Living systematic review methodology – application for pandemic preparedness based on experiences from the COVID-19 pandemic

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I dedicate this dissertation to my sister, Alix, who has always been my greatest source of motivation. I am deeply grateful and proud to call her my sister. She has giving me the confidence and inspiration to pursue this pathway and dedicate my professional career to health research. Through her experiences, I have come to realise the importance of human health and the ongoing need for health research. There is no greater gift than our health, and therefore, we need to protect and maintain it in the best possible way. I would like to contribute to this achievement by enhancing population health through the powerful tool of evidence-based medicine.

Abstract

Background

A living systematic review (LSR) is an emerging review type that incorporates continual updating. During the COVID-19 pandemic, authors were confronted with a shifting epidemiological landscape, clinical uncertainties, and an evolving evidence base. These unexpected challenges compelled us to amend standard LSR methodology. Therefore, LSRs are most suitable for high-priority topics marked by substantial uncertainty and the ongoing publication of new evidence.

Objective

The primary objective of this cumulative dissertation was to explore the methodology of the novel review type, *living systematic review,* in the context of the Coronavirus disease 2019 (COVID-19) pandemic and to devise methods to respond to emerging challenges. The secondary objective was to apply the explored methodology and conduct a living systematic review on a COVID-19 related topic.

Methods

This research involved a methodology concept paper, a scoping review and a Cochrane living systematic review:

- **Concept paper**: A concept paper to explore and discuss the main challenges faced when conducting living systematic reviews during the COVID-19 pandemic, and to provide methodological guidance for similar future endeavours.
- **Scoping review**: A scoping review to systematically provide a comprehensive overview of the available literature on guidance for conducting, reporting, publishing, and appraising living systematic reviews. This aimed to identify areas of lacking evidence.
- **Living systematic review**: A living systematic review with meta-analysis to assess the effectiveness and safety of convalescent plasma transfusion in treating people with COVID-19, using a living approach to ensure the inclusion of the latest evidence.

Results

<u>Methodological results</u>

The concept paper on methodological challenges for LSRs underscored the suitability of the methodology for rapidly emerging diseases. It addresses challenges and considerations specific to LSRs, emphasising the potential need to continuously adapt eligibility criteria and the need for transparent reporting of these changes. Experiences during the COVID-19 pandemic highlighted that updating a LSR depends not solely on the evolving disease or emerging evidence, but also on the review question and the available financial resources.

The scoping review systematically summarised available methodological guidance for conducting, reporting, publishing, appraising LSRs. Identified evidence gaps, especially regarding reporting and appraising quality of LSR, informed the development of a PRISMA 2020 extension for LSR.

The methodological findings were applied in the fifth update version of a living systematic review on convalescent plasma treatment for people with COVID-19.

Clinical results of the conducted living systematic review

The results suggested that convalescent plasma transfusion does not reduce mortality and has little to no impact on clinical improvement or worsening when compared to standard of care alone, with or without placebo, for individuals with moderate to severe COVID-19. Evidence further suggested that the treatment probably has an impact on (serious) adverse events. Limited evidence exists on potential impacts on quality of life and for the comparison to standard plasma and to human immunoglobulin. The effects of convalescent plasma on individuals with mild COVID-19 and vulnerable patient groups (e.g. people with comorbidities or immunosuppression) remain uncertain.

Conclusion

The doctoral projects addressed critical methodological considerations for LSRs conducted on a COVID-19 topic and suggested potential solutions, lessons learned, and implications for future research. Important gaps in LSR guidance were identified and systematically summarized in an evidence map to inform necessary updates. The application of LSR methods to a COVID-19 research topic endorsed key methodological findings. While highly suitable for a pandemic context of rapidly emerging diseases, stakeholders must consider the LSR specific features and adapt to arising challenges. Further research is needed for remaining questions, such as when to ‘retire’ and discontinue the updating of a LSR.

Deutsche Kurzzusammenfassung

Hintergrund

Ein Living Systematic Review (LSR) ist eine aufkommende Form der Übersichtsarbeit „Systematic Review“ und unterscheidet sich hauptsächlich durch die kontinuierliche Suche und Aktualisierung. Während der COVID-19-Pandemie wurden wir mit kritischen Herausforderungen konfrontiert, wie die rasch steigenden Fallzahlen, klinische Unsicherheit und stetig neu auftretenden Erkenntnissen. Diese leiteten uns dazu, die Standardmethodik von LSRs anzupassen. LSRs eignen sich am besten für hochpriorisierte Themen zu denen regelmäßig neue Erkenntnisse veröffentlicht werden.

Ziel

Das primäre Ziel dieser kumulativen Dissertation war es, die Methodik der Review Form Living Systematic Review im Kontext der COVID-19 Pandemie zu untersuchen und herauszufinden, wie diese Methodik an die aufkommenden Herausforderungen angepasst werden kann. Das sekundäre Ziel bestand darin, die erforschte Methodik anzuwenden und ein Living Systematic Review zu einem COVID-19-Thema durchzuführen.

Methodik

Ein Methodik Konzeptpapier, ein Scoping Review (Übersichtsarbeit) und ein Cochrane Living Systematic Review (LSR) wurden durchgeführt:

- **Konzeptpapier**: Ein Konzeptpapier zur Untersuchung der wichtigsten Herausforderungen und möglichen Lösungsansätzen bei der Durchführung von LSRs während der COVID-19-Pandemie. Zudem soll eine methodische Anleitung bereitgestellt werden, für die zukünftige Durchführung ähnlicher Arbeiten.
- **Scoping Review**: Ein Scoping Review zur systematischen Erstellung eines umfassenden Überblicks über die verfügbaren Leitlinien zur Durchführung, Berichterstattung, Veröffentlichung und Bewertung von Living Systematic Reviews, sowie zur Identifizierung von Bereichen mit fehlender Anleitung.
- **Living Systematic Review**: Ein Living Systematic Review mit Meta-Analyse zur Bewertung der Wirksamkeit und Sicherheit der Rekonvaleszentenplasma Transfusion zur Behandlung von Menschen mit COVID-19. Es wurde ein lebender Ansatz verwendet, um die Einbeziehung neuester Erkenntnissen sicherzustellen.

Ergebnisse

Methodische Ergebnisse

Im Konzeptpapier wurde die Eignung der Methodik für schnell auftretende Krankheiten hervorgehoben und auf die sich daraus ergebenden Herausforderungen und Aspekte spezifisch für LSRs eingegangen. In einer lebenden Methodik müssen die Zulassungskriterien für eingeschlossene Studien kontinuierlich angepasst werden. Die zwischen den Aktualisierungen des LSRs vorgenommenen Änderungen sollten transparent berichtet werden. Die Erfahrungen während der COVID-19-Pandemie haben gezeigt, dass die Entscheidung über die Aktualisierung eines LSRs nicht nur von der sich entwickelnden Krankheit oder neuen Erkenntnissen abhängt, sondern auch von der jeweiligen Fragestellung und den verfügbaren finanziellen Ressourcen.

Im Scoping Review wurden die verfügbaren methodischen Leitlinien zur Durchführung, Berichterstattung, Veröffentlichung und Bewertung von LSRs systematisch zusammengefasst. Große Evidenzlücken, insbesondere für die Berichterstattung in LSRs und die Bewertung ihrer Qualität, wurden aufgezeigt und genutzt, um eine PRISMA 2020-Erweiterung für LSRs zu erstellen.

Die methodischen Erkenntnisse wurden in der fünften aktualisierten Version des LSRs zur Untersuchung der Behandlung mit Rekonvaleszentenplasma für Menschen mit COVID-19 angewandt.

Klinische Ergebnisse des durchgeführten Living Systematic Reviews

Die Ergebnisse des durchgeführten LSRs deuten darauf hin, dass die Rekonvaleszentenplasmatransfusion die Sterblichkeit nicht senkt. Im Vergleich zur Standardbehandlung mit oder ohne Placebo, weist die Transfusion bei Personen mit moderater bis schwerer COVID-19-Erkrankung geringe, bis keine Auswirkungen auf die klinische Verbesserung oder Verschlechterung auf. Außerdem gibt es Hinweise darauf, dass die Behandlung wahrscheinlich einen Einfluss auf (schwerwiegende) unerwünschte Ereignisse hat. Darüber hinaus gibt es nur begrenzte Evidenz für mögliche Auswirkungen auf die Lebensqualität und für den Vergleich zu Standardplasma und zu Immunglobulinen. Die Antworten auf die Frage nach der Wirkung von Rekonvaleszentenplasma bei Personen mit leichter COVID-19-Erkrankung und besonders bei gefährdeten Populationsgruppen (Personen mit Begleiterkrankungen oder Immunsuppression) sind mit großer Unsicherheit behaftet.

Schlussfolgerung

Die Projekte der kumulativen Dissertation befassten sich mit kritischen methodischen Aspekten zu LSRs, die zu einem COVID-19-Thema durchgeführt wurden, und präsentierten mögliche Lösungsansätze, Erkenntnisse und Implikationen für zukünftige Forschung. Es wurden große Evidenzlücken in der methodischen Anleitung zur Berichterstattung und Qualitätsbewertung von LSRs identifiziert und systematisch in einer Übersicht zusammengefasst. Diese sollen darauf hinweisen welche methodischen Leitlinien aktualisiert werden müssen. Durch die Anwendung der LSR-Methodik und Durchführung eines LSR zu einem COVID-19 Forschungsthema, konnten diese methodischen Erkenntnisse bekräftigt werden. LSRs eignen sich sehr gut für einen pandemischen Kontext. Die spezifischen Merkmale von LSRs müssen berücksichtigt werden und die Durchführung muss an aufkommenden Herausforderungen anpasst werden. Für einige verbleibende Fragen, wie beispielsweise ab wann ein LSR "in den Ruhestand" versetzt und nicht mehr aktualisiert werden sollte, sind weitere Forschungsarbeiten erforderlich.

Contents

1. Background

1.1 Systematic reviews of interventions

A systematic review (SR) is a crucial methodology for providing evidence-based responses to clinical or public-health related research questions. It employs a priori formulated systematic, explicit, and reproducible methods, grounded in the PICO framework (the acronym for **P**opulation, **I**ntervention, **C**omparison, **O**utcome). This framework defines the scope of the research question (1, 2), aiding authors in formulating a precise research question and defining the eligibility criteria for the selection of studies to be included. It provides information on the population of interest, the intervention(s) of interest, the comparator(s) of interest and the outcome(s) of interest. Ideally, a multidisciplinary team, including at least one author with methodological expertise and at least one author with clinical expertise, conducts a systematic review (1).

Both Cochrane and non-Cochrane systematic reviews should adhere to the gold standard methodology proposed by the *Cochrane Handbook for Systematic Reviews of Interventions* (1). This handbook provides step-by-step guidance, ensuring robust data management, good project management, and quality assurance. Authors should register the title of a proposed review to prevent duplication of work. A protocol documenting the pre-specified research question(s) and the methods, based on the PCIO, should be published to ensure a transparent and traceable review process and minimize any bias (1).

However, standard systematic reviews are not designed for continuous updates and, thus, may not ensure the currency of evidence. In scenarios involving rapidly emerging diseases, such as during the COVID-19 pandemic, a systematic review might prove less suitable. A potential solution to this challenge is the promising methodology of living systematic reviews, providing high-quality, relevant and up-to-date information for health decision-makers (3).

1.2 Living systematic reviews as emerging review type

Living systematic review methodology

A living systematic review (LSR) is a dynamic systematic review type continually updated and incorporating ongoing surveillance and regular searches for the most current evidence available (4). To achieve this, LSR authors commit to specific methods and frequencies of updating the review. Cochrane Reviews have the option to transition into and discontinue the living mode, when there is no necessity anymore, based on pre-specified criteria (3). Thus, the LSR methodology is well-suited for highly relevant research areas with substantial uncertainty and continuously updated evidence bases (4). The intricacies of LSRs have been explored and discussed

in a four-paper series (4-7), and their prominence has increased (8) since first LSRs were published in 2016 (9, 10). Cochrane published the first version of a living review in 2017 (11) and a guidance on the conduct and publication of Cochrane LSRs has been released in 2019 (3).

Difference between systematic reviews and living systematic reviews

While LSRs use the standard systematic review methodology following the required key steps, there are certain methodological decisions specific to LSRs that must be predefined at protocol stage (3). The main differences between SRs and LSRs are outlined in comparison table 1, based on the Cochrane guidance (3). A key distinction is the frequency of seeking and screening new evidence. The Cochrane guidance suggests that bibliographic databases and trial registries should be specifically mentioned in the methods and searched monthly. Additional sources, such as grey literature can be searched less frequently.

	Living systematic review	**Standard systematic review**	**Frequently updated review**
Explicit, pre-defined methods describing search frequency	✓	×	×
Explicit, pre-defined methods describing when new evidence is incorporated into the review	✓	×	×
Continual evidence surveillance	✓	×	?
New evidence is immediately flagged for reader or incorporated into review	✓	×	?
Standard SR methods (e.g. screening, data extraction and risk of bias assessment)	✓	✓	✓

Table 1. Distinction between LSR, standard SR and frequently updated review (based on Cochrane guidance (3))

Key steps in the conduct of living systematic reviews

As displayed in table 1, LSRs follow standard SR methods for key steps of conduct (1). After title registration and protocol publication, where the inclusion and exclusion criteria, the search strategy and methods and additional considerations specific to LSRs are documented, the conduction process is initiated (3). Figure 1 illustrates the circular, continuous process of the living systematic review methodology, including the key steps. The first step is the literature search, conducted by an information specialist, with ongoing evidence surveillance, where key data-

bases and trial registries are searched monthly. LSRs require searching certain databases, including CENTRAL[1], MEDLINE[2] and Embase[3], the registries ClinicalTrials.gov and WHO ICTRP[4] and continuous reference checking of new included studies. The subsequent step is the screening of title and abstract, followed by full text screening of references to select eligible studies. The third step is the data extraction of the included studies, focusing on the pre-specified study characteristics and patient-relevant outcomes. The fourth step encompasses the methodological quality and risk of bias assessment in included studies using, for instance, the Cochrane Risk of Bias 2.0 tool (12) for randomized controlled trials. Different tools are available for assessing the risk of bias for different types of studies. Step two to four are conducted by at least two authors independently to avoid random errors and risk of bias in the LSR conduction process.

Fifthly, the extracted results on the outcome of interests are synthesised, either narratively or if suitable data is available, quantitatively in meta-analyses. Sixthly, the certainty in the evidence needs to be assessed, using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (13). The seventh step consists in writing up the results of the LSR, usually with the input of the clinical experts. The subsequent step is the publication of the review, after the peer review process, either in the Cochrane Library or in another journal of choice. The ultimate step is specific to LSRs and consists of the revision of the eligibility criteria and refinement of the search methods, before commencing the process of a new update version. In this last step, the review scope and the underlying PICO will be assessed, the search strategy and the search frequency will be revised, and the resources of the author team need to be reconsidered. Updating a review requires a high level of resources that need to be available throughout the living period.

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[1] The Cochrane Central Register of Controlled Trials (CENTRAL) contains journal articles of randomised and quasi-randomised controlled trials (www.cochranelibrary.com/central/about-central).

[2] MEDLINE is the National Library of Medicine's (NLM) primary bibliographic database containing journal articles in life sciences and biomedicine (www.nlm.nih.gov/medline/medline_overview.html).

[3] Embase is the medical research database for high-quality, comprehensive evidence (https://www.elsevier.com/products/embase)

[4] The International Clinical Trial Registry Platform (ICTRP) provides a complete view of research is accessible to all those involved in health care decision making (https://www.who.int/clinical-trials-registry-platform)

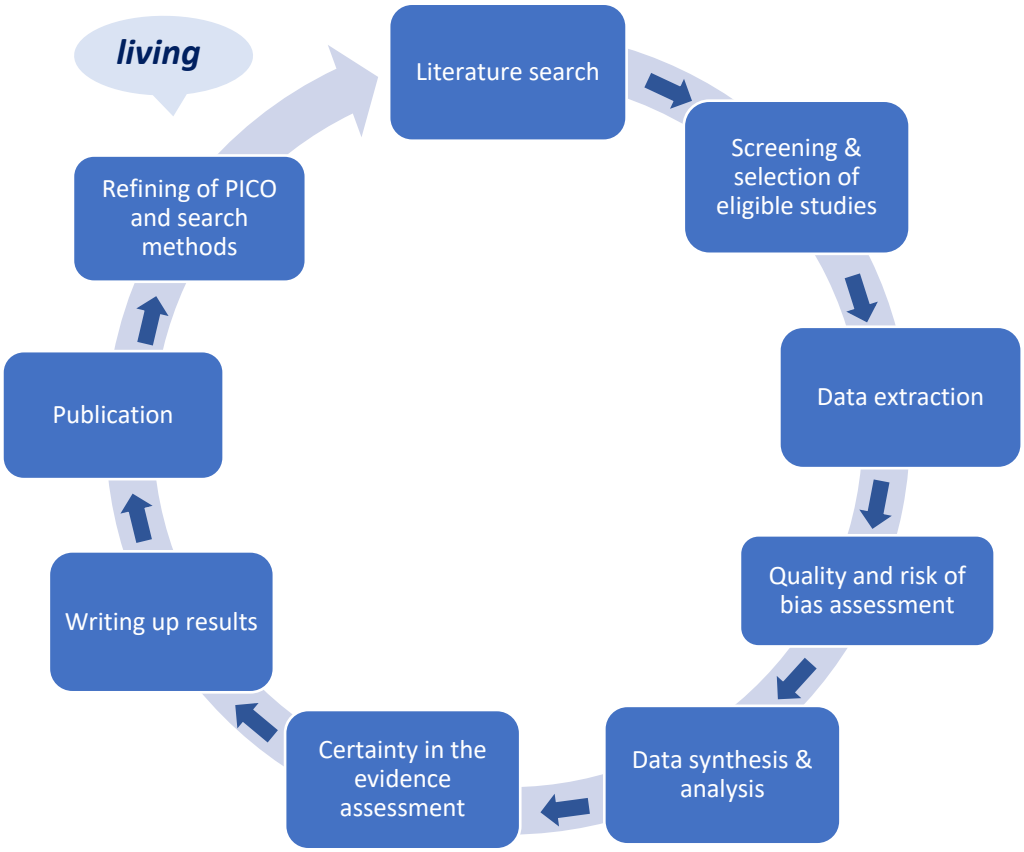

Figure 1. Key steps in the methodology of conducting LSRs (own representation)

Why and when to do living systematic reviews

As described by Elliott and colleagues (4), a LSR is an appropriate review type when all of the following three criteria are met. First, the review question(s) must be a particular priority for evidence-based decision-making. Second, a crucial level of uncertainty exists in the currently available evidence. Third, the field of interest is rapidly evolving with emerging evidence likely to be produced continuously, which might have an impact on the conclusion of the LSR.

1.3 Updating living systematic reviews

A defining feature of LSRs is the continuous updating of evidence. For Cochrane LSRs, it is usual to update and publish a completely new review version in the Cochrane Library, however, this can differ for LRSs published with other journals. Regarding the frequency of updating a LSR, Cochrane suggests two options. The first option proposes to update the review when the newly identified and included evidence is likely to have an impact on the conclusion of the current LSR (3). In this case, there are three possible scenarios to follow, after completing the search and screening of the evidence. In scenario one, no new evidence, including studies, additional data, or information, has been identified and thus, the review conclusion remains up to date. In scenario two, new evidence has been identified, but is unlikely to have a crucial impact

on the current review results and therefore, it can be incorporated subsequently. The conclusion of the review will be considered up to date as well. In scenario three, new important evidence has been identified and is likely to have a valuable impact on the review results and thus, change the review conclusion. In this scenario a full review update is usually conducted (3).

The second option suggests to update the review on a fixed interval schedule when an important number of new studies can be expected (3). In this case, often similar scenarios to those from the first option arise. However, decisions need to be made at protocol stage on whether to still update the review even if no new evidence, or evidence unlikely to have an impact on the review findings, is identified in the ongoing search, despite the fixed updating schedule (3).

1.4 The COVID-19 pandemic and LSR methodology

COVID-19 - burden of disease

The World Health Organization (WHO) declared on March 11, 2020, the Coronavirus disease 2019 (COVID-19) outbreak to be a global pandemic (14). The clinical syndrome COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a rapidly spreading zoonotic infections disease (15). As of December 17, 2023, global reports indicated more than 772 million confirmed COVID-19 cases and nearly seven million deaths (16, 17). With over 850 000 new cases reported, the number of new cases increased by 52% during the 28-day period of November 20 to December 17, 2023, compared to the previous 28-day period (17).

COVID-19 and its emerging evidence suitable for LSRs?

In comparison to previous coronavirus outbreaks like the severe acute respiratory syndrome (SARS) with 813 deaths or the Middle East respiratory syndrome (MERS) with 858 deaths (18, 19), COVID-19 is unprecedented. Despite intense global efforts to curb its spread, SARS-CoV-2 has continued with an ongoing increase of new weekly cases and deaths in various regions worldwide (16). Concurrently, the emergence of new SARS-CoV-2 variants has introduced new challenges and complexities. Factors such as the median incubation time and time to symptom onset highly depend on the SARS-CoV-2 variant. The Omicron SARS-CoV-2 variant exhibits a shorter estimated incubation time (three days for an infection), compared to the Delta SARS-CoV-2 variant and other non-Delta SARS-CoV-2 variants that circulated previously (20, 21). A new variant can potentially alter the disease transmission, the course, and characteristics of the disease, which could affect the effectiveness of vaccines, diagnostic measures, therapeu-

tics, as well as public health and social measures (22). Ultimately, this puts new critical challenges to decision-making and their strategies to control disease spread (22). Thus, COVID-19 disease management, encompassing clinical and public-health care and prevention strategies, has become a top priority for global decision-makers.

The rapidly evolving nature of COVID-19, with constantly new evidence emerging, necessitates decision-making to continuously update evidence-based recommendations and clinical guidelines on COVID-19 management (23). Living guidelines and living systematic reviews are particularly well-suited for investigating an emerging disease like COVID-19. However, the unique challenges posed by the pandemic context must be addressed, despite the inherent adaptability of living systematic review methodology, being constructed for continuous updates and ongoing evidence surveillance. Based on lessons learned from this pandemic, adjustments to the LSR methodology may be necessary to enhance future pandemic preparedness.

2. Objectives

The primary objective of this cumulative dissertation was to explore the methodology of the novel review type, living systematic review, in the context of the COVID-19 pandemic. The exploration aimed to adapt the methods to effectively address the emerging challenges posed by the pandemic. The secondary objective was to apply the investigated methodology and conduct a living systematic review during the COVID-19 pandemic. This cumulative dissertation encompasses a methodological concept paper, a scoping review on LSR methods guidance and a Cochrane living systematic review. An overview of the objectives, projects, and their connections is visually depicted in figure 2 (p.9).

Publication 1: Methodological challenges for living systematic reviews conducted during the COVID-19 pandemic: A concept paper

The concept paper aimed to explore and discuss significant challenges encountered when conducting living systematic reviews during the COVID-19 pandemic. Additionally, it sought to provide methodological guidance and share lessons learned for others engaged in similar work (24). In chapter 3 of the dissertation, a visual abstract (p.13) and a written summary (p.14) of the concept paper are provided.

Publication 2: Methods and guidance on conducting, reporting, publishing and appraising living systematic reviews: a scoping review

The primary aim of the scoping review was to systematically provide a comprehensive overview of available literature on guidance for the conduct, report, publication, and appraisal of living systematic reviews. The secondary aim was to identify areas with lack of evidence and to inform research who plan to adapt standard systematic review guidance to suit the living methodology (25). In chapter 3 of the dissertation, a visual abstract (p.17) and a written summary (p.18) of the scoping review are provided.

Publication 3: Convalescent plasma for people with COVID-19: a living systematic review

The aim of the living systematic review with meta-analysis was to assess the effectiveness and safety of convalescent plasma transfusion in the treatment of people with COVID-19. To ensure the currency of the evidence, the living approach with continuously updated searches was applied (26). In chapter 3 of the dissertation, a visual abstract (p.21) and a written summary (p.22) of the review are provided.

Figure 2. Graphical overview of doctoral projects and objectives (own representation made in Canva)

3. Dissertation project synopses

Publication 1. Methodological challenges for living systematic reviews conducted during the COVID-19 pandemic: A concept paper

In the main body of this dissertation a comprehensive summary of the concept paper in the form of a visual abstract and a written summary are provided. The summary entails sentences and text excerpts from the original published manuscript (24), which is available in Appendix B.

Citation of the published article:

Iannizzi C, Dorando E, Burns J, Weibel S, Dooley C, Wakeford H, Estcourt LJ, Skoetz N, Piechotta V. Methodological challenges for living systematic reviews conducted during the COVID-19 pandemic: A concept paper. J Clin Epidemiol. 2022 Jan;141:82-89. doi: 10.1016/j.jclinepi.2021.09.013.

Visual abstract

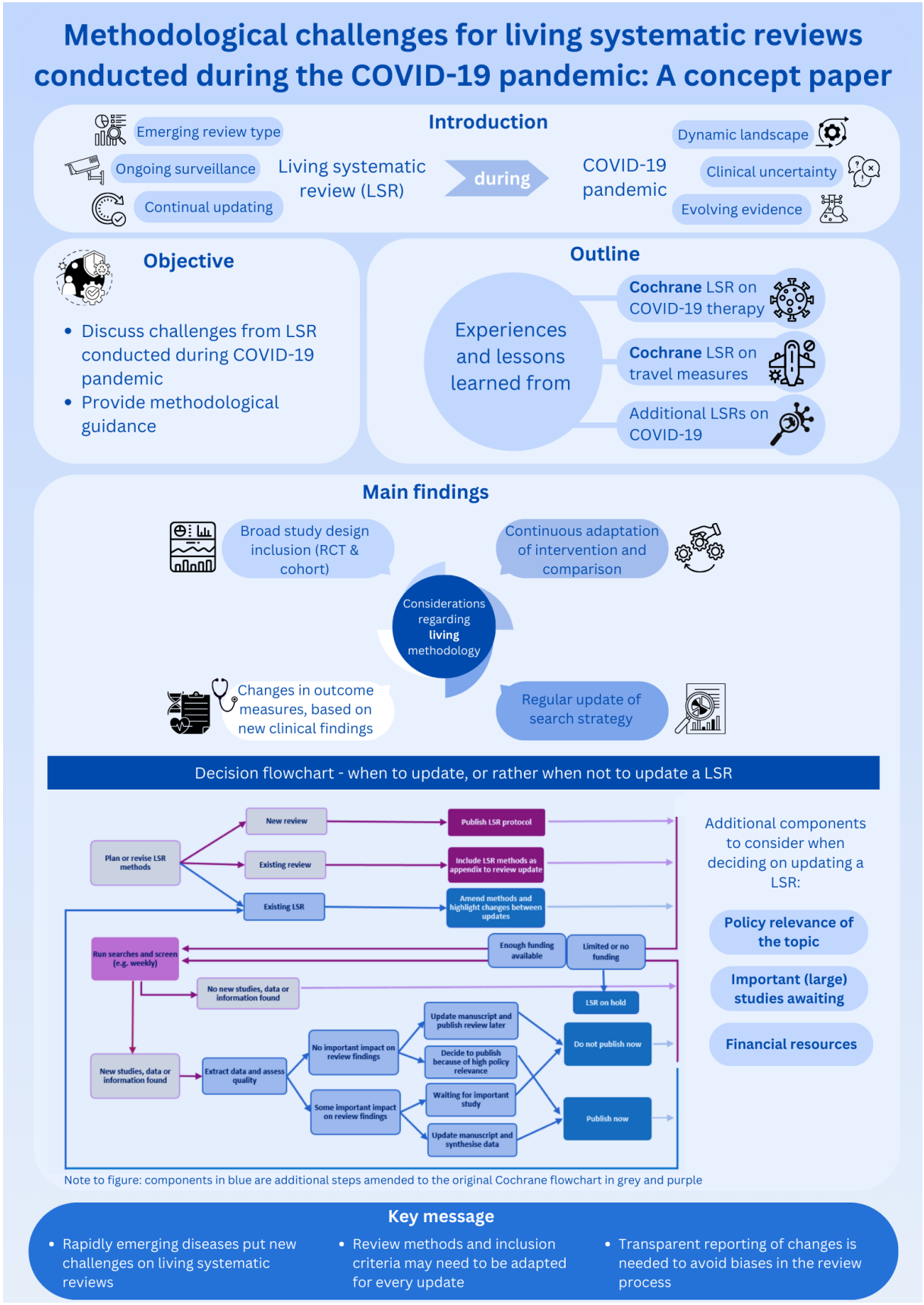

Figure 3. Visual abstract of methodological concept paper

Written summary and main results

Introduction

A living systematic review (LSR) is an emerging review type continuously updated to include the latest evidence (4). In the COVID-19 pandemic, LSR authors were confronted with a shifting epidemiological landscape, clinical uncertainties, and evolving evidence. These unexpected challenges compelled us to amend standard LSR methodology.

Objective and outline

The primary objective was to discuss the emergence and methodology of LSRs considering significant challenges faced when conducting LSRs in the context of the COVID-19 pandemic. The secondary objective was to provide methodological guidance for others engaged in similar work. Based on experiences and lessons learned from two Cochrane LSRs and challenges identified in several non-Cochrane LSRs, the paper highlighted methodological considerations, particularly with regards to the study design, interventions and comparators, changes in outcome measure, and the search strategy. It also discussed when to update, or rather when not to update the review, and the importance of transparency when reporting changes.

Main findings and lessons learned

This concept paper emphasizes the suitability of LSRs for high-priority topics with substantial clinical uncertainty, particularly in the context of the evolving COVID-19 pandemic.

Considerations regarding a living methodology – experiences from a pandemic

Regarding the study design to include when planning a LSR, authors should rely on the best available evidence, which depends on the research question and will likely evolve rapidly. Authors also experienced that the investigated interventions and comparators might change throughout the pandemic and therefore, needed to be adapted in the review process, especially between updates. Similarly, as more evidence became available, outcome measures needed to be refined and the outcome set was never "final", but constantly evolving. The search strategy of a review also required reassessments, due to the dynamic nature of electronic databases in the pandemic.

When to update, or rather when *not* to update

In the context of the COVID-19 pandemic, the paper defined additional components that can affect the decision of whether to update, publish, neither or both. These include policy relevance of the topic, awaiting important studies and available funding. This process i depicted in the *LSR decision flowchart*, displayed in the visual abstract.

Transparency in the reporting of changes

The paper discussed the relevance of transparent reporting of the differences between the protocol and first review version, as well as changes between the review update versions. An overview tables enabling the comprehensive reporting in LSRs is presented in the original manuscript.

Conclusion

Rapidly emerging diseases pose new challenges on LSRs. For a living methodology, inclusion criteria of LSRs may need to be adapted continuously and these changes made must be transparently reported. Author´s experiences during the COVID-19 pandemic showed that the decision for updating a LSR depends not solely on the evolving disease or the emerging evidence, but also on the individual review question and the availability of financial resources. The lessons learned described in the paper could be valuable for future pandemic preparedness. The question on when to ‘retire’ and discontinue the updating of a LSR could be an implication for further research and discussion.

Publication 2. Methods and guidance on conducting, reporting, publishing and appraising living systematic reviews: a scoping review

In the main body of this dissertation a comprehensive summary of the scoping review in the form of a visual abstract and a written summary are provided. The summary entails sentences and text excerpts from the original published manuscript (25), which is available in Appendix C.

Citation of the published article:

Iannizzi C, Akl EA, Anslinger E, Weibel S, Kahale LA, Aminat AM, Piechotta V, Skoetz N. Methods and guidance on conducting, reporting, publishing, and appraising living systematic reviews: a scoping review. Syst Rev. 2023 Dec 14;12(1):238. doi: 10.1186/s13643-023-02396-x.

Visual abstract

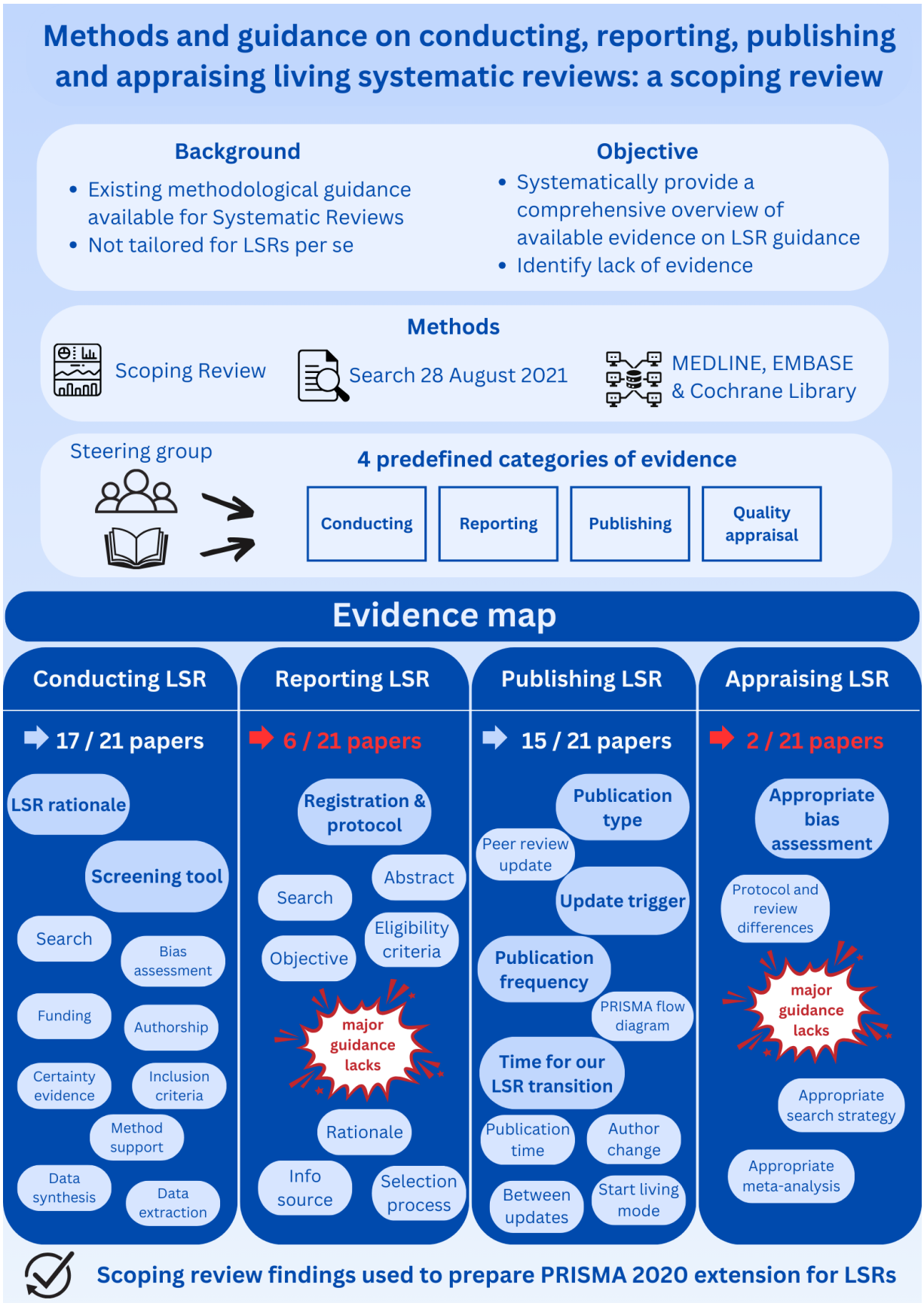

Figure 4. Visual abstract of methodological scoping review

Written summary and main results

Background

The living systematic review (LSR) approach is based on ongoing surveillance of the literature and continual updating (4). Most currently available guidance documents address the conduct, reporting, publishing, and appraisal of systematic reviews (SRs), but are not suitable for LSRs per se and miss additional LSR-specific considerations.

Objective

The primary aim of the scoping review was to systematically provide a comprehensive overview of available literature on guidance for the conduct, report, publication, and appraisal of living systematic reviews. The secondary aim was to identify areas with lack of evidence and to inform research who plan to adjust standard systematic review guidance to suit the living methodology. This scoping review was part of a larger project to develop an extension of the reporting guidance *PRISMA 2020 statement* for living systematic reviews (27).

Methods

Standard scoping review methodology was used (28). The Databases MEDLINE (Ovid), EMBASE (Ovid), and The Cochrane Library were searched on August 28, 2021. As for searching grey literature, existing guidelines, and handbooks on LSRs from organizations that conduct evidence syntheses were looked at. Screening was conducted by two authors independently in Rayyan and data extraction was done in duplicate using a pilot-tested data extraction form in Excel. Data was extracted according to four pre-defined categories for (i) conducting, (ii) reporting, (iii) publishing, and (iv) appraising LSRs and mapped in visualizing overview tables created in Microsoft Word.

Results

Of the 21 included papers, methodological guidance was found in 17 papers for conducting, in six papers for reporting, in 15 papers for publishing, and in two papers for appraising LSRs. Some of the identified key items for (i) conducting LSRs, were identifying the rationale; screening tools; or re-evaluating inclusion criteria. Identified items of (ii) the original PRISMA checklist, included reporting the registration and protocol; title; or synthesis methods. For (iii) publishing, there was guidance available on publication type and frequency or update trigger and for (iv) appraising, guidance on the appropriate use of bias assessment or reporting funding of included studies was found. Our search revealed major evidence gaps, particularly for guidance on certain PRISMA items such as reporting results; discussion; support and funding; and availability of data and material of a LSR.

Conclusion

Important evidence gaps were identified for guidance on how to report in LSRs and appraise their quality. Our findings were applied to inform and prepare a PRISMA 2020 extension for LSR.

Publication 3. Convalescent plasma for people with COVID-19: a living systematic review

In the main body of this dissertation a comprehensive summary of the living systematic review in the form of a visual abstract and a written summary are provided. The summary entails sentences and text excerpts from the original published manuscript (26), which is available in Appendix D.

Citation of the published article:

Iannizzi C, Chai KL, Piechotta V, Valk SJ, Kimber C, Monsef I, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Jindal A, Cryns N, Estcourt LJ, Kreuzberger N, Skoetz N. Convalescent plasma for people with COVID-19: a living systematic review. Cochrane Database of Systematic Reviews 2023, Issue 5. Art. No.: CD013600. DOI: 10.1002/14651858.CD013600.pub6.

Visual abstract

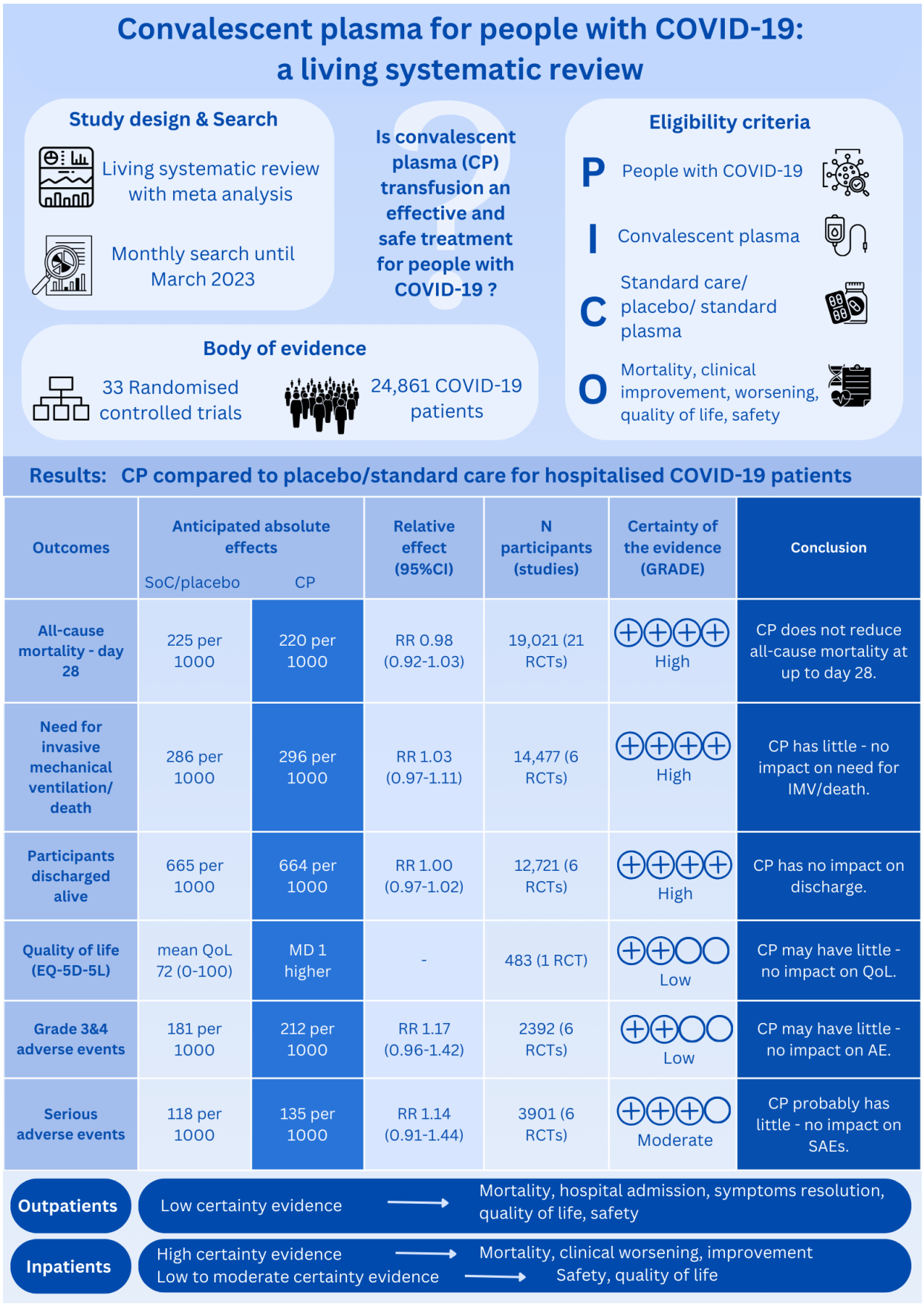

Figure 5. Visual abstract of living systematic review

Written summary and main results

Background

Description of the condition

The clinical syndrome COVID-19 is a rapidly emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (15). The World Health Organization (WHO) declared on 11 March 2020 (14), the current COVID-19 outbreak to be a pandemic, with the outbreak resulting in more than 772 million confirmed cases and nearly seven million deaths globally as of December 2023 (16, 17). Concurrently, new SARS-CoV-2 variants emerged, potentially having an effect on the transmission and characteristics of the disease, the effectiveness of vaccines and treatments, or on public health and social measures (22).

Description of the intervention

Convalescent plasma, obtained from people who have recovered from an infection disease, such as the SARS-CoV-2 infection, has been used in the past to treat conditions when no vaccine or pharmacological interventions were available (29). It contains pathogen-specific neutralising antibodies, which can neutralise viral particles and may confer passive immunity to recipients (30). The duration of conferred protection can differ depending on the timing of administration, ranging from weeks to months after treatment (30). There is conflicting evidence about the effect of convalescent plasma for treating severe acute respiratory infections (31). Convalescent plasma may reduce mortality in patients with viral respiratory diseases and is being investigated as a potential therapy for COVID-19 (32). Therefore, a thorough understanding of the current body of evidence regarding effectiveness and safety of this intervention is required.

Objectives

The primary objective of this living systematic review with meta-analysis was to assess the effectiveness and safety of convalescent plasma transfusion in the treatment of people with COVID-19. The secondary objective was to maintain the currency of the evidence and conduct continuous (monthly) update searches using a living systematic review approach.

Methods

The methods recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* were followed.

Selection criteria

Randomised controlled trials (RCTs), if performed appropriately, give the best evidence for experimental therapies in highly controlled therapeutic settings, were included. Studies on populations with other coronavirus diseases (SARS or MERS), as well as studies evaluating standard immunoglobulin were excluded. Detailed eligibility criteria are listed in table 2.

Population	**I**ntervention	**C**omparator	**O**utcome (critical)
Individuals with a confirmed diagnosis of COVID-19 • with any disease severity • with no age, gender or ethnicity restrictions	Convalescent plasma from people who had recovered from SARS-CoV-2 infection	(1) Standard of care or placebo (i.e. saline solution) (2) Standard plasma (i.e. fresh frozen plasma) (3) Control treatment, e.g. drug treatments (including but not limited to hydroxychloroquine, remdesivir) or standard immunoglobulin	All-cause mortality at up to day 28, worsening and improvement of clinical status (for individuals with moderate to severe disease), hospital admission or death, COVID-19 symptoms resolution (for individuals with mild disease), quality of life, grade 3 or 4 adverse events, and serious adverse events

Table 2. Eligibility criteria of LSR on convalescent plasma transfusion

Search methods

To identify completed and ongoing studies, the World Health Organization (WHO) COVID-19 Global literature on coronavirus disease Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, and the Epistemonikos COVID-19 L*OVE Platform were search monthly until March 03, 2022.

Data collection and analysis

To assess the risk of bias in included studies the Cochrane RoB 2 tool was used. The certainty of evidence was rated using the GRADE approach. All the steps in the review development process were conducted independently by at least two review authors, except for the electronic searches (conducted by an experienced information specialist). Discrepancies were resolved through discussion and by involving a third author.

Further details on study selection, data extraction, dealing with missing data, assessment of heterogeneity, data synthesis and other information are reported in the full manuscript.

Main results

In this fifth review update version, 33 RCTs with 24,861 participants, of whom 11,432 received convalescent plasma were included. More detailed information on the included studies and participants are reported in the full manuscript. Separate analyses were conducted for individuals with moderate to severe COVID-19 disease and for individuals with mild COVID-19 disease.

Further results of secondary outcomes and subgroup, as well as sensitivity analyses can be found in the full manuscript.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

Data from 29 RCTs investigating the use of convalescent plasma for 22,728 participants with moderate to severe disease were analysed. 23 RCTs with 22,020 participants compared convalescent plasma to placebo or standard of care alone, five compared to standard plasma and one compared to human immunoglobulin. We evaluate subgroups on detection of antibodies detection, symptom onset, country income groups and several co-morbidities in the full manuscript.

Convalescent plasma versus placebo or standard of care alone

The analyses showed that convalescent plasma does not reduce all-cause mortality at up to day 28 (risk ratio (RR) 0.98, 95% confidence interval (CI) 0.92 to 1.0; 19,021 participants; high-certainty evidence). It has little to no impact on need for invasive mechanical ventilation, or death (RR 1.03, 95% CI 0.97 to 1.11; 14,477 participants; high-certainty evidence) and has no impact on whether participants are discharged from hospital (RR 1.00, 95% CI 0.97 to 1.02; 12,721 participants; high-certainty evidence). Convalescent plasma may have little to no impact on quality of life (MD 1.00, 95% CI −2.14 to 4.14; 483 participants; low-certainty evidence). Convalescent plasma may have little to no impact on the risk of grades 3 and 4 adverse events (RR 1.17, 95% CI 0.96 to 1.42; 2392 participants; low-certainty evidence). It has probably little to no effect on the risk of serious adverse events (RR 1.14, 95% CI 0.91 to 1.44; 3901 participants; moderate-certainty evidence). Further details for this comparison are displayed in the visual abstract.

Convalescent plasma versus standard plasma

Regarding the comparison with standard plasma, we were uncertain whether convalescent plasma reduces or increases all-cause mortality at up to day 28 (RR 0.73, 95% CI 0.45 to 1.19; 484 participants; very low-certainty evidence). Similarly, we were uncertain whether convalescent plasma reduces or increases the need for invasive mechanical ventilation, or death (RR 5.59, 95% CI 0.29 to 108.38; 34 participants; very low-certainty evidence) and the risk of serious adverse events (RR 0.80, 95% CI 0.55 to 1.15; 327 participants; very low-certainty evidence). No further outcomes were reported for this comparison.

Convalescent plasma versus human immunoglobulin

When comparing convalescent plasma to human immunoglobulin, it may have little to no effect on all-cause mortality at up to day 28 (RR 1.07, 95% CI 0.76 to 1.50; 190 participants; low-certainty evidence). No further outcomes were reported for this comparison.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease

Data from two RCTs with 536 participants, comparing convalescent plasma to placebo or standard care alone, and two RCTs with 1597 participants, comparing convalescent plasma to standard plasma was analysed.

Convalescent plasma versus placebo or standard care alone

We were uncertain whether convalescent plasma reduces all-cause mortality at up to day 28 (odds ratio (OR) 0.36, 95% CI 0.09 to 1.46; 536 participants; very low-certainty evidence). It may have little to no effect on admission to hospital or death within 28 days (RR 1.05, 95% CI 0.60 to 1.84; 376 participants; low-certainty evidence), on time to COVID-19 symptom resolution (hazard ratio (HR) 1.05, 95% CI 0.85 to 1.30; 376 participants; low-certainty evidence), on the risk of grades 3 and 4 adverse events (RR 1.29, 95% CI 0.75 to 2.19; 376 participants; low-certainty evidence) and the risk of serious adverse events (RR 1.14, 95% CI 0.66 to 1.94; 376 participants; low-certainty evidence). We did not identify any study reporting other key outcomes.

Convalescent plasma versus standard plasma

We were uncertain whether convalescent plasma reduces all-cause mortality at up to day 28 (OR 0.30, 95% CI 0.05 to 1.75; 1597 participants; very low-certainty evidence). It probably reduces admission to hospital or death within 28 days (RR 0.49, 95% CI 0.31 to 0.75; 1595 participants; moderate-certainty evidence). Convalescent plasma may have little to no effect on initial symptom resolution at up to day 28 (RR 1.12, 95% CI 0.98 to 1.27; 416 participants; low-certainty evidence). We did not identify any study reporting other key outcomes.

Authors' conclusions

Implication for practice

For the comparison of convalescent plasma versus placebo or standard of care alone, our certainty in the evidence that convalescent plasma for individuals with moderate to severe disease does not reduce mortality and has little to no impact on clinical improvement or worsening is high. It probably has little to no effect on SAEs. For individuals with mild disease, we have low certainty evidence for our primary outcomes.

Implication for research

There are 49 ongoing studies, and 33 studies reported as complete in the trial registries. Publication of ongoing studies might resolve some of the uncertainties around convalescent plasma therapy for people with asymptomatic or mild disease and for certain subgroups.

4. Discussion

4.1 Summary of doctoral projects

The primary objective of this dissertation was to explore the methodology of the novel review type *living systematic review* in the context of the COVID-19 pandemic and how to adapt the methods to respond to the emerging challenges. The secondary objective was to apply the explored methodology and conduct a living systematic review during the COVID-19 pandemic.

To achieve the primary objective, a concept paper exploring the methodological challenges and discussing lessons learned from LSRs conducted on a COVID-19 topic (24) was included in this dissertation. The concept paper emphasised on the suitability of the methodology for rapidly emerging diseases and addressed considerations specific to LSRs. It discussed the living mode of eligibility criteria, the timing of LSR updates, and how to transparently report changes between LSR update versions. Additionally, a scoping review providing a systematic overview of available methodological guidance for LSRs (25) was included in this dissertation. The overview exposed major evidence gaps, particularly for guidance on reporting in LSRs and appraise their quality. The findings were used to prepare an extension of the PRISMA 2020 checklist for LSRs.

To achieve the secondary objective, the LSR methodology was applied in the fifth update version of the living systematic review on convalescent plasma for the treatment of COVID-19 (26). This exemplar review applied and reinforced some of the explored findings and lessons learned on the LSR methodology during the COVID-19 pandemic. The critical revision of the living search strategy, frequency of search, and inclusion criteria was considered. Similarly, the decision flowchart on whether to update the review was consulted when new evidence was identified in the ongoing search. An overview table presenting the methodological changes between the five update versions was incorporated to provide a transparent report on the differences in the methods. While most of the research questions could be answered with the identified evidence, uncertainties remained for individuals with mild COVID-19 and vulnerable patient groups (e.g. people with comorbidities or immunosuppression).

4.2 Implications for living systematic review methodology

Certain aspects and features of the LSR methodology require special consideration due to potential limitations is the conduction process. The continuous and active monitoring of new evidence and ongoing search impose an intensive burden of resources for authors. Monthly con-

ducted searches need to be regularly screened, which can be exhaustive depending on the evidence volume. Producing a Cochrane review, with a full update of the LSR, is highly time-consuming, as each section requires special attention and might need to be refined and sometimes rewritten. Moreover, Cochrane reviews are known to be longer than LSRs published in other journals and their production, including long editorial and peer review processes, can last up to two years. During the pandemic, COVID-19 related LSRs were prioritised as "fast track" reviews by the Cochrane Central Editorial Service, allowing completion in three to six months (33). Other methodological challenges and considerations remain unsolved in practice application and need further guidance. A key challenge is determining when a LSR is (still) useful or when to "retire" it, as given criteria might not be easily transferable to practice. Regarding the lack of LSR-specific guidance, an extension of the PRISMA 2020 checklist (34) for reporting of LSRs is currently under production (27). Urgent guidance is needed for appraising the quality of LSRs, suggesting that the current AMSTAR 2 - A MeaSurement Tool to Assess systematic Reviews – tool (35) should be updated for LSRs. Further methodological implications, particularly regarding challenges raised during the COVID-19 pandemic, are discussed in the concept paper (24) included in this dissertation.

4.3 Implications for research

Evolution of the evidence base for the convalescent plasma LSR

In the protocol of the LSR on convalescent plasma (36), it was planned to include any study design determined by the availability of sufficient evidence and by priority of highest evidence level. Study designs were intended to be included from highest to lowest priority, considering RCTs at the top, followed by prospective controlled non-randomised studies of interventions (NRSIs), prospective observational studies with a control group, and, lastly, prospective non-comparative study designs (e.g. case series). It is interesting to compare the study designs incorporated throughout the various review versions, reflecting the development of the evidence base of published studies on COVID-19, specifically on convalescent plasma treatment, during the pandemic. The base version of the LSR published in May 2020 (37) found only prospective non-comparative study designs to include, as this was the best available evidence at the beginning of the pandemic. The first update version of the LSR published in July 2020 (38) could include one RCT, three prospective controlled NRSI, and further safety data from non-controlled NRSIs. The second update version published in October 2020 (39) incorporated a second RCT, eight controlled NRSIs, and further safety data from nine non-controlled NSRI. There was enough data from controlled studies available in both versions; thus, only safety data was

added from non-controlled studies. The third update version published in March 2021 (40) included 12 RCTs and one prospective registered single-arm study with more than 500 participants for safety data. The fourth and the fifth (an amendment) update version published in 2023 (26) included a total of 33 RCTs that reported enough safety data, leading to exclusion of single-arm studies. Among the 33 RCTs, with a total of 24,861 participants, the majority were small to moderately large trials ranging from 30 to 350 participants, with only a few larger trials with nearly 2000 participants (RECOVERY and REMAP-CAP trials) (41, 42). The evolution of the study design inclusion reflects the paucity of high-quality evidence, especially the preferred RCT design, at the beginning of the pandemic. The objective was to synthesise and critically appraise all available evidence at a given time and to update the review as more and potentially more trustworthy evidence became available, leading to the multiple update versions published. As more RCT data became available, the certainty in the evidence increased considerably.

The rapid emergence and evolution of new knowledge and evidence on COVID-19 was also reflected in the primary studies included in the review. Studies did not consistently report outcomes for instance. Similarly, they did not always consider changes in standard of care treatment throughout the pandemic, impeding comparability in terms of co-interventions administered within and between studies. Regarding the reporting of adverse events, studies mostly failed to report safety consistently for both the intervention and the control arm, and to blind at least the outcome assessors, leading to an elevated risk of bias. Moreover, there was no evidence on convalescent plasma treatment in asymptomatic people. It would be highly interesting to assess whether the intervention is more effective if given earlier in the disease course. Limited evidence was available for people with mild COVID-19 disease severity and for subgroups, including immune-suppressed patients and subgroup data of plasma from SARS-CoV-2 variants. However, there are more than 40 ongoing studies and 30 completed studies with awaiting publication of results that are being tracked, as they might potentially resolve some of the mentioned uncertainties.

The evidence produced for this LSR was also used in living clinical guidelines and recommendations, specifically the German COVID-19 evidence ecosystem (CEOsys) (43), one of 13 projects within a research network of medical faculties and university hospitals in Germany.

The COVID-19 pandemic and its impact on the evidence pipeline

Carley and colleagues stated that "The COVID-19 pandemic has arguably been one of the greatest challenges to evidence-based medicine since the term was coined in the last century" (44). After more than three years since the beginning of the pandemic, major weaknesses have been exposed in the production and usage of evidence-based evidence. More than 2,900 clinical trials related to a COVID-19 research topic were registered (33). However, the large majority of trials were too small or poorly designed and reported to provide meaningful results and robust and trustworthy evidence (33). A similar scenario, described in the previous section of the discussion, was observed in the LSR on convalescent plasma. At the same time, exemplary trials of good practice, rigorous evidence, and having large sample sizes were conducted for various potential COVID-19 treatments. RECOVERY (41) and REMAP-CAP (42), two multi-factorial adaptive platform trials (45), are shining examples of these good practices and brought evidence related to COVID-19 treatments significantly forward. The RECOVERY trial, for instance, enrolled more that 45,000 people at 188 active sites and produced results changing the standard treatment of COVID-19 significantly (33). One crucial lesson learned for further pandemics or comparable situations with vivid research fields is that more large-scale national and international clinical trials are needed between countries to rapidly initiate high-quality evidence.

4.4 Strengths and limitations of this cumulative dissertation

An important strength of this dissertation is that it includes two publications on LSR methodology and contributes to the refinement and adaptation of outdated parts of this method when applied to emerging research fields. The concept paper revealed challenges and weaknesses of the methods experienced by authors conducting LSRs related to COVID-19 during the pandemic. Lessons learned and potential solutions were provided for others doing similar work. The scoping review identified lacking guidance on LSR methodology and presented items of guidance to be adjusted in the current literature. Furthermore, this cumulative dissertation includes a living systematic review following high-quality methodological standards suggested by Cochrane (1, 3). In addition, previous LSR author experiences were used, and the lessons learned from the method papers were applied in the production of the LSR. As a result, the methodological syntheses and findings from the concept paper, the scoping review, and the LSRs might contribute to inform and guide future researcher and be valuable for future pandemic preparedness. Moreover, the results could be used to prepare the development of new methodological guidance. A main limitation of the methodological concept paper is that expe-

riences and challenges reported from a selection of conducted LSRs on COVID-19 were considered, as a matter of time and resources. Thus, the findings and lessons learned are based on this specific sample of LSRs and their authors' perspectives. However, it can be assumed that the results are largely applicable and generalisable to the general LSR conduction during a pandemic. Major challenges and limitations that were encountered when conducting the LSR update versions were discussed in the previous section 4.3 on implications of research.

5. Conclusion

This cumulative dissertation provided valuable and critical considerations and implications on the methodology of living systematic reviews and showed how to apply these methods on a vivid and emerging research topic. The dissertation projects addressed important methodological aspect for LSRs related to a COVID-19 topic and suggested potential solutions, lessons learned and implication for future research. Crucial lack of guidance for LSRs was identified and systematically presented in an evidence map to inform where current guidance needs to be updated. The application of the methods to conduct a living systematic review on convalescent plasma for people with COVID-19 has endorsed main methodological findings. LSRs are highly suitable for a pandemic context of rapidly emerging diseases and are increasingly used for decision-making. However, appropriateness of the method must be carefully evaluated and LSR specific features need to be recognised, considered, and adapted when new challenges arise. Further research is needed to address certain remaining questions and limitations.

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Conflicts of interest disclosure

No conflicts of interest to declare.

List of abbreviations

Abbreviation	Definition
AE	Adverse Event
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trial
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CP	Convalescent Plasma
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
ICTRP	International Clinical Trial Registry Platform
LSR	Living Systematic Review
MEDLINE	National Library of Medicine's (NLM) primary bibliographic database
MERS	Middle East Respiratory Syndrome
MD	Mean Difference
NRSI	Non-randomised studies of interventions
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomised Controlled Trial
RR	Risk of Bias
SAEs	Serious Adverse Events
SARS	Severe acute respiratory syndrome
SR	Systematic Review
WHO	World Health Organization

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List of figures and tables

Figures

All the figures have been self-created, and figure 2-5 have been created using the CANVA online software.

Tables

Appendices

Appendix A. Scientific contributions of authors

Scientific contribution to publication 1, concept paper

The doctoral candidate Claire Iannizzi contributed to the concept paper by accomplishing the following activities: the conceptualisation of the concept paper, investigation of the content, writing up the original draft and reviewing and editing the reviewers' comments. Ms. Iannizzi also presented the project results at the European Public Health Congress and the Cochrane Methods Symposium. The co-authors have supported with the conceptualization, writing and editing of the manuscript (a detailed list of individual contributions is provided in the following table).

Methodological challenges for living systematic reviews conducted during the COVID-19 pandemic: A concept paper

- Published in the Journal of Clinical Epidemiology

Author	Contributions
Claire Iannizzi	Conceptualisation, Investigation, Writing - Original Draft, Writing - Review & Editing
Elena Dorando	Writing - Review & Editing
Jacob Burns	Conceptualisation, Writing - Review & Editing
Stephanie Weibel	Conceptualisation, Writing - Review & Editing
Clare Dooley	Writing - Review & Editing
Helen Wakeford	Writing - Review & Editing
Lise J Estcourt	Writing - Review & Editing
Nicole Skoetz	Conceptualisation, Writing - Review & Editing, Funding acquisition
Vanessa Piechotta	Conceptualisation, Supervision, Writing - Review & Editing

Scientific contribution to publication 2, scoping review

The doctoral candidate Claire Iannizzi contributed to the following activities: the conceptualization of the scoping review; development of the protocol; screening of the systematic literature search results; study selection; development of the data extraction form; data extraction; building the evidence map; writing up of the results; preparation of the final manuscript and editing of the reviewers' comments. The results of this work were presented at the EbM Kongress - Netzwerk Evidenzbasierte Medizin (poster) and at the Cochrane Colloquium 2023 (oral presentation). The scoping review was part of an overarching project, led by Prof. Dr. Akl, to develop a PRISMA 2020 Extension for Living Systematic Reviews. The co-authors have supported with the conceptualization, writing and editing of the manuscript (a detailed list of individual contributions is provided in the following table).

Methods and guidance on conducting, reporting, publishing and appraising living systematic reviews: a scoping review

- Published in the Journal Systematic Reviews

Author	Contributions
Claire Iannizzi	Conceptualization, methodology, analysis, investigation, visualization, writing – original draft preparation, writing – review & editing
Elie A Akl	Conceptualization, methodology, investigation, writing – review & editing
Eva Anslinger	Methodology, analysis, investigation, visualisation
Stephanie Weibel	Conceptualisation, Investigation, Writing – Review & Editing
Lara A Kahale	Conceptualization, methodology
Abina Mosunmola Aminat	Investigation
Vanessa Piechotta	Conceptualization, investigation, methodology, writing – review & editing
Nicole Skoetz	Conceptualization, methodology, investigation,funding acquisition, supervision, and writing—review and editing

Scientific contribution to publication 3, living systematic review

The doctoral candidate Claire Iannizzi was responsible for the methodological expertise and the execution of the associated steps and coordinated the collaboration of an international team of methodological and clinical experts for this review. She contributed to the review process as follows: screening of the systematic literature search results; study selection; development of the data extraction form; data extraction; quality assessment (risk of bias assessment of the included studies); data synthesis; assessment of confidence in the evidence using the GRADE method; interpretation and writing up of the results; preparation of the final manuscript and editing of the reviewers' comments. The co-authors have supported with methodological or clinical expertise (a detailed list of individual contributions is provided in the following table).

Convalescent plasma for people with COVID-19: a living systematic review

- Published in the Cochrane Library

Author	Contributions
Claire Iannizzi	Methodological expertise, study selection, data extraction and assessment, conception and writing of the manuscript
Khai Li Chai	Clinical expertise, study selection and advice
Vanessa Piechotta	Methodological expertise, study selection and data extraction
Sarah J Valk	Clinical expertise, study selection and advice
Catherine Kimber	Clinical expertise, study selection, and advice
Ina Monsef	Development of the search strategy
Erica M Wood	Clinical expertise and advice
Abigail A Lamikanra	Clinical expertise and advice
David J Roberts	Clinical expertise and advice
Zoe McQuilten	Clinical expertise and advice
Cynthia So-Osman	Clinical expertise and advice
Aikaj Jindal	Clinical expertise and advice

Nora Cryns	Data extraction and assessment
Lise J Estcourt	Clinical expertise, and conception and writing of the manuscript
Nina Kreuzberger,	Methodological expertise, study selection, data extraction and assessment
Nicole Skoetz	Methodological expertise, study selection, data extraction and assessment, conception and writing of the manuscript

Appendix B. Publication 1

Methodological challenges for living systematic reviews conducted during the COVID-19 pandemic: A concept paper

Journal of Clinical Epidemiology 141 (2022) 82–89

COVID SERIES

Methodological challenges for living systematic reviews conducted during the COVID-19 pandemic: A concept paper

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Abstract

Background: A living systematic review (LSR) is an emerging review type that makes use of continual updating. In the COVID-19 pandemic, we were confronted with a shifting epidemiological landscape, clinical uncertainties and evolving evidence. These unexpected challenges compelled us to amend standard LSR methodology.

Objective and outline: Our primary objective is to discuss some challenges faced when conducting LSRs in the context of the COVID-19 pandemic, and to provide methodological guidance for others doing similar work. Based on our experience and lessons learned from two Cochrane LSRs and challenges identified in several non-Cochrane LSRs, we highlight methodological considerations, particularly with regards to the study design, interventions and comparators, changes in outcome measure, and the search strategy. We discuss when to update, or rather when *not* to update the review, and the importance of transparency when reporting changes.

Lessons learned and conclusion: We learned that a LSR is a very suitable review type for the pandemic context, even in the face of new methodological and clinical challenges. Our experience showed that the decision for updating a LSR depends not only on the evolving disease or emerging evidence, but also on the individual review question and the review teams' resources.

Keywords: Living systematic review; Experience report; COVID-19 pandemic; Emerging disease; Lessons learned; Experiences during pandemic

1. Introduction

A living systematic review (LSR) is an emerging systematic review type, which makes use of continual updating and ongoing surveillance of emerging research evidence [1]. Regular searches ensure that the systematic review includes the latest available findings and remains up to date [1]. Therefore, LSRs are most suitable for high-priority topics with substantial uncertainty, and where new evidence is published regularly [1]. In a series of four papers, the various aspects of LSRs have been discussed and elaborated on in detail [1-4]. Cochrane published the first version of a Cochrane LSR series in 2017 [5], and in 2019 released guidance on the conduct and publication of Cochrane LSRs [6].

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What is new?

- Rapidly emerging diseases put new challenges on living systematic reviews.
- Review methods and inclusion criteria may need to be adapted for every update.
- Policy relevance and important studies may influence the updating decision.
- Transparent reporting of changes in methodology between review updates is key.
- Transparent reporting is needed to avoid biases in the review process.

In the context of the Coronavirus disease 2019 (COVID-19) pandemic, we are confronted with a shifting epidemiological landscape, clinical uncertainties, a lack of evidence and a rapidly evolving evidence base. As methodologists conducting LSRs during the pandemic, we have recognised the need and opportunity to respond to new and unexpected challenges by amending our standard systematic review methodology.

2. Objectives

Our primary objective is to discuss some of the challenges faced when conducting LSRs in the context of the COVID-19 pandemic, and to provide methodological guidance for others doing similar work.

3. Outline

To accomplish these objectives we draw on the experience and lessons learned from the author teams of two Cochrane LSRs [7, 8] and the methodological approaches used in other selected LSRs [9-14]. When referring to 'our' experiences, we refer either to 'review one', investigating convalescent plasma for COVID-19 treatment [7] or 'review two', investigating international travel-related control measures for containing the COVID-19 pandemic [8]. The additional six LSRs were selected based on several characteristics (journal, complexity of methodology and topic, number of included studies and update strategy) to cover a broad variety in terms of LSR characteristics, see supplementary table 1. We highlight methodological considerations related to when a living review question is reasonable, particularly with regards to study designs, types of interventions and comparators, changes in outcome measures and the search strategy. We discuss when to update, or rather when *not* to update the review and the importance of transparency when reporting methodological changes.

4. Considerations regarding a living PICO – our experiences from a pandemic

To address the uncertainties related to COVID-19 research and adapt to the evolving evidence landscape, certain methodological elements needed special consideration for ensuring that LSRs are a reliable, up-to-date source of evidence that respond to the urgent health situation. Our experiences and further methodological approaches identified through other LSRs are elaborated in the following sections and summarized in Table 1 (and in more detail, in supplementary table 2).

4.1. Relevant design of studies? – a choice based on new conditions

Traditionally, evidence-based medicine has applied a hierarchy of evidence according to study design to achieve an adequate quality of evidence in systematic reviews and draw meaningful and valid conclusions. For standard intervention reviews, for example, randomised controlled trials (RCTs) are at the top of this hierarchy, followed by cohort studies and case-control studies in the middle of the evidence pyramid, and case series or reports at the bottom [15].

As response to clinical uncertainties in the COVID-19 pandemic and to ensure that no relevant evidence was excluded, in conducting review one we initially started with broad study design inclusion criteria. We planned to include RCTs preferentially, and to include other study designs, e.g. observational studies, only if insufficient RCT-evidence was available. We had to eventually adapt this initial plan, as we soon realised that refining inclusion criteria is an interactive process [7]. Identified studies did not report data for all our review outcomes, and in particular, some of the RCTs did not report safety data for the control group. Thus, for a better understanding of the frequency of unintended effects, we made the post-hoc decision to also include safety data from prospectively registered controlled and uncontrolled studies. Similarly, other selectively identified LSRs included observational studies at an early stage of the COVID-19 pandemic due to a paucity of RCTs [7,9-11,13]. The lesson learned here is that authors should always rely on the best available evidence, which may be dependent on the outcome and will likely evolve and change rapidly over time. As LSR authors, we aim to synthesise and critically appraise all available evidence at a given time, but to update the review as more and potentially more trustworthy evidence becomes available. For example, we have seen that observational studies reported on positive outcomes for several interventions, e.g. convalescent plasma [7] or hydroxychloroquine [11], but were later shown to have little or no therapeutic effect against COVID-19 in higher quality studies and systematic review updates.

Table 1. Summary of challenges identified from the methodological approaches used in selected LSRs.

Methodological elements with special LSR consideration and related challenges	LSRs reporting on these challenges	How the LSRs handled these challenges
Living methodology		
Choice of study design: e.g. lack of RCTs/high quality studies	Juul, et al.; Schüneman, et al; Hernandez, et al; Wynants, et al; Allotey, et al; John, et al;	Inclusion of other designs, such as observational study or modelling studies
Choice of study type: e.g. inclusion of preprints	All	Inclusion of preprint
Intervention and comparators challenges	None	/
Changes in outcome measures	Juul, et al;	Post-hoc changes of the inclusion criteria for outcome measures
Search strategy	Juul, et al; Schüneman, et al; Hernandez, et al; Wynants, et al; Allotey, et al; John, et al	Included a variety of databases and search approaches (e.g. preprint server, hand search)
Handling of preprints	Juul, et al; Schüneman, et al; Hernandez, et al; Wynants, et al; Allotey, et al; John, et al	Added preprint server to their search, but no solution reported on how to track preprint updates
When to update, or rather when not to update		
Updating triggers in general	Juul, et al; Schüneman, et al; Hernandez, et al; Wynants, et al; Allotey;, et al	/
Updating trigger: important studies	Schüneman, et al; Hernandez, et al; Wynants, et al;	/
Updating trigger: policy relevance	Juul, et al; Wynants, et al; John, et al	/
Information on funding	Juul, et al; Schüneman, et al; Hernandez, et al; Allotey, et al; John, et al	/
Transparent reporting of changes		
Reporting updates between protocol and review	Juul, et al	Update changes mentioned in a section at the end of the text
Reporting updates between review updates if applicable	Juul, et al; Schüneman, et al; Hernandez, et al; Wynants, et al; Allotey, et al; John, et al	Update changes mentioned in the results, discussion or data supplement, trough update alerts or in a separate paragraph placed before the review introduction

Generally ignored by the classical hierarchy of evidence, modelling studies have rarely been used in answering questions of intervention effectiveness, with systematic reviews focusing instead on experimental and sometimes observational evidence. This lack of consideration of modelling studies is at least partially because such studies simulate data on interventions and/or outcomes, which often require multiple sometimes questionable assumptions, rather than observing and measuring them directly. For some COVID-19 questions, modelling studies represented the sole evidence source, and it became clear early on, that decision-makers, despite the limitations of such studies, were using such studies to inform decisions. In the first version of review two [8], we included any type of modelling study due to the lack of experimental and even observational evidence.

Separate from study design, we also discussed which types of publication to consider for our reviews, e.g. peer-reviewed articles, preprints, abstracts, letters, etc. The experiences during this pandemic have shown the risks and benefits of using preprints, i.e. prompt availability versus validity and reliability (or lack thereof). Due to the prompt availability, several LSRs included preprints [7-14]. However, preprints must be handled with caution as they are not peer reviewed and results might still change [7-9,12,13]. Using preliminary preprint findings instead of data from the most updated preprint version, or the peer-reviewed journal publication could lead to different results or implications for review updates. It is challenging to identify updates of preprints, especially when the DOI remains unchanged [9-14]. As soon as the full-text journal publications became available, some review authors prioritised these and reassessed the preprints [7,8,12,13]. To address remaining uncertainties, sensitivity analysis excluding preprints can be helpful to investigate the robustness of results [7].

4.2. Interventions and comparators

We learned that the interventions and comparators assessed by LSRs in the pandemic context evolved over time and needed adaptations. According to the *Cochrane Handbook for Systemic Reviews of Interventions*, it is important to consider and minimise the clinical and methodological heterogeneity between studies, to allow a valid comparison and a reliable pooled effect [16]. For review one [7], our overall main comparison remained unchanged; however we did adapt how we defined the specific intervention and comparator. Specifically, we noticed that, because there was and is no real standard care available, the best supportive care options differed widely across contexts. For instance, we observed that Chinese studies often used Traditional Chinese Medicine as part of patient care [17]. Studies that were initiated early in the pandemic often used hydroxychloroquine [18], and studies that recruited patients after July 2020 often used corticosteroids [19]. Another challenge was that for most co-interventions the evidence on safety and effectiveness remained uncertain. Hence, we tried to account for bias due to unequal distribution of co-interventions across study groups. We analysed individuals with mild and moderate to severe symptoms separately, based on existing hypotheses regarding the intervention modes of activity and our evolving understanding of COVID-19 progression to assure comparability of study participants [7].

4.3. How to deal with changes in outcome measures

At the beginning and throughout the course of the pandemic, robust and relevant outcome measures were not clear. We based our outcome selection on the COMET (Core Outcome Measures in Effectiveness Trials) initiative for COVID-19 patients [20]. As more evidence became available, we found that outcome measures needed to be refined. Thus, our outcome set was never "final" but constantly evolving. We noted for instance in review one [7], that there was broad diversity in the assessment and reporting of the clinical status or disease progression, with standard reporting measures changing over time as well. This increased the potential for heterogeneity in outcome measurement and reporting across studies. We could not find a solution to reasonably combine data and provided narrative syntheses without meta-analysis for respective outcomes. Changing outcomes were also identified in the Juul review, which added an additional post-hoc outcome for their update [9].

4.4. Developing the search strategy

We used the Cochrane guidance for LSR search methods to develop our initial search strategy. According to this guidance, there is a particular interest for LSRs to keep ongoing and emerging evidence up to date through regular searches of electronic databases, clinical trial registries and other potential sources [6]. The search strategies also need to be updated, as relevant terms, keywords or database filters may change [6].

One challenge for review two, related to maintaining searches over time [8]. The changing database landscape required constant amendments to the search strategy and literature sources. For example, the Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database, an early and comprehensive source of pre-print articles, was discontinued in mid-2020, but is now completely covered by the WHO COVID-19 Global literature on coronavirus disease database. A challenge for review one involved the dynamic nature of electronic databases [7], with existing databases changing and new ones becoming available. Therefore, it was not sufficient to rely only on the traditionally utilised databases such as PubMed, Embase or CENTRAL. Some reviews also explored new COVID-19 registries, such as the Cochrane COVID-19 Study Register (CCSR), [7-10] a regularly updated public database for study references, particularly efficient for update searches of LSRs [21]. Also, the L*VE platform, was used in some LSRs [7,10,14]. The information specialists involved in review one used the website of "COVID-END" [22] and the EPPI Centre [23], providing guidance and listing the various COVID-19 registries, to get an overview of the numerous newly available and often overlapping registries. Another challenge identified in review one was that no suitable screening software exists to respond to the evolving inclusion criteria [7]. Because of the rapid emergence of new evidence, most LSRs decided to run a complete search each week [7,9,10,14] or month [11].

A further challenge with review one was tracking the ongoing studies [7], as the estimated study completion dates indicated in the study registries were sometimes unreliable. Therefore, it was of utmost importance to track ongoing studies through regular contact with the main investigators. For previously identified ongoing platform trials [7] or preprints [9-14] some authors decided to perform regular manual checks for new updates.

5. When to update, or rather when not to update

When to update is an important issue to discuss when planning and conducting a LSR, and is highly context dependent. There is no clear standard for how frequent or at which time point updates of LSRs should be performed and published [1]. According to Cochrane, updates can be planned either when it is likely that newly identified evidence has an impact on the review conclusions or at a fixed-interval schedule when more emerging evidence is expected [6]. The panel for updating guidance for systematic reviews recommends an individualised updating approach, where the responsibility for the update decision depends on the personal resources of the authors and the

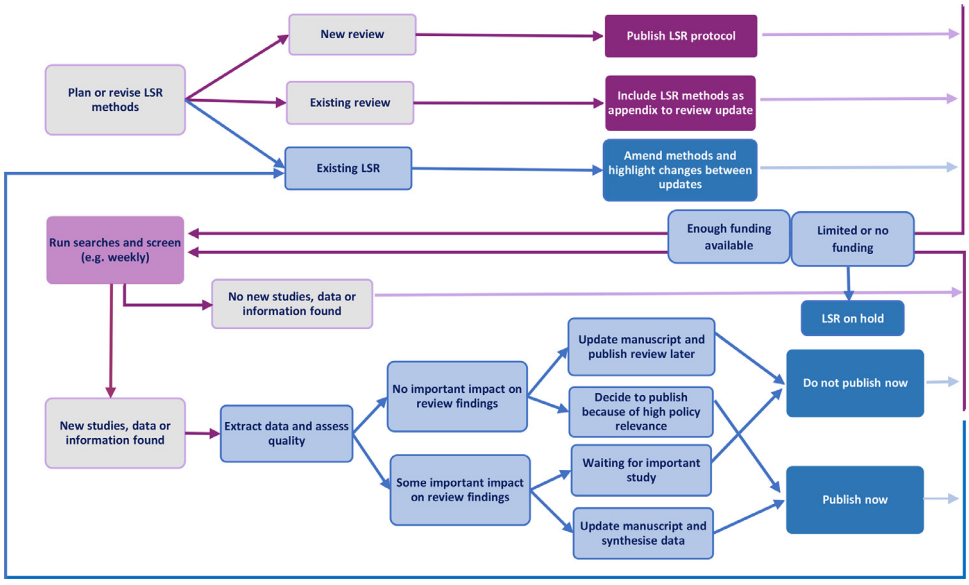

Fig. 1. LSR decision flowchart for updating and publishing the review, adjusted for the context of rapidly emerging diseases (amendments: components in blue are the additional steps we took with the original Cochrane flowchart in grey and purple [6]).

editorial team [24]. The Annals of Internal Medicine provides detailed author guidance on updating and publishing paths for LSRs, which suggests committing to publish either surveillance comments, alerts of new evidence or a new article with major updates [25].

In the context of the COVID-19 pandemic, we defined additional components to consider when deciding on updating a LSR. Based on a figure from the Cochrane LSR guidance illustrating the LSR workflow [6], we reproduced a similar figure and adapted it according to our experience (blue components), to visualise the decision process for updating or publishing a LSR (see Fig 1). The part of the flowchart that we altered most relates to running the search. Here we added three additional considerations that can affect the decision of whether to update, publish, neither or both: the policy relevance, the importance of the study and funding. Each of these three considerations is described in more detail below.

5.1. Policy relevance

We added 'policy relevance' as an additional component influencing the updating decision, as policy triggers can indicate the need for an update. For example the Emergency Use Authorization and statement by the US Food and Drug Administration (FDA) that convalescent plasma may be effective in treating COVID-19 was an important consideration [26] in deciding to publish an update of review one [7], even though the conclusion of our review did not change after considering additional study data. Regarding review two [8], the development of WHO guidance on COVID-19 mitigation in the aviation sector heavily influenced the decision of when to update [27].

5.2. Important studies

We also added "waiting for important study" as an additional aspect to consider in the updating decision. As ongoing studies identified in previous versions of review one came to completion [7], we faced the decision of when to update. To make optimal use of resources, we ultimately decided to tie our updates to the completion of larger, well-planned studies, e.g. platform trials. These were most likely to produce higher-certainty evidence, and we felt that an update including such studies would be of optimal value to the end user. Through regular communication with study investigators, we were able to identify when an 'important' study for our PICO was going to be published. For review two [8], and potentially for other less clinical, more public health-type PICOs, diverse modelling studies and smaller observational studies can be important. The author guidance of the annals of internal medicine for instance suggests a "major update" when new evidence is substantive. Here an "important study" could be a large, well designed study in case of previous inconsistent or lower quality studies, or could be several new studies of differing size and quality [25].

5.3. Funding

Funding could influence or delay the conduct of updates and should therefore be considered already before starting a review update and running the search. If there are no resources to conduct the review update it is possible that the steps following the search cannot be conducted. This concerns not only financial resources but also to time and personnel. In one LSR the review authors indicated that they excluded grey literature for instance due to resource

Table 2. Summary of PICO development from protocol stage to current review version.

	Participants (inclusion and exclusion)	*Intervention*	Comparator	*Outcomes (primary and secondary)*	*Study design*	*Methods changes*	*Results*	*Authors conclusion*
Protocol (date)								
Update 1 (date)								
→Changes								
Update 2 (date)								
→Changes								
Update 3 (date)								
→Changes								
Update 4 (date)								
→Changes								

limitations, which could have hindered identification of important new evidence [13].

6. Transparency in the reporting of changes

Transparent and traceable reporting of changes to the methodology of LSRs is a challenge, and there is currently no PRISMA reporting guideline for LSRs. According to Cochrane guidance, a LSR requires the explicit reporting of certain factors, such as the screening, whether the review incorporated new evidence, and the methods changes [6]. Cochrane has established a transparent structure for reporting the differences between protocol and review in standard reviews [6]. This standard structure can be used for any review, but it may not be adequate for LSRs. Thus, we feel that there is a need for a similar structure specific for LSRs.

In the context of a living PICO and methodology, we found it highly relevant to report in a transparent way the differences between the protocol and first version of the review, as well as between the review updates. When looking at how changes from other LSRs were reported, one LSR included a section at the end of the review on "changes between protocol and review" [9]. Others indicated mainly the changes between review versions or updates, either briefly in the discussion, data supplements [9,12,14], or through update alerts published between review versions [10,11]. One review included a section "Updates from version 1" before the introduction of the review [13]. For review one [7], we decided to include an overview table of changes titled 'Summary of PICO development from protocol stage to current review version', which can be incorporated by other LSR authors. This table summarises the main PICO elements (e.g. participants, interventions, comparators, outcomes, study design and methodological changes) of the protocol and review version changes. For the latter, it is also important to report changes of the reviewś results (e.g. the number of included studies, the certainty of the evidence) and the authors conclusion (see Table 2).

We found it important to emphasise that the choice of study design eligibility was not a selective post-hoc approach. Ideally, the methodology for each update should be adapted and (re)finalised at the beginning of each version. Studies that are excluded based on different criteria for the updated PICO could be listed chronologically in a 'supplemental evidence set' or incorporated in a modified PRISMA flowchart, and thereby increase transparency of the screening and study selection process [28].

7. Lessons learned and conclusion

Based on our experiences in the planning and conducting of LSRs in a pandemic environment and challenges identified from approaches used in other LSRs, we can conclude that a LSR is a highly suitable review type for the pandemic context, even in the face of new methodological and clinical challenges. Our experience also demonstrated that updating the methods of a LSR, or the LSR itself, is dependent not only on the evolving disease or the emerging evidence, but also on the individual PICO and the capacity as well as resources of the review team. For a living PICO, we described the importance of transparently reporting the differences between the protocol and the review, as well as between each review update. These lessons learned could be valuable for future pandemic preparedness. An implication for further research and discussion is when to 'retire' and discontinue the updating of a review.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.09.013.

CRediT authorship contribution statement

Claire Iannizzi: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Elena Dorando:** Writing – review & editing. **Jacob Burns:** Conceptualization, Writing – review & editing. **Stephanie Weibel:** Conceptualization, Writing – review & editing. **Clare Dooley:** Writing – review & editing. **Helen Wakeford:** Writing – review & editing. **Lise J Estcourt:** Writing – review & editing. **Nicole Skoetz:** Conceptualization, Writing – review & editing, Funding acquisition. **Vanessa Piechotta:** Conceptualization, Supervision, Writing – review & editing.

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Appendix C. Publication 2

Methods and guidance on conducting, reporting, publishing and appraising living systematic reviews: a scoping review

Systematic Reviews

METHODOLOGY

Open Access

Methods and guidance on conducting, reporting, publishing, and appraising living systematic reviews: a scoping review

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Abstract

Background and objective The living systematic review (LSR) approach is based on ongoing surveillance of the literature and continual updating. Most currently available guidance documents address the conduct, reporting, publishing, and appraisal of systematic reviews (SRs), but are not suitable for LSRs per se and miss additional LSR-specific considerations. In this scoping review, we aim to systematically collate methodological guidance literature on how to conduct, report, publish, and appraise the quality of LSRs and identify current gaps in guidance.

Methods A standard scoping review methodology was used. We searched MEDLINE (Ovid), EMBASE (Ovid), and The Cochrane Library on August 28, 2021. As for searching gray literature, we looked for existing guidelines and handbooks on LSRs from organizations that conduct evidence syntheses. The screening was conducted by two authors independently in Rayyan, and data extraction was done in duplicate using a pilot-tested data extraction form in Excel. Data was extracted according to four pre-defined categories for (i) conducting, (ii) reporting, (iii) publishing, and (iv) appraising LSRs. We mapped the findings by visualizing overview tables created in Microsoft Word.

Results Of the 21 included papers, methodological guidance was found in 17 papers for conducting, in six papers for reporting, in 15 papers for publishing, and in two papers for appraising LSRs. Some of the identified key items for (i) conducting LSRs were identifying the rationale, screening tools, or re-revaluating inclusion criteria. Identified items of (ii) the original PRISMA checklist included reporting the registration and protocol, title, or synthesis methods. For (iii) publishing, there was guidance available on publication type and frequency or update trigger, and for (iv) appraising, guidance on the appropriate use of bias assessment or reporting funding of included studies was found. Our search revealed major evidence gaps, particularly for guidance on certain PRISMA items such as reporting results, discussion, support and funding, and availability of data and material of a LSR.

Conclusion Important evidence gaps were identified for guidance on how to report in LSRs and appraise their quality. Our findings were applied to inform and prepare a PRISMA 2020 extension for LSR.

Keywords Living systematic reviews, Methods and guidance, Scoping review, Conducting LSRs, Reporting, Appraisal

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Introduction

Systematic reviews (SRs) are essential to provide evidence-based answers to clinical and public health-related questions. Due to the continuous publishing of relevant primary studies in some areas, it is important to keep these SRs up-to-date [1]. One could achieve that goal by adopting the living systematic review (LSR) approach, which is based on an ongoing surveillance of the literature and continual updating [2]. Regular searches ensure that the SR includes the latest available evidence and remains up-to-date [2]. Therefore, LSRs are most suitable for high-priority topics with substantial uncertainty and frequent publications. When continually updating a review, it is important to report changes to the methodology and the findings in transparent and traceable ways, which can be challenging.

Few guidance documents address the conduct, reporting, publishing, and appraisal of LSRs. The Living Evidence Network developed in 2019 the "Guidance for the production and publication of Cochrane living systematic reviews" [3]. However, this guidance lacks certain aspects of the LSR methodology, which have been shown to be important in the last years with the rising number of LSRs conducted. While the recent update of the "Preferred Reporting Items for Systematic reviews and Meta-Analyses" (PRISMA) can be used for reporting LSRs, the statement indicates there may be some additional considerations that need to be addressed [4]. Also, the AMSTAR 2—Assessing the Methodological Quality of Systematic Reviews—tool [5] which was developed for the critical appraisal of the quality of SRs, does not consider LSRs.

Therefore, it is of high interest to summarize the literature evaluating methods of conducting, reporting, publishing, and appraising LSRs, as well as any guidance on those methods. Scoping reviews are particularly useful in the context of emerging evidence and act as a precursor for other topic-related projects [6]. This scoping review is part of a larger project to develop an extension of the PRISMA 2020 statement for living systematic reviews.

Objective

The main objective is to systematically collate methodological literature on guidance on how to conduct, report, publish, and appraise the quality of LSRs and to systematically map how much and what kind of evidence is currently available.

Methods

A protocol elaborating on the detailed methodology of this scoping review was already published [7]. The main differences in methods between the protocol and this scoping review are displayed in the Supplementary Table 1.

Scoping review methodology

To achieve the objective, we conducted a scoping review to identify and evaluate existing evidence and map the availability of methods papers, evidence gaps, and associated primary research gaps [6]. We followed the standard scoping review methodology guidance of the Joanna Briggs Institute [6] and applied the following steps:

a) Identification of the research question
b) Identification of relevant studies
c) Study selection
d) Charting the data
e) Collating, summarizing, and reporting of the results [8]

Moreover, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist (see Supplement Table 2) for transparent reporting of the results [9].

Eligibility criteria

We included articles that devoted at least one paragraph to discuss methods or conceptual approaches on how to conduct, report, publish, or appraise LSRs. Such articles were ideally methodological or concept papers describing methods for LSRs, guidance (e.g., handbooks) for undertaking LSRs, issued by organizations that conduct evidence syntheses, and commentaries or editorials that discuss methods for LSR.

We excluded from our search, LSRs themselves, LSR protocols, and non-LSR-specific papers.

Identification of relevant studies

We searched MEDLINE (Ovid), EMBASE (Ovid), and The Cochrane Library. All searches were completed on August 28, 2021, and we searched from database inception. The search strategy was initially developed by a researcher experienced in developing literature search strategies with support from an information specialist (LH), as part of a larger project to develop an extension of the PRISMA 2020 statement for LSRs [10, 11]. The strategy was peer-reviewed and updated by another information specialist (IM). Please see Box 1 of the Appendix for the complete search strategy.

As for searching the "gray literature," we looked for existing guidelines and handbooks on LSRs from organizations that conduct evidence syntheses (e.g., Cochrane

handbook, Living Evidence network, JBI) using the Lens.org website. Additionally, we conducted an ancestry search to identify relevant LSR handbooks and guidance documents from the reference list of published LSRs. We performed a descendency search, using certain seminal documents (e.g., papers defining LSRs and Cochrane guidance), and tracked their citations via Google Scholar.

Article selection

Two authors (from among CI, NS, EA) contributed to screening independently and in duplicate titles and abstracts. We used a web-based systematic review software Rayyan (RRID:SCR_017584) for the screening process. To ensure a consistent screening procedure and optimize agreement, we developed and used a detailed written instruction form. We then screened for full text assessing eligibility, based on our predefined eligibility criteria. Disagreements and conflicts were solved by consulting a third author.

Data extraction and presentation

Two review authors (from among CI, NS, VP, SW, EA) extracted and cataloged the data on LSR-specific methodological aspects into a standardized and pilot-tested data extraction form in Microsoft Excel (RRID:SCR_016137). We extracted the main article characteristics and LSR-specific guidance data according to our predefined categories on (i) conducting, (ii) reporting, (iii) publishing, and (iv) appraising LSRs. The identified evidence was mapped by visualizing overview tables created in Microsoft Word. The items of the conducting category are based on the standard process of conducting a systematic review from the Cochrane Handbook [12], including the intermediate steps from describing the rationale to evidence synthesis. The reporting category includes the 27 items of the original PRISMA 2020 checklist [4] to identify whether LSR-specific reporting guidance exists for each of these items. The items of the publishing category are partly based on standard Cochrane guidance for systematic reviews [12] and the experiences of LSR authors within this author team. The LSR appraisal category is based on the 16 questions from the AMSTAR 2 tool [5]. Even though we extracted and classified the data according to these categories, we considered that items from one category (e.g., conducting LSR) could have an impact on items from another category (e.g., publishing LSR) and might even overlap. The extracted study characteristics and category items are listed in Supplementary Table 3.

Results

We identified 4590 references, potentially relevant to our research question. After having removed 1171 duplicates, we screened 3436 records on title and abstract and excluded 3379 records that did not meet the pre-defined eligibility criteria. We screened the full text of the remaining 57 records and included 17 papers from the database search in the scoping review. We also searched for "gray literature" and identified 49 potential records, from which we included five papers in the scoping review. In total, 21 articles from both searches were included in the scoping review. The detailed selection process and results are reported in the PRISMA flow diagram (see Fig. 1) [4].

The evidence map

The 21 included papers provided data for 40 of our predefined LSR-specific items. Methodological guidance was found in 17 papers for conducting LSRs, in six papers for reporting LSRs, in 15 papers for publishing LSRs, and in two papers for appraising LSRs (see Tables 1 and 2).

LSR conducting guidance

From the 17 papers including guidance on conducting LSRs, we mapped and summarized the reported guidance for each of our pre-defined items and sub-items (see Table 3). We found evidence for all the pre-defined items on conducting and almost all the sub-items. A particular high frequency of papers, more than half of the 17 included papers, provided guidance on certain sub-items such as the rationale for conducting a LSR and the screening tool of the search. Between one and five papers presented guidance on other sub-items, including changing and re-evaluating the inclusion criteria, the search (frequency, database, and who), the data extraction (frequency, who, and how), the quality and bias assessment (frequency and how), the data synthesis with meta-analysis if applicable (frequency, who, and how), the frequency of the certainty of evidence assessment, authorship changes, ongoing method support, and funding. Also, we found that some papers established very broad guidance on several steps of conducting a LSR [1, 3, 13–15, 25, 29]. The remaining papers reported more specific guidance on certain particular steps of the LSR conduction process. We could not identify any evidence for guidance on two sub-items: who carries out the quality and bias assessment and the certainty of evidence assessment.

LSR reporting guidance

From the six papers providing guidance on reporting LSRs, we mapped the available data for each of the

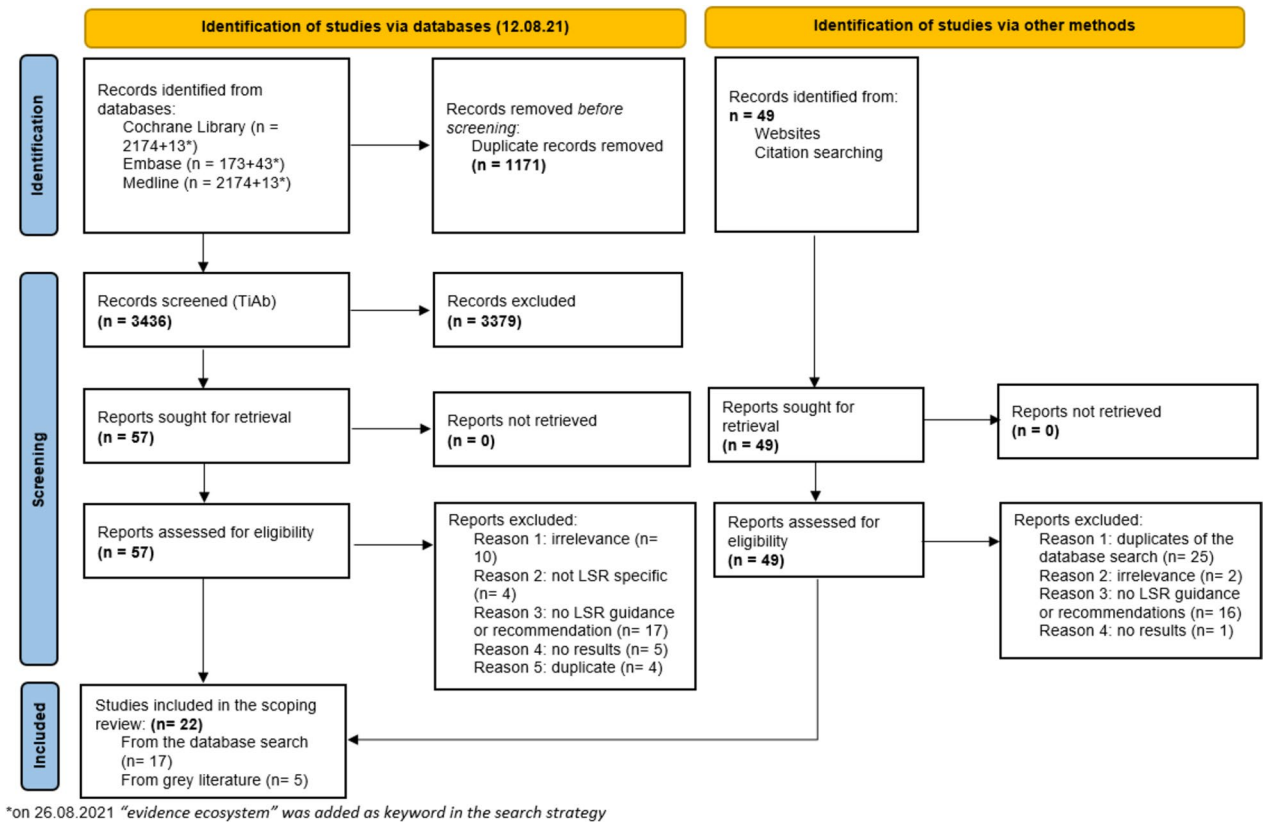

Fig. 1 Flowchart of the database search and gray literature

PRISMA items and sub-items and summarized the identified guidance (see Table 4). We found guidance on 13 out of the 27 PRISMA items for reporting a LSR. We identified a higher frequency of papers, three out of the six, providing guidance for PRISMA item 24 on the registration and protocol. One or two papers provided guidance for PRISMA items one until eight, 11, 13, 16, and 25. We noted that one paper [3] included particularly elaborated guidance on some of the PRISMA items, and the remaining papers provided guidance on a particular PRISMA item.

We could not identify any guidance for the PRISMA items on reporting the methods, including data collection process (9), data items (10), effect measure (12), reporting bias assessment (14), and certainty assessment (15). Further, there was no guidance identified for the reporting of results, including study characteristics (17), presenting the risk of bias in studies (18), results of individual studies (19), results of synthesis (20), reporting bias (21), and certainty of evidence (22). No data was found on reporting the three items (23a, 23bc, and 23d) of the discussion, on the item reporting support and funding (25), and on the availability of data and material (27).

LSR publishing guidance

From the 15 papers including guidance on publishing LSRs, we mapped the available data for our pre-defined items and sub-items and summarized the identified guidance (see Table 5). We found guidance for all of the pre-defined items and all the sub-items. We identified a particular high frequency of papers, more than half of the 15 included papers, providing guidance on certain sub-items such as the publication type, publication frequency, update publication trigger, and time point for transitioning out of the living mode. A lower frequency of papers included guidance on the remaining sub-items. Also, we note that some papers provide very broad guidance on several aspects of publishing a LSR [3, 14, 19, 29]. The other remaining papers provided more specific guidance on particular steps of the LSR publication process.

LSR appraisal guidance

From the two papers including guidance on LSRs appraisal, we mapped the available data for each AMSTAR 2 tool question and some additional items and summarized the identified guidance (see Table 6). We found guidance on appraising LSRs for four of the

Table 1 Evidence map on the four categories of LSR guidance

Papers	Extracted data: aim and guidance evidence				
	Paper-specific aims	**Conducting LSRs**	**Reporting LSRs**	**Publishing LSRs**	**Appraising LSRs**
Brooker 2019 [3] Guidance for the production and publication of Cochrane living systematic reviews: Cochrane Reviews in living mode	To provide detailed guidance on the production and publication process of a Cochrane living systematic review	√	√	√	√
Crequit 2020 [13] Future of evidence ecosystem series: 2. current opportunities and need for better tools and methods	To consider how the access to new sources and data types and the recent developments of new methods, technologies, and tools presents a great opportunity to create and sustain an ecosystem designed to support the production of updated high-quality evidence syntheses	√		√	
Elliott 2014 [1] Living Systematic Reviews: An Emerging Opportunity to Narrow the Evidence-Practice Gap	To describe several recent developments that have the potential to improve dramatically the efficiency of conventional SRs and enable the widespread production of LSRs			√	
Elliott 2017 [14] Living systematic review: 1. Introduction—the why, what, when, and how	To introduce what LSRs are and discuss the main issues in LSRs, including searching, updating scenarios, production processes, editorial and peer review, and publication	√		√	
Harrington 2021 [15] COVID-19 Technology-Enabled Living Systematic Reviews to Enhance Knowledge Translation	To provide details on how machine learning can be used for LSR and nursing implications	√		√	
Kahale 2021 [11] Tailored PRISMA 2020 flow diagrams for living systematic reviews: a methodological survey and a proposal	To assess how published LSRs report on the flow of studies through the different phases of the review for the different updates and to propose an approach for documentation and reporting		√		
Lansky 2020 [16] Living Systematic Reviews and Other Approaches for Updating Evidence	To introduce a new method for updating SRs called "living" SRs and indications for updating	√		√	
Lerner 2019 [17] Automatic screening using word embeddings achieved high sensitivity and workload reduction for updating living network meta-analyses	To develop and evaluate an algorithm for automatically screening citations when updating living network meta-analysis (NMA)	√			
MacDonald 2020 [18] Living systematic reviews at The BMJ	To give insights into how living SRs (in fast-moving research areas) at The BMJ will be handled by the research team and of their usual methodological standards	√			
Millard 2019 [19] Feasibility and acceptability of living systematic reviews: results from a mixed-methods evaluation	To provide details on the feasibility of LSRs, barriers, and facilitators	√		√	
Negrini 2021 [20] A systematic review that is "rapid" and "living": A specific answer to the COVID-19 pandemic	To describe "rapid living" systematic reviews, an innovative methodological design used to systematically synthesize emerging evidence in the field of rehabilitation during the COVID-19 pandemic	√		√	
Page 2020 [4] The PRISMA 2020 statement: An updated guideline for reporting systematic reviews	To provide an updated guideline for reporting SRs with the PRISMA 2020 checklist and statement		√		

Table 1 (continued)

Papers	Extracted data: aim and guidance evidence				
	Paper-specific aims	**Conducting LSRs**	**Reporting LSRs**	**Publishing LSRs**	**Appraising LSRs**
Ravaud 2020 [21] Future of evidence ecosystem series: 3. From an evidence synthesis ecosystem to an evidence ecosystem	To introduce a new approach and innovative solution to the current problems of need to provide up-to-date evidence synthesis for a specific clinical question	√	√	√	
Simmonds 2017 [22] Living systematic reviews: 3. Statistical methods for updating meta-analyze	To compare and consider the application of four methods to avoid specific statistical problems when updating meta-analyses for LSRs	√		√	
Slaugther 2015 [23] Enabling Living Systematic Reviews and Clinical Guidelines through Semantic Technologies	To provide a brief review of various efforts to produce semantic technologies for sharing and reusing content from clinical investigations (RCTs and other clinical primary studies)			√	
Ter Schure 2019 [24] Accumulation bias in meta-analysis: the need to consider time in error control	To investigate various ways in which time influences error control in meta-analysis testing and to introduce an Accumulation Bias Framework	√			√
Thomas 2017 [25] Living systematic reviews: 2. Combining human and machine effort	To specifically focus on ways in which the use of new human and machine "technologies" can make the standard SR process more efficient	√			
Thomas 2021 [26] Cochrane Handbook Chapter 22: Prospective approaches to accumulating evidence	To provide detailed guidance on prospective approaches to accumulating evidence for LSRs	√		√	
Vergara-Merino 2020 [27] Living systematic review: new inputs and challenges	To describe LSR's relevance, the considerations that should be taken when producing one, and the challenges proper of this type of review	√	√	√	
Winters 2020 [28] Stay alive! What are living systematic reviews and what are their advantages and challenges?	To introduce living SRs and to discuss its advantages and challenges	√		√	
Xu 2020 [29] A brief INTRODUCTION to living systematic reviews (Chinese)	To introduce the development, characteristics, conditions, implementation, and applications of living systematic reviews	√	√	√	
Total number		**17/21**	**6/21**	**15/21**	**2/21**

Table 2 Summary of the number of papers reporting on each category, reported pre-defined items/sub-items, and gaps of guidance evidence

	Conducting LSRs	Reporting LSRs[a]	Publishing LSRs	Appraising LSRs[b]
N of papers reporting on a category	17 of 21	6 of 21	15 of 21	2 of 21
N of pre-defined items/sub-items reported on	19 of 21 sub-items	13 of the 27 PRISMA items	14 of 14 sub-items	4 of 18 (16 AMSTAR two tool questions & 2 additional items)
Pre-defined items/sub-items reported by at least half of identified papers	LSR rationale, Screening tools	Registration & protocol	Publication type, publication frequency, update publication trigger and time point for transitioning out of the living mode	Use of appropriate risk of bias assessment technique and funding of included studies reported
Pre-defined items/sub-items reported by less than half of identified papers	Changing of inclusion criteria, search (frequency, database and who), data extraction (frequency, who and how), quality and bias assessment (frequency and how), data synthesis with meta-analysis if applicable (frequency, who and how), frequency of the certainty of evidence assessment, authorship changes, ongoing method support and funding	PRISMA items on reporting: title (1), abstract (2), rationale (3), objective (4), eligibility criteria (5), information sources (6), search strategy (7), selection process (8), bias assessment (11), synthesis methods (13), study selection (16) and competing interests (26)	Type of information in an update, publication of review status, new citation & added to PubMed, publication of an update, specific time point of publication, when starting living mode publication, publication of between updates information, transition out of living mode trigger, peer review updates, publish authorship changes, publish PRISMA flow diagram	Assessment of protocol and review differences, use of comprehensive search strategy, and appropriate methods for meta-analysis
Identified gaps of guidance evidence	Who carries out bias assessment & certainty of evidence assessment	PRISMA items on reporting: data collection process (9), data items (10), effect measure (12), reporting bias assessment (14), certainty assessment (15), reporting of results, including study characteristics (17), presenting risk of bias in studies (18), results of individual studies (19), results of synthesis (20), reporting bias (21) and certainty of evidence (22), discussion (23a, 23bc and 23d) and reporting support and funding (25) the availability of data and material (27)	None	Eligibility criteria, explain study selection, assessments in duplicate, list of studies, funding, heterogeneity, RoB impact, preprints

[a] For the reporting category, the pre-defined items and sub-items were based on the existing PRISMA 2020 checklist (Page, et al. 2021)

[b] For the appraisal category, the pre-defined items were based on the AMSTAR 2 tool questions (SHEA, et al. 2017)

Table 3 Evidence table on identified guidance for conducting LSRs with a narrative summary of extracted data

Items of guidance	Subgroups of items & *N of* papers	Narrative summary of extracted data
Criteria/rationale for conducting LSR	Rationale (*N* = 10/17)	• High prevalence of condition/RQ [13, 15] • Existing results change [3, 15] • Priority for decision making [3, 20, 22, 26, 27, 29] • Low certainty of evidence or rapidly emerging evidence [3, 15, 18, 21, 26, 27, 29]
Inclusion criteria	Emerging change (*N* = 1/17)	• Adaption is needed, if inclusion criteria are changed [3]
	Re-evaluate (*N* = 2/17)	• Based on the evolving quality of evidence, a new understanding of context, with the involvement of experts with different expertise [20] • Identify and re-define most relevant RQs [13]
Search	Frequency (*N* = 8/17)	• Set up auto alerts to provide a regular feed of new citations [14] • Continuous search (e.g., varying between weekly and monthly) [1, 3, 13, 14, 16, 19, 28, 29]
	Database (*N* = 2/17)	• Bibliographic databases, clinical trials registries, gray literature [3, 14]
	Who (*N* = 1/17)	• Information specialists or librarians, using technological enablers [3]
	Screening tool (*N* = 10/17)	• Computer-supported & automated [3, 13–15, 17, 19, 26–29] • Continuous database search with push notification [25, 26] • Guidance on eligibility: machine-learning classifier, crowdsourced inclusion decisions [25]
Data extraction	Frequency (*N* = 3/17)	• Continuous search (trigger-dependent) [1] • Immediately after study identification [22] • Once new evidence has been identified for inclusion, the update process including data extraction starts [29]
	Who (*N* = 1/17)	• Machine-learning information-extraction systems [25] • Linkage of existing structured data sources (e.g., clinical trials registries) [25]
	How (*N* = 6/17)	• AI, machine learning, and automated structured data [3, 13, 15, 26, 29] • Crowd-sourcing [13, 26, 27]
Quality & bias assessment	Frequency (*N* = 2/17)	• Regular updating, at a defined time interval [3] • Once new evidence has been identified for inclusion, the update process including RoB assessment starts [29]
	Who (*N* = 0/17)[a]	
	How (*N* = 2/17)	• Machine learning-assisted RoB tools (e.g., RobotReviewer) [25] • AI-assited tools [26]
Data synthesis with meta-analysis (if applicable)	Frequency (*N* = 5/17)	• Immediately after new study inclusion [22, 24] • When deciding to update [14], on a continuous base [1] • Once new evidence has been identified for inclusion, the update process including data synthesis starts [29]
	Who (*N* = 1/17)	• People responsible for performing the initial evidence synthesis [21]
	How (*N* = 5/17)	• AI, e.g., automatic text generation tools [3] • Error controls, e.g., by trial sequential analysis [24, 29], sequential methods, or Bayesian framework [1] • Follow the description of the planned statistical approach to update a meta-analyze [14]
Certainty of the evidence assessment	Frequency (*N* = 1/17)	• Regular updating [3]
	Who (*N* = 0/17)[a]	
Authorship changes	Authorship (*N* = 4/17)	• Regularly updated for each new review version, according to contribution [1, 3] • Contribution of each member of the group was assessed as sufficient for authorship (and meeting ICMJE criteria) or not [14, 29]
Ongoing method support	Method support (*N* = 2/17)	• Involvement of different methodological expertise [20] • Team of clinicians, researchers, and graduate students with SR expertise [29]
Funding	Funding (*N* = 4/17)	• Impact on maintaining LSR [3] • Direct funding for personnel [19], a consistent flow of funding to research groups is needed [13, 16]

[a] The two items for which no data could be identified are grayed out

Table 4 Evidence table on identified guidance for reporting LSRs with narrative summary of extracted data

PRISMA items (number)	Subgroups of items & *N* of papers reporting evidence	Narrative summary of extracted data
(1)Title	*N* = 2/6	• Transition to and out of living mode must be recognized in the title, responsible parties must be informed [3] • Additional information regarding the indication of an update or "living" SR approach must be provided in the title [4]
(2)Abstract	*N* = 1/6	• Abstract must indicate identification as an LSR; updated search results must be reported [3]
Introduction	(3) Rationale (*N* = 1/6)	• Rational for the LSR approach: Previous updates must be mentioned [3]
	(4) Objective (*N* = 1/6)	• Previously performed updates must be mentioned [3]
Methods	(5) Eligibility criteria (*N* = 1/6)	• Remain the same as for standard SRs [3]
	(6) Information sources (*N* = 1/6)	• Accurate reporting is necessary, including the PRISMA flow diagram [3]
	(7) Search strategy (*N* = 1/6)	• Must be specified and reported in the protocol [3]
	(8) Selection process (*N* = 1/6)	• Report whether any new citations retrieved by the monthly searches was immediately screened; using technical support tools [3]
	(9) Data collection process (*N* = 0/6)[a]	
	(10) Data items (*N* = 0/6)[a]	
	(11) Study risk of bias assessment (*N* = 1/6)	• Report the use of machine learning and automated structured data extraction tools [3]
	(12) Effect measure (*N* = 0/6)[a]	
	(13) Synthesis methods (*N* = 2/6)	• Specify statistical methods used to correct type 1 and 2 errors [27] • Enables for data synthesis [3]
	(14) Reporting bias assessment (*N* = 0/6)[a]	
	(15) Certainty assessment (*N* = 0/6)[a]	
Results	(16) Study selection (*N* = 1/6)	• Record in detail the search results, a spreadsheet is recommended. Present either the results of the base and updates separately, all combined or only the updated versions combined [11]
	(17) Study characteristics (*N* = 0/6)[a]	
	(18) Present risk of bias in studies (*N* = 0/6)[a]	
	(19) Present results of individual studies (*N* = 0/6)[a]	
	(20) Results of synthesis (*N* = 0/6)[a]	
	(21) Reporting bias (*N* = 0/6)[a]	
	(22) Certainty of evidence (*N* = 0/6)[a]	
Discussion (23)	(23a) General interpretation (*N* = 0/6)[a]	
	(23bc) Limitations (*N* = 0/6)[a]	
	(23d) Implications for practice (*N* = 0/6)[a]	
Registration and protocol (24)	*N* = 3/6	• Justify the use of the "living" format in their protocol and mention pre-established criteria to abandon the "living" format for the conventional method [27] • Based on SR protocol [29] and the use of a template on how to create protocol [3]
Support and funding (25)	*N* = 0/6[a]	
Competing interests (26)	*N* = 1/6	• Role of each work group member and their COI should be transparent [21]
Availability of data & material (27)	*N* = 0/6[a]	

[a] Items for which no evidence was identified are grayed out

Table 5 Evidence table on identified guidance for publishing LSRs with a narrative summary of extracted data

Items of guidance	Subgroups of items & *N* of papers reporting evidence	Narrative summary of extracted data
Publication type of new findings	Publication types *N* = 9/15	• Latest findings published on website [14, 28] • Depending on changes for the conclusion (major changes: new DOI and citation) [1] • Interactive living evidence map and dynamic table [20] • What's a new table, update alert [3] • Full review update [19] • [21, 23, 29]]
	Type of information in an update *N* = 2/15	• The format of LSR publication and dissemination must accommodate its frequent updates [29] • Date of last search, numbers of citations screened, studies awaiting inclusion [14]
Publication of review status	*N* = 4/15	• Regular and transparent statements [3], alerts [14] • Monthly/daily/three monthly statements to reader about review status [3, 19] • Status and information of the update process should be disclosed to users, and the update results should be published in a timely manner [29]
New citation & added to PubMed	*N* = 5/15	• DOI & citation adaption as appropriate [3, 19] • Depending on changes for the conclusion (major changes: new doi and citation) [1, 27] • [29]
Publication of an update	Publication frequency *N* = 8/15	• Regular updating process [3] • Trigger dependent [13, 14, 19, 22, 26, 29] • When a certain number of new publications [28]
	Specific time point of publication *N* = 5/15	• Between immediately when new evidence is identified to every 4 or 6 months [3, 14, 19, 29] • Explicit and a priori commitment to a predetermined frequency of review updating [22]
	Updating trigger *N* = 7/15	• Criteria-dependent (evidence dependent) [28] • When new information is likely to impact the review conclusion [3, 14, 26] • Independent from trigger, when new evidence is identified [19, 22, 29]
	When starting living mode publication *N* = 4/15	• Priority & relevance dependent [3, 19] • Happens when the normal SR is released or this action usually occurs when the normal SR is released or updated [29] • (1) new priority of topic, (2) inadequate evidence available, and (3) research moving quickly and emerging evidence impacting conclusion [15]
Publication of between updates information	*N* = 4/15	• Interactive living evidence map and dynamic table [20] • When new evidence is included: the reader should be notified of the process [3, 14, 19]
Transition out of living mode	Time point *N* = 7/15	• Evidence/trigger dependent [3, 29] • Specific thresholds for transitioning out of a Living systematic review mode, if known. [14] • When "enough evidence" but statistically unreasonable anymore [13, 16, 22] • Explicit discouraged from editor/journal [21]
	Transition out trigger *N* = 6/15	• When no rapidly iterating and new evidence is emerging, no priority [21, 29] • Evidence unlikely to change conclusion [3, 13, 16, 22]
Peer review updates	*N* = 5/15	• Peer review [3], dependent on update [14, 19] • Depending on whether new studies are identified and if new studies are included, then evidence impacts on conclusion [1] • Inclusion of new evidence requires editorial and optional peer review [29]

Table 5 (continued)

Items of guidance	Subgroups of items & *N* of papers reporting evidence	Narrative summary of extracted data
Publish authorship changes	*N* = 4/15	• LSR publication should have an appropriate author labeling mechanism, and all authors should conform to the ICMJE specification [14, 29] • Transparent and appropriate contribution fulfilling authorship criteria [1, 3]
Publication of Prisma flow diagram	*N* = 2/15	• Should regularly be updated [3], evidence-dependent to see live progress [19]

pre-defined items. Among the two included papers, both provided guidance on the use of appropriate risk of bias assessment techniques and funding of included studies reported. One of each provided guidance on the assessment of protocol and review differences, the ongoing search, searched study registries, and gray literature. Moreover, we noted that one paper included more elaborated guidance on several aspects of quality appraisal [3]. We found no data for guidance on the remaining 14 items and two sub-items.

Table 6 Evidence table on identified guidance for appraising LSRs with a narrative summary of extracted data

Items of guidance & *N* of papers	Sub-items & narrative summary of extracted data
(1)RQ & inclusion criteria (*N* = 0/2)[a]	
(2)Methods established prior to the conduct & justify deviation from the protocol (*N* = 1/2)	Whether/how the difference between protocol and review was assessed: • Authors should note that the updated review includes additional methods pertaining to the LSR and refer the reader to the living systematic review protocol appendix [3] Whether/how the difference between review versions was assessed: no evidence[a]
(3)Explain study selection (*N* = 0/2)[a]	
(4)Use of comprehensive search strategy (*N* = 1/2)	• Ongoing search is recommended [3] Conducted search within a certain month of LSR completion: no evidence[a] • Searched study registries are recommended [3] • Searched reference list/gray literature is recommended [3]
(5)Study selection in duplicate (*N* = 0/2)[a]	
(6)Data extraction in duplicate (*N* = 0/2)[a]	
(7)List of excluded studies & justification (*N* = 0/2)[a]	
(8)Adequate description of included studies (*N* = 0/2)[a]	
(9)Use of appropriate RoB assessment technique (*N* = 2/2)	• Accumulation bias [24] • If new relevant methods emerged that would be appropriate to integrate into the methods it is recommended (risk of bias tools) new evidence will be assessed with risk of bias tool [3]
(10)Funding of included studies reported (*N* = 0/2)[a]	
(11)Use of appropriate methods for meta-analysis (*N* = 1/2)	• Refer to overview of the Framework for Adaptive Meta-analysis [3]
(12)(if meta-analysis) assessment of potential RoB impact on pooled results (*N* = 0/2)[a]	
(13)Accounted for RoB when interpreting/discussing the results (*N* = 0/2)[a]	
(14)Explanation & discussion of heterogeneity observed in results (*N* = 0/2)[a]	
(15)(if quantitative synthesis) adequate investigation of publication bias & impact on result (*N* = 0/2)[a]	
(16)Report of potential COI sources (funding) (*N* = 0/2)[a]	
Use & handling of preprints (*N* = 0/2)[a]	
Guidance on using a specific checklist (*N* = 0/2)[a]	

[a] Items for which no guidance was be identified are grayed out

Discussion

To summarize the results, we included 21 articles from both search approaches in the scoping review. These papers included data for 40 of our pre-defined LSR-specific sub-items. Methodological guidance was found in 17 papers for conducting LSRs, in six papers for reporting LSRs, in 15 papers for publishing LSRs, and in two papers for appraising LSRs. We identified guidance on conducting LSRs for all of our pre-defined items of interest. Lacking evidence only exists for two sub-items on who carries out the quality and bias assessment and on the certainty of evidence assessment. Thus, we can state from our findings that there is enough guidance available in the literature on how to conduct a LSR and no major evidence gaps have been found.

We identified major evidence gaps in literature on guidance for reporting LSRs. There is lacking guidance for many of the PRISMA sub-items, such as reporting on the methods, the results, the discussion, reporting support and funding, and the availability of data and material. We did not find any evidence gaps in the literature for guidance on publishing LSRs. The identified papers included guidance for all of the pre-defined items and sub-items on publishing LSRs.

Regarding the literature on guidance for appraising the quality of LSRs, we can state that most of the important key items are lacking, indicating major evidence gaps. These include appraisal aspects on eligibility criteria, explaining study selection, assessments of data in duplicate, the list and description of included studies, funding sources and COI declarations reporting, assessing the heterogeneity of results, impact of risk of bias assessment on results, and use as well as handling of preprints.

This scoping review has certain limitations. The search was conducted in 2021 and within this 2-year gap, we could have failed to identify additional literature published since. We only focused on our four predefined categories of LSR methodological aspects, including conducting, reporting, publishing, and appraisal of LSRs. Even though these categories were drafted based on existing LSR methods handbooks, the PRISMA reporting checklist for SRs and the AMSTAR 2 tool for appraisal, a different author team may have chosen different categories or emphasized other LSR aspects. Moreover, we included quantitative guidance literature, rather than qualitative reviews or reports, as these would have sat outside the scope of this paper. The methodology of a scoping review itself includes some limitations as well. The scoping review is an approach to inform research and decision-making on existing evidence gaps and the availability of literature within a certain field of interest. The main purpose is to map, identify, and inform for future systematic reviews or other types of syntheses. Thus, the scope of a scoping review is often limited to presenting what kind of evidence exists, without further investigating and synthesizing the data of each included reference.

For the specific objective of our project, the scoping review approach has important strengths. We used a sensitive search strategy developed by an experienced researcher and information specialist. The article selection process, including the screening and data extraction that have been conducted independently and in duplicate, adds to the quality of the systematic approach. Also, the data extraction form was piloted before by the author group. We developed and published a detailed a priori protocol for this scoping review, which pre-defines our objective, the methods used, and the reporting of the review.

Our findings are of utmost importance, as they reveal important evidence gaps in methodological guidance on the reporting and quality appraisal of LSRs. We cannot provide any rational explanation as to why there is a lack of guidance for certain LSR-specific aspects, such as reporting and appraisal, and for other aspects, higher frequencies of guidance exist. We believe that the first obvious methodological question that authors need to address when a LSR becomes a relevant approach for their investigation, is how to conduct this novel review type. Thus, the need for LSR-specific guidance on conduct was probably acknowledged very early and researchers addressed this question in handbooks and guidance papers. Regarding the aspect of reporting or appraisal, guidance already exists for similar review types and the need for updating this literature is increasingly being acknowledged and addressed, for instance, in the PRISMA 2020 extensions for LSRs. The results of this scoping review will inform other authors, researchers, and decision-makers and show them what guidance literature is available or needs to be updated.

Conclusion

From this scoping review, we can conclude that there is some important evidence for guidance on LSRs available. In terms of the numbers of identified sources including guidance, there is a high frequency of guidance papers on conducting and publishing a LSR. However, we identified less guidance on the reporting of a LSR and the least guidance on the quality appraisal of LSRs.

When considering our results from the scoping review, there is a particular need to develop and publish more guidance on how to adequately report in LSRs. An

updated LSR-specific guidance document on reporting can be highly relevant for LSR authors, reviewers, editors, and other stakeholders involved in the LSR process. The scoping review results on reporting guidance have been used as a precursor and have been applied to inform and prepare a project on developing a PRISMA 2020 checklist extension for LSRs. The findings on the categories other than the reporting LSRs could be used by further author teams to re-evaluate and update existing guidance on SRs. Hence, we identified major evidence gaps for guidance on LSR appraisal. The AMSTAR 2 tool, which is currently used to assess the quality of SRs is not updated yet for the use of LSRs. This could be considered for further research, since there is an emerging need to develop an AMSTAR2 tool extension for novel methodological approaches to evidence syntheses, such as LSRs. Data can be made available upon author request.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-023-02396-x.

Additional file 1. Box 1. Study search strategy.

Additional file 2: Table S1. Differences between protocol and scoping review. **Table S2.** Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. **Table S3.** List of extracted study characteristics and extracted items of the categories.

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Contributors of this scoping review protocol: Gladis Honein and Matthew Page
Contributors of this scoping review: Joanne McKenzie

Authors' contributions

CI: conceptualization, methodology, analysis, investigation, visualization, writing – original draft preparation, and writing—review and editing. EAA: conceptualization, methodology, investigation, and writing—review and editing. EA: methodology, analysis, investigation, and visualization. SW: conceptualization, investigation, and writing—review and editing. LAK: conceptualization and methodology. AMA: investigation. VP: conceptualization, investigation, methodology, and writing—review and editing. NS: conceptualization, methodology, investigation,funding acquisition, supervision, and writing—review and editing.

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Declarations

Competing interests

The authors declare that they have no competing interests.
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Publisher's Note

Appendix D. Publication 3

Convalescent plasma for people with COVID-19: a living systematic review

Cochrane Library

Cochrane Database of Systematic Reviews

Convalescent plasma for people with COVID-19: a living systematic review (Review)

Iannizzi C, Chai KL, Piechotta V, Valk SJ, Kimber C, Monsef I, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Jindal A, Cryns N, Estcourt LJ, Kreuzberger N, Skoetz N

Iannizzi C, Chai KL, Piechotta V, Valk SJ, Kimber C, Monsef I, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Jindal A, Cryns N, Estcourt LJ, Kreuzberger N, Skoetz N.
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TABLE OF CONTENTS

[Intervention Review]

Convalescent plasma for people with COVID-19: a living systematic review

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ABSTRACT

Background

Convalescent plasma may reduce mortality in patients with viral respiratory diseases, and is being investigated as a potential therapy for coronavirus disease 2019 (COVID-19). A thorough understanding of the current body of evidence regarding benefits and risks of this intervention is required.

Objectives

To assess the effectiveness and safety of convalescent plasma transfusion in the treatment of people with COVID-19; and to maintain the currency of the evidence using a living systematic review approach.

Search methods

To identify completed and ongoing studies, we searched the World Health Organization (WHO) COVID-19 Global literature on coronavirus disease Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, and the Epistemonikos COVID-19 L*OVE Platform. We searched monthly until 03 March 2022.

Selection criteria

We included randomised controlled trials (RCTs) evaluating convalescent plasma for COVID-19, irrespective of disease severity, age, gender or ethnicity.

We excluded studies that included populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)), as well as studies evaluating standard immunoglobulin.

Data collection and analysis

We followed standard Cochrane methodology.

To assess bias in included studies we used RoB 2. We used the GRADE approach to rate the certainty of evidence for the following outcomes: all-cause mortality at up to day 28, worsening and improvement of clinical status (for individuals with moderate to severe disease), hospital admission or death, COVID-19 symptoms resolution (for individuals with mild disease), quality of life, grade 3 or 4 adverse events, and serious adverse events.

Main results

In this fourth review update version, we included 33 RCTs with 24,861 participants, of whom 11,432 received convalescent plasma. Of these, nine studies are single-centre studies and 24 are multi-centre studies. Fourteen studies took place in America, eight in Europe, three in South-East Asia, two in Africa, two in western Pacific and three in eastern Mediterranean regions and one in multiple regions. We identified a further 49 ongoing studies evaluating convalescent plasma, and 33 studies reporting as being completed.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

29 RCTs investigated the use of convalescent plasma for 22,728 participants with moderate to severe disease. 23 RCTs with 22,020 participants compared convalescent plasma to placebo or standard care alone, five compared to standard plasma and one compared to human immunoglobulin. We evaluate subgroups on detection of antibodies detection, symptom onset, country income groups and several co-morbidities in the full text.

Convalescent plasma versus placebo or standard care alone

Convalescent plasma does not reduce all-cause mortality at up to day 28 (risk ratio (RR) 0.98, 95% confidence interval (CI) 0.92 to 1.03; 220 per 1000; 21 RCTs, 19,021 participants; high-certainty evidence). It has little to no impact on need for invasive mechanical ventilation, or death (RR 1.03, 95% CI 0.97 to 1.11; 296 per 1000; 6 RCTs, 14,477 participants; high-certainty evidence) and has no impact on whether participants are discharged from hospital (RR 1.00, 95% CI 0.97 to 1.02; 665 per 1000; 6 RCTs, 12,721 participants; high-certainty evidence). Convalescent plasma may have little to no impact on quality of life (MD 1.00, 95% CI −2.14 to 4.14; 1 RCT, 483 participants; low-certainty evidence). Convalescent plasma may have little to no impact on the risk of grades 3 and 4 adverse events (RR 1.17, 95% CI 0.96 to 1.42; 212 per 1000; 6 RCTs, 2392 participants; low-certainty evidence). It has probably little to no effect on the risk of serious adverse events (RR 1.14, 95% CI 0.91 to 1.44; 135 per 1000; 6 RCTs, 3901 participants; moderate-certainty evidence).

Convalescent plasma versus standard plasma

We are uncertain whether convalescent plasma reduces or increases all-cause mortality at up to day 28 (RR 0.73, 95% CI 0.45 to 1.19; 129 per 1000; 4 RCTs, 484 participants; very low-certainty evidence). We are uncertain whether convalescent plasma reduces or increases the need for invasive mechanical ventilation, or death (RR 5.59, 95% CI 0.29 to 108.38; 311 per 1000; 1 study, 34 participants; very low-certainty evidence) and whether it reduces or increases the risk of serious adverse events (RR 0.80, 95% CI 0.55 to 1.15; 236 per 1000; 3 RCTs, 327 participants; very low-certainty evidence). We did not identify any study reporting other key outcomes.

Convalescent plasma versus human immunoglobulin

Convalescent plasma may have little to no effect on all-cause mortality at up to day 28 (RR 1.07, 95% CI 0.76 to 1.50; 464 per 1000; 1 study, 190 participants; low-certainty evidence). We did not identify any study reporting other key outcomes.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease

We identified two RCTs reporting on 536 participants, comparing convalescent plasma to placebo or standard care alone, and two RCTs reporting on 1597 participants with mild disease, comparing convalescent plasma to standard plasma.

Convalescent plasma versus placebo or standard care alone

We are uncertain whether convalescent plasma reduces all-cause mortality at up to day 28 (odds ratio (OR) 0.36, 95% CI 0.09 to 1.46; 8 per 1000; 2 RCTs, 536 participants; very low-certainty evidence). It may have little to no effect on admission to hospital or death within 28 days (RR 1.05, 95% CI 0.60 to 1.84; 117 per 1000; 1 RCT, 376 participants; low-certainty evidence), on time to COVID-19 symptom resolution (hazard ratio (HR) 1.05, 95% CI 0.85 to 1.30; 483 per 1000; 1 RCT, 376 participants; low-certainty evidence), on the risk of grades 3 and 4 adverse events (RR 1.29, 95% CI 0.75 to 2.19; 144 per 1000; 1 RCT, 376 participants; low-certainty evidence) and the risk of serious adverse events (RR 1.14, 95% CI 0.66 to 1.94; 133 per 1000; 1 RCT, 376 participants; low-certainty evidence). We did not identify any study reporting other key outcomes.

Convalescent plasma versus standard plasma

We are uncertain whether convalescent plasma reduces all-cause mortality at up to day 28 (OR 0.30, 95% CI 0.05 to 1.75; 2 per 1000; 2 RCTs, 1597 participants; very low-certainty evidence). It probably reduces admission to hospital or death within 28 days (RR 0.49, 95% CI 0.31

to 0.75; 36 per 1000; 2 RCTs, 1595 participants; moderate-certainty evidence). Convalescent plasma may have little to no effect on initial symptom resolution at up to day 28 (RR 1.12, 95% CI 0.98 to 1.27; 1 RCT, 416 participants; low-certainty evidence). We did not identify any study reporting other key outcomes.

This is a living systematic review. We search monthly for new evidence and update the review when we identify relevant new evidence.

Authors' conclusions

For the comparison of convalescent plasma versus placebo or standard care alone, our certainty in the evidence that convalescent plasma for individuals with moderate to severe disease does not reduce mortality and has little to no impact on clinical improvement or worsening is high. It probably has little to no effect on SAEs. For individuals with mild disease, we have very-low to low certainty evidence for most primary outcomes and moderate certainty for hospital admission or death. There are 49 ongoing studies, and 33 studies reported as complete in a trials registry. Publication of ongoing studies might resolve some of the uncertainties around convalescent plasma therapy for people with asymptomatic or mild disease.

PLAIN LANGUAGE SUMMARY

Is plasma from the blood of people who have recovered from COVID-19 an effective treatment for other people with COVID-19?

Key messages

• We are very confident that plasma from the blood of people who have recovered from COVID-19 (convalescent plasma) has no benefits for the treatment of people with moderate to severe COVID-19.

• Convalescent plasma may have little to no benefit for treating people with mild COVID-19.

• We found 49 ongoing studies and 33 finished studies with unpublished results. We will update our review with evidence from these studies as soon as possible. New evidence may answer our remaining questions, especially for people with mild COVID-19 or who have no symptoms.

What is convalescent plasma?

The body produces antibodies as one of its defences against infection. Antibodies are found in part of the blood called plasma. Plasma from people who have recovered from the COVID-19 virus contains COVID-19 antibodies, and it can be used to make convalescent plasma, which is plasma that contains these antibodies.

Convalescent plasma has been used successfully to treat some viruses. This treatment (given by a drip or injection) is generally well-tolerated, but can cause unwanted effects.

What did we want to find out?

We wanted to find out whether convalescent plasma is an effective treatment for people with confirmed COVID-19. We looked at:

• deaths from any cause after treatment with convalescent plasma;

• worsening of patients' condition, measured by the number of people who needed support from a ventilator (a machine that helps people breathe if they cannot breathe on their own) or died; and improvement of patients' condition, measured by participants discharged from hospital;

• quality of life; and

• unwanted effects.

What did we do?

We searched for studies that investigated convalescent plasma to treat people with COVID-19. Studies could take place anywhere in the world and include people of any age, gender or ethnicity, with mild, moderate or severe COVID-19.

Where possible we pooled (added up) the studies' results to analyse them. We rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 33 studies with 24,861 participants that investigated convalescent plasma. Among these, 29 studies included people with moderate to severe COVID-19 and four studies included people with mild COVID-19. Studies mainly took place in hospitals, in countries all over the world. The following findings apply to convalescent plasma compared with placebo (the same treatment but with no active ingredients) or standard care.

People with moderate to severe COVID-19

• Convalescent plasma makes no difference to **deaths from any cause** at up to 28 days after treatment, about 225 in 1000 people died, compared to 220 in 1000 people who had been given convalescent plasma (21 studies, 19,021 people).

• Convalescent plasma makes little to no difference to **needing invasive mechanical ventilation or dying**. About 287 in 1000 people needed invasive mechanical ventilation support or died, compared to 296 in 1000 people given convalescent plasma (6 studies, 14,477 people). It makes no difference to**participants being discharged from hospital.** About 665 in 1000 people were discharged from hospital, compared to 665 in 1000 people given convalescent plasma (6 studies, 12,721 people).

• Convalescent plasma probably makes no difference to **serious unwanted effects,** about 118 in 1000 people may be at risk to have serious unwanted effects compared to 133 in 1000 people given convalescent plasma (6 studies, 4901 people).

• Convalescent plasma may result in no difference in **quality of life** (1 study, 483 people).

People with mild COVID-19
• Convalescent plasma may result in no difference to **deaths from any cause** up to 28 days after treatment. About 22 in 1000 people given placebo or standard care died, compared to 9 in 1000 people given convalescent plasma (2 studies, 536 people).

• Convalescent plasma may result in no difference to **admission to hospital or death within 28 days** after treatment. About 112 in 1000 people given placebo or standard care were admitted to hospital or died, compared to 117 in 1000 people given convalescent plasma (1 study, 376 people).

• Convalescent plasma may result in no difference in the **time until COVID-19 symptoms resolved** (1 study, 376 people).

• Convalescent plasma may result in no difference to **serious unwanted effects**.

What are the limitations of the evidence?

• We are very confident in the evidence for deaths from any cause, and worsening and improvement of patients' condition in people with moderate to severe COVID-19, as the results are consistent and are from many high-quality studies.

• Our confidence in the other evidence for people with moderate and severe, and mild COVID-19 is still limited, as we could not identify enough consistent results from a lot of studies.

• We still have little evidence on quality of life and for people with mild disease, and none for people without COVID-19 symptoms.

How up to date is this evidence?

This is the fifth version of our review. The evidence is up to date to 03 March 2022.

Summary of findings 1. Summary of findings table - Convalescent plasma compared to placebo or standard care alone for individuals with moderate to severe disease

Convalescent plasma compared to placebo or standard care alone for individuals with moderate to severe disease

Patient or population: individualswith moderate to severe disease
Setting: inpatient
Intervention: convalescent plasma
Comparison: placebo or standard care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or standard care alone	Risk with convalescent plasma				
All-cause mortality at up to day 28 - total	225 per 1000	**220 per 1000** (207 to 232)	**RR 0.98** (0.92 to 1.03)	19021 (21 RCTs)	⊕⊕⊕⊕ High	Convalescent plasma does not reduce all-cause mortality at up to day 28.
Clinical worsening: need for invasive mechanical ventilation, or death at up to day 28	287 per 1000	**296 per 1000** (278 to 319)	**RR 1.03** (0.97 to 1.11)	14477 (6 RCTs)	⊕⊕⊕⊕ High	Convalescent plasma has little to no impact on the need for invasive mechanical ventilation, or death at day 28.
Clinical improvement: participants discharged from hospital	665 per 1000	**665 per 1000** (645 to 678)	**RR 1.00** (0.97 to 1.02)	12721 (6 RCTs)	⊕⊕⊕⊕ High	Convalescent plasma has no impact on whether participants are discharged from hospital.
Quality of life, assessed with EQ-5D-5L-questionnaire, at day 28 (0 indicates worst heath and 100 best health)	The mean quality of life, assessed with EQ-5D-5L-questionnaire, at day 28 was **72**	MD **1 higher** (2.14 lower to 4.14 higher)	-	483 (1 RCT)	⊕⊕⊖⊖ Low[a]	Convalescent plasma may have little to no impact on quality of life at up to day 28.
Grades 3 and 4 adverse events follow-up: 28 days	181 per 1000	**212 per 1000** (174 to 257)	**RR 1.17** (0.96 to 1.42)	2392 (6 RCTs)	⊕⊕⊖⊖ Low[b,c]	Convalescent plasma may have little to no impact on the risk of grades 3 and 4 adverse events.

Serious adverse events - total follow-up: 28 days	118 per 1000	**135 per 1000** (108 to 170)	**RR 1.14** (0.91 to 1.44)	3901 (6 RCTs)	⊕⊕⊕⊖ Moderate[c]	Convalescent plasma probably has little to no effect on the risk of serious adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423533352409190077.

[a] Downgraded two levels for very serious imprecision, because of few participants and wide confidence interval.
[b] Downgraded one level for serious indirectness, because some studies did not provide clear definitions of how the adverse events were measured and the number of events are inconsistent.
[c] Downgraded one level for publication bias, because safety outcomes were assessed and reported in most studies for convalescent plasma group only.

Summary of findings 2. Summary of findings table - Convalescent plasma compared to standard plasma for individuals with moderate to severe disease

Convalescent plasma compared to standard plasma for individuals with moderate to severe disease

Patient or population: individuals with moderate to severe disease
Setting: inpatient
Intervention: convalescent plasma
Comparison: standard plasma

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard plasma	Risk with convalescent plasma				
All-cause mortality at up to day 28	177 per 1000	**129 per 1000** (80 to 210)	**RR 0.73** (0.45 to 1.19)	484 (4 RCTs)	⊕⊖⊖⊖ Very low[a,b]	We are uncertain whether convalescent plasma reduces or increases all-cause mortality at up to day 28.

Clinical worsening: need for invasive mechanical ventilation, or death at up to day 28	56 per 1000	**311 per 1000** (16 to 1000)	**RR 5.59** (0.29 to 108.38)	34 (1 RCT)	⊕⊖⊖⊖ Very low[c]	We are uncertain whether convalescent plasma reduces or increases the risk of need for invasive mechanical ventilation, or death at day 28.
Clinical improvement: participants discharged from hospital - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Quality of life, assessed with standardised scales at longest follow-up - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Grades 3 and 4 adverse events follow-up: 28 days	The identified study reported the number of participants experiencing any event of grade 3 (27/147 in CP group versus 17/72 in SP group), or grade 4 (26/147 in CP group versus 15/72 in SP group).			248 (1 RCT)	⊕⊖⊖⊖ Very low[d,e]	We are uncertain whether convalescent plasma reduced or increases the risk for grades 3 and 4 adverse events.
Serious adverse events follow-up: 28 days	295 per 1000	**236 per 1000** (162 to 340)	**RR 0.80** (0.55 to 1.15)	327 (3 RCTs)	⊕⊖⊖⊖ Very low[f,g]	We are uncertain whether convalescent plasma reduces or increases the risk of serious adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423575562054934976.

[a] Downgraded one level for serious inconsistency, because direction of effect is not consistent in all the studies.
[b] Downgraded two levels for very serious imprecision, because of few participants and because optimal information size is not met at a power of 0.80.
[c] Downgraded three levels due to extreme imprecision, because of extremely few participants, extremely few events, very wide confidence interval and optimal information size is not met at a power of 0.80.
[d] Downgraded one level for serious indirectness, because definition of outcomes was different to the definition used in our review.

[e] Downgraded two levels for very serious imprecision, because of few participants, and few events.
[f] Downgraded two levels for very serious imprecision, because of few participants, and few events and optimal information size is not met at a power of 0.80.
[g] Downgraded one level for publication bias, because safety outcomes were assessed and reported in most studies for convalescent plasma group only.

Summary of findings 3. Summary of findings table - Convalescent plasma compared to human immunoglobulin for individuals with moderate to severe disease

Convalescent plasma compared to human immunoglobulin for individuals with moderate to severe disease

Patient or population: individuals with moderate to severe disease
Setting: inpatient
Intervention: convalescent plasma
Comparison: human immunoglobulin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with human immunoglobulin	Risk with convalescent plasma				
All-cause mortality at up to day 28	433 per 1000	**464 per 1000** (329 to 650)	**RR 1.07** (0.76 to 1.50)	190 (1 RCT)	⊕⊕⊖⊖ Low[a]	Convalescent plasma may have little to no effect on all-cause mortality at up to day 28.
Clinical worsening: need for invasive mechanical ventilation, or death at up to day 28 - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Clinical improvement: participants discharged from hospital - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Quality of life - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Grades 3 and 4 adverse events - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Serious adverse events - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_432005298021526745.

[a] Downgraded by two levels for very serious imprecision, because of few events, few participants and because optimal information size is not met at a power of 0.90.

Summary of findings 4. Summary of findings table - Convalescent plasma compared to placebo or standard care alone for individuals with mild disease

Convalescent plasma compared to placebo or standard care alone for individuals with mild disease

Patient or population: outpatients withmild disease
Setting: outpatient
Intervention: convalescent plasma
Comparison: placebo or standard care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or standard care alone	Risk with convalescent plasma				
All-cause mortality at up to day 28	22 per 1000	**8 per 1000** (2 to 32)	**OR 0.36** (0.09 to 1.46)	536 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]	We are uncertain whether or not convalescent plasma reduces all-cause mortality at up to day 28.
Admission to hospital or death within 28 days	112 per 1000	**117 per 1000** (67 to 206)	**RR 1.05** (0.60 to 1.84)	376 (1 RCT)	⊕⊕⊖⊖ Low[b]	Convalescent plasma may have little to no impact on admission to hospital or death within 28 days.

Symptom resolution- all initial symptoms resolved - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Time to symptom resolution (absolute effect calculated for day 12) follow-up: 60 days	Low 500 per 1000	 **483 per 1000** (406 to 555)	**HR 1.05** (0.85 to 1.30) [symptoms resolution]	376 (1 RCT)	⊕⊕⊖⊖ Low[b]	Convalescent plasma may have little to no impact on time to symptom resolution.
Quality of life, assessed with standardised scales at longest follow-up - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Grades 3 and 4 adverse events follow-up: 28 days	112 per 1000	**144 per 1000** (84 to 245)	**RR 1.29** (0.75 to 2.19)	376 (1 RCT)	⊕⊕⊖⊖ Low[b]	Convalescent plasma may have little to no impact on the risk of grades 3 and 4 adverse events.
Serious adverse events follow-up: 28 days	117 per 1000	**133 per 1000** (77 to 227)	**RR 1.14** (0.66 to 1.94)	376 (1 RCT)	⊕⊕⊖⊖ Low[b]	Convalescent plasma may have little to no impact on the risk of serious adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard Ratio; **OR:** odds ratio; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423575913930302502.

[a] Downgraded one level for serious indirectness, because outcome definition did not exactly match our definition (defined as death associated with COVID-19).
[b] Downgraded two levels for very serious imprecision, because of few participants, few events, wide confidence intervals and because optimal information size is not met for a power of 0.90.

Summary of findings 5. Summary of findings table - Convalescent plasma compared to standard plasma for outpatients with mild disease

Convalescent plasma compared to standard plasma for outpatients withmild disease

Patient or population: outpatients withmild disease
Setting: outpatient
Intervention: convalescent plasma
Comparison: standard plasma

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard plasma	Risk with convalescent plasma				
All-cause mortality at up to day 28	5 per 1000	**2 per 1000** (0 to 9)	**OR 0.30** (0.05 to 1.75)	1597 (2 RCTs)	⊕⊖⊖⊖ Very low[a]	We are uncertain whether or not convalescent plasma reduces all-cause mortality at up to day 28.
Admission to hospital or death within 28 days	73 per 1000	**36 per 1000** (23 to 55)	**RR 0.49** (0.31 to 0.75)	1595 (2 RCTs)	⊕⊕⊕⊖ Moderate[b]	Convalescent plasma probably reduces admission to hospital or death at up to day 28.
Symptom resolution- all initial symptoms resolved follow-up: 28 days	657 per 1000	**736 per 1000** (644 to 835)	**RR 1.12** (0.98 to 1.27)	416 (1 RCT)	⊕⊕⊖⊖ Low[c]	Convalescent plasma may have little to no effect on symptom resolution at up to day 28.
Time to symptom resolution - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Quality of life, assessed with standardised scales - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Grades 3 and 4 adverse events - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.
Serious adverse events - not reported	-	-	-	-	-	We did not identify any study reporting this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_432020765287988004.

[a] Downgraded by three levels for extremely serious imprecision, because few events, extremely wide confidence intervals and because optimal information size is not met for a power of 0.90.
[b] Downgraded one level for serious imprecision, because optimal information size is not met for a power of 0.90.
[c] Downgraded by two levels for very serious imprecision, because few events, very wide confidence intervals and because optimal information size is not met for a power of 0.90.

BACKGROUND

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Description of the condition

The clinical syndrome coronavirus disease 2019 (COVID-19) is a new, rapidly emerging zoonotic infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; WHO 2020a). On 22 March 2020, the World Health Organization (WHO) declared the current COVID-19 outbreak to be a pandemic, with the outbreak resulting in more than 535 million confirmed cases and over 6.3 million deaths worldwide as of June 2022 (WHO 2020b; WHO 2021a). Although there are similarities with historic coronavirus epidemics, with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) responsible for 813 and 858 deaths respectively, the scale and impact of the COVID-19 pandemic present unprecedented challenges to health facilities and healthcare workers all over the world (WHO 2007; WHO 2019). Concurrently, new SARS-CoV-2 variants emerged, potentially having an effect on the transmission and characteristics of the disease, the effectiveness of vaccines and treatments, or on public health and social measures (WHO 2022b).

Early reports suggested case fatality rates between 0.7% and 4% (WHO 2020a; WHO 2020c). More recent reports estimate wide-ranging case fatality rates, as low as 0. 1% in Singapore and up to 5.2% in Peru (Johns Hopkins 2022). However, these numbers should be interpreted with great care due to testing availability, underreporting of cases and delays from confirmation of a case to time of death (Kim 2020), ethnicity, underlying health conditions, access to health care, and socioeconomic status (Williamson 2020).

The median incubation period and time to symptom onset of SARS-CoV-2 was reported to be five days, with 97.5% of cases developing symptoms within 11.5 days of infection (Brandal 2021; Lauer 2020). However, the median incubation time depends on the virus variant and is estimated to be only three days (range: 0 to 8 days) in case of the Omicron variant, which is shorter compared to the estimate for the Delta variant, for instance, or other previous variants (Brandal 2021). Common signs and symptoms can include fever, dry cough, fatigue and sputum production (WHO 2020a). Postviral olfactory dysfunction is reported in 5% to 85% of cases, with loss of both smell and taste reported (Izquierdo-Dominguez 2020). Other less commonly reported signs and symptoms are shortness of breath, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhoea, haemoptysis and conjunctival congestion (WHO 2020a). Of the reported cases, 80% are estimated to have a mild or asymptomatic course of infection, and an estimated 5% of cases are admitted to the intensive care unit (ICU) with acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure, or all three conditions (Team 2020; WHO 2020a). A risk factor for developing infection and progressing to severe disease is old age, with people aged over 80 years at highest risk of mortality. Other risk factors are cardiovascular disease, obesity, hypertension, diabetes, chronic respiratory disease, cancer and compromised immune status (Chen 2020a; Huang 2020; Liang 2020; WHO 2020a; Wu 2020a). Individuals who are immune-compromised are at higher risk of adverse outcomes from COVID-19, including people who have received recent chemotherapy and chemoimmunotherapy, recipients of solid organ and allogeneic transplants and individuals with haematological malignancies and solid organ cancer (Chavez-MacGregor 2022; Fung 2020).

SARS-CoV-2 is a positive-sense, single-stranded ribonucleic acid (RNA) virus with a large genome. There are indications that the virus is capable of inducing an excessive immune reaction in the host, with highly activated but decreased numbers of $CD4^+$ and $CD8^+$ T cells detected in the peripheral blood of people with COVID-19 (Xu 2020a). Early reports also showed that people critically ill with COVID-19 frequently exhibit a hypercoagulable state and endothelial inflammation, which is hypothesised to lead to the high burden of thromboembolic events seen in this population (Driggin 2020). SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2). ACE2 is a protein that functions as the receptor, facilitating entry of SARS-CoV-2 into the host cell, and is most abundant on type II alveolar cells in the lungs (Tolouian 2020; Van de Veerdonk 2020).

Widespread availability of vaccines against SARS-CoV-2 has reduced infections and the risk of severe disease. However, individuals who are immunocompromised have reduced rates of seroconversion following vaccination and therefore remain susceptible to severe COVID-19 and in need of effective therapies (Lee 2022; Teh 2022).

Description of the intervention

Convalescent plasma and convalescent serum prepared from convalescent plasma are interventions that have been used in the past to treat conditions when no vaccine or pharmacological interventions were available. Diphtheria, pneumococcal pneumonia, hepatitis A and B, mumps, polio, measles, and rabies are conditions where convalescent plasma has been shown to be effective (Eibl 2008).

A systematic review has shown that convalescent plasma may have clinical benefit for people with influenza and SARS (Mair-Jenkins 2015). This systematic review included observational studies and randomised controlled trials (RCTs) that investigated the use of convalescent plasma or serum for treating severe acute respiratory infections of laboratory-confirmed or suspected viral aetiology, and included investigations with patients of any age and sex. Control interventions consisted of sham or placebo therapy and no therapy. Although the included studies were generally small and of low quality, with a moderate to high risk of bias, the review authors concluded that the use of convalescent plasma may reduce mortality, and appears safe (Mair-Jenkins 2015). The authors also suggested that the effectiveness of convalescent plasma in reducing hospital length of stay is dependent on early administration of the therapy, and use as prophylaxis is more likely to be beneficial than treating severe disease. However, the optimal timing and dosage of convalescent plasma therapy are unknown.

There is conflicting evidence about the effect of convalescent plasma for treating severe acute respiratory infections. For instance, studies that investigated the effectiveness of immune plasma for influenza showed no benefit (Beigel 2017; Beigel 2019).

Although convalescent plasma is generally thought to be a well-tolerated therapy, adverse events can occur. Limited information is available about specific adverse events related to convalescent plasma therapy, but symptoms that have been reported are similar to those for other types of plasma blood components, including fever or chills, allergic reactions, and transfusion-related

acute lung injury (TRALI; Beigel 2019; Chun 2016; Luke 2006). Furthermore, the transfer of coagulation factors present in plasma products is potentially harmful for people with COVID-19, who are already at an increased risk of thromboembolic events (Driggin 2020). Plasma transfusions are also known to cause transfusion-associated circulatory overload (TACO). TACO and TRALI are especially important to consider, because COVID-19 patients with comorbidities, who might be eligible for experimental treatment with convalescent plasma therapy, are at an increased risk of these adverse events. Risk-mitigation strategies can be implemented to prevent TRALI. These include limiting donations from female donors, especially those with a history of pregnancy, and screening donors for antibodies that are implicated in TRALI (Otrock 2017). In addition to the aforementioned adverse events, transfusion-transmitted infections, red blood cell allo-immunisation and haemolytic transfusion reactions have also been described following plasma transfusion, although they are less common (Pandey 2012). Pathogen inactivation can be implemented to decrease the risk of transmitting infections by transfusion (Rock 2011), with likely preservation of neutralising antibodies (Focosi 2021; Kostin 2021; Larrea 2022).

A theoretical risk related to virus-specific antibodies, which are transferred with convalescent plasma administration, is antibody-dependent enhancement of infection (Morens 1994). Here, virus-binding antibodies facilitate the entry and replication of virus particles into monocytes, macrophages and granulocytic cells and thereby increase the risk of more severe disease in the infected host. Although antibody-dependent enhancement has not been demonstrated in COVID-19, it has been seen with previous coronavirus infections when the antibodies given targeted a different serotype of the virus (Wan 2020; Wang 2014). A mechanism for antibody-dependent enhancement in COVID-19 has recently been proposed, with non-neutralising antibodies to variable S domains potentially enabling an alternative infection pathway via Fc receptor-mediated uptake (Ricke 2020). Antibody-dependent enhancement is therefore a potentially harmful consequence of convalescent plasma therapy for COVID-19.

In summary, the benefits of the intervention for convalescent plasma should be carefully considered in view of the risks of adverse events.

How the intervention might work

Convalescent plasma contains pathogen-specific neutralising antibodies, which can neutralise viral particles and may confer passive immunity to recipients. The duration of conferred protection can differ depending on the timing of administration, ranging from weeks to months after treatment (Casadevall 2020).

By neutralising SARS-CoV-2 particles, early treatment with convalescent plasma is postulated to increase the patient's own capacity to clear the initial inoculum (Casadevall 2020; Robbins 1995). This could lead to a reduction in mortality and fewer hospitalised patients progressing to the ICU. Furthermore, convalescent plasma may reduce the length of ICU stay in critically ill patients (Mair-Jenkins 2015), thus helping to lift pressure from global healthcare systems and increasing ICU capacity.

Although, initially re-infection was not thought to be likely (Bao 2020a; Wu 2020b), this has changed since the end of 2021 when Omicron variants of SARS-CoV-2 became dominant (ONS 2022). This implies that convalescent plasma from people who have recovered from SARS-CoV-2 infection may be capable of conferring passive immunity. Retrospective studies also observed a potential correlation between the level of antibody titres in convalescent plasma and recovery after treatment (Joyner 2021; Shen 2020). It is important to note, however, that research in other coronavirus species has shown that immunity may not be long-lasting, with two to three years of protection estimated from work with SARS and MERS (Mo 2006; Payne 2016). Furthermore, there are indications that the severity of infection has an impact on antibody titres, with less-severe disease leading to lower neutralising antibody response in people with SARS and COVID-19 (Ho 2005; Zhao 2020). It is unclear exactly how often reinfection occurs, with the burden of reinfection likely to be underestimated, while at the same time a number of case reports of severe reinfection have been published (Iwasaki 2021).

Why it is important to do this review

There is an ongoing need for information to guide clinical decision making for COVID-19 patients. Pharmacological treatment options have been and are continuing to be investigated in many ongoing trials, with treatment guidelines updated accordingly (WHO 2022a). Current treatments that have been shown to be effective in non-severe COVID-19 at risk of hospitalisation include nirmatrelvir-ritonavir, remdesivir and molnupiravir (WHO 2022a), and in severe or critical COVID-19 systemic corticosteroids, interleukin-6 receptor blockers (tocilizumab and sarilumab), and baracitinib (Janus kinase inhibitor) (Beigel 2020; Horby 2020; Horby 2021a; WHO 2022a). Current treatment also consists of supportive care with extracorporeal membrane oxygenation in severe cases and oxygen supply in less severe cases (CDC 2020; WHO 2020d). Although the risk of hospitalisation and death has decreased during the course of the pandemic with emergence of different variants including omicron (Adjei 2022; Nyberg 2022; Ulloa 2022), even with current therapies, patients with COVID-19 remain at increased risk of mortality, particularly older individuals and those with comorbidities (Adjei 2022).

Currently approved and available COVID-19 vaccines have been shown to be well-tolerated and effective (CDC 2022). They can prevent transmission to those who are at risk for becoming seriously ill and reduce the risk for developing severe disease (CDC 2022). However, even with the available effective vaccines, not everyone can be effectively vaccinated; for example, people who are temporarily or permanently immune-compromised. Convalescent plasma can be prepared and made rapidly available by blood banks and hospitals when enough potential donors have recovered from the infection, using readily available materials and methods (Bloch 2020). However, its safety and efficacy are not well-characterised, and there are costs associated with pursuing the use of convalescent plasma for treatment of COVID-19.

A multitude of clinical trials investigating the safety and effectiveness of convalescent plasma have been announced, and their results will need to be interpreted with care. Thus, there needs to be a thorough understanding of the current body of evidence regarding the use of convalescent plasma for people with COVID-19, and an extensive review of the available literature is required.

OBJECTIVES

To assess the effectiveness and safety of convalescent plasma transfusion in the treatment of people with COVID-19; and to maintain the currency of the evidence using a living systematic review approach.

METHODS

Criteria for considering studies for this review

Types of studies

The main description of methods is based on a template from Cochrane Haematology and is in line with a series of Cochrane Reviews investigating treatments and therapies for COVID-19. The protocol for this review was registered with the Center for Open Science on 17 April 2020 (Piechotta 2020a). Amendments that have been made since are summarised in Differences between protocol and review and Table 1.

To assess the benefits and safety of convalescent plasma therapy for the treatment of COVID-19, we included RCTs, as such studies, if performed appropriately, give the best evidence for experimental therapies in highly controlled therapeutic settings. We used the methods recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022a). If we had identified non-standard RCT designs, such as cluster-randomised trials and cross-over trials, we would have considered only the results from the first cycle of cross-over RCTs.

We included full-text publications, preprint articles, abstract publications, and results published in trials registries, if sufficient information was available on study design, characteristics of participants, interventions and outcomes. We did not apply any limitation with respect to the length of follow-up.

Types of participants

We included individuals with a confirmed diagnosis of COVID-19, with no age, gender or ethnicity restrictions.

We included trials that included participants with any disease severity. We performed separate analyses for populations with ambulatory mild disease and for hospitalised participants with moderate to severe disease, according to the latest WHO clinical progression score (see Table 2; WHO 2020e).

We excluded studies that included populations with other coronavirus diseases (SARS or MERS). We also excluded studies that included populations with mixed viral diseases (e.g. influenza), unless the trial authors provided subgroup data for people with COVID-19.

Types of interventions

We included the following intervention.

- Convalescent plasma from people who had recovered from SARS-CoV-2 infection

We did not include studies on standard immunoglobulin as intervention.

We included the following comparisons for the control arm.

- Convalescent plasma therapy versus control treatment, for example, drug treatments (including but not limited to hydroxychloroquine, remdesivir), standard immunoglobulin. Co-interventions were allowed, but must have been comparable between intervention groups.
- Convalescent plasma versus standard care or placebo (i.e. saline solution)
- Convalescent plasma versus standard plasma (i.e. fresh frozen plasma)

Types of outcome measures

We evaluated core outcomes as predefined by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2020), and additional outcomes that have been prioritised by consumer representatives, referees of previous versions of this review, and the German guideline panel for inpatient therapy of people with COVID-19.

We defined outcome sets for two populations: individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, and individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, according to the WHO clinical progression scale (WHO 2020e).

We assessed disease severity with need for respiratory support according to the WHO clinical progression scale (WHO 2020e).

Timing of outcome measurement

For time-to-event outcomes, such as mortality, discharge from hospital, and improvement of clinical symptoms, we included outcome measures representing the longest follow-up time available.

We included all other outcome categories for the observational periods that the study publications reported. We included those adverse events occurring during active treatment and had planned to include long-term adverse events as well. If sufficient data had been available, we planned to group the measurement time points of eligible outcomes, for example, adverse events and serious adverse events, into those measured directly after treatment (up to seven days after treatment), medium-term outcomes (15 days after treatment) and longer-term outcomes (over 30 days after treatment).

Primary outcomes

These critical outcomes will be included in the summary of findings tables.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

- All-cause mortality at day 28, day 60, time to death and during hospital stay
- Clinical status, at day 28, day 60, and up to the longest follow-up, including the following:
  - worsening of clinical status: participants with clinical deterioration (new need for invasive mechanical ventilation) or death;
  - improvement of clinical status: participants discharged from hospital. Participants should be discharged without clinical deterioration

- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100, a standardised scale for assessing quality of life) at up to 7 days, up to 28 days, and longest follow-up available
- Adverse events (any grade, grades 1-2, grades 3-4), defined as the number of participants with any event and including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, transfusion-associated dyspnoea (TAD), acute transfusion reactions, headache, thromboembolic events)
- Serious adverse events, defined as the number of participants with any serious adverse event (serious as defined according to CTCAE (Common Terminology Criteria for Adverse Events))

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

- All-cause mortality at day 28, day 60, time to event, and at the longest follow-up
- Admission to hospital or death within 28 days
- Symptom resolution:
  - all initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up;
  - time to symptom resolution
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 28 days, and longest follow-up available;
- Adverse events (any grade, grades 1-2, grades 3-4)
- Serious adverse events, defined as the number of participants with any serious adverse event (serious as defined according to CTCAE (Common Terminology Criteria for Adverse Events))

Secondary outcomes

These outcomes will not be included in the summary of findings tables.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

- Improvement of clinical status, at day 28 and up to the longest follow-up, including:
  - weaning or liberation from invasive mechanical ventilation in surviving participants;
  - ventilator-free days (defined as days alive and free from mechanical ventilation);
  - liberation from supplemental oxygen in surviving participants
- Need for dialysis at up to 28 days
- Admission to the ICU on day 28
- Duration of hospitalisation
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, and up to 3, 7, and 14 days.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

- Worsening of clinical status, at day 28 and up to the longest follow-up, including (moderate to severe COVID-19 symptoms):
  - need for hospitalisation with oxygen by mask or nasal prongs, or death;
  - need for invasive mechanical ventilation, or death
- Viral clearance, assessed with RT-PCR for SARS-CoV-2 at baseline, and up to 3, 7, and 14 days

Search methods for identification of studies

We carried out weekly searches until 11 August 2021 and from August 2021 onwards, we carried out monthly searches for completed and ongoing studies. In order to limit language bias, studies reported in all languages were eligible. We checked review search methods and strategies approximately monthly to ensure they reflected any terminology changes in the topic area, or in the databases. We adapted the strategy where necessary.

Electronic searches

We designed and tested search strategies for electronic databases according to methods suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022a). One review author (CD) developed the original strategies and Cochrane Haematology's Information Specialist (IM) peer-reviewed and revised them at various times, to reflect the current state of knowledge. In this emerging field, we expected that at least study abstracts would be in English. If studies were published in other languages than those our review team could accommodate (English, Dutch, German, French, Italian, Malay and Spanish), we involved Cochrane TaskExchange to identify people within Cochrane to translate these studies.

As publication bias might influence all subsequent analyses and conclusions, we searched all potentially relevant trials registries in detail to detect ongoing studies as well as studies that had been completed but not yet published. It is mandatory to provide trial results in the trials registry, so we planned to extract and analyse these data, in case results were not published elsewhere. However, no outcome data have yet been added to the trials registries.

We searched the following databases and sources from 1 January 2019 to 03 March 2022.

- Databases of medical literature (Appendix 1):
  - MEDLINE Ovid (1 January 2020 to 02 March 2022);
  - Embase Ovid (1 January 2020 to 02 March 2022);
  - Cochrane COVID-19 Study Register (covid-19.cochrane.org; inception to 03 March 2022)*
  - PubMed (for epublications ahead of print only; 1 January 2020 to 03 March 2022)
  - World Health Organization COVID-19 Global literature on coronavirus disease (bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov; inception to 03 March 2022) without references of MEDLINE and PubMed)
  - Epistemonikos, L*OVE List Coronavirus disease (COVID-19) (app.iloveevidence.com; inception to 03 March 2022)

*The Cochrane COVID-19 Study Register is a specialised register built within the Cochrane Register of Studies (CRS) and is maintained by Cochrane Information Specialists. Complete data sources and search methods for the register are available at community.cochrane.org/about-covid-19-study-register. The register contains study reports from several sources, including:

- weekly searches of PubMed;
- daily searches of ClinicalTrials.gov;

- weekly searches of Embase.com;
- weekly searches of the WHO International Clinical Trials Registry Platform (ICTRP);
- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL).

Searching other resources

We handsearched the reference lists of all identified studies, relevant review articles and current treatment guidelines for further literature. We also contacted experts in the field, drug manufacturers and regulatory agencies in order to retrieve information on unpublished studies.

Data collection and analysis

Selection of studies

Using Covidence software, two review authors (from among SJV, KLC, VP, CK, CI and NS) independently screened the results of the search strategies for eligibility, by reading the abstracts. We coded the abstracts as either 'retrieve' or 'do not retrieve'. In the case of disagreement, or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Two review authors assessed the full-text articles of selected studies. If the two review authors were unable to reach a consensus, they consulted a third review author to reach a final decision.

We documented the study selection process in a flow chart, as recommended in the PRISMA statement (Moher 2009), and show the total numbers of retrieved references and the numbers of included and excluded studies. We list all studies that we excluded after full-text assessment and the reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (from among CI, NK, and EA) independently assessed eligible studies obtained in the process of study selection (as described above) for methodological quality and risk of bias. If the review authors were unable to reach a consensus, we consulted a third review author.

Two review authors (from among CI, NK, NC, and EA) extracted data using a customised data extraction form, developed in Microsoft Excel (Microsoft Corporation 2018). Another review author (CI, NK, or NS) verified the accuracy and (where applicable) the plausibility of extractions and assessment. We conducted data extraction according to the guidelines proposed by Cochrane (Li 2022). If the review authors were unable to reach a consensus, we consulted a third review author.

We collated multiple reports of one study so that the study, and not the report, is the unit of analysis.

We extracted the following information.

- General information: author, title, source, publication date, country, language, duplicate publications
- Quality assessment: study design, bias arising from the randomisation process, due to deviations from the intended interventions, due to missing outcome data, in measurement of the outcome, and in selection of the reported results
- Study characteristics: trial design, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, treatment cross-overs, compliance with assigned treatment, length of follow-up
- Participant characteristics: age, sex, ethnicity, number of participants recruited/allocated/evaluated, disease, severity of disease, additional diagnoses, previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation), whether the donors were tested by nasal swabs or whether the plasma was tested
- Interventions: convalescent plasma therapy, concomitant therapy, duration of follow-up, donors' disease severity, how donations were tested for neutralising antibody
  - For studies that included a control group: comparator (type)
- Outcomes: as specified in Types of outcome measures

Assessment of risk of bias in included studies

We used the RoB 2 to analyse the risk of bias in the underlying study results (Sterne 2019). Of interest for this review was the effect of the assignment to the intervention (the intention-to-treat (ITT) effect) and we performed all assessments with RoB 2 on this effect. The outcomes that we addressed are those specified for inclusion in Summary of findings table 1. Accordingly, the outcomes had been prioritised according to the COMET Initiative for COVID-19 patients (COMET 2020).

Two review authors (from among CI, VP and EA) independently assessed the risk of bias for each study result. In case of discrepancies among their judgements or inability to reach consensus, we consulted a third review author to reach a final decision. We assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For cluster-RCTs, we had planned to add an additional domain to assess bias arising from the timing of identification and recruitment of participants in relation to timing of randomisation, as recommended in the archived RoB 2 guidance for cluster-randomised trials (Eldridge 2016), and in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b).

To address these types of bias we used the signalling questions recommended in RoB 2 and made a judgement using the following options:

- 'yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'no': if there is firm evidence that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question);

- 'probably no': a judgement has been made that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'no information': if the study report does not provide sufficient information to allow any judgement.

We used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias:

- low risk of bias;
- some concerns;
- high risk of bias.

Subsequently, we derived a risk of bias rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judged the trial to be at low risk of bias for all domains for this result.
- 'Some concerns': we judged the trial to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judged the trial to be at high risk of bias in at least one domain for the result or we judged the trial to have some concerns for multiple domains in a way that substantially lowers confidence in the results.

We used the RoB 2 Excel tool to implement RoB 2 (available on the riskofbiasinfo.org website), added our judgements to the analysis for each assessed study and outcome, and stored our detailed RoB 2 assessments as supplementary online material. We used the overall risk of bias judgement, derived from the RoB 2 Excel tool, to inform our GRADE decision on downgrading for risk of bias.

Measures of treatment effect

For continuous outcomes, we recorded the mean, standard deviation and total number of participants in both the treatment and control groups. For dichotomous outcomes, we recorded the number of events and total number of participants in both the treatment and control groups.

For continuous outcomes using the same scale, we performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we performed analyses using the standardised mean difference (SMD). For interpreting SMDs, we re-expressed SMDs in the original units of a particular scale with the most clinical relevance and impact.

If available, we extracted and reported hazard ratios (HRs) for time-to-event outcomes (e.g. time to symptom resolution). If HRs were not available, we made every effort to estimate the HR as accurately as possible using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007). If sufficient studies provided HRs, we used HRs rather than risk ratios (RRs) or MDs in a meta-analysis.

For dichotomous outcomes, we planned to report the pooled RR with a 95% CI (Deeks 2022). If the number of observed events had been small (less than 5% of sample per group), and if studies had balanced treatment groups, we planned to report the Peto odds ratio (OR) with 95% CI (Deeks 2022).

Unit of analysis issues

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022c), for studies with multiple treatment groups, we planned to combine arms if they could be regarded as subtypes of the same intervention.

When arms could not be pooled this way, we planned to compare each arm with the common comparator separately. For pair-wise meta-analysis, we planned to split the 'shared' group into two or more groups with smaller sample sizes, and include two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, both the number of events and the total number of participants would be divided up, and for continuous outcomes, the total number of participants would be divided up with unchanged means and standard deviations (SDs).

Dealing with missing data

Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data, which we needed to take into account: at study level, at outcome level and at summary data level (Higgins 2022c). In the first instance, it is of the utmost importance to differentiate between data 'missing at random' and 'not missing at random'.

We handled missing data by conducting an available-case analysis and extracted all the available data. Further, we requested missing data from the study authors. For the previous update version, we contacted 11 principal investigators from included studies (Agarwal 2020; AlQahtani 2021; Avendano-Sola 2021; Bajpai 2020; Gharbharan 2021; Hamdy Salman 2020; Horby 2021b; Li 2020; Libster 2020; Ray 2022; Simonovich 2020). We received six responses: one each from Agarwal 2020; AlQahtani 2021; Avendano-Sola 2021; Gharbharan 2021; Horby 2021b and Li 2020, providing all requested information. For this current update version, we contacted another 11 principal investigators from included studies (Baldeon 2022; Bar 2021; Bennett-Guerrero 2021; De Santis 2022; Devos 2021; Holm 2021; Koerper 2021; Menichetti 2021; NCT04421404; Ortigoza 2022; Sekine 2021). We received three responses (De Santis 2022; Baldeon 2022; Bennett-Guerrero 2021).

We further contacted all principal investigators (where contact information was available) from ongoing studies, asking for their prospective completion dates, as well as completed or terminated studies without published results, and invited them to share their data with us for this update. We received a response from one study (NCT04374526), informing us that their trial was completed, but that the results will not be published soon and that they are willing to share their data for this update (no data were received from the investigators before submission of our review).

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$, and visual examination. We used the I^2 statistic (Higgins 2003), to quantify possible heterogeneity ($I^2 > 30\%$ to signify moderate heterogeneity, $I^2 > 75\%$ to signify considerable heterogeneity; Deeks 2022). If heterogeneity had been above 80%, we would have explored potential causes through sensitivity and subgroup analyses. If we had not found a reason for heterogeneity, we would not have performed a meta-analysis, but would have only commented on results from all studies and presented these in tables.

Assessment of reporting biases

As mentioned above, we searched trials registries to identify completed studies that have not been published elsewhere, to minimise or determine publication bias. We included studies irrespective of their publication status, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2022).

For meta-analyses involving at least 10 studies, we intended to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test (Sterne 2019). We considered $P < 0.1$ as significant for this test.

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data in meta-analysis. We performed separate analyses for populations with ambulatory mild disease and for hospitalised participants with moderate to severe disease, according to the latest WHO clinical progression score (WHO 2020e). We performed analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). We did not conduct meta-analyses that included different study designs. We conducted separate meta-analyses for each comparison.

We used RevMan Web 2022 software for analyses. One review author entered the data into the software, and a second review author checked the data for accuracy.

We used the random-effects model for all analyses, as we anticipated that true effects in included studies would be related but would not be the same. For binary outcomes, we based the estimation of the between-study variance using the Mantel-Haenszel method. We used the inverse variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. We planned to explore heterogeneity above 80% with subgroup analyses. If we could not find a cause for the heterogeneity or if study outcomes were too clinically heterogeneous to be combined, we did not perform a meta-analysis, but commented on the results in a narrative analysis, with the results from all studies presented in tables.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses of the following characteristics for our prioritised outcomes, as specified in the Summary of findings section.

- Severity of condition for inpatients only (assessed with need for respiratory support according to WHO clinical progression scale (WHO 2020e) are divided into:
  - moderate, when at least 90% of participants are WHO level 4 or higher, and below WHO level 6,
  - severe disease, when at least 90% of participants are WHO level 6 or higher, and
  - moderate to severe, when 90% of participants are in both the 'moderate' and severe' categories
- Length of time since symptom onset (divided into up to and including 7 days and more than 7 days)
- Antibodies in recipients detected at baseline (divided into 'detected in a maximum of 20% of recipients' versus 'detected in at least 80% of recipients')
- Age of participants (divided into age groups: children, 18 to 64 years, 65 years and older)
- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression)
- Level of antibody titre in donors (divided into high and low titres, using the US Food and Drug Administration (FDA) definition for 'low' and 'high' titre using the definition provided by the study)
- Equity impact: sex (divided into female and male)
- Equity impact: country income groups, according to the World Bank definitions (divided into high- and low- or middle-income countries; The World Bank 2022)

We used the tests for interaction to test for differences between subgroup results.

We had further planned to perform additional subgroup analyses of the following characteristics, but we did not find outcome data for:

- SARS-CoV-2 variants (e.g. B1.1.7, B.1.351, P.1, and other variants that may occur in the future)
- Equity impact: ethnicity

Sensitivity analysis

We performed sensitivity analyses for the following.

- Risk of bias assessment components (studies with a low risk of bias or some concerns versus studies with a high risk of bias)
- Influence of completed, but not published studies (preprints)
- Influence of premature termination of studies

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the following outcomes. We prepared three summary of findings tables for the population of individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, and two summary of findings tables for individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

- All-cause mortality at day 28 and if not reported, all-cause mortality at day 60, time-to-event estimate, or during hospital stay
- Clinical status, at day 28 and if not reported, clinical status at day 60, or up to the longest follow-up, including the following:
  - worsening of clinical status: participants with clinical deterioration (new need for invasive mechanical ventilation) or death;
  - improvement of clinical status: participants discharged from hospital. Participants should be discharged without clinical deterioration.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100, a standardised scale for assessing quality of life) at up to 7 days, up to 28 days, or longest follow-up available
- Grade 3 or 4 adverse events, defined as the number of participants with any event and including potential relationship between intervention and adverse reaction (e.g. TRALI,

transfusion-transmitted infection, TACO, TAD, acute transfusion reactions, headache, thromboembolic events)

- Serious adverse events, defined as the number of participants with any serious adverse event (serious as defined according to CTCAE (Common Terminology Criteria for Adverse Events)).

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

- All-cause mortality at day 28 and if not reported, all-cause mortality at day 60, or time-to-event estimate
- Symptom resolution:
  - all initial symptoms resolved (asymptomatic) at day 28 and if not reported, at day 14 or up to the longest follow-up;
  - length of time to symptom resolution
- Quality of life, including fatigue and functional independence; assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available
- Grade 3 or 4 adverse events
- Serious adverse events, defined as the number of participants with any serious adverse event (serious as defined according to CTCAE (Common Terminology Criteria for Adverse Events))

We followed the current GRADE guidance for these assessments in its entirety, as recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022). We used GRADEpro GDT software to create a summary of findings table (Schünemann 2022). For RCTs, we used the overall risk of bias judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading for risk of bias. For time-to-event outcomes, we calculated absolute effects at specific time points, as recommended in the GRADE guidance 27 (Skoetz 2020). We phrased the findings and certainty of the evidence as suggested in the informative statement guidance (Santesso 2020).

RESULTS

Description of studies

Results of the search

As of 3 March 2022, we identified for this update 7625 new records, in addition to the 22,570 potentially relevant records from the previous versions (altogether 30,195 references). After removing duplicates, we screened 6455 new records for this update (altogether 22,267 records) based on their titles and abstracts, and we excluded 21,929 records that did not meet the prespecified inclusion criteria. We evaluated the remaining 338 records and screened the full texts, or, if these were not available, abstract publications or trial registry entries. See Figure 1 for the study flow diagram (Moher 2009).

Figure 1. Study flow diagram

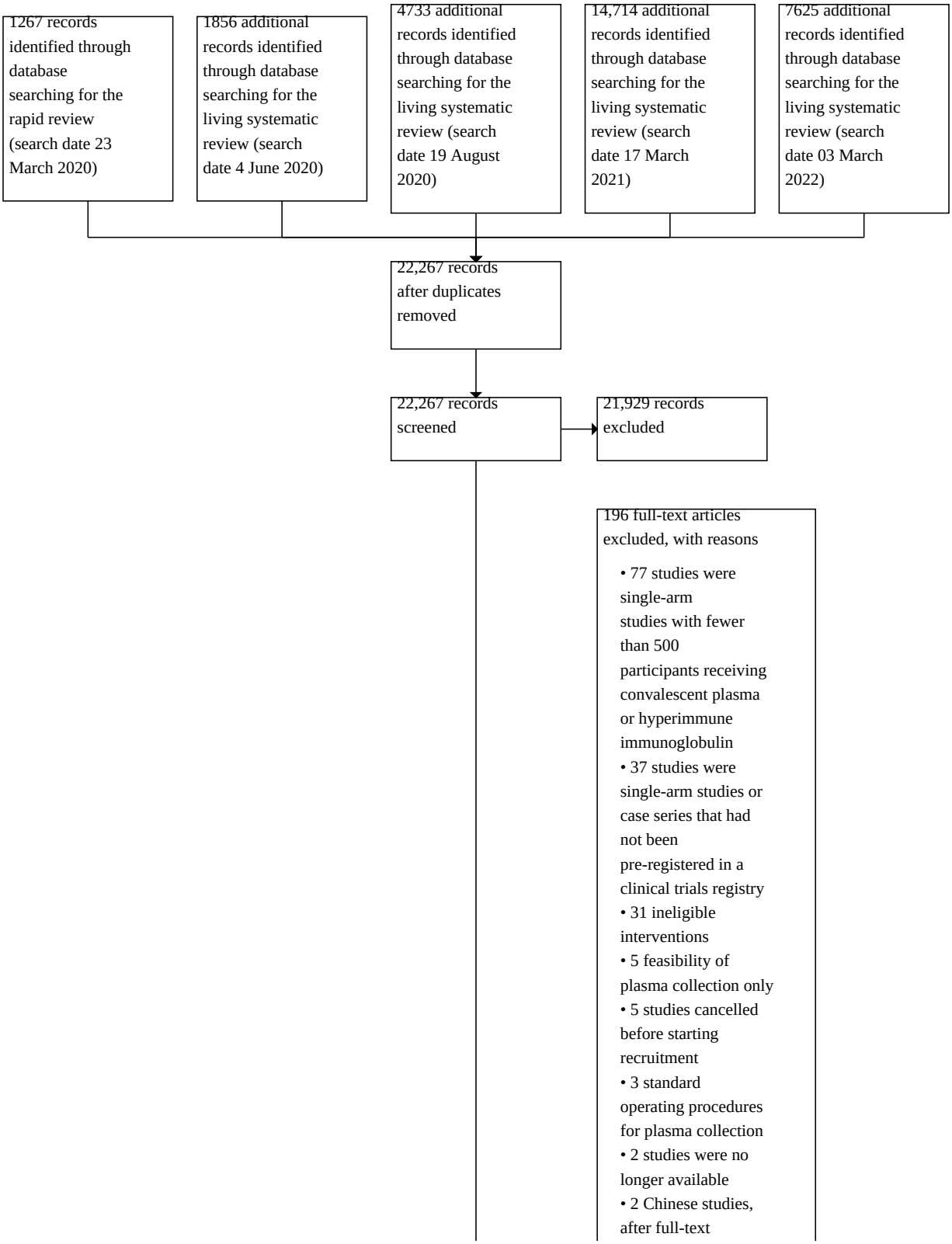


Figure 1. (Continued)

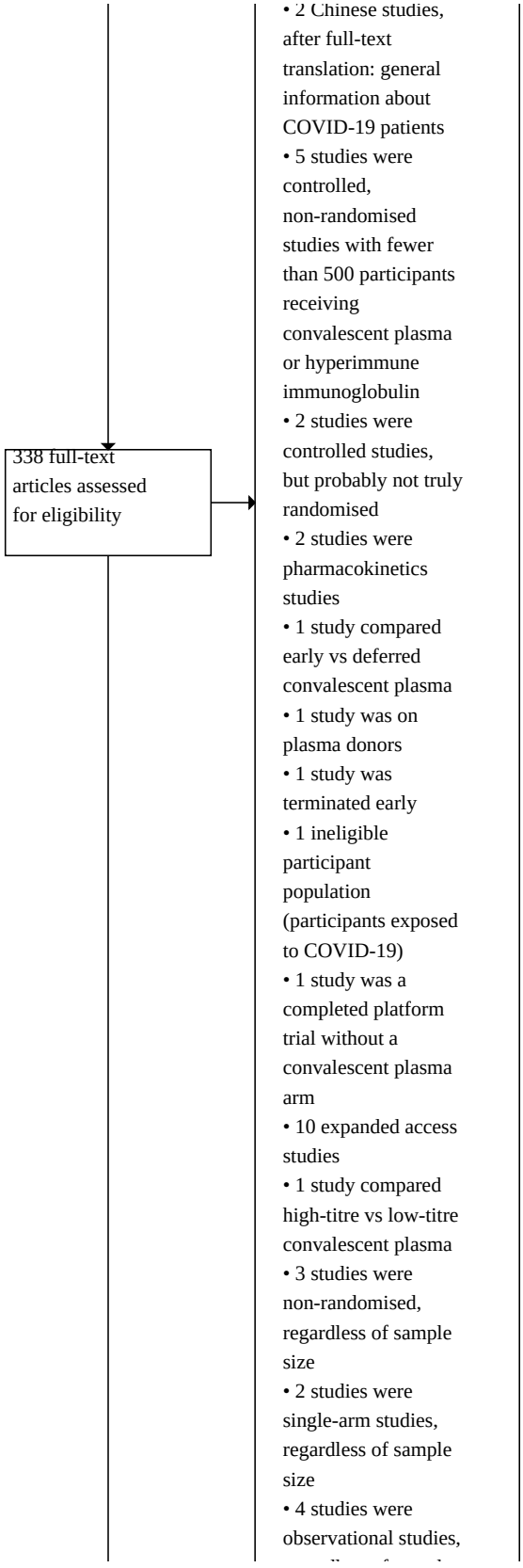
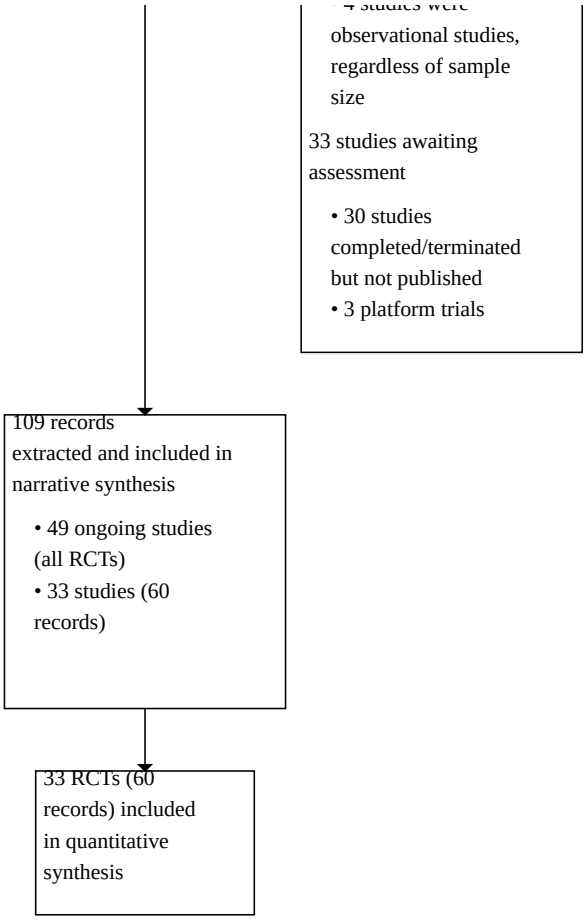


Figure 1. (Continued)



We identified 82 eligible studies within 108 citations: 33 included studies (60 records) (Agarwal 2020; Alemany 2022; AlQahtani 2021; Avendano-Sola 2021; Bajpai 2020; Baldeon 2022; Bar 2021; Begin 2021; Beltran Gonzalez 2021; Bennett-Guerrero 2021; CoV-Early; De Santis 2022; Devos 2021; Estcourt 2021; Gharbharan 2021; Hamdy Salman 2020; Holm 2021; Horby 2021b; Kirenga 2021; Koerper 2021; Korley 2021; Li 2020; Libster 2020; Menichetti 2021; NCT04421404; Ortigoza 2022; O'Donnell 2021; Pouladzadeh 2021; Ray 2022; Sekine 2021; Simonovich 2020; Sullivan 2022; Van den Berg 2022) and 49 ongoing studies (see 'Ongoing studies' below).

Included studies

We included 33 studies reporting on 24,861 participants, of whom 11,432 received convalescent plasma (Agarwal 2020; Alemany 2022; AlQahtani 2021; Avendano-Sola 2021; Bajpai 2020; Baldeon 2022; Bar 2021; Begin 2021; Beltran Gonzalez 2021; Bennett-Guerrero 2021; CoV-Early; De Santis 2022; Devos 2021; Estcourt 2021; Gharbharan 2021; Hamdy Salman 2020; Holm 2021; Horby 2021b; Kirenga 2021; Koerper 2021; Korley 2021; Li 2020; Libster 2020; Menichetti 2021; NCT04421404; Ortigoza 2022; O'Donnell 2021; Pouladzadeh 2021; Ray 2022; Sekine 2021; Simonovich 2020; Sullivan 2022; Van den Berg 2022).

Design and sample size

All included studies were RCTs and their sample size ranged from 29 participants in Bajpai 2020 to 11,558 participants in Horby 2021b.

Setting

The included studies differed considerably in their settings.

Six studies were conducted in the USA (Bar 2021; Bennett-Guerrero 2021; Korley 2021; NCT04421404; Ortigoza 2022; Sullivan 2022). Three were conducted in India (Agarwal 2020; Bajpai 2020; Ray 2022). Two were done in Brazil (De Santis 2022; Sekine 2021), two in Spain (Alemany 2022; Avendano-Sola 2021), two in Argentina (Libster 2020; Simonovich 2020), and two in the Netherlands (CoV-Early; Gharbharan 2021). One was carried out in each of China (Li 2020), Bahrain (AlQahtani 2021), Belgium (Devos 2021), Ecuador (Baldeon 2022), Egypt (Hamdy Salman 2020), Germany (Koerper 2021), Iran (Pouladzadeh 2021), Italy (Menichetti 2021), Mexico (Beltran Gonzalez 2021), South Africa (Van den Berg 2022), Sweden (Holm 2021), Uganda (Kirenga 2021), and the UK (Horby 2021b). One study was conducted partly in Brazil, Canada, and the USA (Begin 2021), one was partly in Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK and the USA (Estcourt 2021), and one was conducted partly in the USA and partly in Brazil (O'Donnell 2021).

Nine studies are single-centre studies (Bajpai 2020; Beltran Gonzalez 2021; Bennett-Guerrero 2021; Hamdy Salman 2020; Kirenga 2021; Pouladzadeh 2021; Ray 2022; Sekine 2021; Sullivan 2022), and 24 are multi-centre studies (Agarwal 2020; Alemany 2022; AlQahtani 2021; Avendano-Sola 2021; Baldeon 2022; Bar 2021; Begin 2021; CoV-Early; De Santis 2022; Devos 2021; Estcourt 2021; Gharbharan 2021; Holm 2021; Horby 2021b; Koerper 2021; Korley 2021; Li 2020; Libster 2020; Menichetti 2021; NCT04421404; Ortigoza 2022; O'Donnell 2021; Simonovich 2020; Van den Berg 2022), with a minimum of two centres for AlQahtani 2021, Bar 2021, Holm 2021 and Ortigoza 2022 and a maximum of 177 centres for Horby 2021b.

Among the RCTs, 29 were performed in an inpatient setting (Agarwal 2020; AlQahtani 2021; Avendano-Sola 2021; Bajpai 2020; Baldeon 2022; Bar 2021; Begin 2021; Beltran Gonzalez 2021; Bennett-Guerrero 2021; De Santis 2022; Devos 2021; Estcourt 2021; Gharbharan 2021; Hamdy Salman 2020; Holm 2021; Horby 2021b; Kirenga 2021; Koerper 2021; Korley 2021; Li 2020; Menichetti 2021; NCT04421404; Ortigoza 2022; O'Donnell 2021; Pouladzadeh 2021; Ray 2022; Sekine 2021; Simonovich 2020; Van den Berg 2022). Four studies were performed in an outpatient setting (Alemany 2022; CoV-Early; Libster 2020; Sullivan 2022).

Participants

The RCTs by Agarwal 2020, AlQahtani 2021, Avendano-Sola 2021, Baldeon 2022, Holm 2021, Kirenga 2021, Korley 2021, Menichetti 2021 and Simonovich 2020 included participants with moderate disease, and the RCTs by Bar 2021, Beltran Gonzalez 2021, De Santis 2022, Estcourt 2021 and Li 2020 included individuals with severe disease, according to the latest WHO clinical progression score (WHO 2020e). The RCTs by Bajpai 2020, Begin 2021, Bennett-Guerrero 2021, Devos 2021, Gharbharan 2021, Hamdy Salman 2020, Horby 2021b, Koerper 2021, NCT04421404, O'Donnell 2021, Ortigoza 2022, Pouladzadeh 2021, Ray 2022, Sekine 2021 and Van den Berg 2022 included individuals with both moderate and severe disease, according to the latest WHO clinical progression score (WHO 2020e). The RCTs by Alemany 2022, CoV-Early, Libster 2020 and Sullivan 2022 included populations with mild disease.

Interventions

Twenty-five RCTs compared convalescent plasma with standard care, with or without placebo (Agarwal 2020; Alemany 2022; AlQahtani 2021; Avendano-Sola 2021; Bar 2021; Begin 2021; De Santis 2022; Devos 2021; Estcourt 2021; Gharbharan 2021; Hamdy Salman 2020; Holm 2021; Horby 2021b; Kirenga 2021; Koerper 2021; Korley 2021; Li 2020; Libster 2020; Menichetti 2021; Ortigoza 2022; Pouladzadeh 2021; Ray 2022; Sekine 2021; Simonovich 2020; Van den Berg 2022), and seven RCTs compared convalescent plasma with standard plasma (Bajpai 2020; Baldeon 2022; Bennett-Guerrero 2021; CoV-Early; NCT04421404; O'Donnell 2021; Sullivan 2022). One RCT compared convalescent plasma with human immunoglobulin (Beltran Gonzalez 2021).

The dose and volume of plasma given in the studies that we evaluated for efficacy and safety varied. The total volume of convalescent plasma transfused varied between 200 mL and 600 mL of plasma, with participants receiving between one dose of plasma (Alemany 2022; Avendano-Sola 2021; Baldeon 2022; Bar 2021; Bennett-Guerrero 2021; CoV-Early; Gharbharan 2021; Hamdy Salman 2020; Korley 2021; Li 2020; Libster 2020; NCT04421404; O'Donnell 2021; Ortigoza 2022; Simonovich 2020; Sullivan 2022; Van den Berg 2022), one to two doses of plasma (Begin 2021; Pouladzadeh 2021), and two or more doses of plasma (Agarwal 2020; AlQahtani 2021; Bajpai 2020; Beltran Gonzalez 2021; De Santis 2022; Devos 2021; Estcourt 2021; Holm 2021; Horby 2021b; Kirenga 2021; Koerper 2021; Menichetti 2021; Ray 2022; Sekine 2021).

Plasma donors

All included RCTs determined antibody titres in donors, except one (Baldeon 2022). Twelve RCTs reported antibody titres in donors' plasma (AlQahtani 2021; Bajpai 2020; Begin 2021; Beltran Gonzalez 2021; Holm 2021; Kirenga 2021; Libster 2020; Menichetti 2021; O'Donnell 2021; Simonovich 2020; Sullivan 2022; Van den Berg 2022), 12 RCTs reported neutralising antibody titres in donors' plasma (Agarwal 2020; Alemany 2022; Avendano-Sola 2021; Bar 2021; Bennett-Guerrero 2021; De Santis 2022; Devos 2021; Gharbharan 2021; Koerper 2021; Korley 2021; Pouladzadeh 2021; Sekine 2021), and eight did not report antibody titre in donors (CoV-Early; Estcourt 2021; Hamdy Salman 2020; Horby 2021b; Li 2020; NCT04421404; Ortigoza 2022; Ray 2022).

Of the included studies, 30 RCTs reported the donors' eligibility criteria (Agarwal 2020; Alemany 2022; AlQahtani 2021; Avendano-Sola 2021; Bajpai 2020; Baldeon 2022; Bar 2021; Begin 2021; Beltran Gonzalez 2021; Bennett-Guerrero 2021; De Santis 2022; Devos 2021; Gharbharan 2021; Hamdy Salman 2020; Holm 2021; Horby 2021b; Kirenga 2021; Koerper 2021; Korley 2021; Li 2020; Libster 2020; Menichetti 2021; Ortigoza 2022; O'Donnell 2021; Pouladzadeh 2021; Ray 2022; Sekine 2021; Simonovich 2020; Sullivan 2022; Van den Berg 2022). They also reported some descriptive information about donors, such as their age, gender and disease severity, and the time from disease recovery or RT-PCR virus detection, or both. Among those RCTs reporting the sex of donors, in Agarwal 2020, Avendano-Sola 2021, Gharbharan 2021, Kirenga 2021, Koerper 2021 and Sekine 2021, most of the donors were male (94%, 88%, 91%, 96%, 59% and 65% respectively). In Bajpai 2020, Baldeon 2022 and Holm 2021, all donors were male.

Please refer to the Characteristics of included studies for more detailed information.

Outcomes

A list of outcomes and the applied method for which transformation of data and recalculations were made can be found in Appendix 2.

Efficacy outcomes

We prioritised different efficacy outcomes, based on the setting and the disease severity in participants of the included RCTs (see Types of outcome measures).

Among the RCTs that included individuals with moderate to severe disease, 26 studies reported 28-day mortality (Agarwal 2020; AlQahtani 2021; Avendano-Sola 2021; Bajpai 2020; Baldeon 2022; Bar 2021; Begin 2021; Beltran Gonzalez 2021; Bennett-Guerrero 2021; De Santis 2022; Devos 2021; Estcourt 2021; Gharbharan 2021; Holm 2021; Horby 2021b; Kirenga 2021; Koerper 2021; Korley 2021; Li 2020; Menichetti 2021; O'Donnell 2021; Ortigoza 2022; Ray 2022; Sekine 2021; Simonovich 2020; Van den Berg 2022) and five studies also reported all-cause mortality during hospital stay (Agarwal 2020; Beltran Gonzalez 2021; Estcourt 2021; Gharbharan

2021; O'Donnell 2021). Nine RCTs reported worsening of clinical status, assessed by the need for invasive mechanical ventilation or death (Agarwal 2020; Alemany 2022; Begin 2021; Estcourt 2021; Horby 2021b; Korley 2021; Menichetti 2021; NCT04421404; Simonovich 2020). Six RCTs reported improvement of clinical status, assessed by the number of participants discharged from hospital (Devos 2021; Gharbharan 2021; Horby 2021b; Li 2020; Sekine 2021; Simonovich 2020). One of the included RCTs reported quality of life (Devos 2021). Nine RCTs reported the safety outcome, adverse event of any grade (Holm 2021; Kirenga 2021; Koerper 2021; NCT04421404; Ortigoza 2022; O'Donnell 2021; Sekine 2021; Simonovich 2020; Van den Berg 2022); six RCTs reported the safety outcome, grade 3 or 4 adverse events (Agarwal 2020; Avendano-Sola 2021; Begin 2021; Menichetti 2021; Sekine 2021; Simonovich 2020); and 10 RCTs reported serious adverse events (Bar 2021; Begin 2021; Bennett-Guerrero 2021; Devos 2021; Estcourt 2021; Horby 2021b; Koerper 2021; NCT04421404; O'Donnell 2021; Simonovich 2020).

Among the RCTs that included individuals with asymptomatic or mild disease, four reported 28-day mortality (Alemany 2022; CoV-Early; Libster 2020; Sullivan 2022). Three RCTs reported admission to hospital or death within 28 days (Alemany 2022; Sullivan 2022; CoV-Early). One RCT reported symptom resolution, assessed by 'all initial symptoms resolved' (CoV-Early), and one RCT reported time to symptom resolution (Alemany 2022). No RCTs for individuals with asymptomatic or mild disease reported quality of life. One RCT reported the safety outcomes, grade 3 or 4 adverse events and serious adverse events (Alemany 2022).

Safety outcomes

Eighteen RCTs (Agarwal 2020; Alemany 2022; AlQahtani 2021; Bar 2021; Begin 2021; Bennett-Guerrero 2021; Devos 2021; Estcourt 2021; Holm 2021; Kirenga 2021; Koerper 2021; Menichetti 2021; NCT04421404; O'Donnell 2021; Ortigoza 2022; Sekine 2021; Simonovich 2020; Van den Berg 2022), reported adverse events or serious adverse events, or both, for all the participants. From these 18 studies, we extracted safety data from 7953 participants, with safety data for 4913 participants who received convalescent plasma and 3040 participants who did not receive convalescent plasma. All the other included RCTs reported transfusion-related adverse events for the participants receiving convalescent plasma (Avendano-Sola 2021; Bajpai 2020; Baldeon 2022; Beltran Gonzalez 2021; CoV-Early; De Santis 2022; Gharbharan 2021; Hamdy Salman 2020; Horby 2021b; Korley 2021; Li 2020; Libster 2020; Pouladzadeh 2021; Ray 2022; Sullivan 2022), and for the participants receiving standard plasma (Bajpai 2020; Baldeon 2022; CoV-Early; Sullivan 2022). From these studies, we extracted safety data from 7528 participants who received convalescent plasma only and 903 participants who received the standard plasma.

Please refer to the Characteristics of included studies for more detailed information.

Ongoing studies

Of the 49 ongoing studies, all are RCTs (see Table 3). Of the 49 RCTs, 16 were scheduled to be completed in 2020 and planned to evaluate between 15 and 480 participants, but according to the trial registry, five are not yet recruiting, and nine are still recruiting. Twenty-three RCTs were expected to be completed in 2021, and planned to evaluate between 15 and 2400 participants. They were scheduled to be completed by the time of writing, but according to the trial registry, five are not yet recruiting, three are still recruiting and 15 are active, but not recruiting. Eight further RCTs are planned to be completed in 2022: CTRI/2020/05/025346, randomising 90 participants; EUCTR2020-001632-10 randomising 174 participants; ISRCTN49832318 randomising 210 participants, NCT04333251, randomising 115 participants; NCT04390503, randomising 150 participants; NCT04415086, randomising 120 participants; NCT04558476, randomising 500 participants; NCT05077930, randomising 200 participants.

Please refer to Characteristics of ongoing studies (Ongoing studies) for more detailed information and Table 3 for further details on the planned completed dates and planned number of participants per study.

Studies awaiting assessment

In the process of finalising the review, two of our tracked ongoing studies were terminated early for futility and the trials stopped recruiting participants (NCT04361253, NCT04539275).

According to the trials registries, 28 RCTs have been completed, or had their recruitment completed, but no results have been published yet (CTRI/2020/05/025299; CTRI/2020/05/025328; CTRI/2020/06/025803; EUCTR2020-001860-27-GB; IRCT20120215009014N353; IRCT20150808023559N21; IRCT20200404046948N1; IRCT20200413047056N1; IRCT20200501047258N1; IRCT20200503047281N1; IRCT20201004048922N1; NCT04332835; NCT04345991; NCT04358783; NCT04362176; NCT04374526; NCT04385199; NCT04405310; NCT04425915; NCT04428021; NCT04442958; NCT04468009; NCT04497324; NCT04521309; NCT04542967; NCT04547127; NCT04649879; NCT04681430). For this reason, we have placed these studies in the category of 'Studies awaiting classification'.

Three studies are platform trials, A platform trial is an adaptive, multistage study design in which numerous interventions can be evaluated through interim analyses. These three trials do not currently include the convalescent plasma intervention, however, in a platform trial new study arms can be added within the study period to examine further interventions (Park 2020). We are tracking these studies, in case they add an arm on convalescent plasma (NCT04501978; NCT04315948; NCT04801940).

Excluded studies

We excluded in total 196 studies that did not match our inclusion criteria as follows.

162 studies are excluded from the review based on unchanged exclusion criteria:

- 76 studies were single-arm studies with fewer than 500 participants receiving convalescent plasma (Abdullah 2020; Bradfute 2020; ChiCTR2000029850; ChiCTR2000030039; ChiCTR2000031501; ChiCTR2000033798; CTRI/2020/04/024804; CTRI/2020/08/027285; Donato 2020; Duan 2020; Dulipsingh 2020; Ibrahim 2020; IRCT20151228025732N53; IRCT20200406046968N2; IRCT20200414047072N1; IRCT20200416047099N1; Jin 2020; Liu 2020a; Madariaga 2020; NCT04264858; NCT04292340; NCT04321421; NCT04327349;

NCT04332380; NCT04333355; NCT04345679; NCT04346589; NCT04348877; NCT04353206; NCT04354831; NCT04355897; NCT04356482; NCT04365439; NCT04374565; NCT04376034; NCT04377672; NCT04383548; NCT04384497; NCT04388527; NCT04389710; NCT04389944; NCT04390178; NCT04392232; NCT04397523; NCT04407208; NCT04408209; NCT04411602; NCT04412486; NCT04418531; NCT04432103; NCT04438694; NCT04458363; NCT04462848; NCT04471051; NCT04474340; NCT04476888; NCT04502472; NCT04513158; NCT04516954; NCT04535063; NCT04554992; NCT04565197; NCT04569188; NCT04570982; NCT04614012; NCT04616976; NCT04622826; NCT04644198; Olivares-Gazca 2020; PER-031-20; Perotti 2020; RBR-4vm3yy; RPCEC00000323; Salazar 2020a; Xia 2020; Zeng 2020);

- 37 studies were single-arm studies or case series that had not been pre-registered in a clinical trials registry (Ahn 2020; Anderson 2020; Bao 2020b; Bobek 2020; Cantore 2020; Çınar 2020; Clark 2020; Enzmann 2020; Erkurt 2020; Fan 2020; Figlerowicz 2020; Grisolia 2020; Im 2020; Jamous 2020; Jiang 2020a; Karatas 2020; Kong 2020; Liu 2020b; Martinez-Resendez 2020; McCuddy 2020; Mira 2020; Niu 2020; Pei 2020; Peng 2020; Salazar 2020b; Shen 2020; Soleimani 2020; Taher 2020; Tan 2020; Wang 2020; Wright 2020; Xu 2020b; Yang 2020; Ye 2020; Zhang 2020a; Zhang 2020b; Zhang 2020c);
- 17 studies were performed with an intervention other than convalescent plasma (Cao 2020a; Chen 2020b; Chen 2020c; Díez 2020; Hu 2020; ISRCTN86534580; Jiang 2020b; Lin 2020; NCT04261426; NCT04344379; NCT04350580; NCT04368013; Robbiani 2020; Shi 2020; Xie 2020; de Assis 2020; CTRI/2020/10/028547);
- five studies pertained to feasibility of collection of convalescent plasma only (Budhai 2020; Hashim 2020; NCT04344015; NCT04344977; NCT04360278);
- five studies were cancelled by the investigator before recruiting participants into the study (ChiCTR2000030312; ChiCTR2000030381; ChiCTR2000030442; NCT04325672; NCT04467151);
- three studies reported standard operating procedure related to plasma donation (Brasil Ministerio 2020; Franchini 2020; Ministerio de Salud 2020);
- Two references were in Chinese (Qiu 2020; Tu 2020); both were translated and assessed by Rujan Shrestha and Ya-Ying Wang via Cochrane TaskExchange. The papers reported on a generalised collection of information about the COVID-19 infection of two participants relating to aetiology, pathology, symptoms, clinical presentation and some generalised pharmacological treatment methods;
- five studies were controlled, non-randomised studies with fewer than 500 participants receiving convalescent plasma (Abolghasemi 2020; NCT04347681; NCT04384588; Allahyari 2021; IRCT20200525047562N1);
- two studies were controlled studies, but probably not truly randomised (Baklaushev 2020; Rasheed 2020);
- two studies were pharmacokinetics studies (NCT04638634; NCT04661839);
- two studies were withdrawn or suspended (NCT04377568; RBR-5r8gv8p);
- one study included an irrelevant participant population (participants exposed to COVID-19; NCT04323800);
- one study was a single-arm study with fewer than 500 participants receiving hyperimmune immunoglobulin (NCT04721236);
- one study compared early to deferred convalescent plasma (Balcells 2020);
- one study was on plasma donors (NCT04555109);
- one study was terminated early and stopped because the sponsor was changed and a new study on convalescent plasma sponsored by the Italian Medicines Agency (AIFA) was started in Italy (NCT04393727);
- one study is a completed platform trial that did not include a convalescent plasma arm (NCT04593940).

We excluded 34 more studies based on the updated exclusion criteria for this review version (update 4):

- 14 studies included hyperimmune immunoblogulin as intervention, which is being investigated in a separate review (CTRI/2020/09/027903; jRCT2031200174; IRCT20200508047346N1; NCT04366245; NCT04395170; NCT04468958; NCT04469179; NCT04514302; NCT04546581; NCT04555148; NCT04573855; Gaborit 2021; NCT04610502; EUCTR2020-005979-12-GR);
- 10 studies are expanded access studies from the USA (Joyner 2020; NCT04338360; NCT04360486; NCT04363034; NCT04374370; NCT04420988; NCT04445207; NCT04472572; NCT04358211; NCT04372368). These studies are non-RCTs, and the expanded access programme is an FDA-initiated, national, multicentre programme providing access to convalescent plasma for patients with serious or life-threatening COVID-19 disease, for investigations outside clinical trials when no alternative therapy options are available (US Covid Plasma 2022);
- three studies were non-randomised studies, excluded regardless of their sample size (NCT04492501; NCT04408040; NCT04432272);
- two studies were single-arm studies studies, excluded regardless of their sample size (NCT04352751; NCT04642014);
- two studies were observational cohort studies (NCT04497779; NCT04545047) and two were prospective case-only studies (NCT04463823; NCT04669990), excluded regardless of their sample size;
- one study compared high-titre convalescent plasma to low-titre convalescent plasma (NCT04524507).

Risk of bias in included studies

We assessed methodological quality and risk of bias for all 33 included RCTs using RoB 2, recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a). The completed RoB 2 tool with responses to all assessed signalling questions is available online at zenodo.org/record/6685234#.YrMlYEZByHs.

Overall judgements for studies that included individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

All-cause mortality

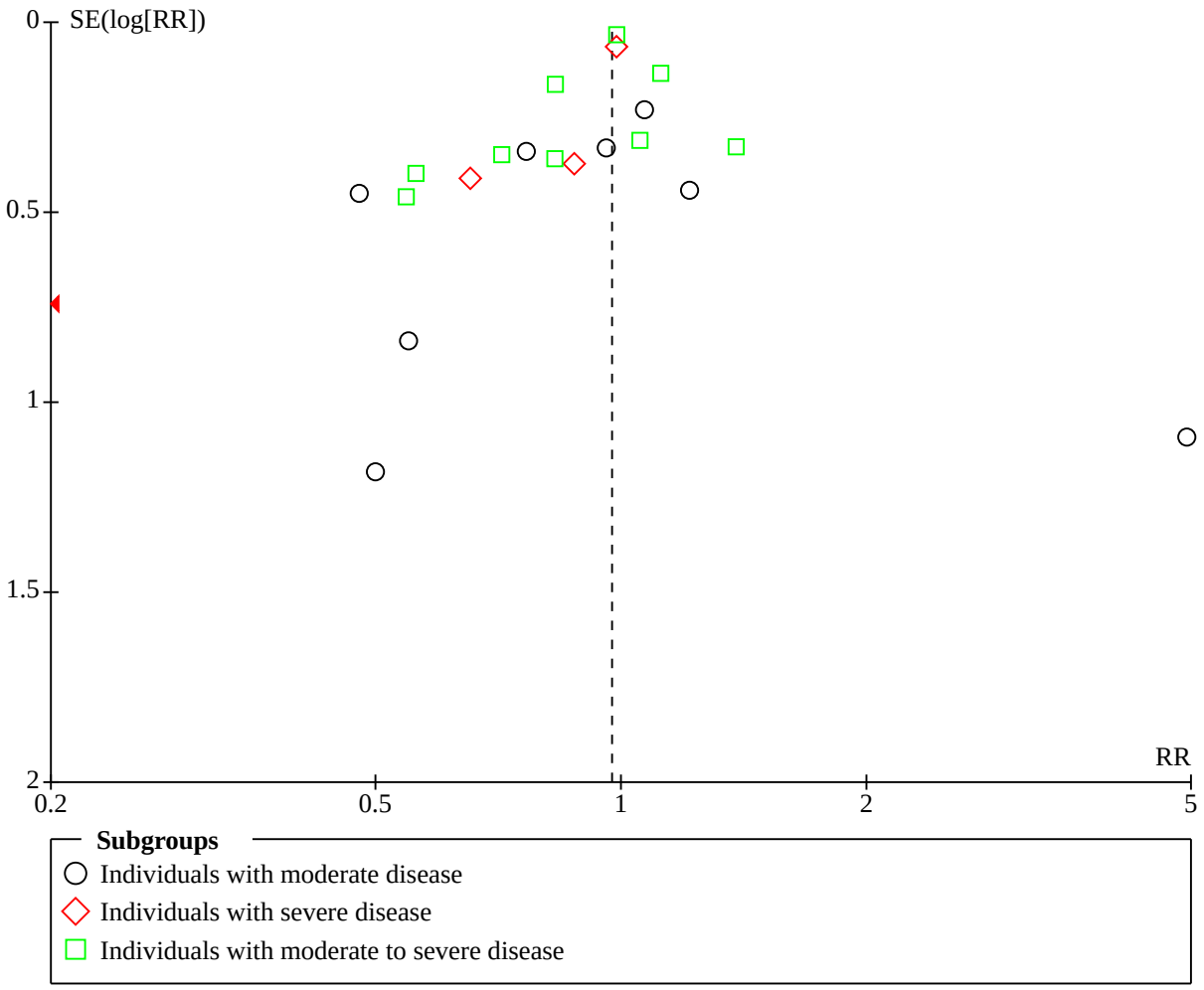
Among those studies reporting a mortality outcome, we rated the overall risk of bias to be of some concern in Agarwal 2020, AlQahtani

2021, Baldeon 2022, Bar 2021, Beltran Gonzalez 2021, De Santis 2022, Gharbharan 2021, Holm 2021, Pouladzadeh 2021 and Ray 2022. We assessed this outcome on a study level at day 28, day 60 and time to event. For Agarwal 2020, there were some inconsistencies in the adherence to the allocated interventions, which could be due to awareness of the intervention in this open-label trial (see Risk of bias table for Analysis 1.1; Risk of bias table for Analysis 1.4). In AlQahtani 2021, the outcome analysed was not in accordance with the prespecified analysis plan, as the time point of the mortality outcome was not specified in the study protocol (see Risk of bias table for Analysis 1.1). Baldeon 2022 provided no information on the concealment of the allocation sequence (see Risk of bias table for Analysis 2.1; Risk of bias table for Analysis 2.2). In one study (Bar 2021), information on whether the allocation sequence was concealed is missing (see Risk of bias table for Analysis 1.1; Risk of bias table for Analysis 1.3). Also, Beltran Gonzalez 2021 and De Santis 2022 provide no information on the concealment of the allocation sequence (see Risk of bias table for Analysis 3.1; Risk of bias table for Analysis 3.2; Risk of bias table for Analysis 3.3; and see Risk of bias table for Analysis 1.1; Risk of bias table for Analysis 1.2; Risk of bias table for Analysis 1.3). Gharbharan 2021 provided insufficient information on whether co-interventions were balanced across arms (see Risk of bias table for Analysis 1.1; Risk of bias table for Analysis 1.3; Risk of bias table for Analysis 1.4). For one study (Holm 2021), the time point of measurement is not consistent with the time point indicated in the trial registry (see Risk of bias table for Analysis 1.1). Pouladzadeh 2021 did not publish a protocol and the data that produced this result were not mentioned as predefined outcomes in the trial registration (see Risk of bias table for Analysis 1.2). Ray 2022 did not provide enough information on the randomisation process and allocation concealment, and the trial registry only indicates concealment through "Case Record Numbers" (see Risk of bias table for Analysis 1.1; Risk of bias table for Analysis 1.3).

We rated the overall risk of bias to be high in Korley 2021, because of baseline differences in hospitalisation between the groups (see Risk of bias table for Analysis 1.1).

We also assessed with a funnel plot the potential risk of publication bias for the outcome all-cause mortality up to day 28, and there is no indication for publication bias, see Figure 2.

Figure 2.



Clinical status

Among those studies reporting at least one of the two outcomes addressing clinical status, we rated the overall risk of bias to be of some concern for Agarwal 2020 and Gharbharan 2021. We assessed clinical status on a study level, including both improvement of clinical status by the number of participants discharged from hospital and worsening of clinical status by need for invasive mechanical ventilation or death. For Gharbharan 2021, we judged the risk of bias for need for invasive mechanical ventilation or death to be of some concern, as the study provided insufficient information on whether co-interventions were balanced across arms (see Risk of bias table for Analysis 1.6). For Agarwal 2020, we judged the risk of bias for participants discharged from hospital to be of some concern, because of some inconsistencies in adherence to the allocated interventions, which could be due to awareness of the intervention in this open-label trial, as well as because the outcome analysed was not prespecified in the trials registry and a study protocol was not available (see Risk of bias table for Analysis 1.5).

In Korley 2021, we rated the overall risk of bias to be high. There are some baseline differences in hospitalisation between the two groups (see Risk of bias table for Analysis 1.5).

Quality of life

Only one study reported a quality-of-life outcome (Devos 2021). In this study, we rated the overall risk of bias to be of some concern, because the assessors were aware of the intervention received and it is possible that the assessment could have been influenced by knowledge of intervention received (see Risk of bias table for Analysis 1.7).

Safety

Among those studies that reported at least one of the safety outcomes, we rated the overall risk of bias to be of some concern for Agarwal 2020, AlQahtani 2021, Bar 2021, Begin 2021, Bennett-Guerrero 2021, Devos 2021, Estcourt 2021, Holm 2021, Kirenga 2021, Koerper 2021, Menichetti 2021, Sekine 2021 and Van den Berg 2022. We assessed safety outcomes on a study level and included any adverse events, grade 1 or 2 adverse events, grade 3 to 4 adverse events and serious adverse events.

For Agarwal 2020, we judged the risk of bias for grade 3 to 4 adverse events to be of some concern, because of some inconsistencies in the adherence to the allocated interventions, which could be due to awareness of the intervention in this open-label trial. For Agarwal 2020 and AlQahtani 2021, the safety data were provided at our request by the study authors, and it is not clear whether data for this outcome were collected from all, or nearly all the participants randomised. There is also no information available on how safety was measured (see Risk of bias table for Analysis 1.10). Bar 2021 gave no information on whether the allocation sequence was concealed and the outcome assessors were aware of the intervention received (see Risk of bias table for Analysis 1.11). In Begin 2021, too, the outcome assessors were aware of the interventions received, but external monitoring was performed at all sites to assess protocol adherence, reporting of adverse events and accuracy of data entry (see Risk of bias table for Analysis 1.10; Risk of bias table for Analysis 1.11). There is not enough information available in Bennett-Guerrero 2021 to evaluate the measurement of the outcome and the outcome is not predefined in the registry of supplemental material (see Risk of bias table for Analysis 2.6). Devos 2021 and Estcourt 2021did not blind the assessor, so the assessment could have been influenced by knowledge of the intervention received (see Risk of bias table for Analysis 1.11). Holm 2021 did not predefine the outcome in the clinical trials registry and there is no protocol available (see Risk of bias table for Analysis 1.8). Kirenga 2021 did not clearly indicate whether all the participants were included in the analysis and the assessors were aware of the intervention allocation (see Risk of bias table for Analysis 1.8). In Koerper 2021 and in Menichetti 2021, the assessment of the outcome could have been influenced by knowledge of intervention received (see Risk of bias table for Analysis 1.8; Risk of bias table for Analysis 1.10; Risk of bias table for Analysis 1.11). Sekine 2021 did not provide information on whether the outcome measure was appropriate and the outcome assessors were not blinded (see Risk of bias table for Analysis 1.8; Risk of bias table for Analysis 1.9; Risk of bias table for Analysis 1.10). Van den Berg 2022 did not blind the assessors either, the data that produced this result were not analysed in accordance with the predefined outcomes stated in the trials registry and the protocol was not available (see Risk of bias table for Analysis 1.8).

Overall judgements for studies that included individuals with a confirmed diagnosis of COVID-19 and mild disease

All-cause mortality

Among those studies reporting a mortality outcome, we rated the overall risk of bias to be of some concern for CoV-Early. There is not enough information available on the allocation sequence concealment, as the full-text article is not published yet. In addition, the trials registry does not provide enough information on missing data (see Risk of bias table for Analysis 5.1).

Admission to hospital or death

Among those studies reporting admission to hospital or death, we rated the overall risk of bias to be of some concern for CoV-Early. The trials registry did not provide enough information on the allocation sequence concealment and there are not enough information on missing data and the measurement of the outcome (see Risk of bias table for Analysis 5.2).

Symptom resolution

We assessed symptom resolution on a study level, including symptom resolution by all initial symptoms resolved (asymptomatic) at day 14, day 28, and at longest follow-up available, and time to symptom resolution. We rated the overall risk of bias to be of some concern for CoV-Early for the outcome all initial symptoms resolved (asymptomatic) at day 14 and day 28. There is not enough information available yet on the allocation sequence concealment, as the full-text article has not yet been published. In addition, the trials registry does not provide enough information on missing data (see Risk of bias table for Analysis 5.4; Risk of bias table for Analysis 5.3)

Quality of life

None of the studies that included individuals with a confirmed diagnosis of COVID-19 and mild disease examined quality-of-life outcomes.

Safety

Among those studies reporting at least one of the safety outcomes, we rated the overall risk of bias to be of some concern for Alemany 2022. This study does not provide enough information to judge whether the outcome was measured appropriately (see Risk of bias table for Analysis 4.8; Risk of bias table for Analysis 4.9).

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Convalescent plasma compared to placebo or standard care alone for individuals with moderate to severe disease; **Summary of findings 2** Summary of findings table - Convalescent plasma compared to standard plasma for individuals with moderate to severe disease; **Summary of findings 3** Summary of findings table - Convalescent plasma compared to human immunoglobulin for individuals with moderate to severe disease ; **Summary of findings 4** Summary of findings table - Convalescent plasma compared to placebo or standard care alone for individuals with mild disease; **Summary of findings 5** Summary of findings table - Convalescent plasma compared to standard plasma for outpatients with mild disease

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

We present the summary of findings and the certainty of the evidence for our prioritised outcomes for individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease in Summary of findings 1 (convalescent plasma versus placebo or standard care alone), Summary of findings 2 (convalescent plasma versus standard plasma) and Summary of findings 3 (convalescent plasma versus human immunoglobulin). We assessed disease severity with the need for respiratory support according to the WHO clinical progression scale (WHO 2020e).

Convalescent plasma versus placebo or standard care alone

Primary outcomes (included in the summary of findings table)

All-cause mortality

We assessed all-cause mortality at day 28, day 60, by time until death and during hospital stay.

Twenty-one studies reported all-cause mortality for 19,021 participants. Considering the reported event rates across studies, we estimated that 225 of 1000 participants die at up to 28 days when treated with placebo or standard care alone. Treatment with convalescent plasma does not reduce all-cause mortality at up to day 28 (RR 0.98, 95% CI 0.92 to 1.03; 220 per 1000; 21 studies, 19,021 participants; I^2 = 1%; high-certainty evidence; Analysis 1.1); at day 60 (RR 0.74, 95% CI 0.49 to 1.12; 3 studies, 272 participants; I^2 = 0%; Analysis 1.2); when measured over time (HR 0.98, 95% CI 0.92 to 1.04; 16 studies, 17,070 participants; I^2 = 0%; Analysis 1.3); or during hospital stay (RR 0.97, 95% CI 0.87 to 1.08; 4 studies, 2556 participants; I^2 = 0%; Analysis 1.4).

- **Subgroup analyses**
  - **Severity of disease:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to all-cause mortality for people with moderate disease (WHO score 4 and 5) or severe disease (WHO score ≥ 6), according to the WHO Clinical Progression Scale (WHO 2020e; Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4).
  - **Antibodies in recipients detected at baseline:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the detection of antibodies in the recipients at baseline (Analysis 6.1).
  - **Length of time since symptom onset:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the length of time since symptom onset(Analysis 7.1).
  - **Other subgroups:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the pre-existing condition of immunosuppression at baseline (Analysis 10.1); diabetes at baseline (Analysis 12.1); respiratory disease at baseline (Analysis 14.1); or hypertension at baseline (Analysis 15.1); participants' age (Analysis 16.1), sex (Analysis 18.1), or country income groups according to the World Bank definitions (The World Bank 2022; Analysis 20.1).
  - We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus standard placebo or standard care alone and the outcome all-cause mortality.
- **Sensitivity analyses**
  - We summarised the effects of sensitivity analyses in Table 4. Reported effects of our main analysis were robust when we removed studies at high risk of bias or studies that were terminated early. We did not include any preprint articles in the main analysis of this outcome.

Clinical status

We assessed the clinical status of participants by the need for invasive mechanical ventilation or death (worsening of clinical status) and by participants discharged from hospital (improvement of clinical status) up to day 28, day 60, and up to longest follow-up.

- **Worsening of clinical status:** six studies reported the need for invasive mechanical ventilation or death for 14,477 participants. Considering the reported event rates within the study, we estimated that 287 of 1000 participants not treated with convalescent plasma needed invasive mechanical ventilation or died. Evidence suggests that treatment with convalescent plasma has little to no impact on the need for invasive mechanical ventilation or death when compared to no convalescent plasma (RR 1.03, 95% CI 0.97 to 1.11; 296 per 1000; I^2 = 13%; high-certainty evidence; Analysis 1.5).
- **Improvement of clinical status:** six studies reported the number of participants discharged from hospital for 12,721 participants. Considering the reported event rates within the study, we estimated that 665 of 1000 participants not treated with convalescent plasma were discharged from hospital. Evidence suggests that treatment with convalescent plasma has no impact on whether participants are discharged from hospital when compared to no convalescent plasma (RR 1.00, 95% CI 0.97 to 1.02; 665 per 1000; I^2 = 0%; high-certainty evidence; Analysis 1.6).
- **Subgroup analyses**
  - **Severity of disease:** we did not identify any significant subgroup difference in the effectiveness of convalescent

plasma with regard to the need for invasive mechanical ventilation or death for people with moderate disease (WHO score 4 and 5) or severe disease (WHO score ≥ 6), according to WHO Clinical Progression Scale (WHO 2020e; Analysis 1.5). We did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the number of participants discharged from hospital for people with moderate disease (WHO score 4 and 5), or severe disease (WHO score ≥ 6), according to WHO Clinical Progression Scale (WHO 2020e; Analysis 1.6).

- **Antibodies in recipients detected at baseline:** for both clinical status outcomes, the test for subgroup differences suggests significant subgroup differences in the effectiveness of convalescent plasma with regard to antibodies in recipients detected at baseline (P = 0.02; I^2 = 82.8%; 2 studies; Analysis 6.3); (P = 0.04; I^2 = 76.9%; 2 studies; Analysis 6.4), however, due to the small number of studies included in both subgroup analyses and the high heterogeneity, we are uncertain whether the analyses produced useful findings.
- **Length of time since symptom onset:** for the outcome 'need for invasive mechanical ventilation or death', we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the length of time since symptom onset onset; Analysis 7.3). For the outcome 'participants discharged from hospital, we identified significant subgroup differences in the effect of convalescent plasma with regard to the length of time since symptom onset (P = 0.09; I^2 = 65.2%; 2 studies; Analysis 7.4), however, due to the small number of studies included in the subgroup analysis and the high heterogeneity, we are uncertain whether the analysis produced useful findings.
- **Other subgroups**
  - For the outcome 'need for invasive mechanical ventilation or death', we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the pre-existing condition of diabetes at baseline (Analysis 12.2); or respiratory disease at baseline (Analysis 14.2). We identified significant subgroup differences for the effect of convalescent plasma with regard to participants' age (P = 0.02; I^2 = 68%; 2 studies; Analysis 16.2) and sex (P = 0.04; 3 studies; I^2 = 75.6%, Analysis 18.2), however due to the small number of studies included in the subgroup analyses and the high heterogeneity, we are uncertain whether the analyses produced useful findings. We did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to country income groups, according to the World Bank definitions (The World Bank 2022; Analysis 20.2).
  - For the outcome 'participants discharged from hospital', we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the pre-existing condition of immunosuppression at baseline (Analysis 10.2); diabetes at baseline (Analysis 12.3); respiratory disease at baseline (Analysis 14.3); or hypertension at baseline (Analysis 15.2); or with regard to participants' age (Analysis 16.3), sex (Analysis 18.3); or country income groups, according to the World Bank definitions (The World Bank 2022; Analysis 20.3).
- We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus placebo or standard care alone for both outcomes summarised under 'clinical status'.

- **Sensitivity analyses:** we summarised the effects of sensitivity analyses in Table 4. Reported effects of our main analyses were robust when we removed studies at high risk of bias, or studies that were terminated early. We did not include any preprint articles in the main analysis of this outcome.

Quality of life

We assessed quality of life, including fatigue and neurological functioning of participants, if assessed with standardised scales (e.g. WHOQOL-100) for the following time points: at up to 7 days, up to 28 days, and longest follow-up available.

One study reported quality of life, assessed with the standardised scale EQ-5D-5L questionnaire at day 28, for 483 participants (Devos 2021). Considering the reported event rates within the study, we estimated a mean quality of life of 72 when treated without convalescent plasma. Evidence suggests that treatment with convalescent plasma may have little to no impact on quality of life up to day 28 when compared to no convalescent plasma (MD 1.00, 95% CI −2.14 to 4.14; low-certainty evidence; Analysis 1.7). Our main reasons for downgrading were very serious imprecision, because of few participants and wide confidence interval.

- **Subgroup analyses:** we could not perform any of our planned subgroup analyses for the comparison of convalescent plasma versus placebo or standard care alone.
- **Sensitivity analyses:** we summarised the effects of sensitivity analyses in Table 4. We did not include any studies at high risk of bias, preprint articles, or studies terminated early in the main analysis of this outcome.

Adverse events (grade 3 to 4)

We defined the outcome as the number of participants with any grades 3 to 4 adverse event. We summarised data in Table 5, including the potential relationship between the intervention and the adverse event, as reported in the primary studies.

Six studies reported grade 3 to 4 adverse events for both groups in a total of 2392 participants. Considering the reported event rates across studies, we estimated that 181 of 1000 participants not treated with convalescent plasma experience a grade 3 or 4 adverse event. Evidence suggests that treatment with convalescent plasma may have little to no effect on the risk of grades 3 and 4 adverse events (RR 1.17, 95% CI 0.96 to 1.42; 212 per 1000; I^2 = 31%; low-certainty evidence; Analysis 1.10). Our main reasons for downgrading were serious indirectness, because some studies did not provide clear definitions of how the adverse events were measured and the number of events are inconsistent, and suspected publication bias, because most studies assessed and reported safety outcomes for the convalescent plasma group only.

- **Subgroup analyses**
  - **Severity of disease:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to grade 3 or 4 adverse events for people with moderate disease (WHO score 4 and 5), or moderate to severe disease (WHO score ≥ 4), according to WHO Clinical Progression Scale (WHO 2020e; Analysis 1.10).
  - **Other subgroups:** we identified significant subgroup differences for the effect of convalescent plasma with regard

to country income groups, according to the World Bank definitions (The World Bank 2022; P = 0.07; I^2 = 68.5%; 5 studies; Analysis 20.4), however due to the small number of studies included in the subgroup analyses and the high heterogeneity, we are uncertain whether the analyses produced useful findings.
    - We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for any adverse events.
- **Sensitivity analyses:** we summarised the effects of sensitivity analyses in Table 4. The effects of our main analysis for the outcome grade 3 or 4 adverse events were robust when we removed a study that was terminated early. We did not include any studies at high risk of bias or preprint articles in the main analysis of this outcome.

Serious adverse events

We summarised data on serious adverse events reported only in participants who received convalescent plasma without reporting in the control group, and adverse events with a potential relationship to transfusion in Table 6.

Six studies reported serious adverse events for both groups and a total of 4901 participants. Considering the event rates reported across studies, we estimated that 118 of 1000 participants not treated with convalescent plasma experienced a serious adverse event. Evidence suggests that treatment with convalescent plasma probably has little to no effect on the risk of serious adverse events (RR 1.14, 95% CI 0.91 to 1.44; 135 per 1000; 6 studies, 3901 participants; I^2 = 45%%; moderate-certainty evidence; Analysis 1.11). Our main reason for downgrading was suspected publication bias because most studies assessed and reported transfusion-related events only; that is, they reported safety data only for the intervention group.

- **Subgroup analyses**
    - **Severity of disease:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to serious adverse events for people with moderate disease (WHO score 4 and 5), or moderate to severe disease (WHO score ≥ 4), according to WHO Clinical Progression Scale (WHO 2020e; Analysis 1.11).
    - **Other subgroups:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to country income groups, according to the World Bank definitions (The World Bank 2022; Analysis 20.5).
    - We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for any outcome that summarised adverse events.
- **Sensitivity analyses**
    - We summarised the effects of sensitivity analyses in Table 4. Reported effects of our main analysis for the outcome serious adverse events were robust when we removed a study that was terminated early. We did not include any studies at high risk of bias, or preprint articles in the main analysis of this outcome.

Secondary outcomes (not included in the summary of findings table)

Improvement of clinical status

We assessed improvement of clinical status up to day 28, and up to longest follow-up.

Two studies reported weaning or liberation from invasive mechanical ventilation in surviving patients for 630 participants; the subgroup of participants who were ventilated at baseline (i.e. WHO ≥ 7). Evidence suggests that treatment with convalescent plasma may have little to no impact on being weaned or liberated from invasive mechanical ventilation (RR 1.04, 95% CI 0.57 to 1.93; I^2 = 75%; Analysis 1.12). Two studies reported ventilator-free days by day 28 for 1028 participants. Evidence suggests that treatment with convalescent plasma could have little to no impact on ventilator-free days (MD −0.53, 95% CI −1.90 to 0.84; I^2 = 0%; Analysis 1.13). Two studies reported liberation from supplemental oxygen in surviving patients for 560 participants; the subgroup of participants requiring any supplemental oxygen or ventilator support at baseline. Evidence suggests little to no difference in the chance of being liberated from supplemental oxygen when treated with convalescent plasma (RR 0.99, 95% CI 0.91 to 1.08; I^2 = 0%; Analysis 1.14).

Need for dialysis

Two studies reported the need for dialysis at up to 28 days for 12,325 participants. Evidence suggests little to no difference between participants receiving convalescent plasma or not (OR 1.03, 95% CI 0.86 to 1.23; I^2 = 0%; Analysis 1.15).

Admission to the ICU

Two studies reported admission to the ICU for 816 participants. Evidence suggests that treatment with convalescent plasma may have little to no impact on being admitted to the ICU (RR 0.93, 95% CI 0.77 to 1.11; I^2 = 0%; Analysis 1.16).

Duration of hospitalisation

Two studies reported duration of hospitalisation for 97 participants. Evidence suggests that treatment with convalescent plasma may have little to no impact on the duration of hospitalisation when compared to placebo or standard care alone (MD −1.04, 95% CI −6.87 to 4.79; I^2 = 96%; Analysis 1.17).

Viral clearance

We included data of viral clearance if assessed with RT-PCR test for SARS-CoV-2 for the following time points: at baseline, up to 3, 7, and 14 days.

Four studies reported viral clearance for 674 participants. Evidence suggests that more people treated with convalescent plasma may achieve viral clearance at up to day 3 (RR 1.29, 95% CI 0.76 to 2.18; 4 studies, 619 participants; I^2 = 86%; Analysis 1.18) day 7 (RR 1.24, 95% CI 0.85 to 1.79; 4 studies, 674 participants; I^2 = 80%; Analysis 1.19), and day 14 (RR 1.46, 95% CI 0.58 to 3.68; 2 studies, 212 participants; I^2 = 93%; Analysis 1.20).

Adverse events (any grade and grades 1 to 2)

We summarised data in Table 5, including the potential relationship between the intervention and the adverse event, as reported in the primary studies.

Seven studies reported adverse events of any grade for both groups and a total of 1809 participants. Evidence suggests little to no difference in the occurrence of any adverse events when treated with convalescent plasma (RR 1.05, 95% CI 0.95 to 1.17; I^2 = 0%; Analysis 1.8).

One study reported adverse events of grades 1 to 2 for both groups and a total of 160 participants (Sekine 2021). Evidence suggests little to no difference in the occurrence of grades 1 to 2 events when treated with convalescent plasma (RR 1.11, 95% CI 0.87 to 1.41; Analysis 1.9).

Convalescent plasma versus standard plasma

Primary outcomes (included in the summary of findings table)

All-cause mortality

We assessed all-cause mortality at day 28, day 60, by time until death and during hospital stay.

Four studies reported all-cause mortality for 484 participants. Considering the reported event rates within the study, we estimated that 177 of 1000 participants not treated with convalescent plasma die up to 28 days after treatment. We are uncertain whether convalescent plasma reduces or increases all-cause mortality up to day 28 when compared to standard plasma (RR 0.73, 95% CI 0.45 to 1.19; 129 per 1000; 4 studies, 484 participants; I^2 = 16%, very low-certainty evidence; Analysis 2.1); or when measured over time (HR 0.94, 95% CI 0.41 to 2.14; 4 studies, 484 participants; I^2 = 48%; Analysis 2.2). Our main reasons for downgrading were serious inconsistency because direction of effect was not consistent in both studies, and serious imprecision due to few participants and wide confidence intervals. All-cause mortality at day 60 and during hospital stay was not reported in the studies.

- Subgroup analyses
  - **Length of time since symptom onset:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the length of time since symptom onset (Analysis 8.1).
  - **Other subgroups:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to country income groups, according to the World Bank definitions (The World Bank 2022; Analysis 21.1). We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus standard plasma and the outcome all-cause mortality.
- **Sensitivity analyses:** we summarised the effects of sensitivity analyses in Table 7. The effects of our main analysis were robust when we removed preprint articles and studies that were terminated early. We did not include any studies with high risk of bias in the main analysis of this outcome.

Clinical status

We assessed the clinical status of participants by the need for invasive mechanical ventilation or death (worsening of clinical status) and by participants discharged from hospital (improvement of clinical status) up to day 28, day 60, and up to longest follow-up.

- **Worsening of clinical status:** one study reported the need for invasive mechanical ventilation or death for 34 participants (NCT04421404). Considering the reported event rates within the study, we estimated that 56 of 1000 participants treated with standard plasma needed invasive mechanical ventilation or died. Evidence is uncertain whether treatment with convalescent plasma reduces or increases the need for invasive mechanical ventilation or death when compared to standard plasma (RR 5.59, 95% CI 0.29 to 108.38; 311 per 1000; 1 study, 34 participants; very low-certainty evidence; Analysis 2.3). Our main reasons for downgrading were extreme imprecision due to very few participants, very few events, and very wide confidence intervals.
- **Improvement of clinical status:** we did not identify any study reporting this outcome.
- **Subgroup analyses:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to country income groups, according to the World Bank definitions (The World Bank 2022; Analysis 21.2). We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for the outcome, clinical worsening.
- **Sensitivity analyses:** we summarised the effects of sensitivity analyses in Table 7. We did not see the reported effects of our main analysis when we removed the study with no published peer-reviewed results. We did not include a study with high risk of bias, or a study that was terminated early in the main analysis of this outcome.

Quality of life

We did not identify any study reporting this outcome.

Adverse events (grades 3 to 4)

We defined the outcome as the number of participants with any grades 3 or 4 events. We summarised data in Table 5, including the potential relationship between intervention and adverse event, as reported in the primary studies.

None of the studies reported the number of participants who experienced grades 3 or 4 adverse events. However, O'Donnell 2021 reported separately the number of participants who experienced any grade 3 adverse event (27 events in 147 participants treated with convalescent plasma versus 17 events in 72 participants without convalescent plasma) and any grade 4 adverse event (26 events in 147 participants treated with convalescent plasma versus 15 events in 72 participants without convalescent plasma). We are uncertain whether convalescent plasma reduces or increases the risk of grade 3 or 4 adverse events compared to standard plasma. Our main concerns were serious indirectness, because outcome definitions differed from the definitions used in our review, and very serious imprecision because of few participants and few events.

Serious adverse events

We summarised data on serious adverse events reported only in participants who received convalescent plasma, with no reporting in the control group and including potential relationships between events and transfusion in Table 6.

Three studies reported serious adverse events for both groups and a total of 327 participants. Considering the reported event rates across studies, we estimated that 295 of 1000 participants not treated with convalescent plasma experience a serious adverse event. We are uncertain whether treatment with convalescent

plasma reduces or increases the risk of serious adverse events when compared to standard plasma (RR 0.80, 95% CI 0.55 to 1.15; 236 per 1000; 3 studies, 327 participants; I^2 = 0%; very low-certainty evidence; Analysis 2.6). Our main reasons for downgrading were serious imprecision because of few participants and few events, and suspected publication bias because most studies assessed and reported transfusion-related events only; that is, they reported safety data only for the intervention group.

- **Subgroup analyses**
  - **Severity of disease:** we could not investigate subgroup differences between participants with moderate and severe disease, because the three studies included in the main analysis for this outcome included participants with moderate disease only (WHO score 4 and 5), according to WHO Clinical Progression Scale (WHO 2020e; Analysis 2.6).
  - **Other subgroups:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to country income groups, according to the World Bank definitions (The World Bank 2022; Analysis 21.3).
  - We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for any outcome that summarised adverse events.
- **Sensitivity analyses:** we summarised the effects of sensitivity analyses in Table 7. Reported effects of our main analysis were robust when we removed preprint articles and studies that were terminated early. We did not include any studies with high risk of bias in the main analysis of this outcome.

Secondary outcomes (not included in the summary of findings table)

Improvement of clinical status

We did not identify any study reporting this outcome.

Need for dialysis

We did not identify any study reporting this outcome.

Admission to the ICU

We did not identify any study reporting this outcome.

Duration of hospitalisation

Two studies reported duration of hospitalisation for 189 participants. Evidence suggests that treatment with convalescent plasma may have little to no impact on the duration of hospitalisation when compared to standard plasma (MD −2.14, 95% CI −5.24 to 0.95; I^2 = 52%; Analysis 2.4).

Viral clearance

We did not identify any study reporting this outcome.

Adverse events (any grade and grade 1 to 2)

We defined the outcome as the number of participants with events of any grade and grades 1 to 2. We summarised data in Table 5, including the potential relationship between the intervention and the adverse event, as reported in the primary studies.

Two studies reported adverse events of any grade for both groups and a total of 253 participants. Evidence suggests an increase of any adverse events when treated with convalescent plasma (RR 1.18, 95% CI 0.93 to 1.50; I^2 = 0%; Analysis 2.5). None of the studies reported the number of participants who experienced grade 1 or 2 adverse events.

Convalescent plasma versus human immunoglobulin

Primary outcomes (included in the summary of findings table)

All-cause mortality

We assessed all-cause mortality at day 28, day 60, by time until death and during hospital stay.

One study reported all-cause mortality for 190 participants (Beltran Gonzalez 2021). Considering the reported event rates across studies, we estimated that 433 of 1000 participants die at up to 28 days when treated with human immunoglobulin. Convalescent plasma may have little to no effect on all-cause mortality at up to day 28 (RR 1.07, 95% CI 0.76 to 1.50; 464 per 1000; 1 study, 190 participants; low-certainty evidence; Analysis 3.1); when measured over time (HR 1.14, 95% CI 0.84 to 1.54; 1 study, 190 participants; or low-certainty evidence; Analysis 3.2); or during hospital stay (RR 1.01, 95% CI 0.76 to 1.34; 1 study, 190 participants; low-certainty evidence; Analysis 3.3). Our main reason for downgrading was very serious imprecision due to few events and few participants. This study did not report all-cause mortality at day 60.

- **Subgroup analyses:** we could not perform any of our planned subgroup analyses for the comparison of convalescent plasma versus human immunoglobulin.
- **Sensitivity analyses:** we did not summarise the effects of sensitivity analyses in a separate table, as we included only one study in the analysis for this outcome. We did not see the reported effects of our main analysis after we removed the study as a preprint article. We did not judge the study at high risk of bias, nor was it terminated early.

Clinical status

We did not identify any study reporting this outcome.

Quality of life

We did not identify any study reporting this outcome.

Adverse events (grades 3 to 4)

We did not identify any study reporting this outcome.

Serious adverse events

We did not identify any study reporting this outcome.

Secondary outcomes (not included in the summary of findings table)

Improvement of clinical status

We did not identify any study reporting this outcome.

Need for dialysis

We did not identify any study reporting this outcome.

Admission to the ICU

We did not identify any study reporting this outcome.

Duration of hospitalisation

We did not identify any study reporting this outcome.

Viral clearance

We did not identify any study reporting this outcome.

Adverse events (any grade and grades 1 to 2)

We did not identify any study reporting this outcome.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

We present certainty of the evidence for our prioritised outcomes for individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease in Summary of findings 4 and Summary of findings 5 (please see 'Summary of findings and assessment of the certainty of the evidence' in Methods). Summary of findings 4 includes the comparison of convalescent plasma versus placebo or standard care alone and Summary of findings 5 includes the comparison of convalescent plasma versus standard plasma.

Convalescent plasma versus placebo or standard care alone

Primary outcomes (included in the summary of findings table)

All-cause mortality

We assessed all-cause mortality at day 28, day 60, by time until death, and at longest follow-up available.

Two studies reported all-cause mortality for 536 participants. Considering the reported event rates across studies, we estimated that 22 of 1000 participants die at up to 28 days when treated with placebo or standard care alone. Evidence is uncertain whether or not treatment with convalescent plasma reduces all-cause mortality at up to day 28 (OR 0.36, 95% CI 0.09 to 1.46; 8 per 1000; 2 studies, 536 participants; I^2 = 0%; very low-certainty evidence; Analysis 4.1); or at up to day 60 (OR 0.13, 95% CI 0.01 to 2.16, 1 study, 376 participants; Analysis 4.2). Our main reasons for downgrading were serious indirectness, because in one study (Libster 2020), the authors defined the outcome as deaths associated with COVID-19, and may not have reported other causes of mortality, and serious imprecision due to few events and wide confidence intervals. None of the studies reported all-cause mortality measured over time.

- **Subgroup analyses**
  - **Other subgroups:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to country income groups, according to the World Bank definitions (The World Bank 2022; Analysis 22.1).
  - We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus placebo or standard care alone for this outcome.

Admission to hospital or death within 28 days

One study reported admission to hospital or death within 28 days for 376 participants (Alemany 2022). Considering the reported event rates across studies, we estimated that 112 of 1000 participants are admitted to hospital or died within 28 days when treated with placebo or standard care alone. Evidence suggests that the treatment with convalescent plasma may have little to no impact on admission to hospital or death within 28 days (RR 1.05, 95% CI 0.60 to 1.84; 117 per 1000; low-certainty evidence; Analysis 4.3). Our main reason for downgrading was very serious imprecision, due to very few events, few participants and wide confidence intervals.

- **Subgroup analyses:** we could not perform any of our planned subgroup analyses for the comparison of convalescent plasma versus placebo or standard care alone for this outcome.

Symptom resolution

We assessed the outcome symptom resolution by all initial symptoms resolved (asymptomatic) at day 14, day 28, and at longest follow-up available and by time to symptom resolution.

- **All initial symptoms resolved:** we did not identify any study reporting this outcome.
- **Time to symptom resolution:** one study reported time to symptom resolution for 376 participants (Alemany 2022). Considering the reported event rates across studies, we estimated that 500 of 1000 participants' symptoms resolved after 12 days when treated with placebo or standard care alone. Evidence suggests that treatment with convalescent plasma may have little to no impact on the time to symptom resolution (HR 1.05, 95% CI 0.85 to 1.30; 483 per 1000; low-certainty evidence; Analysis 4.4). Our main reason for downgrading was very serious imprecision due to very few events, few participants, and wide confidence intervals.
- **Subgroup analyses:** we could not perform any of our planned subgroup analyses for the comparison of convalescent plasma versus placebo or standard care alone for both outcomes of symptom resolution.

Quality of life

We did not identify any study reporting this outcome.

Adverse events (grades 3 to 4)

We defined the outcome as the number of participants with any adverse events of grades 3 to 4. We summarised data in Table 5, including the potential relationship between the intervention and the adverse event, as reported in the primary study.

One study reported grades 3 or 4 adverse events for both groups and a total of 376 participants (Alemany 2022). Considering the reported event rates across studies, we estimated that 112 of 1000 participants not treated with convalescent plasma experience a grade 3 or 4 adverse event. Evidence suggests that treatment with convalescent plasma may have little to no impact on the risk of grade 3 and 4 adverse events (RR 1.29, 95% CI 0.75 to 2.19; 144 per 1000; low-certainty evidence; Analysis 4.8). Our main reason for downgrading was very serious imprecision, due to few participants, few events and wide confidence intervals. One study reported that convalescent plasma was not associated with any "solicited adverse events" (Libster 2020). Because the definition was unclear and we were unsure whether only drug-related adverse events were assessed, and we did not receive additional information from the study authors, we did not include this outcome in the analysis. We do not know whether convalescent plasma is associated with a higher risk for grades 3 or 4 adverse events (very low-certainty evidence).

- **Subgroup analyses:** we could not investigate the difference in the effectiveness of convalescent plasma with regard to country income groups, according to the World Bank definitions (The

World Bank 2022), as the study included in this analysis was from a high-income country (Alemany 2022; Analysis 22.2).

- We could not perform any of our planned subgroup analyses for the comparison of convalescent plasma versus placebo or standard care alone for the adverse events analyses.

Serious adverse events

One study reported serious adverse events for both groups and a total of 376 participants (Alemany 2022). Considering the reported event rates across studies, we estimated that 117 of 1000 participants not treated with convalescent plasma experience a serious adverse event. Evidence suggests that treatment with convalescent plasma may have little to no impact on the risk of serious adverse events (RR 1.14, 95% CI 0.66 to 1.94; 133 per 1000; low-certainty evidence; Analysis 4.9). Our main reason for downgrading was very serious imprecision, due to few participants, few events and wide confidence intervals. One study reported that convalescent plasma was not associated with any "solicited serious adverse events" (Libster 2020). Because the definition was unclear and we were unsure whether only drug-related serious adverse events were assessed, and we did not receive additional information from the study authors, we did not include this outcome in the analysis. We do not know whether convalescent plasma is associated with a higher risk for serious adverse events (very low-certainty evidence).

- **Subgroup analyses**: we could not investigate the difference in the effectiveness of convalescent plasma with regard to country income groups, according to the World Bank definitions (The World Bank 2022), as the study included in this analysis was from a high-income country (Alemany 2022; Analysis 22.3).
- We could not perform any of our planned subgroup analyses for the comparison of convalescent plasma versus placebo or standard care alone for the serious adverse events analysis.

Secondary outcomes (not included in the summary of findings table)

Worsening of clinical status

We assessed worsening of clinical status at day 28, and up to the longest follow-up available, by need for hospitalisation with oxygen by mask or nasal prongs, or death, and by need for invasive mechanical ventilation, or death.

Two studies reported the need for hospitalisation with oxygen by mask or nasal prongs, or death, at up to 28 days for 536 participants. Evidence suggests little to no difference between participants receiving convalescent plasma or not (RR 0.76, 95% CI 0.36 to 1.59; I^2 = 68%; Analysis 4.5). One study reported need for invasive mechanical ventilation or death up to day 28 and up to day 60 for 376 participants (Alemany 2022). Evidence suggests that fewer people treated with convalescent plasma may need invasive mechanical ventilation or die at up to day 28 (OR 0.51, 95% CI 0.10 to 2.55; Analysis 4.6), or at up to day 60 (OR 0.51, 95% CI 0.10 to 2.55; Analysis 4.7)

Viral clearance (assessed with RT-PCR)

We did not identify any study reporting this outcome.

Adverse events (any grade and grades 1 to 2)

We identified no study reporting adverse events of any grade or grades 1 to 2.

Convalescent plasma versus standard plasma

Primary outcomes (included in the summary of findings table)

All-cause mortality

We assessed all-cause mortality at day 28, day 60, by time until death, and at longest follow-up available.

Two studies reported all-cause mortality for 1597 participants. Considering the reported event rates across studies, we estimated that 5 of 1000 participants die at up to 28 days when treated with standard plasma. We are uncertain whether convalescent plasma reduces all-cause mortality at up to day 28 (OR 0.30, 95% CI 0.05 to 1.75; 2 per 1000; 2 studies, 1597 participants; I^2 = 19%; very low-certainty evidence; Analysis 5.1). Our main reason for downgrading was very serious imprecision due to few events and very wide confidence intervals. The studies did not report all-cause mortality at up to day 60, or measured over time.

- **Subgroup analyses**
  - **Length of time since symptom onset:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the length of time since symptom onset (Analysis 9.1).
  - **Other subgroups:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the pre-existing condition of diabetes at baseline (Analysis 13.1), or participant's age (Analysis 17.1). We could not calculate the difference in the effectiveness of convalescent plasma with regard to the sex of participants, as none of the female participants died in either group (out of 43 with convalescent plasma and 52 with standard plasma), and one of the male participants died in each group (out of 163 with convalescent plasma and 158 with standard plasma; Analysis 19.1). We could not investigate the difference in the effectiveness of convalescent plasma with regard to country income groups, according to the World Bank definitions (The World Bank 2022), as both studies included in this analysis were set in high-income countries (Analysis 23.1).
  - We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for this outcome.

Admission to hospital or death within 28 days

Two studies reported admission to hospital or death within 28 days for 1595 participants. Considering the reported event rates across studies, we estimated that 73 of 1000 participants treated with standard plasma are admitted to hospital or died within 28 days. Evidence suggests that treatment with convalescent plasma probably reduces admission to hospital or death within 28 days (RR 0.49, 95% CI 0.31 to 0.75; 36 per 1000; I^2 = 0%; moderate-certainty evidence; Analysis 5.2). Our main reason for downgrading was serious imprecision because the optimal information size is not met for a power of 0.90.

- **Subgroup analyses**
  - **Length of time since symptom onset:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the length of time since symptom onset (Analysis 9.2).

- **Other subgroups:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the pre-existing condition of diabetes at baseline (Analysis 13.2), sex of participants (Analysis 19.2), or age of participants (Analysis 17.2).
- We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for this outcome.

Symptom resolution

We assessed the outcome symptom resolution by all initial symptoms resolved (asymptomatic) at day 14, day 28, and at longest follow-up available and by time to symptom resolution.

- **All initial symptoms resolved:** one study reported all initial symptoms resolved for 417 participants (CoV-Early). Considering the reported event rates across studies, we estimated that all symptoms of 657 of 1000 participants treated with standard plasma would be resolved at up to 28 days. Evidence suggests that treatment with convalescent plasma may have little to no effect on resolution of all initial symptoms up to day 28 (RR 1.12, 95% CI 0.98 to 1.27; 736 per 1000; 1 study, 416 participants; low-certainty evidence; Analysis 5.3) or at up to day 14 (RR 1.00, 95% CI 0.83 to 1.21; 1 study, 417 participants; Analysis 5.4). Our main reason for downgrading was very serious imprecision due to few events, few participants, and wide confidence intervals.
- **Time to symptom resolution:** we did not identify any study reporting this outcome.
- **Subgroup analyses**
  - **Length of time since symptom onset:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to length of time since symptom onset (Analysis 9.3).
  - **Other subgroups:** we did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the pre-existing condition of diabetes at baseline (Analysis 13.3), participants' age (Analysis 17.3), or sex (Analysis 19.3).
  - We could not perform any further planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for the outcome of all initial symptoms resolved.

Quality of life

We did not identify any study reporting this outcome.

Adverse events (grades 3 to 4)

We did not identify any study reporting this outcome.

Serious adverse events

We did not identify any study reporting this outcome.

Secondary outcomes (not included in the summary of findings table)

Worsening of clinical status

We assessed worsening of clinical status at day 28, and up to the longest follow-up available, by need for hospitalisation with oxygen by mask or nasal prongs, or death, and by need for invasive mechanical ventilation, or death.

One study reported the need for hospitalisation with oxygen by mask or nasal prongs, or death, at up to 28 days for 1181 participants (Sullivan 2022). Evidence suggests that fewer people treated with convalescent plasma may need hospitalisation and receive oxygen by mask or nasal prongs, or die up to day 28 (RR 46, 95% CI 0.23 to 0.90; Analysis 5.5). One study reported need for invasive mechanical ventilation or death up to day 28 for 414 participants (CoV-Early). Evidence suggests that fewer people treated with convalescent plasma may need invasive mechanical ventilation or die up to day 28 (OR 0.30, 95% CI 0.05 to 1.77; Analysis 5.6).

Viral clearance (assessed with RT-PCR)

We did not identify any study reporting this outcome.

Adverse events (any grade and grades 1 to 2)

We did not identify any study reporting adverse events of any grade or grades 1 to 2.

DISCUSSION

Summary of main results

The aim of this review was to assess the effectiveness and safety of convalescent plasma in the treatment of COVID-19. This is the fifth version of our living systematic review.

We identified 33 RCTs that evaluated 24,861 participants, of whom 11,432 received convalescent plasma. We identified a further 49 ongoing studies evaluating convalescent plasma. We also identified 28 completed but not yet published studies and two studies terminated early for futility, that we categorised as 'Awaiting classification', as well as three platform trials that we have also placed in that category.

Effects of interventions

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

29 RCTs investigated the use of convalescent plasma for 22,728 participants with moderate to severe disease, of which 23 RCTs compared convalescent plasma to placebo treatment or standard care alone, five compared convalescent plasma to standard plasma, and one RCT compared convalescent plasma to human immunoglobulin.

Convalescent plasma versus placebo or standard care alone

Convalescent plasma does not reduce all-cause mortality at up to day 28 (RR 0.98, 95% CI 0.92 to 1.03; 220 per 1000; 21 RCTs, 19,021 participants; high-certainty evidence). It has little to no impact on need for invasive mechanical ventilation or death (RR 1.03, 95% CI 0.97 to 1.11; 296 per 1000; 6 RCTs, 14,477 participants; high-certainty evidence) and has no impact on whether participants are discharged from hospital (RR 1.00, 95% CI 0.97 to 1.02; 665 per 1000; 6 studies, 12,721 participants; high-certainty evidence). Convalescent plasma may have little to no impact on quality of life, assessed with standardised scale EQ-5D-5L questionnaire (MD 1.00, 95% CI −2.14 to 4.14; 1 RCT, 483 participants; low-certainty evidence). Convalescent plasma may have little to no impact on the risk of grade 3 and 4 adverse events (RR 1.17, 95% CI 0.96 to 1.42; 212 per 1000; 6 RCTs, 2392 participants; low-certainty evidence). Convalescent plasma probably has little to no effect on the risk of serious adverse events (RR 1.12, 95% CI 0.96 to 1.31; 133 per 1000; 6 RCTs, 4901 participants; moderate-certainty evidence).

We did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to the detection of antibodies in the recipients at baseline, to length of time since symptom onset, disease severity, country income groups, or certain pre-existing conditions. For improvement and worsening of clinical status, we identified significant subgroup differences for the effect of convalescent plasma with regard to antibodies in recipients detected at baseline and age of people, but we are uncertain whether the analyses produced useful findings.

Convalescent plasma versus standard plasma

We are uncertain whether convalescent plasma reduces or increases all-cause mortality at up to day 28 (RR 0.73, 95% CI 0.45 to 1.19; 129 per 1000; 4 studies, 484 participants; very-low-certainty evidence). We are uncertain whether convalescent plasma reduces or increases need for invasive mechanical ventilation or death (RR 5.59, 95% CI 0.29 to 108.38; 311 per 1000; 1 study, 34 participants; very low-certainty evidence). None of the studies reported the number of participants who experienced grade 3 or 4 adverse events, only one study reported the number of participants with any adverse event of grade 3 and grade 4 separately. However, we are uncertain whether convalescent plasma reduces or increases the risk of grade 3 or 4 adverse events and the risk of serious adverse events (RR 0.80, 95% CI 0.55 to 1.15; 236 per 1000; 3 studies, 327 participants; very low-certainty evidence). We identified no study reporting quality of life.

We did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to length of time since symptom onset, country income groups, or disease severity.

Convalescent plasma versus human immunoglobulin

Convalescent plasma may have little to no effect on all-cause mortality at up to day 28 (RR 1.07, 95% CI 0.76 to 1.50; 464 per 1000; 1 study, 190 participants; low-certainty evidence).

We identified no study reporting on clinical status, quality of life or safety.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease

We identified four RCTs that investigated the use of convalescent plasma for 2133 participants with mild disease, of which two RCTs with 536 participants compared convalescent plasma to placebo or standard care alone, and two RCTs with 1597 participants compared convalescent plasma to standard plasma.

Convalescent plasma versus placebo or standard care alone

We are uncertain whether convalescent plasma reduces all-cause mortality at up to day 28 (OR 0.36, 95% CI 0.09 to 1.46; 8 per 1000; 2 RCTs, 536 participants; very low-certainty evidence). Evidence suggests that it may have little to no impact on admission to hospital or death within 28 days (RR 1.05, 95% CI 0.60 to 1.84; 117 per 1000; 1 study, 376 participants; low-certainty evidence) and on time to COVID-19 symptom resolution (HR 1.05, 95% CI 0.85 to 1.30; 483 per 1000; 1 study, 376 participants; low-certainty evidence). Convalescent plasma may have little to no impact on the risk of grade 3 and 4 adverse events (RR 1.29, 95% CI 0.75 to 2.19; 144 per 1000; 1 study, 376 participants; low-certainty evidence) and the risk of serious adverse events (RR 1.14, 95% CI 0.66 to 1.94; 133 per 1000; 1 study, 376 participants; low-certainty evidence). We identified no study reporting symptom resolution or quality of life.

We did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to length of time since symptom onset. We were unable to perform any further subgroup analysis.

Convalescent plasma versus standard plasma

We are uncertain whether convalescent plasma reduces all-cause mortality at up to day 28 (OR 0.30, 95% CI 0.05 to 1.75; 2 per 1000; 2 studies, 1597 participants; very low-certainty evidence). It probably reduces admission to hospital or death within 28 days (RR 0.49, 95% CI 0.31 to 0.75; 36 per 1000; 2 studies, 1595 participants; moderate-certainty evidence). Convalescent plasma may have little to no effect on resolution of all initial symptoms at up to day 28 (RR 1.12, 95% CI 0.98 to 1.27; 736 per 1000; 1 study, 416 participants; low-certainty evidence). We did not identify any study reporting time to symptom resolution, quality of life or safety.

We did not identify any significant subgroup difference in the effectiveness of convalescent plasma with regard to country income groups, pre-existing condition, sex, or age of participants.

Overall completeness and applicability of evidence

Most of the included participants had received additional treatment options to convalescent plasma or control, including, for instance, antivirals, antimicrobials, corticosteroids, hydroxychloroquine, respiratory support (extracorporeal membrane oxygenation, mechanical ventilation or oxygen), or a combination of those.

Thanks to high-certainty evidence, we are confident that treatment with convalescent plasma does not reduce all-cause mortality at up to 28 days, has little to no impact on need for invasive mechanical ventilation or death at day 28, and has no impact on whether participants are discharged from hospital when compared to placebo treatment or standard care alone. For the same comparison, we found low-certainty evidence. Convalescent plasma may have little to no impact on quality of life and may result in a clinically relevant increased risk of grade 3 or 4 adverse events, but the treatment probably has little to no effect on the risk of serious adverse events (moderate-certainty evidence). Not all the included RCTs reported adverse events for the control arm. When compared to standard plasma, we are uncertain about the effect of convalescent plasma on all-cause mortality at up to 28 days, and very uncertain whethe convalescent plasma therapy increases the risk of need for invasive mechanical ventilation or death at day 28. For the same comparison, the evidence for grade 3 and 4 adverse events is uncertain (very-low evidence), but convalescent plasma therapy may result in little to no impact on serious adverse events (low-certainty evidence). When comparing the treatment to human immunoglobulin, we have low-certainty evidence; convalescent plasma may have little to no impact on all-cause mortality at up to 28 days.

Four RCTs investigated the use of convalescent plasma treatment for individuals with mild disease, of which two RCTs compared the therapy to placebo or standard care alone, and two RCTs compared it to standard plasma. We have low confidence in the evidence; treatment with convalescent plasma may have little to no impact on all-cause mortality at up to day 28, on admission to hospital

or death within 28 days and on time to symptom resolution. For the same comparison, convalescent plasma may result in a clinically relevant increased risk of grade 3 or 4 adverse events and serious adverse events (low-certainty evidence). When compared to standard plasma, we have low certainty evidence; convalescent plasma may have little to no impact on all-cause mortality at up to day 28, and on time to symptom resolution. For the same comparison, convalescent plasma probably reduces admission to hospital or death within 28 days (moderate-certainty evidence).

28 RCTs have been completed, or completed their recruitment, and two RCTs have been terminated early, but no results have been published yet. We are also keeping track of three ongoing platform trials that might potentially add an intervention arm on convalescent plasma. Therefore, we categorised all these as 'Awaiting classification' and we will consider including them in an update of this review, once results are available.

We identified 49 ongoing studies, all RCTs assessing the benefits and safety of convalescent plasma therapy for the treatment of COVID-19.

Quality of the evidence

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

We included data from 23 RCTs to assess effectiveness and safety of convalescent plasma when compared to treatment with placebo or standard care alone. We were very confident in the identified evidence for effectiveness outcomes, but less confident in the identified evidence for safety outcomes. Our main concerns were that some studies still assessed and reported safety outcomes for the convalescent plasma group only, indicating publication bias and serious imprecision because the optimal information size was not met for a power of 0.90 (the optimal information size indicates the threshold for the number of included participants for an adequately powered trial or meta-analysis; Guyatt 2011).

We included data from five RCTs to assess effectiveness and safety of convalescent plasma when compared to treatment with standard plasma. Our confidence in the evidence was very low to low for effectiveness and safety outcomes. Our main concerns were serious inconsistency for the outcome mortality at up to day 28, very serious imprecision for mortality and safety outcomes, and extreme serious imprecision for clinical worsening due to wide confidence intervals, few to extremely few participants and events, and because the optimal information size was not met for a power of 0.80. Also, some studies still reported safety outcomes for the convalescent plasma group only, indicating publication bias.

We included data from one RCT to assess effectiveness of convalescent plasma when compared to treatment with human immunoglobulin. We had low confidence in the identified evidence for mortality. Our main concern was very serious imprecision due to few events and few participants.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and mild disease

We included data from two RCTs to assess effectiveness and safety of convalescent plasma when compared to treatment with placebo or standard care alone. We had low confidence in the identified evidence for effectiveness and safety outcomes. Our main concerns were serious to very serious imprecision due to the small information size and serious indirectness for all the reported outcomes, and serious indirectness for mortality, because the outcome definition did not precisely match our outcome definition.

We included data from two RCTs to assess effectiveness of convalescent plasma when compared to treatment with standard plasma. We had moderate to low confidence in the identified evidence for effectiveness. Our main concerns were serious imprecision for admission to hospital or death, because the optimal information size was not met for a power of 0.90. and very serious imprecision for mortality and symptom resolution, due to few events and very wide confidence intervals.

Potential biases in the review process

To avoid potential biases in the review process, we planned to include the best available evidence and adhered to the guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* in all steps of the review (Higgins 2022). Even though COVID-19 is still a novel disease, we identified more high-quality evidence and included only RCTs in this version, as we have identified a large number of RCTs since the last update (Piechotta 2021). For this update, we were able to include 33 RCTs. To increase the informative value of our review, we are tracking all registered trials and will continually update this review as more evidence becomes available. There are currently still many new trials being registered in trials registries, as can be seen from the additional 49 RCTs added to the list of ongoing studies in this update of the review.

Two experienced information specialists developed a sensitive search strategy, to identify all ongoing and completed studies. We searched all relevant databases and trials registries, and two review authors conducted all review steps independently and in duplicate.

Another consideration for this rapidly evolving field is the availability of preprint articles that have not yet undergone peer review. We included preprints in this review, however, we are aware of the potentially lower quality of these publications, and investigated the robustness of our results in sensitivity analyses.

The necessary adaptation of review methods to the development of research output, as described in Table 1, is in general a potential source of bias in the review process. Since the available evidence has changed rapidly in a comparably short period of time during the COVID-19 pandemic, we needed to take this approach to give a comprehensive answer to the review question. Before we start an update, our interdisciplinary team of review authors meets to review the methods and to discuss necessary amendments. We follow the methods we agreed upon before starting the update, and adhere to these decisions throughout each update process.

For this review update, we removed 'hyperimmune immunoglobulin' from the eligibility criteria because we identified several studies that evaluated this intervention treatment and therefore, we decided to assess this as a separate research question in a new review. We do not think that the bias arising from this adaptation was substantial, since the change was driven by objective reasons.

For changes in outcomes and outcome measurement, we specified the outcome 'worsening of clinical status' from standardised scales (WHO 2020e; WHO 2020f), in the third (Chai 2020), and fourth

version (Piechotta 2021), to 'worsening of clinical status, assessed by need for invasive mechanical ventilation or death' and added the competing event of death to the outcome. We do not think that this change has led to any bias in the review process. Instead, we think that changing the inclusion criteria for outcome measurement to a standardised scale can facilitate identifying studies with objective and higher-quality results and, additionally, can contribute to a lower heterogeneity among included studies. We also added a new secondary outcome 'quality of life' from version 2 of this review (Piechotta 2020b) onward, but do not suspect that this had an impact on bias since the outcome was suggested by an external patient representative.

For inclusion criteria regarding different study designs, we tried to anticipate possible changes of the evidence landscape already at protocol stage and therefore excluded study designs of lower-level evidence, as more RCTs were published. So, for this update, we decided to only include RCTs, as enough RCT data were available to investigate the research question.

In previous versions of this review (Piechotta 2020b), we used RoB 1 for RCTs (Higgins 2011). We started using ROB 2 (Sterne 2019) from the second update (Chai 2020). This led to changes in the risk of bias rating and the GRADE assessment for the mortality, clinical status and safety outcomes of one included study (Li 2020). We think using RoB 2 corrected our judgement from potential personal biases, since it is less sensitive to subjective interpretations and allows for more nuanced assessment of potential bias in open-label trials.

Agreements and disagreements with other studies or reviews

In the previous version of this systematic review, we compared our findings to two systematic reviews, Janiaud 2021, which included only RCTs, and Klassen 2021, which included RCTs together with other study designs. For the current update, we have been looking for more recent high-quality, RCT-only systematic reviews on the effect and safety of convalescent plasma for people with COVID-19, to compare them to our RCT-based findings.

Jorda 2022 aggregated data from 16 RCTs with 16,317 participants with moderate to severe disease, except one included trial (Libster 2020), and they found similar results to our review. Their meta-analysis of 16 RCTs indicated that there is high-certainty evidence for convalescent plasma not being associated with lower all-cause morality (RR 0.97, 95% CI 0.90 to 1.04), lower initiation of mechanical ventilation (RR 0.97, 95% CI 0.88 to 1.07), and increased time to hospital discharge (HR 0.95, 95% CI 0.89-1.02). They did not identify any subgroup differences for disease severity and baseline antibody level in recipients. Their results may be comparable to our findings, as all their included RCTs are also evaluated in our review.

Yang 2022, another systematic review, indicated similar results in their meta-analysis. They included 14 RCTs with 4543 participants and found that convalescent plasma treatment for patients with severe COVID-19 infection, who were critically ill, did not reduce mortality risk (RR 0.94, 95% CI 0.85 to 1.03, low-certainty evidence) nor increase clinical improvement (RR 1.07, 95% CI 0.97 to 1.17, moderate-certainty evidence). Also, there were no subgroup differences for disease severity.

Fernández-Lázaro 2022, a systematic review that included six studies (classified as RCTs) in a qualitative synthesis, indicated contradictory results to our review. They found that treatment with convalescent plasma in hospitalised COVID-19 patients could decrease mortality, viral load and period of infection, without the occurrence of serious adverse events. One potential reason for the difference between their results and ours could be the inclusion of Liu 2020a, Rasheed 2020 and Zeng 2020, which they had classified as RCTs. We did not identify these studies as RCTs, however, and therefore excluded them from our review analyses. Rasheed 2020, for instance, reported that controls were matched to participants according to the disease stage, age, and sex, and assigned participants to convalescent plasma based on ABO compatibility and limited availability of plasma. In our opinion, this does not fit the criteria for a randomised allocation method and we classified it as a controlled non-randomised study of interventions (NRSI), since we did not receive any further information on their methods.

Also, the FDA and the USA Government considered that there was sufficient evidence of efficacy to widen access to convalescent plasma under the 'Emergency Use Authorization' (EUA) issued on 23 August 2020 (FDA 2020). However, on 11 February 2021, the FDA revised the EUA for convalescent plasma. The authorisation is now limited to the use of high-titre convalescent plasma for hospitalised individuals at an early stage of disease (FDA 2021).

Furthermore, Bartelt 2022, an RCT available in preprint, evaluated the safety and effectiveness of convalescent plasma with high- (> 1:640) compared to lower- (≥ 1:160) neutralising antibody titres. The study authors reported that participants treated with high titre convalescent plasma had earlier hospital discharge and lower occurrences of life-threatening serious adverse events. Even though this study is limited by its small sample size, and further RCTs are needed to confirm their findings, the results might indicate how varying titre levels can have an impact on between-study differences in our analyses. This could be one potential reason why some of our included RCTs have different safety and effectiveness results.

AUTHORS' CONCLUSIONS

Implications for practice

We are very confident in the evidence that convalescent plasma for the treatment of individuals with moderate to severe disease does not reduce mortality and has little to no impact on the need for invasive mechanical ventilation or death (clinical worsening) and participants discharged from hospital (clinical improvement) when compared to placebo or standard care alone. Convalescent plasma probably has little to no effect on the risk of serious adverse events in such patients. Further, we identified very low- to low-certainty evidence for the effects of convalescent plasma when compared to standard plasma in individuals with moderate to severe COVID-19. Convalescent plasma therapy may result in little to no impact on serious adverse events, in such patients. For the same population, when compared to human immunoglobulin treatment, we identified low-certainty evidence for mortality.

For individuals with a diagnosis of SARS-CoV-2 infection and mild disease, we currently have low confidence in the evidence for the effects of convalescent plasma when compared to placebo or standard care alone. For the same comparison, convalescent

plasma may result in a clinically relevant increased risk of grade 3 or 4 adverse events and serious adverse events. When compared to standard plasma, we have low- to moderate confidence in the evidence on the effects of convalescent plasma, in such patients.

Implications for research

For the fifth version of this living systematic review investigating the use of convalescent plasma for people with COVID-19, we included data from 33 randomised controlled trials (RCTs) reporting on the effectiveness and safety of convalescent plasma, and in total considered the experience of 24,861 participants. Studies should more consistently report outcomes and, if relevant, consider the competing event of death. Further, studies should consider standard treatment changes during the pandemic to ensure and improve comparability in terms of co-interventions administered in all study arms. Concerning adverse events, studies should try to blind at least outcome assessors, and report adverse events consistently, and for both the intervention and the control arm.

Additional studies evaluating convalescent plasma treatment in asymptomatic participants would be of interest to assess whether the intervention is more effective if given earlier in the course of the disease. Additional data are needed for patients with any disease severity who are immune-suppressed, as well as subgroup data for plasma from SARS-CoV-2 variants, and different ethnicities. Future studies should also report outcomes based on antibody titre in the donor plasma administered.

There are 49 ongoing studies evaluating convalescent plasma and 30 studies reporting in a trials registry as being completed or terminated. We will also keep track of three platform trials. Publication of the results might resolve some of the uncertainties around convalescent plasma therapy for people with asymptomatic or mild disease and for certain subgroups.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agarwal 2020

Study characteristics	
Methods	• Trial design: open-label, multicentre RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 22 April 2020-14 July 2020 • Country: India • Language: English • Number of centres: 39 • Trial registration number: CTRI/2020/04/024775 • Date of trial registration: 12 April 2020

Participants	• Age (median, IQR; years):
	  ○ CP + SC: 52 (IQR 42-60)
	  ○ SC: 52 (IQR 41-60)
	• Sex (N, or %; female):
	  ○ CP + SC: 58/235 (24.7%)
	  ○ SC: 52/229 (22.7%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 1210/464 (CP 235, SC 229)/464
	• Severity of condition according to study definition: moderate PaO2/FiO2 ratio between 200 mm Hg and 300 mm Hg or a respiratory rate of > 24/min with oxygen saturation ≤ 93% on room air)
	• Severity of condition according to WHO score: levels 4 and 5
	• Comorbidities: diabetes mellitus, hypertension, coronary artery disease, obesity, TB, chronic kidney disease, COPD, cerebrovascular disease, cirrhosis and history of cancer
	• Inclusion criteria
	  ○ Participants admitted with RT-PCR-confirmed COVID-19 illness
	  ○ Age > 18 years
	  ○ Moderate illness with 1 of 2:
	  ■ PaO_2/FiO_2: 200-300
	  ■ respiratory rate > 24/min with oxygen saturation (SaO_2) ≤ 93% on room air
	  ○ Availability of matched donor plasma at the point of enrolment
	  ○ Written informed consent obtained before recruitment
	• Exclusion criteria
	  ○ Pregnant or breastfeeding women
	  ○ Known hypersensitivity to blood products
	  ○ Receipt of pooled immunoglobulin in last 30 days
	  ○ Critically ill patients:
	  ■ PaO_2/FiO_2 ratio < 200 mmHG (moderate-severe ARDS) or
	  ■ shock (requiring vasopressors to maintain a MAP of ≥ 65 mm Hg or MAP of < 65 mm Hg)

Agarwal 2020 *(Continued)*

	○ Participating in any other clinical trial ○ Clinical status precluding infusion of blood product • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR • Donor eligibility criteria ○ Men or nulliparous women ○ Aged 18-65 years ○ Weight of > 50 kg ○ Received a diagnosis of COVID-19 confirmed by an RT-PCR test result ○ Had experienced symptoms of COVID-19 with at least fever and cough ○ the symptoms must have completely resolved for 28 consecutive days before donation or ○ a period of 14 days before donation with 2 negative RT-PCR test results for SARS-CoV-2 from nasopharyngeal swabs collected 24 h apart • Donor exclusion criteria: NR
Interventions	• Details of CP ○ Type of plasma: CP ○ Volume: 200 mL ○ Number of doses: 2 doses ○ Type of antibody test and antibody-titre: micro-neutralisation test, median (IQR) titre of 1:40 (1:30 to 1:80) ○ Pathogen inactivated or not: NR • Details of donors ○ Sex (N, or %; female): 5.7% ○ Age (median, IQR or mean, SD; years): NR ○ HLA and HNA antibody-negative: NR ○ Severity of disease: ■ mild (fever and cough with no oxygen requirement): 94.2% ■ moderate (fever and cough with oxygen requirement): 5.8% ○ Timing of recovery from disease: symptoms must have completely resolved for 28 consecutive days before donation or a period of 14 days before donation with 2 negative RT-PCR test results for SARS-CoV-2 from nasopharyngeal swabs collected 24 h apart. ○ RT-PCR tested: yes • Treatment details, including time of plasma therapy (e.g. early stage of disease): first dose of convalescent plasma was transfused at randomisation, and the second dose after 24 h. • Comparator: standard care alone, including any drugs that are being used in clinical practice • Concomitant therapy: standard care for COVID-19 disease (antivirals (hydroxychloroquine, remdesivir, lopinavir/ritonavir, oseltamivir), broad spectrum antibiotics, immunomodulators (steroids, tocilizumab), and supportive management (oxygen through a nasal cannula, face mask, non-rebreathing face mask; noninvasive or invasive mechanical ventilation; awake proning)) • Duration of follow-up: 28 days • Treatment cross-overs: none • Compliance with assigned treatment: 3 participants from the control group received CP; 2 participants in CP group did not receive CP, and 1 lost to follow-up
Outcomes	• Primary study outcome ○ Composite of progression to severe disease (PaO_2/ FiO_2 < 100 mm Hg) or all-cause mortality at 28 days post-enrolment • Primary review outcomes ○ All-cause mortality during hospital stay: yes ○ 28-day mortality: yes ○ 60-day mortality: NR ○ Mortality (time to event): NR

Agarwal 2020 *(Continued)*

- Clinical status
  - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
  - Improvement of clinical status: participants discharged from hospital: assessed, but NR
- QoL: NR
- Number of participants with adverse events (any grade, grades 1-2, grades 3-4): yes, transfusion-related AEs and grades 3 and 4 AEs provided by study authors
- Number of participants with SAEs: NR

- Secondary review outcomes
  - Improvement of clinical status
    - Weaning or liberation from IMV in surviving patients: NR
    - Ventilator-free days: NR
    - Liberation from supplemental oxygen in surviving patients: NR
  - Need for dialysis at up to 28 days: NR
  - Admission on the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance(RT-PCR) at baseline, up to 3, 7, and 15 days: day 3 and 7
- Additional study outcomes
  - Time to symptom resolution at 1, 3, 5, 7, and 14 days
    - Fever
    - Shortness of breath
    - Fatigue
  - Duration of respiratory support required
    - Duration of IMV
    - Duration of non-IMV
  - Change in oxygen requirement post-transfusion, at 0, 1, 3, 5, 7 and 14 days
  - Change in SOFA pre- and post-transfusion, at 0, 1, 3, 5, 7 and 14 days
  - Correlation between IgG antibody in donor plasma and recipient plasma after transfusion, at 0, 1, 3 and 7 days
  - Levels of biomarkers (CRP, IL6, ferritin) pre- and post-transfusion, at 0 and 3 days
  - Need of vasopressor use
  - Pre- and post-transfusion antibody titres (IgG) in recipient plasma, at 0, 3 and 7 days
  - Radiological improvement at 0, 3 and 7 days
  - Change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR transfusion, at 0, 3 and 7 days

Notes	• Preprint published on 10 September 2020 • Journal article accepted on 12 October 2020 • Sponsor/funding: this multicentric study was funded by ICMR, an autonomous government-funded medical research council • CoI: TB is a member of the National Task Force for covid-19, whichapproved the protocol. AM, AA, GK, AT, TB, VS, KK, RS, SD, GD, SS, RG, AS, DP, CP, SS, KJ, HK, PDY, GS, PA, MM, and RMY are employed by the Indian Council of Medical Research (ICMR), the funding source for the trial. PC was an employee of ICMR during the trial.

Alemany 2022

Study characteristics	
Methods	• Trial design: double-blind, placebo-controlled RCT • Type of publication: journal publication • Setting: outpatient

Alemany 2022 *(Continued)*

- Recruitment dates: 10 November 2020-28 July 2021
- Country: Spain
- Language: English
- Number of centres: 4
- Trial registration number: NCT04621123
- Date of trial registration: 9 November 2020

Participants	• Age (median, IQR; years)
	  ◦ CP + SC: 56 (IQR 52–62)
	  ◦ Placebo: 56 (IQR 53-63)
	• Sex (N, or %; female):
	  ◦ CP + SC: 44%
	  ◦ Placebo: 48%
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 909/376/ (CP 188, SC 188)/376
	• Severity of condition according to study definition: mild and moderate COVID-19, defined according to international guidelines
	• Severity of condition according to WHO score: WHO level 3 (ambulatory mild disease)
	• Comorbidities: obesity, cardiovascular disease, lung disease, diabetes, chronic renal failure, immune-compromised
	• Inclusion criteria
	  ◦ Participants admitted with positive PCR or validated antigen rapid test result confirmed COVID-19 illness
	  ◦ Age ≥ 50 years
	  ◦ Mild to moderate COVID-19 defined according to international guidelines:
	  ■ mild: patients with fever, cough, sore throat, malaise, headache, and muscle pain
	  ■ moderate: evidence of lower respiratory disease by clinical assessment or imaging and saturation of oxygen 94% or more on room air
	  ◦ Non-hospitalised
	• Exclusion criteria
	  ◦ Severe COVID-19
	  ◦ Required hospitalisation for any cause
	  ◦ A history of a previous SARS-CoV-2 infection
	  ◦ Received 1 or 2 doses of a COVID-19 vaccine
	  ◦ Contraindications to the investigational product
	  ◦ Increased thrombotic risk
	  ◦ History of clinically significantly abnormal liver function(e.g. Child-Pugh C), or chronic kidney disease ≥ stage 4
	  ◦ Pregnant, breastfeeding, or planning a pregnancy during the study period.
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
	• Donor eligibility criteria
	  ◦ Convalescent plasma units were sourced from the central blood bank located 12 km or less from the two large study sites, and 90 km or less from all study sites
	  ◦ High anti-SARS-CoV-2 IgG titres with ELISA (EUROIMMUN ratio ≥ 6)
	• Donor exclusion criteria: NR

Interventions	• Details of CP
	  ◦ Type of plasma: fresh frozen CP
	  ◦ Volume: 250–300 mL
	  ◦ Number of doses: 1 dose
	  ◦ Type of antibody test and antibody-titre: anti-SARS-CoV-2 IgG titres with ELISA (EUROIMMUN ratio ≥ 6)
	  ◦ Pathogen inactivated or not: yes, methylene blue treatment
	  ◦ ABO-compatible

Alemany 2022 *(Continued)*

- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative:
  - Severity of disease:
    - mild (fever and cough with no oxygen requirement):
    - moderate (fever and cough with oxygen requirement):
  - Timing from recovery from disease:
  - RT-PCR tested:
- Treatment details, including time of plasma therapy (e.g. early stage of disease):
- Comparator: saline placebo (0.9% saline solution)
- Concomitant therapy: NR
- Duration of follow-up: 60 days
- Treatment cross-overs: NR
- Compliance with assigned treatment: reported

Outcomes

- Primary study outcome
  - Incidence of hospitalisation within 28 days from baseline
  - Mean change in viral load (in log10 copies per mL) in nasopharyngeal swabs from baseline to day 7
- Primary review outcomes
  - 28-day mortality: yes (provided by study authors)
  - 60-day mortality: yes (provided by study authors)
  - Mortality (time to event): NR
  - Admission to hospital or death within 28 days: yes
  - Symptom resolution
    - All initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up: NR
    - Time to symptom resolution: yes
  - QoL: NR
  - Number of participants with adverse events (any grade, grades 1-2, grades 3-4): grades 3-4 AE
  - Number of participants with SAEs: yes (provided by study authors)
- Secondary review outcomes
  - Worsening of clinical status
    - Need for IMV or death: yes (provided by authors, day 28 and day 60
    - Need for hospitalisation with oxygen by mask or nasal prongs, or death: yes (provided by authors)
  - Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR, viral load at day 7 reported
- Additional study outcomes
  - Hospitalisations by day 28
  - Data or appendix provided including treatment- and COVID-related SAE, viral load at day 7 and 28, and WHO progression scale status per measured time point

Notes

- Journal article published on 9 February 2022
- Sponsor/funding:
  - Grifols, Crowdfunding campaign YoMeCorono
  - Fight AIDS and Infectious Diseases Foundation (Badalona, Spain) with funding from the pharmaceutical company, Grifols Worldwide Operations (Dublin, Ireland)
- CoI: "We declare no competing interests."

AlQahtani 2021

Study characteristics

Methods	• Trial design: RCT, open-label • Type of publication: preprint publication • Setting: inpatient • Recruitment dates: April 2020-June 2020 • Country: Bahrain • Language: English • Number of centres: 2 • Trial registration number: NCT04356534 • Date of trial registration: 22 April 2020

Participants	• Age (mean, SD; years):
	  ○ CP + SC: 52.6 (14.9)
	  ○ SC: 50.7 (12.5)
	• Sex (N, or %; female):
	  ○ CP + SC: 15%
	  ○ SC: 25%
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 40/40/40 (20 in CP arm and 20 in control arm)
	• Severity of condition according to study definition: severe (requiring oxygen therapy and radiological evidence of pneumonia)
	• Severity of condition according to WHO score: according to WHO 10-point scale: level 5 (90% of participants)
	• Comorbidities: diabetes, hypertension, cardiac disease, chronic kidney disease, chronic lung disease, chronic liver disease
	• Inclusion criteria
	  ○ Signed informed consent
	  ○ Aged at least 21 years
	  ○ COVID-19 diagnosis based on PCR testing
	  ○ Hypoxia (oxygen saturation of ≤ 92% on air, or PO_2 < 60 mmHg in arterial blood gas, or arterial partial pressure 90 of oxygen (PaO_2)FIO_2) of ≤ 300) and patient requiring oxygen therapy
	  ○ Pneumonia confirmed by chest imaging
	• Exclusion criteria
	  ○ Mild disease not requiring oxygen therapy
	  ○ Normal chest X-ray and CT scan
	  ○ Requiring ventilatory support (invasive or non-invasive)
	  ○ History of allergy to plasma, sodium citrate or methylene blue
	  ○ History of autoimmune disease or selective IGA deficiency
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
	• Donor eligibility criteria
	  ○ Ability to give informed consent
	  ○ Men or nulliparous women (all women had a pregnancy test except for postmenopausal women)
	  ○ PCR COVID-19-negative from respiratory tract and symptom-free
	  ○ Recovered from COVID-19 and discharged from hospital for > 2 weeks
	  ○ Patients > 21 years of age
	  ○ Bodyweight > 50 kg
	  ○ Met all donor selection criteria employed for routine plasma collection and plasmapheresis procedures at the collection centre
	• Donor exclusion criteria: NR

AlQahtani 2021 *(Continued)*

Interventions	• Details of CP
	  ○ Type of plasma: CP frozen within 24 h
	  ○ Volume: 400 mL
	  ○ Number of doses: 200 mL x 2 (2 consecutive days)
	  ○ Type of antibody test and antibody-titre: Lansionbio COVID-19 IgM/IgG Test kit
	  ○ Pathogen inactivated or not: NR
	• Details of donors
	  ○ Sex (N, or %; female): NR
	  ○ Age (median, IQR or mean, SD; years): NR
	  ○ HLA and HNA antibody-negative: NR
	  ○ Severity of disease: NR
	  ○ Timing from recovery from disease: recovered from COVID-19 and had been discharged from hospital for > 2 weeks
	  ○ RT-PCR tested: yes (negative)
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• Comparator (type): local SC, which included antivirals and supportive care
	• Concomitant therapy: SC included control of fever (paracetamol) and antiviral medications, tocilizumab, and antibacterial medication)
	• Duration of follow-up: 30 days
	• Treatment cross-overs: none
	• Compliance with assigned treatment: good compliance

Outcomes	• Primary study outcome
	  ○ Requirement for ventilation (invasive or noninvasive)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: yes
	  ○ 28-day mortality: yes
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: no
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with adverse events (any grade, grades 1-2, grades 3-4): grades 3 and 4 AEs provided by study authors
	  ○ Number of participants with SAEs: NR
	• Secondary review outcomes
	  ○ Improvement of clinical status
	  ■ Weaning or liberation from IMV in surviving patients: NR
	  ■ Ventilator-free days: NR
	  ■ Liberation from supplemental oxygen in surviving patients: NR
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission on the ICU on day 28: NR
	  ○ Duration of hospitalisation: yes
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional outcomes
	  ○ Reduction in white cell count, CRP, LDH, procalcitonin, D-Dimer, ferritin, troponin T, brain natriuretic peptide measurements (time frame: 10 days or until discharge)

AlQahtani 2021 *(Continued)*

Notes	• Preprint published: 4 November 2020 • Full text published: 11 May 2021 • Sponsor/funding: Royal College of Surgeons in Ireland, Medical University of Bahrain and Ministry of Health Bahrain • CoI: "The authors declare no competing interests."

Avendano-Sola 2021

Study characteristics

Methods	• Trial design: multicentre, open-label RCT • Type of publication: journal publication • Recruitment dates: 4 April 2020-5 February 2021 • Setting: hospital • Country: Spain • Language: English • Number of centres: 14 • Trial registration: NCT04345523 • Date of trial registration: 14 April 2020

Participants	• Age (median, IQR; years):
	  ○ CP + SC: 63 (50.0 to 75)
	  ○ SC: 61 (55.0 to 75.0)
	• Sex (N, % female):
	  ○ CP + SC: 61/179 (34.1%)
	  ○ SC: 60/171 (35.1%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 359/350/350
	• Severity of condition according to study definition: patients requiring hospitalisation for COVID-19 without mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices
	• Severity of condition according to WHO score: levels 4 and 5
	• Comorbidities: diabetes mellitus, hypertension, cardiac disorder, chronic lung disease, chronic kidney disease, immunodeficiency, obesity, cancer, chronic liver disease, neurological or neuro-muscular disorder
	• Inclusion criteria
	  ○ Written informed consent prior to performing study procedures. Witnessed oral consent will be accepted in order to avoid paper handling
	  ○ Not > 12 days between the onset of symptoms (fever or cough) and treatment administration day
	  ○ Participants requiring hospitalisation for COVID-19 without mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices and at least 1 of the following:
	  ■ radiographic evidence of pulmonary infiltrates by imaging (chest X-ray, CT scan, etc.), or
	  ■ clinical assessment (evidence of rales/crackles on exam) and $SpO_2 \leq 94\%$ on room air that requires supplemental oxygen
	  ○ Laboratory-confirmed SARS-CoV-2 infection as determined by PCR in naso/oropharyngeal swabs or any other relevant specimen
	• Exclusion criteria
	  ○ Requiring mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices
	  ○ > 12 days since symptoms (fever or cough)
	  ○ Participation in any other clinical trial of an experimental treatment for COVID-19
	  ○ In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 h, irrespective of the provision of treatments

Avendano-Sola 2021 *(Continued)*

- Any incompatibility or allergy to the administration of human plasma
- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated GFR < 30)

- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): SC treatments at baseline were glucocorticoid therapy, anticoagulants, remdesivir, azithromycin, tocilizumab
- Donor eligibility criteria
  - Willing and able to provide written informed consent
  - Fulfilling all the current requirements to be a plasma apheresis donor according to the regulations for donation of blood products (European Guidelines and RD 1088/2005 in Spain)
  - Absence of COVID-19 symptoms within the last 14 days
  - Anti-SARS-CoV-2 IgG antibodies detectable in peripheral blood
  - ≥ 18 years of age at time of donation
  - Weight > 50 kg and good vein access are standard criteria, for which exceptions could be considered according to the criteria of the blood bank and haematologists
- Donor exclusion criteria
  - Plasmapheresis in the previous 7 days
  - Whole blood donation in the previous 30 days
  - Donation of > 25 L of plasma in the previous 12 months

Interventions

- Details of CP
  - Type of plasma: CP
  - Volume: 250-300 mL
  - Number of doses: 1
  - Type of antibody test and antibody-titre:
    - measured by VITROS (Ortho-Clinical Diagnostics, Rochester, New York, USA)
    - anti–SARS-CoV-2 IgG (anti-S) titres median value of 8.2 (IQR 4.5–12.0) measured by VITROS (high titre defined as ≥ 9.5)
  - Pathogen inactivated or not: pathogen reduced
- Details of donors
  - Sex (N, or %; female): 3 (11.54%)
  - Age (mean, SD; years): 37.85 (±11.60)
  - HLA and HNA antibody-negative: yes (tested only in 2 cases with infusion-related AE and suspected TRALI)
  - Severity of disease: mild (but recovered from severe disease was not an exclusion criteria)
  - Timing from recovery from disease: absence of COVID-19 symptoms within the last 14 days
  - RT-PCR tested: not inclusion criterion, antibody testing
- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage within 12 days
- Comparator (type): SC including any drugs that are being used in clinical practice (e.g. lopinavir/ritonavir; darunavir/cobicistat; hydroxy/chloroquine, tocilizumab, etc.), other than those used as part of another clinical trial
- Concomitant therapy: SC as specified above
- Duration of follow-up: 29 days
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome
  - Proportion of participants in categories 5, 6 or 7 (7-category ordinal scale) at day 15 of the study
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60 day mortality: no
  - Mortality (time to event): yes (up to 29 days)
  - Clinical status

Avendano-Sola 2021 *(Continued)*

- Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
- Improvement of clinical status: participants discharged from hospital: NR

- Quality of life: NR
- Number of participants with adverse events (any grade, grades 1-2, grades 3-4), yes, infusion-related AE
- Number of participants with SAEs: only together with AE grades 3-4

- Secondary review outcomes
  - Improvement of clinical status
    - Weaning or liberation from IMV in surviving patients: NR
    - Ventilator-free days: assessed but NR
    - Liberation from supplemental oxygen in surviving patients: NR
  - Need for dialysis at up to 28 days: NR
  - Admission on the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Category changes in ordinal scale (time frame: 15 days)
    - Proportion of participants in categories 5, 6 or 7 of the 7-point ordinal scale at day 15 ordinal scale:
    - Not hospitalised, no limitations on activities
    - Not hospitalised, limitation on activities
    - Hospitalised, not requiring supplemental oxygen
    - Hospitalised, requiring supplemental oxygen
    - Hospitalised, on non-invasive ventilation or high-flow oxygen devices
    - Hospitalised, on IMV or ECMO
    - Death
  - Time to category 5, 6 or 7 of the ordinal scale (time frame: 29 days)
    - Time to change from baseline category to worsening into 5, 6 or 7 categories of the ordinal scale
  - Oxygenation-free days (time frame: 29 days)
  - Change in biological parameters (time frame: days 1, 3, 5, 8, 11 and 29) - serum levels of CRP, lymphocyte count, LDH, D Dimer, IL-6, coagulation tests at baseline and days 3, 5, 8, 11, 15 and 29
  - Viral load (time frame: days 1, 3, 5, 8, 11 and 29)

Notes

- Interim analysis after randomisation of 81 participants, study terminated afterwards due to fall in recruitment
- First published: 1 September 2020; latest version: 29 September 29
- Sponsor/funding: "This research is funded by the Government of Spain, Ministry of Science and Innovation, Instituto de Salud Carlos III, grant number COV20/00072 (Royal Decree-Law 8/2020, of 17 March, on urgent extraordinary measures to deal with the economic and social impact of COVID-19), co-financed by the European Regional Development Fund (FEDER) A way to make Europe."
- COIs: none

Bajpai 2020

Study characteristics

Methods

- Trial design: open-label RCT
- Type of publication: preprint publication
- Setting: inpatient
- Recruitment dates: 21 April 2020-30 May 2020

Bajpai 2020 *(Continued)*

- Country: India
- Language: English
- Number of centres: 1
- Trial registration number: NCT04346446
- Date of trial registration: 15 April 2020

Participants	• Age (mean, SD; years)
	  ○ CP + SC: 48.1 (9.1)
	  ○ SP + SC: 48.3 ± 10.8
	• Sex (N, %; female)
	  ○ CP + SC: 3/14 (21.4%)
	  ○ SP + SC: 4/15 (26.7%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 51/31/29
	• Severity of condition according to study definition: severe (respiratory rate ≥ 30/min, oxygen saturation level < 93% in resting state, PaO_2/FiO_2 ≤ 300 mmHg, lung infiltrates > 50% within 24-48 h)
	• Severity of condition according to WHO score: level 5-7
	• Comorbidities: BMI
	• Inclusion criteria
	  ○ Written informed consent
	  ○ SARS-CoV-2 infection (positive by RT-PCR assay)
	  ○ Severe COVID-19 (respiratory rate ≥ 30/min, oxygen saturation level < 93% in resting state, PaO_2/FiO_2 ≤ 300 mmHg, lung infiltrates > 50% within 24-48 h)
	• Exclusion criteria
	  ○ Failure to obtain informed consent
	  ○ Patients < 18 years or > 65 years of age
	  ○ Co-morbid conditions (cardiopulmonary disease-structural or valvular heart disease, coronary artery disease, COPD, chronic liver disease, chronic kidney disease)
	  ○ Multi-organ failure or on mechanical ventilation
	  ○ Pregnant females
	  ○ Individuals with HIV
	  ○ Viral hepatitis, cancer, morbid obesity with a BMI > 35 kg/m^2
	  ○ Extremely moribund patients with an expected life expectancy of < 24 h
	  ○ Haemodynamic instability requiring vasopressors
	  ○ Previously known history of allergy to plasma, or a PaO_2/FiO_2 ratio < 150
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
	• Donor eligibility criteria
	  ○ COVID-19-recovered patients after 14 days of complete resolution of symptoms
	  ○ 2 consecutive negative test results (RT-PCR) 24 h apart
	  ○ Due consent
	  ○ Medical history, physical examination, and laboratory tests
	• Donor exclusion criteria: NR

Interventions	• Details of CP
	  ○ Type of plasma: COPLA CP transfusion (ABO blood group compatible plasma)
	  ○ Volume: 500 mL
	  ○ Number of doses: 2 divided doses on consecutive days
	  ○ Type of antibody test and antibody titre:
	  ■ ELISA (SARS-CoV-2 Spike S1-RBD IgG Detection Kit, Genscript, USA) A S1 RBD IgG titre of 1:80 or above was preferred
	  ■ neutralizing Ab (SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) Kit (Genscript, USA))
	  ○ Pathogen inactivated or not: NR
	• Details of donors

Bajpai 2020 *(Continued)*

- Sex (N, or %; female): 0
- Age (median, IQR or mean, SD; years): NR
- HLA and HNA antibody-negative: NR
- Severity of disease: NR
- Timing from recovery from disease: 14 days of complete resolution of symptoms
- RT-PCR tested: yes

- Treatment details, including time of plasma therapy (e.g. early stage of disease): transfusion within 3 days of onset of symptoms of severe COVID-19
- Comparator (type): FFP
- Concomitant therapy: SC
  - All participants received supplemental oxygen and a course of hydroxychloroquine 400 mg (twice daily) on day 1, followed by 200 mg (twice daily) for 5 days along with oral azithromycin 500 mg (once daily) for 5 days. Standard medications for the control of diabetes and hypertension were given when required
- Duration of follow-up: 28 days
- Treatment cross-overs: no
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome
  - Proportion of participants remaining free of mechanical ventilation (day 7)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-mortality: NR
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with adverse events (any grade, grades 1-2, grades 3-4): only transfusion-related reactions
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status
    - Weaning or liberation from IMV in surviving participants: NR
    - Ventilator-free days: NR
    - Liberation from supplemental oxygen in surviving patients: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional review outcomes
  - Improvement in Pa02/Fi02 ratio (day 2, day 7)
  - SOFA scores reduction (day 2, day 7)
  - Requirements of Vasopressor (day 28)
  - Days free of dialysis (day 28)
  - Clinical assessment of patients was done by assessing reduction in respiratory rate, and improvement in oxygen saturation (day 2 and day 7)
  - Laboratory effects of plasma therapy by improvement in lymphocyte count Ct value (day 7)
  - Any adverse transfusion events with plasma transfusion

Notes

- Preprint published: 27 October 2020
- Journal article accepted: not yet

Bajpai 2020 *(Continued)*

- Sponsor/funding: Institute of Liver and Biliary Sciences, India
- CoI: no conflict of interest declared

Baldeon 2022

Study characteristics

Methods	• Trial design: double-blind RCT • Type of publication: journal publication • Setting: inpatients • Recruitment dates: May 2020-January 2021 • Country: Ecuador • Language: English • Number of centres: 3 • Trial registration: ISRCTN85216856 • Date of registration: 6 May 2020

Participants	• Age (mean, SD; years):
	  ○ CP + SC: 56.3 (12.7)
	  ○ SP + SC: 55.0 (13.3)
	• Sex (N, or %; female):
	  ○ CP + SC: 21/63 (33.3%)
	  ○ SP + SC: 30/95 (31.6%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 190/158/158
	• Severity of condition according to study definition: patients with impairment of previously normal lung function defined with a SaO_2 < 90% at 0.5FiO_2 and/or with an increased O_2 need in the previous 24 h upon admission
	• Severity of condition according to WHO score: moderate
	• Comorbidities: hypertension, diabetes, overweight, obesity
	• Inclusion criteria
	  ○ Aged ≥ 18 years
	  ○ Clinical, molecular (using IgM/IgG or RT-PCR), or lung imaging diagnosis of COVID-19
	  ○ Deterioration of previously normal lung function defined as SaO_2 of < 90% in 0.5 FiO_2, and/or a higher requirement of O_2 than in the previous 24 h
	  ○ A score of 5-7 on the early warning scale for COVID-19 patients or a SOFA score between 2 and 10
	  ○ Informed consent provided by participants or their representatives
	• Exclusion criteria
	  ○ Diagnosis and/or treatment for cancer
	  ○ HIV infection
	  ○ Currently receiving immunosuppressants for a condition other than SARS-CoV-2 infection
	  ○ Superimposed systemic infections
	  ○ Liver or kidney failure
	  ○ COPD, previous pulmonary fibrosis, and/or restrictive lung disease
	  ○ Have received previous transfusions
	  ○ Pregnant or lactating
	  ○ Participating in another trial
	  ○ History of previous blood/derivate transfusion
	• Donor eligibility criteria
	  ○ According to country regulation for blood banks
	  ○ Male

Baldeon 2022 *(Continued)*

- Age 18-65 years
- No history of transfusions
- Fully recovered from SARS-CoV-2 infection
- Negative for SARS-CoV-2 infection by RT-PCR or have passed at least 20 days from diagnosis

- Donor exclusion criteria: NR

Interventions	• Details of CP
	  ◦ Type of plasma
	  ■ Volume: 5 mL of plasma/kg of body weight IV
	  ■ Number of doses: 1
	  ◦ Type of antibody test and antibody-titre
	  ■ Roche's Elecsys SARS-CoV-2 (qualitative assay)
	  ■ Pathogen inactivated or not: NR
	  ■ AB0-matched
	• Details of donors
	  ◦ Sex (N, or %; female): male only
	  ◦ Age (median, IQR or mean, SD; years): NR
	  ◦ HLA and HNA antibody: NA, male donors only
	  ◦ Severity of disease: NR
	  ◦ Timing from recovery from disease: at least 20 days after diagnosis
	  ◦ RT-PCR tested: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
	• Comparator (type): SP (collected in 2018)
	• Concomitant therapy: SC (supportive common treatments included oxygen administration, antibacterial medication, steroids, other anti-inflammatory drugs, and anti-coagulants)
	• Duration of follow-up: 21 days
	• Treatment cross-overs: none
	• Compliance: 100%

Outcomes	• Primary study outcome
	  ◦ Case fatality rate assessed through data collected from the follow-up instrument and medical records at 21 and 28 days
	• Primary review outcomes
	  ◦ All-cause mortality during hospital stay: NR
	  ◦ 28-day mortality: yes
	  ◦ 60-day mortality: NR
	  ◦ Mortality (time to event): yes
	  ◦ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
	  ■ Improvement of clinical status: participants discharged: NR
	  ◦ QoL: NR
	  ◦ Number of participants adverse events (any grade, grades 1-2, grades 3-4): NR
	  ◦ Number of participants with SAEs: NR
	• Secondary review outcomes
	  ◦ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: NR
	  ◦ Need for dialysis at up to 28 days: NR
	  ◦ Admission to the ICU on day 28: NR
	  ◦ Duration of hospitalisation: NR
	  ◦ Viral clearance (RT-PCR): NR

Baldeon 2022 *(Continued)*

	• Additional outcomes
	  ○ SOFA, thoracic X-ray and/or tomography documented at discharge
	  ○ Demographic information, including age and sex collected using the specific instrument created to screen potential patients at baseline
	  ○ Time of initiation of treatment in relation to the evolution of the disease assessed using the follow-up instrument, completed daily from baseline to 21 days)
	  ○ Sequelae at discharge (liver, kidney functions, pulmonary, cardiac and neurological) assessed by the follow-up instrument at discharge

Notes	• Journal article accepted on 9 January 2022 • Sponsor/funding: SalvarVidasEC (Ecuador) • CoI: "The authors declare no conflict of interest."

Bar 2021

Study characteristics	
Methods	• Trial design: open-label RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 18 May 2020-8 January 2021 • Country: USA • Language: English • Number of centres: 2 • Trial registration number: NCT04397757 • Date of registration: 13 May 2020

Participants	• Age (median, IQR; years)
	  ○ CP + SC and SC arm together: 63 (52 - 74)
	• Sex (N, %: female)
	  ○ CP + SC: 24/39 (61.5%)
	  ○ SC: 19/40 (47.5%)
	• Ethnicity:
	  ○ African American: 53%
	  ○ Asian: 5%
	  ○ White: 38%
	  ○ Hispanic: 4%
	• Number of participants (recruited/allocated/evaluated): 930/80/79
	• Severity of condition according to study definition: maximum WHO score 5 on 8-point scale: hospitalised, requiring supplemental oxygen
	• Severity of condition according to WHO score:
	  ○ WHO 5, 6
	• Comorbidities: diabetes, obesity, hypertension, coronary artery disease, congestive heart failure, pulmonary disease, chronic kidney disease, cancer, immune deficiency
	• Inclusion criteria
	  ○ Adult ≥ 18 years of age
	  ○ Laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other authorised or approved assay in any specimen collected within 72 h prior to enrolment
	  ○ Hospitalised in participating facility
	  ○ Documentation of pneumonia with radiographic evidence of infiltrates by imaging (e.g., chest X-ray or CT scan).

Bar 2021 *(Continued)*

- Abnormal respiratory status that is judged worse than baseline by the investigator and as documented at any point within 24 h prior to randomisation, consistent with ordinal scale levels 5, 6 or 7, specifically defined as:
  - room air saturation of oxygen (SaO2) < 93%, or
  - requiring supplemental oxygen, or
  - tachypnoea with respiratory rate ≥ 30
- Patient or proxy is willing and able to provide written informed consent and comply with all protocol requirements

- Exclusion criteria
  - Contraindication to transfusion (e.g. severe volume overload, history of severe allergic reaction to blood products), as judged by the investigator
  - Clinical suspicion that the aetiology of acute illness (acute decompensation) is primarily due to a condition other than COVID-19
  - Receipt of other investigational therapy as a part of another clinical trial
- Previous treatments: remdesivir, steroids hydroxychloroquine
- Donor eligibility criteria:
  - individuals who would otherwise qualify as blood donors
  - diagnosed with SARS-CoV-2 by RT-PCR testing during acute COVID-19 infection
  - at least 28 days from symptoms
- Donor exclusion criteria
  - NR

Interventions

- Details of CP
  - Type of plasma: CP
  - Volume: 2 units
  - Number of doses: probably as 1 dose, 2 units both on day 1
  - Type of antibody test and antibody-titre: SARS-CoV-2 IgG by ELISA, all plasma had IgG > 0.48 au/mL, median 3.69 (IQR 1.61–8.56); combined titre (total over both units): 8.180 au/mL (IQR 4.195–20.980)
  - Pathogen inactivated or not: NR
- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: yes
  - Severity of disease: NR
  - Timing from recovery from disease: at least 28 days
  - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): early in their disease course, at a median of 6 days (IQR 4–9) from COVID-19 symptom onset and 1 day (IQR 1–2) from hospital admission
- Comparator (type): SC
- Concomitant therapy: SC
- Duration of follow-up: 28 days
- Treatment cross-overs: 2 participants in CP group did not receive CP (declined)
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome
  - Participants with serious events
  - Comparison of clinical severity score between participants on the experimental vs control arm
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): yes

Bar 2021 *(Continued)*

- Clinical status
  - Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: NR
  - Improvement of clinical status: participants discharged from hospital: as Kaplan Meier curve only
- QoL: NR
- Number of participants with adverse events (any grade, grades 1-2, grades 3-4): reported as median AE per person and number of AEs
- Number of participants with SAEs: yes

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving patients: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission on the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - 14- and 28-day WHO 8 score
  - Duration of supplemental oxygenation
  - Use and duration of mechanical ventilation
  - Presence and quantity of SARS-CoV-2 RNA in respiratory samples
  - Anti–SARS-CoV-2 antibody levels

Notes	• Journal article published on 15 December 2021 • Sponsor funding: University of Pennsylvania and approved by its institutional review board, located in Philadelphia, Pennsylvania, USA • CoI: JLP reports consultancy fees from Pfizer; WRS reports consultancy fees from Viiv, Gilead, and Janssen; IF reports consultancy fees from Gilead and Merck; SEH reports consultancy fees from Sanofi Pasteur, Lumen, Novavax, and Merck; PT reports consultancy fees from Merck, Gilead, Janssen, and Viiv.

Begin 2021

Study characteristics

Methods	• Trial design: open-label RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 14 May 2020-29 January 2021 • Country: Brazil, Canada, USA • Language: English • Number of centres: 27 • Trial registration number: NCT04348656 • Date of trial registration: 16 April 2020

Participants	• Age (median, IQR; years)
	  ◦ CP + SC: 69 (58 - 80)
	  ◦ SC: 68 (58 - 78)
	• Sex (N, %; female)
	  ◦ CP + SC: 256/625 (41.0%)

Begin 2021 *(Continued)*

- SC: 128/313 (40.9%)
- Ethnicity:
  - White 458/938 (48.8%)
  - Asian 150 (16.0 %)
  - Hispanic or Latino 43/938 (4.6 %)
  - Black 36/938 (3.8 %)
  - other 66 (7.0 %)
  - unknown 185 (19.7 %)
- Number of participants (recruited/allocated/evaluated): NR/940/921 (614 plasma and 307 control)
- Severity of condition: moderate and severe, 505 (80.8%) participants on ward, 120 (19.2%) participants in ICU
- Severity of condition according to WHO score: WHO levels 5-7
- Comorbidities:
  - diabetes: 220/938 (35.2 %)
  - cardiac disease: 385/938 (61.6 %)
  - baseline respiratory diseases: 147/938 (23.5%)
- Inclusion criteria
  - ≥ 16 years old in Canada or ≥ 18 in the USA and Brazil
  - Admitted to hospital with confirmed COVID-19 respiratory illness
  - Receiving supplemental oxygen
  - 500 mL of ABO-compatible CP is available
- Exclusion criteria
  - Onset of symptoms > 12 days prior to randomisation
  - Intubated or plan in place for intubation
  - Plasma is contraindicated (e.g. history of anaphylaxis from transfusion)
  - Decision in place for no active treatment
- Donor inclusion criteria:
  - Prior diagnosis of COVID-19 documented by a PCR test at time of infection or by positive anti-SARS-CoV-2 serology following infection
  - Male donors, or female donors with no pregnancy history or with negative anti-HLA antibodies
  - At least 6 days since last plasma donation
  - Provided informed consent
  - A complete resolution of symptoms at least 14 days prior to first donation.
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: CP
  - Volume: 500 mL of CP (from 1 single-donor unit of 500 mL or 2 units of 250 mL from 1-2 donations) collected by aphaeresis from donors who have recovered from COVID-19 and frozen (1 year expiration date from date of collection)
  - Number of doses: when administering 2 units of 250 mL, the 2nd unit will be administered after the first, and no longer than 12 h later
  - Type of antibody test and antibody-titre: NR
  - Pathogen inactivated or not: NR
- Details of donors: NR
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: NR
  - Severity of disease: NR
  - Timing from recovery from disease: NR
  - RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

Begin 2021 *(Continued)*

	• Comparator (type): SC • Concomitant therapy: NR • Duration of follow-up: 30 days • Treatment cross-overs: yes, in the CP group: 7 participants refused to receive CP and switched to the control group • Compliance with assigned treatment: yes

Outcomes	• Primary study outcome
	  ○ Need for intubation or participant death by day 30 in hospital
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: yes
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): yes
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: yes
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with adverse events (any grade, grades 1-2, grades 3-4): yes, transfusion-related adverse events and grades 3-4 adverse events
	  ○ Number of participants with SAEs: yes
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: yes
	  ■ liberation from supplemental oxygen in surviving participants: NR
	  ○ Need for dialysis at up to 28 days: yes
	  ○ Admission on the ICU on day 28: NR
	  ○ Duration of hospitalisation: NR
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 day: NR
	• Additional outcomes
	  ○ Need for renal replacement therapy (time frame: day 30)
	  ○ Development of myocarditis (time frame: day 30)

Notes	• Preprint: published 3 July 2021 • Full text published November 2021 • Sponsor/funding: Hamilton Health Sciences Corporation, Canada • Grant support: Canadian Institutes of Health Research – COVID-19 May 2020 Rapid Research Funding Opportunity – Operating Grant; Ontario COVID-19 Rapid Research Fund; Toronto COVID-19 Action Initiative 2020 (University of Toronto); University Health Network Emergent Access Innovation Fund; University Health Academic Health Science Centre Alternative Funding Plan (Sunnybrook Health Sciences Centre); Ministère de l'Économie et de l'Innovation (Québec); Fond de Recherche du Québec en Santé; Saskatchewan Ministry of Health; University of Alberta Hospital Foundation; Alberta Health Services COVID-19 Foundation Competition; Sunnybrook Health Sciences Centre Foundation; Fondations CHU Ste-Justine; The Ottawa Hospital Academic Medical Organization; The Ottawa Hospital Foundation COVID-19 Research Fund; Fondation du CHUM; Sinai Health System Foundation and McMaster University

Beltran Gonzalez 2021

Study characteristics

Beltran Gonzalez 2021 *(Continued)*

Methods	• Trial design: RCT • Type of publication: preprint publication • Setting: inpatient • Recruitment dates: 5 May-17 October 2020 • Country: Mexico • Language English • Number of centres: 1 • Trial registration number: NCT04381858 • Date of trial registration: 11 May 2020

Participants	• Age (median, IQR; years):
	  ○ CP + SC: 60 (48 - 74)
	  ○ IVIg + SC: 55 (46.5 - 67)
	• Sex (N, %; female):
	  ○ CP + SC: 50/130 (38.5%)
	  ○ IVIg + SC: 21/60 (35%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 193/190/165
	• Severity of condition according to study definition: severe (IMV: 85.2 %; remaining participants managed with high-oxygen flow devices)
	• Severity of condition according to WHO score: level > 6
	• Comorbidities: obesity, systemic arterial hypertension, diabetes, stroke, smoker, alcohol, drugs, heart disease, pulmonary disease, chronic kidney disease, hypothyroidism, HIV, cancer, transplant, autoimmunity
	• Inclusion criteria
	  ○ Fulfilled the operational definition of a suspected or confirmed case of COVID-19, and presented with criteria of severe pneumonia according to the ATS/IDSA guidelines
	  ○ Positive nasopharyngeal and oropharyngeal swab RT-PCR for SARS-CoV-2
	  ○ Pneumonia diagnosed by high-resolution CT scan of the chest, and a pattern suggesting coronavirus infection
	  ○ Recently developed hypoxaemic respiratory failure or acute clinical exacerbation of pre-existing pulmonary or heart disease
	  ○ Requirement of respiratory support with a high-flow nasal cannula, defined as 60 L with a 90% inspired oxygen fraction or IMV with an orotracheal tube
	  ○ The availability of ABO-compatible convalescent plasma from donors who had recovered from COVID-19 infection was an eligibility requirement
	• Exclusion criteria
	  ○ Viral infection other than COVID-19
	• Previous treatments: antibiotics, carbapenem drugs, dexamethasone, ivermectin
	• Donor inclusion criteria
	  ○ Reactive SARS-CoV-2 nasopharyngeal swab and 2nd negative swab, and asymptomatic in previous 14 days or initially positive test, minimum disease course 28 days, and remained asymptomatic 14 days prior to donation
	  ○ Mexican official norms for plasma donation
	• Donor exclusion criteria: NR

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 400 mL
	  ○ Number of doses: 2
	  ○ Antibody-titre: when assay available > 1:640 by immunochemiluminescence (ARCHITECT ABBOTT) (after plasma administration)
	  ○ Pathogen inactivated: NR
	• Donor details

Beltran Gonzalez 2021 *(Continued)*

- Sex (N, or %; female): NR
- Age (median, IQR or mean, SD; years): NR
- HLA and HNA antibody-negative: NR
- Severity of disease: NR
- Timing from recovery from disease: asymptomatic during the 14 days prior to donation
- RT-PCR tested: yes

- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: human immunoglobulin 0.3 g/kg/day for 5 days
- Concomitant therapy: NR
- Duration of follow up: 14 days
- Treatment cross-overs: NR
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome: mean hospitalisation time
- Primary review outcomes reported
  - All-cause mortality during hospital stay: yes
  - 28 day mortality: yes
  - 60 day mortality: NR
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with adverse events (any grade, grades 1-2, grades 3-4): transfusion related AEs
  - Number of participants with SAEs: NR
- Secondary review outcomes reported
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
- Need for dialysis at up to 28 days: NR
- Admission to the ICU on day 28: NR
- Duration of hospitalisation: only reported as median
- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional outcomes
  - Time to viral PCR negativisation

Notes

- Full-text article published on 31 March 2021
- Sponsor/funding: Centenario Hospital Miguel Hidalgo
- CoI: not reported

Bennett-Guerrero 2021

Study characteristics

Methods

- Trial design: double-blind RCT
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates: 8 April 2020-24 August 2020
- Country: USA

Bennett-Guerrero 2021 *(Continued)*

- Language: English
- Number of centres: 1
- Trial registration number: NCT04344535
- Date of trial registration: 14 April 2020

Participants	• Age (mean, SD; years)
	  ○ CP + SC: 67 (15.8)
	  ○ SP + SC: 64 (SD 17.4)
	• Sex (N, %; female)
	  ○ CP + SC: 23/59 (39.0%)
	  ○ SP + SC: 7/15 (46.7%)
	• Ethnicity
	  ○ White: CP 42/59 (71.2%), SP 8/15 (53.3%)
	• Number of participants (recruited/allocated/evaluated): 82/74/ (59 CP, 15 SP)
	• Severity of condition according to study definition
	  ○ Nasal cannula or mask: intervention group 50.8% and control group 26.7%
	  ○ Intubated: intervention group 18.6% and control group 20.0%
	• Severity of condition according to WHO score: levels 4, 5 and 6
	• Comorbidities: diabetes, hypertension, COPD, chronic heart failure, chronic renal insufficiency, coronary artery disease, coronary artery bypass graft surgery, percutaneous coronary intervention, myocardial infarction, cerebrovascular disease, immunosuppressant medication
	• Inclusion criteria
	  ○ Adults ≥ 18 years
	  ○ Hospitalised with PCR-positive COVID-19 infection
	  ○ If female, not pregnant or breastfeeding
	• Exclusion criteria
	  ○ Contraindication to transfusion or history of prior reactions to transfusion blood products
	  ○ Receipt of pooled (polyclonal) immunoglobulin or any polyclonal IVIG in past 30 days
	  ○ Women with a positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period
	  ○ In the treating physician's opinion, unable to tolerate a 450-550 mL infusion of plasma over up to 8 h (4 h max per unit)
	  ○ Unable to be randomised within 14 days of admission to Stony Brook Hospital (or any other hospital if a transfer)
	• Previous treatments: NR
	• Donor inclusion criteria
	  ○ Previous SARS-CoV-2 PCR-positive COVID-19 infection
	  ○ Robust antibody response by an immunochromatographic test (at least 145 reflectance light units for IgG)
	• Donor exclusion criteria: NR

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 450-550 mL
	  ○ Number of doses: 1
	  ○ Antibody-titre: ideally > 1:320, but meeting minimum titre per FDA Guidelines for CP
	  ○ Pathogen inactivated or not: NR
	• Donor details
	  ○ Sex (N, or %; female): NR
	  ○ Age (median, IQR or mean, SD; years): NR
	  ○ HLA and HNA antibody-negative: NR
	  ○ Severity of disease: NR
	  ○ Timing from recovery from disease: NR
	  ○ RT-PCR tested: NR

Bennett-Guerrero 2021 *(Continued)*

	• Treatment details, including time of plasma therapy (e.g. early stage of disease): within 14 days of hospitalisation • Comparator (type): 450-550 mL of plasma collected before January 2020 (SP) • Concomitant therapy: glucocorticoids, remdesivir, hydroxychlorocine, tocilizumab, sarilumab • Duration of follow-up: 90 days • Treatment cross-overs: none • Compliance with assigned treatment: 2 participants (1 per arm) did not receive plasma

Outcomes	• Primary study outcome: number of days participant remained ventilator-free (up to 28 days)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28 day mortality: yes
	  ○ 60 day mortality: NR
	  ○ Mortality (time to event): yes (90-day follow up)
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: NR
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants adverse events (any grade, grade 1-2, grade 3-4): NR
	  ○ Number of participants with SAEs: yes
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ Ventilator-free days: reported as median only (28 day FU)
	  ■ Liberation from supplemental oxygen in surviving patients: NR
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission to the ICU on day 28: NR
	  ○ Duration of hospitalisation: NR
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional outcomes:
	  ○ number of days participant remains ventilator-free (up to 28 days)

Notes	• Full text published on 16 April 2021 • Sponsor/funding: Stony Brook University • CoI: Dr. Fries: National Institutes of Health. "The remaining authors have disclosed that they do not have any potential conflicts of interest."

CoV-Early

Study characteristics	
Methods	• Trial design: multi-centre, double-blind, RCT • Type of publication: no publication yet, but results made available by study authors • Setting: outpatient • Recruitment dates: NR • Country: the Netherlands • Language: English • Number of centres: 11 • Trial registration number: NCT04589949 • Date of trial registration: 1 April 2022

CoV-Early *(Continued)*

Participants	• Age (mean, SD; years):
	  ○ CP + SC: 60.57 (SD 7.73)
	  ○ FFP: 63.76 (SD 44.76)
	• Sex (N, or %; female):
	  ○ CP + SC: 43/210 (20.5%)
	  ○ FFP: 52/211 (24.6%)
	• Ethnicity: NR
	• Number of participants (NR/NR/421)
	• Severity of condition according to study definition: NR
	• Severity of condition according to WHO score: NR
	• Comorbidities: cardiac or pulmonary disease, neurological disease, diabetes mellitus, chronic kidney disease, rheumatic disease, immunodeficiency, cancer, untreated HIV, chronic liver disease, obesity
	• Inclusion criteria
	  ○ RT-PCR-confirmed COVID-19
	  ○ Symptomatic (e.g but not limited to fatigue, fever, cough, dyspnoea, loss of taste or smell, diarrhoea, falls or confusion)
	  ○ ≥ 70 years or 50-69 years and ≥ 1 of the risk factors described in the protocol
	• Exclusion criteria
	  ○ Life expectancy < 28 days in the opinion of the treating physician
	  ○ Patient or legal representative is unable to provide written informed consent
	  ○ Symptomatic for ≥ 8 days
	  ○ Being admitted to the hospital with the informed consent procedure
	  ○ Known previous history of TRALI
	  ○ Known IgA deficiency
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
	• Donor eligibility criteria: NR
	• Donor exclusion criteria: NR

Interventions	• Details of CP:
	  ○ Type of plasma: CP
	  ○ Volume: 300 mL
	  ○ Number of doses: 1 dose
	  ○ Type of antibody test and antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Details of donors
	  ○ Sex (N, or %; female): NR
	  ○ Age (median, IQR or mean, SD; years): NR
	  ○ HLA and HNA antibody-negative: NR
	  ○ Severity of disease: NR
	  ○ Timing from recovery from disease: NR
	  ○ RT-PCR tested: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage (see inclusion criteria)
	• Comparator (type): 300 mL FFP
	• Concomitant therapy: NR
	• Duration of follow-up: NR
	• Treatment cross-overs: NR
	• Compliance with assigned treatment: NR

Outcomes	• Primary study outcome ○ Highest disease status on the 5-point ordinal disease severity scale (up to 28 days) • Primary review outcomes

CoV-Early *(Continued)*

- 28-day mortality: yes (provided by study authors)
- 60-day mortality: NR
- Mortality (time to event): NR
- Admission to hospital or death within 28 days: yes (provided by study authors)
- Symptom resolution
  - All initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up: NR
  - Time to symptom resolution: NR
- QoL: NR
- Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
- Number of participants with SAEs: NR

- Secondary review outcomes
  - Worsening of clinical status:
    - need for IMV or death: yes (provided by study authors, day 28 and day 60)
    - need for hospitalisation with for oxygen by mask or nasal prongs, or death: NR
  - Viral clearance (RT-PCR) up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Disease duration in days of symptoms (28 days)
  - Age and clinical frailty score (28 days)

Notes

- Preprint published: not published yet
- Sponsors/funding: Erasmus Medical Center, Sanquin Plasma Products BV, ZonMw: The Netherlands Organisation for Health Research and Development, Leiden University Medical Center
- CoI: NR

De Santis 2022

Study characteristics

Methods

- Trial design: open-label RCT
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates: April-November 2020
- Country: Brazil
- Language: English
- Number of centres: 5
- Trial registration: RBR-7f4mt9f
- Date of registration: NR

Participants

- Age (mean, SD; years)
  - CP + SC: 56.1 (15.2)
  - SC: 59.3 (12.4)
- Sex (N, %; female)
  - CP + SC: 13/36 (36.1%)
  - SC: 27/71 (35.2%)
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 110/110/107
- Severity of condition according to study definition: all participants had severe COVID-19 (> 6 points according to the WHO severity ordinal scale)
- Severity of condition according to WHO score: WHO level > 6
- Comorbidities: hypertension, diabetes mellitus, renal replacement therapy
- Inclusion criteria

De Santis 2022 *(Continued)*

- Diagnosis of COVID-19 based on RT-PCR results
- Respiratory distress (oxygen saturation at room air < 93%, or PaO_2/FiO_2 < 300, or requiring mechanical ventilation) resulting from pneumonia
- Within 10 days of initial symptoms
- Age 18–80 years
- Signed written informed consent by the patient or legal representative

- Exclusion criteria
  - History of previous severe allergy to plasma transfusion
  - Severe congestive heart failure
  - Terminal renal failure
  - Hepatic cirrhosis
  - Any severe illness expected to confer a short life expectancy
  - Participation in any other clinical trial with therapeutic intervention
  - Immunosuppression
- Previous treatments: NR
- Donor eligibility criteria
  - Adult
  - Men or nulliparous women
  - At least 15 days since symptom resolution
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: CP
  - Volume: 600 mL/day
  - Number of doses: 3 doses on 3 consecutive days
  - Antibody test and antibody-titre: median neutralising antibody titre against SARS-CoV-2: 128
  - Pathogen inactivation: no
- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody: NA
  - Severity of disease: NR
  - Timing from recovery from disease: at least 15 days
  - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): patients in ICU
- Comparator (type): SC
- Concomitant therapy: NR
- Duration of follow-up: 60 days
- Treatment cross-overs: 1 participant in CP group did not receive CP
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome
  - Death rate at days 30 and 60 from the day of randomisation
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes (30-day mortality)
  - 60-day mortality: yes
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: NR
    - Improvement of clinical status - participants discharged from hospital: NR
  - QoL: NR

De Santis 2022 *(Continued)*

- Number of participants with AEs (grades 1-2, grades 3-4, any): NR (only AEs to CP reported)
- Number of participants with SAEs: NR

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: only median reported
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional outcomes
  - Inflammatory biomarkers (CRP concentration, IL-6)

Notes	• Full-text published in March 2022 • Sponsor/funding: Fundação de Amparo à Pesquisa do Estado de São Paulo • CoI: NR

Devos 2021

Study characteristics	
Methods	• Trial design: RCT, prospective, randomised, open-label, multicentre clinical trial • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 2 May 2020-26 January 2021 • Country: Belgium • Language: English • Number of centres: 22 • Trial registration number: NCT04429854 • Date of trial registration: 12 June 2020

Participants	• Age (mean, SD; years):
	  ○ CP + SC: 62 (SD 14)
	  ○ SC: 62 (SD 14)
	• Sex (N, %; male):
	  ○ CP + SC: 219/320 (68.4%)
	  ○ SC: 113/163 (69.3%)
	• Ethnicity:
	  ○ White CP 247/320 (77.2%); SC 135/163 (82.8%)
	  ○ North African CP 39/320 (12.2%); SC 20/163 (12.3%)
	  ○ Middle Eastern CP 16/320 (5.0%); SC 2/163 (1.2%)
	  ○ Black or sub-Saharan (Africa) CP 10/320 (3.1%); SC 2/163 (1.2%)
	  ○ Asian CP 5/320 (1.6%); SC 2/163 (1.2%)
	  ○ Latino or Hispanic CP 3/320 (0.9%); SC 2/163 (1.2%)
	• Number of participants (recruited/allocated/evaluated): (499/489/483)
	• Severity of condition according to study definition: moderate and severe with 397/481 participants on ward (82.5%) and 71/481 participants in ICU (14.8%, ER: 13/418 (2.7%)
	• Severity of condition according to WHO score: WHO level > 4 (including level 4)
	• Comorbidities: diabetes, COPD, asthma, heart failure, ischaemic heart disease, kidney disease, cancer, HIV
	• Inclusion criteria

Devos 2021 *(Continued)*

	○ Adults (≥ 18 years) hospitalised patients with laboratory or radiologically confirmed COVID-19 • Exclusion criteria ○ Pregnancy, lactation ○ Previous grade 3 allergic reaction to plasma transfusions ○ Treatment with rituximab or another anti-CD20 monoclonal antibody during the past year • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR • Donor eligibility criteria ○ Patients that were infected with COVID-19 and recovered ○ At least 28 days should have passed since full recovery and disappearance of the symptoms ○ Potential donors must at least fulfil national legal requirements for eligibility of donors to donate blood or plasma ○ The Blood Establishment qualifies donations from donors with neutralising antibody titres ≥ 1/320 as appropriate for this study. • Donor exclusion criteria: NR
Interventions	• Details of CP: ○ Type of plasma: CP with neutralising antibody-titres ≥ 1/320 (NT50) ○ Volume: 200-250 mL within 12 h after randomisation, with a second administration of 2 units 24-36 h after the first administration ○ Number of doses: 2 units ○ Type of antibody test and antibody-titre: anti-SARS-CoV-2 virus neutralisation titres were determined by neutralisation assays, performed in BSL3 laboratories in a 96-well plate format, using heat-inactivated plasma or serum samples (30-60 min at 56 °C) ○ Pathogen inactivated or not: yes • Details of donors: ○ Sex (N, or %; female): NR ○ Age (median, IQR or mean, SD; years): NR ○ HLA and HNA antibody-negative: NR ○ Severity of disease: NR ○ Timing from recovery from disease: NR ○ RT-PCR tested: yes • Treatment details, including time of plasma therapy: median time from randomisation to the first plasma transfusion was 5 h • Comparator: SC • Concomitant therapy: specific treatment for COVID-19 used (chloroquine, hydroxychloroquine, favipiravir, remdesivir, tocilizumab, lopinavir/ritonavir, other), other antiviral drugs, antibiotics, antifungal treatment, systemic corticosteroids (hydrocortisone, methylprednisolone, prednisolone, dexamethasone, other), anticoagulation • Duration of follow up: NR • Treatment cross-over: NR • Compliance with assigned treatment: NR
Outcomes	• Primary study outcome ○ Number and proportion of participants alive without mechanical ventilation at day 15 • Primary review outcomes: ○ All-cause mortality during hospital stay: NR ○ 28-day mortality: yes ○ 60-day mortality: NR ○ Mortality (time to event): yes ○ Clinical status ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR ■ Improvement of clinical status: participants discharged from hospital: yes ○ QoL: yes, at baseline and at 30 days

Devos 2021 *(Continued)*

- Number of participants with AEs (any grade, grades 1-2, grades 3-4): only transfusion related AEs
- Number of participants with SAEs: yes

- Secondary review outcomes:
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: yes
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: yes
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Correlation between the number of transfused CP units from donors with neutralising antibody titres ≥ 1/320 (NT50) and the primary endpoint was analysed

Notes	• Published online 26 August 2021 • Sponsor/funding: Belgian Health Care Knowledge Centre (KCE) • COI: "All authors report support for the present manuscript from the Belgian Healthcare Knowledge Center (KCE). Q. Van Thillo reports grants from Fonds Wetenschappelijk Onderzoek (FWO)–Vlaanderen Basic Research 2019–2021 outside the submitted work. G. Meyfroidt reports a FWO–Vlaanderen Senior Clinical Researcher Grant outside the submitted work."

Estcourt 2021

Study characteristics

Methods	• Trial design: randomised multifactorial adaptive platform (REMAP) • Type of publication: journal article • Recruitment dates: 9 March 2020- 18 January 2021, • Setting: patients in ICU • Country: international (Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK, USA) • Language: English • Number of centres: 90 • Trial registration: NCT02735707 • Date of registration: 13 April 2016

Participants	• Age (median, IQR; years):
	  ○ CP + SC: 61 (52-69)
	  ○ SC: 61 (52-70)
	• Sex (N, %; female):
	  ○ CP + SC: 351 (32.6%)
	  ○ SC: 291 (32.0%)
	• Ethnicity: race and ethnicity, N/total (%)
	  ○ Asian: plasma 144/976 (14.8); control 133/832 (16.0)
	  ○ Black: 51/976 (5.2) 38/832 (4.6); > 1 race 16/976 (1.6) 8/832 (1.0)
	  ○ White: 731/976 (74.9); 619/832 (74.4)
	  ○ Other: 34/976 (3.5); 34/832 (4.1)
	• Number of participants (recruited/allocated/evaluated): (10282/4763/2011 (1084 CP, 11 delayed CP, 916 control))
	• Severity of condition according to study definition: median WHO score of 6 (IQR 3-7)

Estcourt 2021 *(Continued)*

- Severity of condition according to WHO score: WHO levels 6-7
- Comorbidities
  - Diabetes 339/1078 (31.4) 268/907 (29.5)
  - Respiratory disease 245/1078 (22.7) 216/907 (23.8)
  - Kidney disease 107/1000 (10.7) 83/837 (9.9)
  - Severe cardiovascular disease 96/1053 (9.1) 67/890(7.5)
  - Immunosuppressive disease or therapy 67/1066 (6.3) 60/907 (6.6)
- Inclusion criteria
  - Adult patients admitted to an ICU for severe CAP within 48 h of hospital admission with:
    - symptoms or signs or both that are consistent with lower respiratory tract infection and
    - radiological evidence of new onset consolidation (in patients with pre-existing radiological changes, evidence of new infiltrate)
  - Up to 48 h after ICU admission, receiving organ support with one or more of:
    - non-IMV or IMV
    - receiving infusion of vasopressor or inotropes or both
  - COVID inclusion criteria:
    - adult patients (≥ 18 years) admitted to hospital with acute illness due to suspected or proven pandemic infection
- Exclusion criteria
  - Healthcare-associated pneumonia:
    - prior to this illness, is known to have been an inpatient in any healthcare facility within the last 30 days
    - resident of a nursing home or long-term care facility
  - Death is deemed to be imminent and inevitable during the next 24 h and one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
  - Previous participation in this REMAP within the last 90 days
- Previous treatments: NR
- Donor eligibility criteria: Prospective donors were screened for both IgA and IgG antibodies against the Covid-19 spike protein
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: CP
  - Volume: total volume approximately 550 mL ± 150 mL
  - Number of doses: 2 doses, if participant has no serious adverse reaction to first dose
  - Antibody test and antibody-titre: NR
  - Pathogen inactivated or not: NR
- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody: NR
  - Severity of disease: NR
  - Timing from recovery from disease: NR
  - RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): patients in ICU
- Comparator (type): SC (multi-platform adaptive trial)
  - Corticosteroid domain: hydrocortisone
  - Antibiotic domain: multiple
  - Antiviral against influenza: 10-day course of oseltamivir, 5-day course of oseltamivir, nil
  - Antiviral domain: lopinavir/ritonavir, hydroxychloroquine + lopinavir/ritonavir, hydroxychloroquine, nil
  - Anti-inflammatory: tocilizumab, anakinra, sarilumab, hydrocortisone, nil
  - Thrombo prophylaxis domain: SC vs therapeutic anticoagulation

Estcourt 2021 *(Continued)*

- Simvastatin: simvastatin vs nil
- Vitamin C: vitamin C vs nil
- Ig domain: CP (1-2 units) vs nil
- Ventilation: protocolised IMV strategy vs clinician-preferred

- Concomitant therapy: NR
- Duration of follow-up: 6 months
- Treatment cross-overs: NR
- Compliance with assigned treatment: NR

Outcomes

- Primary study outcome
  - All-cause mortality (time frame: day 90)
  - Days alive and not receiving organ support in ICU
- Primary review outcomes
  - All-cause mortality during hospital stay: yes (up to day 28)
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with grade 3 and grade 4 AEs: NR
  - Number of participants with SAEs: yes
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: only median reported
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional outcomes
  - COVID-19 antiviral domain- and COVID-19 immune modulation domain-specific endpoint
  - Occurrence of multi-resistant organism colonisation/infection (time frame: day 90, censored at hospital discharge)
  - Occurrence *Clostridium difficile* (time frame: day 90, censored at hospital discharge)
  - Occurrence of serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death (time frame: day 90, censored at hospital discharge)
  - Change from baseline influenza virus levels in upper and lower respiratory tract specimens (time frame: day 3, up to day 7), characterised as home, rehabilitation hospital, nursing home or long-term care facility, or another acute hospital
  - Proportion of intubated participants who receive a tracheostomy (time frame: day 28)
  - Destination at time of hospital discharge (time frame: day 90)
  - Readmission to the index ICU during the index hospitalisation (time frame: day 90)
  - Organ failure-free days (time frame: day 28)

Notes

- Preprint published on 13 June 2021
- Journal article accepted on 2 November 2021
- Sponsor/funding: MJM Bonten
- CoI: certain members declared their funding/grant sources

Gharbharan 2021

Study characteristics

Methods	• Trial design: RCT, open-label • Type of publication: preprint publication • Setting: hospital • Recruitment dates: 8 April 2020-14 June 2020 • Country: the Netherlands • Language: English • Number of centres: 14 • Trial registration number: NCT04342182 • Date of trial registration: 10 April 2020

Participants	• Age (median, IQR; years):
	  ○ CP: 61 (IQR 56-70)
	  ○ SC: 63 (IQR 55-77)
	• Sex (N, %; female):
	  ○ CP: 14/43 (33%)
	  ○ SC: 10/43 (23%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 204/86/86
	• Severity of condition according to study definition: moderate to severe (defined in the study according to the old WHO 8-point COVID-19 disease severity score)
	• Severity of condition according to WHO score
	  ○ CP: 16% ≤ score 4 and 84% ≥ score 5
	  ○ SC: 2% ≤ score 4 and 98% ≥ score 5
	• Comorbidities: diabetes mellitus, hypertension, cardiac, pulmonary, cancer, immunodeficiency, chronic kidney disease, liver cirrhosis
	• Inclusion criteria
	  ○ PCR-confirmed COVID-19 disease
	  ○ Admitted to hospital
	  ○ Availability of PCR-positive sample < 96 h old
	  ○ Written informed consent by patient or LAR
	  ○ Age ≥ 18 years
	• Exclusion criteria
	  ○ Participation in another intervention trial on the treatment of COVID-19 that falls under the Dutch law human research (WMO) and in which individual patients are randomised to different treatment options
	  ○ Known IgA deficiency
	  ○ Invasive ventilation for > 96 h already
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
	• Donor eligibility criteria:
	  ○ Donors with a history of COVID infection that was documented by PCR, known ABO-rhesus (D) blood group, negative screening for irregular antibodies, asymptomatic for at least 24 h, written informed consent regarding the plasmapheresis procedure
	• Donor exclusion criteria
	  ○ If age < 18 years and > 66 years, weight < 45 kg, medical history of heart failure, history of transfusion with red blood cells, platelets, or plasma

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 300 mL

Gharbharan 2021 *(Continued)*

- Number of doses: 1 (participants without a clinical response and a persistently positive RT-PCR could receive a second plasma unit after 5 days)
- Type of antibody test(s) and antibody-titre(s): antiSARS-CoV-2 neutralising antibodies confirmed by a SARS-COV-2 PRNT and a $PRNT_{50}$ titre > 1:80
- Pathogen inactivated or not: NR

- Details of donors
  - Sex (N, %; female) 10/115 (9%)
  - Age (median, IQR; years): 43 (IQR 31-52 years)
  - HLA and HNA antibody-negative: yes
  - Severity of disease: generally mild, 12% were admitted to hospital
  - Timing from recovery from disease: median 34 days in their convalescent phase
  - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): administered on the day of inclusion
- Comparator (type): SC; off-label use of EMA-approved drugs (e.g. chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, anakinra) as a treatment for COVID-19 was allowed in hospitals where this was part of SC
- Concomitant therapy: NR
- Duration of follow-up: 60 days
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome
  - Overall mortality until discharge from hospital or a maximum of 60 days after admission whichever comes first
- Primary review outcomes
  - All-cause mortality during hospital stay: all-cause mortality reported
  - 28-day mortality: reported in source data appendix
  - 60-day mortality: reported in source data appendix
  - Mortality (time to event): yes
  - Clinical status at day 28, day 60, and up to the longest follow-up, including the following: for day 15 and 30
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: yes
  - QoL: NR
  - Number of participants with grade 3 and grade 4 AEs: NR
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes: NR

Notes

- Preprint published on 3 July 2021
- Journal article accepted on 27 May 2021
- Sponsor/funding: Erasmus Medical Center
- COIs: study authors declared to have no competing interests

Gharbharan 2021 *(Continued)*

- The trial was stopped early after enrolment of 86 participants

Hamdy Salman 2020

Study characteristics

Methods	• Trial design: RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: June 2020-August 2020 • Country: Egypt • Language: English • Number of centres: 1 • Trial registration number: NCT04530370 • Date of trial registration: 28 August 2020

Participants	• Age (median, IQR; years)
	  ○ CP + SC: 57 (49.0 - 68.0)
	  ○ SC: 58.0 (50.0 - 67.0)
	• Sex (N, %; female)
	  ○ CP + SC: 5/15 (33.3%)
	  ○ SC: 4/15 (26.7%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 45/30/30
	• Severity of condition according to study definition: patients with COVID-19 severe conditions (no clear definition reported)
	• Severity of condition according to WHO score: not clear, probably WHO level > 4 (including level 4)
	• Comorbidities: diabetes and respiratory disease
	• Inclusion criteria
	  ○ Hospitalised patients ≥ 18 years
	  ○ Confirmed positive nasopharyngeal/oropharyngeal COVID-19 swab
	  ○ With ≥ 2 of a 4-category illness-severity scale:
	  ■ respiratory frequency ≥ 24/min
	  ■ blood oxygen saturation ≤ 93% on room air
	  ■ PaO_2/FiO_2 < 300 mmHg
	  ■ pulmonary infiltrates occupying > 50% of both lungs
	• Exclusion criteria
	  ○ Any patient with prior allergic history to plasma or plasma products or septic shock or multiple organ failure
	• Previous treatments: all participants received antiviral, antibacterial and antifungal treatment according to co-infections, and steroid and oxygen supportive therapy as required
	• Donor eligibility criteria
	  ○ A history of COVID-19 infection confirmed by positive nasopharyngeal swab/oropharyngeal swab test
	  ○ Complete recovery of symptoms for at least 2 weeks prior to donation, documented with negative nasopharyngeal/oropharyngeal swab
	  ○ All blood products followed standard blood handling and processing procedures and regulations
	• Donor exclusion criteria: NR

Interventions	• Details of CP ○ Type of plasma: CP

Hamdy Salman 2020 *(Continued)*

- Volume: 250 mL
- Number of doses: 1
- Type of antibody test and antibody-titre: neutralising antibody, Cusabio, ELISA Kit Catalog Number. CSBEL23253HU for the qualitative determination of SARS-CoV-2
- Pathogen inactivated or not: NR

- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: NR
  - Severity of disease: NR
  - Timing from recovery from disease: complete recovery of symptoms for at least 2 weeks prior to donation
  - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator (type): SC
- Concomitant therapy: available standard therapy, when appropriate, included:
  - supplemental oxygen
  - non-IMV andIMV
  - antibiotic medication
  - inotrope drugs
  - renal-replacement therapy
  - anticoagulants
  - glucocorticoids
  - intravenous fluids
  - interferon
  - ECMO
- Duration of follow-up: 5 days
- Treatment cross-overs: NA
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome
  - 50% Improvement of severity of illness was defined as achieving a minimum of 2-point reduction on the 4-category illness severity scale:
    - respiratory frequency ≥ 24/min
    - blood oxygen saturation ≤ 93% on room air
    - PaO_2/FiO_2 < 300 mmHg; pulmonary infiltrates occupying > 50% of both lungs, during 5-day study period
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: NR
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with grade 3 and grade 4 AEs: NR, only transfusion related AEs
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR

Hamdy Salman 2020 *(Continued)*

- ventilator-free days: NR
- liberation from supplemental oxygen in surviving participants: NR
- Need for dialysis at up to 28 days: NR
- Admission to the ICU on day 28:
- Duration of hospitalisation: NR
- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: yes, at day 3

- Additional review outcomes
  - Laboratory biomarkers of severe COVID-19 infections were assessed, including serum levels of ferritin, D-dimer, troponin, LDH, creatine phosphokinase, lymphocytic count, and CRP

Notes	• Preprint published on: NR • Journal article accepted on: 3 November 2020 • Sponsor/funding: South Valley University • CoI: "No potential conflict of interest was reported by the authors."

Holm 2021

Study characteristics

Methods	• Trial design: open-label RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: June 2020-January 2021 • Country: Sweden • Language: English • Number of centres: 2 • Trial registration number: NCT04600440 • Date of registration: 23 October 2020

Participants	• Age (median, IQR; years:
	  ◦ CP + SC: 80 (60–86)
	  ◦ SC: 65 (43–84)
	• Sex (N, %; female):
	  ◦ CP + SC: 6/17 (35%)
	  ◦ SC: 6/14 (43%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): NR/33/31
	• Severity of condition according to study definition: hospitalised with need for supplemental oxygen treatment
	• Severity of condition according to WHO score: WHO level 5
	• Comorbidities: BMI, arterial hypertension
	• Inclusion criteria
	  ◦ Admitted to the hospital and a need for supplemental oxygen treatment
	  ◦ Verified diagnosis of COVID-19 (with a nasopharyngeal swab positive for SARS-CoV-2 in RT-PCR no later than 4 days prior to inclusion)
	  ◦ ≥ 18 years
	  ◦ < 94% oxygen saturation
	  ◦ Willingness to participate
	  ◦ Ability to sign informed consent
	• Exclusion criteria

Holm 2021 *(Continued)*

	◦ Inability to understand information and sign informed consent ◦ Severely immunosuppressed patient • Previous treatments: betamethasone, remdesivir, IV antibiotics, anti-coagulants • Donor eligibility criteria ◦ Male only ◦ Mild to moderate disease ◦ Fulfilled the national blood donor selection criteria ◦ 2 weeks after the complete resolution of clinical symptoms • Donor exclusion criteria: NR
Interventions	• Details of CP ◦ Type of plasma: CP ◦ Volume: 200-250 mL ◦ Number of doses: 3 on three consecutive days ◦ Type of antibody test and antibody-titre: high-titre donor plasma, median value of 1:116 ◦ Pathogen inactivated or not: NR • Details of donors ◦ Sex (N, %; female): 0 ◦ Age (median, IQR or mean, SD; years): ◦ HLA and HNA antibody-negative: yes (only male donors) ◦ Severity of disease: mild to moderate disease ◦ Timing from recovery from disease: 2 weeks ◦ RT-PCR tested: yes • Treatment details, including time of plasma therapy (e.g. early stage of disease): symptom duration between 5 and 11 days at inclusion • Comparator (type): SC • Concomitant therapy: NR • Duration of follow-up: max. 28 days • Treatment cross-overs: none • Compliance with assigned treatment: yes
Outcomes	• Primary study outcomes ◦ Number of days within 28 days after inclusion with a need for oxygen therapy to keep an oxygen saturation above 93% • Primary review outcomes ◦ All-cause mortality during hospital stay: NR ◦ 28-day mortality: yes ◦ 60-day mortality: NR ◦ Mortality (time to event): NR ◦ Clinical status ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: NR (IMV and death separately reported) ■ Improvement of clinical status: participants discharged from hospital: NR ◦ QoL: NR ◦ Number of participants with AEs (any grade, grades 1-2, grades 3-4): transfusion related AEs and any AEs ◦ Number of participants with SAEs: NR • Secondary outcomes ◦ Improvement of clinical status: ■ weaning or liberation from IMV in surviving participants: NR ■ ventilator-free days: NR ■ liberation from supplemental oxygen in surviving participants: NR ◦ Need for dialysis at up to 28 days: NR ◦ Admission to the ICU on day 28: NR

Holm 2021 *(Continued)*

- Duration of hospitalisation: as median only
- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR

Notes	• Journal article published on 4 December 2021 • Sponsor/funding: Skane University Hospital • CoI: "The authors declare no competing interests."

Horby 2021b

Study characteristics

Methods	• Trial design: multicentre, randomised adaptive trial • Type of publication: preprint • Setting: inpatient • Recruitment dates: 28 May 2020-15 January 2021 • Country: UK • Language: English • Number of centres: multiple (currently 177 active sites) • Trial registration number: NCT04381936 • Date of trial registration: 11 May 2020

Participants	• Age (mean, SD; years):
	  ◦ CP + SC: 63.5 (14.7)
	  ◦ SC: 63.4 (14.6)
	• Sex (%; female):
	  ◦ CP + SC: 37%
	  ◦ SC: 34%
	• Ethnicity
	  ◦ White 75% in CP and 74% in SC
	  ◦ Black, Asian, and minority ethnic 15% in CP and 15% in SC
	  ◦ Unknown 10% in CP and 10% in SC
	• Number of participants (recruited/allocated/evaluated): 40,000/5795 CP and 5763 SC/5795 CP and 5763 SC
	• Severity of condition according to study definition: 4.8% in plasma group vs 6.7% in control group receiving high-flow oxygen, 85.5% vs 81.9% receiving oxygen by mask or nasal prongs, 9.7% vs 11.4% no oxygen
	• Severity of condition according to WHO score: most WHO levels 4-5
	• Comorbidities: diabetes, heart disease, chronic lung disease, TB, HIV, severe liver disease, severe kidney impairment
	• Inclusion criteria
	  ◦ Hospitalised patients at any age
	  ◦ SARS-CoV-2 infection (clinically suspected or laboratory-confirmed)
	  ◦ No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial
	  ◦ Written informed consent
	• Exclusion criteria
	  ◦ If the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient
	  ◦ For patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial would be considered sufficient reason to exclude them from the trial

Horby 2021b *(Continued)*

- Exclusion for CP randomisation: known moderate or severe allergy to blood components,
- Not willing to receive a blood product

- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): yes
- Donor eligibility criteria
  - Only plasma donations with sample to cut-off (S/CO) ratio of ≥ 6.0 on the EUROIMMUN IgG ELISA test targeting the spike (S) glycoprotein (PerkinElmer, London, UK) were supplied for the RECOVERY trial use
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: ABO-identical CP if possible
  - Volume: 275 mL +/- 75 mL
  - Number of doses: 2 (with a minimum of 12-h interval between 1st and 2nd units)
  - Type of antibody test and antibody-titre: only plasma donations with sample to cut-off (S/CO) ratio of ≥ 6.0 on the EUROIMMUN IgG ELISA test targeting the spike (S) glycoprotein (PerkinElmer, London, UK) were supplied for the RECOVERY trial use
  - Pathogen inactivated or not: NR
- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: NR
  - Severity of disease: NR
  - Timing from recovery from disease: NR
  - RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: standard therapy and/or lopinavir-ritonavir, low-dose corticosteroids, hydroxychloroquine, azithromycin, tocilizumab
- Concomitant therapy: standard therapy and/or lopinavir-ritonavir, low-dose corticosteroids, hydroxychloroquine, azithromycin, tocilizumab or sarilumab, remdesivir
- Duration of follow-up: 6 months
- Treatment cross-overs: participants with progressive COVID-19 (as evidenced by hypoxia and an inflammatory state) may undergo an optional second randomisation: no additional treatment vs tocilizumab. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome: all-cause mortality (time frame: within 28 days after randomisation)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes (up to 6 months after main randomisation)
  - 60-day mortality: NR
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
    - Improvement of clinical status: participants discharged from hospital: yes
  - QoL: NR
  - Number of participants with grade 3 and grade 4 AEs: transfusion related AEs
  - Number of participants with SAEs: NR
- Secondary review outcomes reported
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: yes
    - ventilator-free days: NR

Horby 2021b *(Continued)*

- liberation from supplemental oxygen in surviving participants: NR
- Need for dialysis at up to 28 days: yes
- Admission to the ICU on day 28: NR
- Duration of hospitalisation: median only
- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR

- Additional outcomes
  - Need for renal replacement
  - Development of new major cardiac arrhythmias
  - Proportion of participants discharged from hospital

Notes	• Preprint published 10 March 2021 • Journal article published on 29 May 2021 • Sponsor/funding: UK Research and Innovation (Medical Research Council) and National 48 Institute of Health Research (Grant refs: MC_PC_19056; COV19-RECPLA) • CoI:

Kirenga 2021

Study characteristics

Methods	• Trial design: open-label RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 21 September 2020-2 December 2020 • Country: Uganda • Language: English • Number of centres: 1 • Trial registration number: NCT04542941 • Date of registration: 9 September 2020

Participants	• Age (median, IQR; years)
	  ◦ CP + SC: 48 (35–64)
	  ◦ SC: 53 (44–61)
	• Sex (N, %; female)
	  ◦ CP + SC: 21/69 (30.4%)
	  ◦ SC: 18/67
	• Ethnicity: NR
	• Number of participants (recruited/allocated/ evaluated): 403/136/122
	• Severity of condition according to study definition: at enrolment, 48.5% were on supplemental oxygen, 58.8% were on systemic corticosteroids mainly dexamethasone, 58.8% were on anticoagulants mainly low-molecular-weight heparin and 1 participant was on non-invasive ventilation
	• Severity according to WHO score: moderate with WHO levels 4-5
	• Comorbidies: 58.1% reported at least 1 comorbidity (hypertension 36.0%, diabetes 23.5%, and HIV 11.0%)
	• Inclusion criteria
	  ◦ Adults with documented laboratory RT-PCR-confirmed SARS-CoV-2 infection irrespective of severity of disease
	  ◦ Able to provide informed consent or next of kin or legal surrogate to provide consent
	• Exclusion criteria
	  ◦ Prior diagnosis of IgA deficiency

Kirenga 2021 *(Continued)*

- Inability to return for post-discharge follow-up
- Previous treatments: 80 systematic corticosteroids; 80 anticoagulants (mainly low molecular weight heparin)
- Donor eligibility criteria (Muttamba 2021: see secondary reference under Kirenga 2021)
  - Written informed consent
  - Documented evidence of SARS-CoV-2 infection by RT-PCR test and recovery defined as 2 negative RT-PCR tests performed at least 24 h apart
  - ≥ 18 years old
  - Meet all criteria for blood donation as set by Uganda Blood Transfusion Services (UBTS): age between 17–60 years, weight ≥ 50 kg, pulse rate of 60–100 beats/min, temperature 37 °C ± 0.4°C, haemoglobin level 12.5-16 g/dL for women and 13.5-17 g/dL for men, and last blood donation not less than 3 months and 4 months for men and women respectively
- Exclusion criteria
  - Women with previous history of blood transfusion and/or pregnancy
  - Documented evidence of HIV-positive status

Interventions

- Details of CP
  - Type of plasma: CP
  - Volume: NR
  - Number of doses: 2
  - Antibody-titre: anti-SARS-CoV-2 IgG antibody titres, median 139.5 (IQR 84.3–195.4) Astronomical Units (AU)
  - Pathogen inactivated: not pathogen inactivated
- Details of donors (Muttamba 2021: see secondary reference under Kirenga 2021)
  - Sex (N; female): 6
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: male or nulliparous female
  - Severity of disease: hospitalised
  - Timing from recovery from disease:
  - RT-PCR tested: 2 negative RT-PCR tests performed at least 24 h apart
- Treatment details, including time of plasma therapy: median duration of symptoms was 7 days
- Comparator: SC
- Concomitant therapy: NR
- Treatment cross-overs: none
- Donor CP was cross-matched with the participant's red blood cells to ensure compatibility. CP was administered over 2–3 h at a rate of 1.4–2 mL/min and a second aliquot transfused at the same rate 3 h after completion of the first one

Outcomes

- Primary study outcome
  - Time to viral clearance (RT-PCR negativity) by28 days
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4):): any grade AE
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:

Kirenga 2021 *(Continued)*

- weaning or liberation from IMV in surviving participants: NR
- ventilator-free days: NR
- liberation from supplemental oxygen in surviving participants: NR

- Need for dialysis at up to 28 days: NR
- Admission to the ICU on day 28: NR
- Duration of hospitalisation: NR
- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: : yes, for day 3, 7 and 15

- Additional study outcomes
  - Time to symptom resolution (time frame: 28 days)
  - Time to severe/critical disease (time frame: 28 days)

Notes	• Journal publication: published in August 2021 • Sponsor/funding: Makerere University, Uganda Blood Transfusion Services, Joint Clinical Research Center, Uganda Peoples Defence Forces Medical Services, Mulago Hospital, Uganda • CoI: "None declared"

Koerper 2021

Study characteristics

Methods	• Trial design: open-label RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 30 August 2020-24 December 2020 • Country: Germany • Language: English • Number of centres: 13 • Trial registration number: NCT04433910 or EudraCT2020-001310-38 • Date of registration: 16 June 2020

Participants	• Age (median, IQR; years)
	  ○ CP+ SC: 59 (53–65)
	  ○ SC: 62 (55–66)
	• Sex (N, %; female)
	  ○ CP + SC: 11 (20.8%)
	  ○ SC: 17 (32.7%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 106/105/105
	• Severity of condition according to study definition: 59.1% of participants receiving supplemental oxygen or non-invasive ventilation and 34.3% invasive ventilation
	• Severity of condition according to WHO score: moderate to severe with WHO levels 4-7
	• Inclusion criteria
	  ○ SARS-CoV-2 infection confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swab)
	  ○ Age ≥ 18 years and ≤ 75 years
	  ○ Severe disease, defined by at least 1 of the following:
	  ■ respiratory rate ≥ 30 breaths/minute under ambient air
	  ■ requirement of any type of ventilation support
	  ■ need for ICU treatment
	  ○ Written informed consent by patient or LAR
	• Exclusion criteria
	  ○ Accompanying diseases other than COVID-19 with an expected survival time of < 12 months
	  ○ Previous treatment with any SARS-CoV-2-CP

Koerper 2021 *(Continued)*

- In the opinion of the clinical team, progression to death imminent and inevitable within following 48 h, irrespective of the provision of treatment
- Interval > 72 h since start of ventilation support
- Not eligible for ECMO support (even in case of severe ARDS according to Berlin classification with Horovitz-Index < 100 mgHg)
- COPD, stage 4
- Lung fibrosis with UIP pattern in CT and severe emphysema
- Chronic heart failure NYHA ≥ 3 and/or pre-existing reduction of left ventricular ejection fraction to ≤ 30%
- Shock of any type requiring ≥ 0.5 µg/kg/min noradrenaline (or equivalent) or requiring > 2 types of vasopressor medication for > 8 h
- Liver cirrhosis Child C
- Liver failure: bilirubin > 5 x ULN and elevation of ALT/AST (at least one > 10 x ULN)
- Any history of adverse reactions to plasma proteins
- Known deficiency of IgA
- Pregnant or breastfeeding
- Participation in another clinical trial with an investigational medicinal product

- Donor eligibility criteria
  - Infection with SARS-CoV-2 documented by a positive RT-PCR (from nasal or pharyngeal swab, BAL or stool)
  - Cleared SARS-CoV-2 from nasopharyngeal mucosa by 1 negative RT-PCR result from a nasal or pharyngeal swab prior to start of first plasmaphaeresis
  - Interval of at least 2 weeks since resolution of symptoms of the SARS-CoV-2 infection
  - No residual severe organ dysfunction
  - Written informed consent to donate plasma for the clinical trial
  - Negative test for antibodies against HLA class I, class II and HNA-antigens. This test was performed in all donors – irrespective of gender and previous pregnancies. It was performed prior to first plasmaphaeresis and repeated after an immunisation event.
  - Anti-SARS-CoV-2 antibodies detectable in a neutralisation assay
  - Age: first donors: 18–60 years, repeated donors: 18–68 years
  - Body weight: ≥ 50 kg
  - Additional blood parameters
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: CP
  - Volume: (250-325 mL) on days 1, 3 and 5
  - Number of doses: 3 (transfusion on days 1, 3, and 5)
  - Antibody test and antibody-titre: neutralising Ab $PRNT_{50}$ median titre of transfused plasma units: 1:80; mean titre: 1:115
  - Pathogen inactivation: none
- Details of donors
  - Sex (%; female): 41%
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody: negative
  - Severity of disease: mild or moderate course of COVID-19
  - Timing from recovery from disease: at least 2 weeks
  - RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with severe disease, within 1 day of randomisation
- Comparator: SC
- Concomitant therapy: SC
- Duration of follow-up: 60 days

Koerper 2021 *(Continued)*

- Treatment cross-overs: yes (cross over for participants with progressive disease on day 14 with CP transfusion on day 15, 17 and 19), in total 7 patients

Outcomes

- Primary study outcome
  - Composite endpoint of survival and no longer fulfilling criteria of severe COVID-19 (time frame: day 21)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: yes
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): any AE
  - Number of participants with SAEs: yes
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes (median and IQR only)
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: only time until negative SARS-CoV-2 PCR
- Additional outcomes
  - Laboratory parameters (inflammatory markers, thrombotic markers, anti-SARS-CoV-2-antibody titres correlated with age; sex; severity of COVID-19; interval between resolution of symptoms and plasmaphaeresis of plasma donors, correlation of antibody titres with:
    - "Survival and no longer fulfilling criteria of severe COVID-19"
    - change in WHO ordinal scale
    - time to clinical improvement
    - length of hospital stay
    - length of ICU stay
    - length of mechanical ventilation or ECMO support
  - Percentage of former COVID-19 patients willing to donate qualifying for plasma donation (time frame: through study completion, an average of 8 months)
  - Impact of donor characteristics on anti-SARS-CoV-2 humoral response (time frame: up to 60 days)
  - Course of anti-SARS-CoV-2 titre in both participant groups at different time points related to transfusion of CP (time frame: up to 60 days)

Notes

- Journal article published 31 August 2021
- Sponsor/funding: Bundesministerium für Gesundheit (German Federal Ministry of Health)
- CoI: VMC "is named together with Euroimmun on a patent application filed recently regarding the diagnosis of SARS-CoV-2 by antibody testing" Patent application no. EP3809137A1

Korley 2021

Study characteristics

Methods	• Trial design: single-blind RCT (terminated early for futility based on preplanned interim analysis) • Type of publication: journal publication • Recruitment dates: August 2020-February 2021 • Setting: inpatient • Country: USA • Language: English • Number of centres: 48 • Trial registration number: NCT04355767 • Date of trial registration: 21 April 2020

Participants	• Age (median, IQR; years)
	  ○ CP + SC: 54 (42 - 62)
	  ○ Placebo + SC: 54 (40 - 62)
	• Sex (N, %; female)
	  ○ CP + SC: 135/257 (52.5%)
	  ○ Placebo + SC: 139/254 (54.7%)
	• Ethnicity (N, %):
	  ○ Hispanic or Latino: CP: 83 (32.3%), Placebo: 73 (28.7%)
	  ○ not Hispanic or Latino: CP 170 (66.1%), placebo 179 (70.5%)
	  ○ unknown: CP: 4 (1.6%), Placebo: 2 (0.8%)
	• Number of participants: (3990/511/497)
	• Severity of condition according to study definition: the clinical team determined that the patient's condition was stable for outpatient treatment without new supplemental oxygen (however, participants were probably already hospitalised before randomisation)
	• Severity of condition according to WHO score: WHO level 4
	• Comorbitities: BMI, hypertension, diabetes mellitus, COPD or asthma, coronary artery disease, immunosuppression, chronic lung disease, chronic kidney disease, congestive heart failure, pregnancy, organ transplant recipient, active cancer, sickle-cell disease, liver disease, alcohol abuse, drug abuse, haematological disorder
	• Previous treatments: patients with previous other treatments were excluded
	• Inclusion criteria
	  ○ Age ≥ 18 years
	  ○ People requiring clinical evaluation in the ED but not hospital admission
	  ○ Within 7 days of onset of COVID-19 symptoms
	  ○ COVID-19 confirmed via COVID-19 SARS-CoV-2 RT-PCR testing or rapid RNA assay
	  ○ Agree to storage of specimens for future testing
	  ○ Severity of condition
	• Exclusion criteria
	  ○ Pregnant or breastfeeding
	  ○ Received pooled immunoglobulin in the past 30 days
	  ○ Contraindication to transfusion or history of prior reactions to transfusion blood products
	• Donor eligibility criteria
	  ○ Have recovered from COVID-19 for at least 14 days
	  ○ nAb titre (NT50) of 1:160 and later ID50 of 1:250
	  ○ Men, women who have never been pregnant and women who test negative for HLA antibodies
	• Donor exclusion criteria: NR

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 250 mL
	  ○ Number of doses: 1

Korley 2021 *(Continued)*

- Antibody-titre: > 1:80
- Pathogen inactivated or not: NR

- Donor details
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: yes
  - Severity of disease: NR
  - Timing of recovery from disease: at least 14 days after clinical recovery from COVID-19
  - RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): within 14 days after disease onset
- Comparator: saline coloured with a parenteral multivitamin concentrate to resemble plasma
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: none
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome
  - Number of participants with disease progression (day 15)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): transfusion-related AEs
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Time to disease progression (15 days), on COVID Outpatient Ordinal Outcome Scale
  - Number of hospital-free days during the 30 days following randomisation (30 days)

Notes

- Journal article published on 18 August 2021
- Sponsor/funding: The National Heart, Lung and Blood Institute (NHLBI), The National Institute of Neurological Disorders and Stroke (NINDS)
- CoI: not reported

Li 2020

Study characteristics	
Methods	• Trial design: open-label RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 14 February 2020-1 April 2020 • Country: China • Language: English • Number of centres: 7 • Trial registration number: ChiCTR2000029757 • Date of registration: 12 February 2020

Participants	• Age (median, IQR; years)
	  ○ CP: 70 (62-80)
	  ○ SC: 69 (63-76)
	• Sex (N, %; female):
	  ○ 25/52 (48.1%)
	  ○ 18/51 (35.3%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 148/103/103 (52 CP, 51 standard treatment)
	• Severity of condition according to study definition: severe (respiratory distress and/or hypoxaemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation)
	• Severity of condition according to WHO score: WHO levels 6 to 9
	• Comorbidities: hypertension, cardiovascular disease, cerebrovascular disease, diabetes, liver disease, cancer, kidney disease
	• Inclusion criteria
	  ○ Signed informed consent
	  ○ Aged at least 18 years
	  ○ COVID-19 diagnosis based on PCR testing
	  ○ Positive PCR result within 72 h prior to randomisation
	  ○ Pneumonia confirmed by chest imaging
	  ○ Clinical symptoms meeting the definitions of severe or life-threatening COVID-19
	  ○ Acceptance of random group assignment
	  ○ Hospital admission
	  ○ Willingness to participate in all necessary research studies and be able to complete the study follow-up
	  ○ No participation in other clinical trials, such as antiviral trials, during the study period
	• Exclusion criteria
	  ○ Pregnancy or lactation
	  ○ Immunoglobulin allergy
	  ○ IgA deficiency
	  ○ Pre-existing comorbidity that could increase the risk of thrombosis
	  ○ Life expectancy < 24 h
	  ○ Disseminated intravascular coagulation
	  ○ Severe septic shock
	  ○ PaO_2/FIO_2 of < 100
	  ○ Severe congestive heart failure
	  ○ Detection of high titre of S protein–RBD-specific IgG antibody (≥ 1:640)
	  ○ Other contraindications as determined by the patient's physicians
	  ○ Participation in any antiviral clinical trials for COVID-19 within 30 days prior to enrolment

Li 2020 *(Continued)*

- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antivirals, antibiotics, steroids, human Ig, Chinese herbal medicines, interferon
- Donor eligibility criteria
  - Age 18-55 years, suitable for blood donation, initially diagnosed with COVID-19 but with 2 negative PCR test results from nasopharyngeal swabs (at least 24 h apart) prior to hospital discharge, discharged for > 2 weeks from the hospital, and no persisting COVID-19 symptoms
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: plasmaphaeresis
  - Volume: 4-13 mL/kg of recipient body weight, median 200 mL, IQR 200-300 mL
  - Number of doses: ≥ 1 (96%)
  - Antibody test and antibody-titre: only the plasma units with an S-RBD–specific IgG titre of at least 1:640 were used, correlating to serum neutralisation titre of 1:80
  - Pathogen inactivated or not: NR
- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: NR
  - Severity of disease: NR
  - Timing from recovery from disease: discharged from hospital > 2 weeks
  - RT-PCR tested: lab-confirmed COVID-19 diagnosis, 2 negative PCR results from nasopharyngeal swabs at least 24 h apart prior to hospital discharge
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe to life-threatening
- Comparator: SC
- Concomitant therapy: antivirals, antibiotics, steroids, human Ig, Chinese herbal medicines, interferon
- Duration of follow-up: 28 days
- Treatment cross-overs: none
- Compliance with assigned treatment: 1 participant in control arm received CP, 1 participant in CP arm discontinued study

Outcomes

- Primary study outcome(s): clinical improvement within 28 days (patient discharged from hospital or reduction of 2 points on a 6-point disease-severity scale)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: yes
  - QoL: NR
  - Number of participants with grade 3 and grade 4 AEs: NR
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR

Li 2020 *(Continued)*

- Admission to the ICU on day 28: NR
- Duration of hospitalisation: NR
- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: yes reported at day 3

- Additional study outcomes:

Notes	• Journal article published on 3 June 2020 • Sponsor/funding: this work was supported by the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) grants 2020-I2M-CoV19-006, 2016-I2M-3-024 (Dr Z. Liu), and 2017-I2M-1-009 (Dr L. Li) and the Nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences grant 2018PT32016 (Dr Z. Liu) • COIs: Dr Liu reports holding a pending patent on COVID-19 testing. Dr Wu reports consulting for Verax Medical and Grifols, receiving royalties from UptoDate and AABB, and being a volunteer visiting professor and receiving travel support for giving medical education from the Chinese Institute of Blood Transfusion. No other disclosures were reported.

Libster 2020

Study characteristics

Methods	• Trial design: double-blind RCT • Type of publication: journal publication • Setting: outpatient • Recruitment dates: 9 June 2020-25 October 2020 • Country: Argentina • Language: English • Number of centres: 11 • Trial registration number: NCT04479163 • Date of registration: 21 July 2020

Participants	• Age (mean, SD; years)
	  ◦ CP: 76.4 (8.7)
	  ◦ Placebo: 77.9 (8.4)
	• Sex (N, %; female)
	  ◦ 54/80 (68%)
	  ◦ 46/80 (58%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 165/160 (80 CP, 80 SC)/160
	• Severity of condition according to study definition: mild signs and symptoms for < 48 h at the time of screening for SARS-CoV-2 by RT-PCR
	• Severity of condition according to WHO score: WHO levels 2-3
	• Comorbidities: arterial hypertension, diabetes, obesity, COPD, heart disease, CKD, asthma or other respiratory disease, non-cirrhotic liver disease, cancer (not active), neurologic disease
	• Inclusion criteria
	  ◦ Aged ≥ 75 years irrespective of presenting comorbidities or between 65-74 years of age with at least 1 comorbidity (hypertension or diabetes under pharmacologic treatment, obesity, chronic renal failure, cardiovascular disease, and COPD)
	  ◦ Participants had experienced at least 1 of each in the following 2 categories of signs and symptoms for < 48 h at the time of screening for SARS-CoV-2 by RT-PCR:
	  ■ temperature ≥ 37.5 ° C and/or unexplained sweating and/or chills
	  ■ dry cough, dyspnoea, fatigue, myalgia, anorexia, sore throat, dysgeusia, anosmia, and/or rhinorrhoea

Libster 2020 *(Continued)*

- Confirmed diagnosis SARS-CoV-2 by RT-PCR
- Informed consent

- Exclusion criteria
  - Severe respiratory disease
  - Cardiac insufficiency
  - Chronic renal failure
  - Primary hypogammaglobulinaemias
  - Myelodysplastic syndromes
  - Chronic lymphoproliferative syndromes
  - Monoclonal gammapathies
  - Known hypersensitivity
  - Active cancer
  - HIV, HBV or HCV infection
  - Chronic administration of immunosuppressants
  - Body transplant history
  - Chronic liver disease, chronic lung disease with oxygen requirement
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
- Donor eligibility criteria
  - Infected with SARS-CoV-2 for a minimum of 10 days
  - Asymptomatic for ≥ 3 days, and with 2 negative RT-PCR tests
- Donor exclusion criteria: NR

Interventions	• Details of CP
	  ◦ Type of plasma: CP
	  ◦ Volume: 250 mL
	  ◦ Number of doses: 1
	  ◦ Antibody test and antibody-titre: IgG titre against SARS-CoV-2 spike (S) protein > 1:1000 (COVIDAR IgG, Instituto Leloir, Argentina)
	  ◦ Pathogen inactivated or not: NR
	• Details of donors
	  ◦ Sex (N, or %; female): NR
	  ◦ Age (median, IQR or mean, SD; years): NR
	  ◦ HLA and HNA antibody-negative: NR
	  ◦ Severity of disease: NR
	  ◦ Timing from recovery from disease: infected with SARS-CoV-2 for a minimum of 10 days, asymptomatic for ≥ 3 days
	  ◦ RT-PCR tested: 2 negative RT-PCR tests
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): early-stage within 72 h of mild COVID-19 symptoms
	• Comparator: placebo (250 mL 0.9% normal saline)
	• Concomitant therapy: NR
	• Duration of follow-up: 15 days in general, 25 for participants with persistent symptoms that required medical care
	• Treatment cross-overs: none
	• Compliance with assigned treatment: 1 participant voluntarily abandoned the trial on day 11 of follow-up.

Outcomes	• Primary study outcome(s): development of severe respiratory disease defined as a respiratory rate ≥ 30 and/or an O_2 saturation < 93% when breathing room air determined between 12 h after infusion of the investigational product and day 15 of study participation
	• Primary review outcomes (outpatient)
	  ◦ 28-day mortality: yes
	  ◦ 60-day mortality: NR

Libster 2020 *(Continued)*

- Mortality (time to event): NR
- Admission to hospital or death within 28 days:NR
- Symptom resolution
  - All initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up: NR
  - Time to symptom resolution: NR
- QoL: NR
- Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
- Number of participants with SAEs: NR

- Secondary review outcomes (outpatient)
  - Worsening of clinical status:
    - need for IMV or death: NR
    - need for hospitalisation with oxygen by mask or nasal prongs, or death: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Life-threatening respiratory disease, defined as need for 100% oxygen supplementation and/or non-invasive ventilation and/or admission to ICU and/or mechanical ventilation
  - Critical systemic illness, defined as respiratory failure ($PaO_2/FiO_2 \leq 200$ mmHg) and/or shock and/or multi-organ distress syndrome (defined in supplementary material)
  - Combinatory endpoint death associated with COVID-19, life-threatening respiratory disease or critical systemic illness
  - The distribution of serum titres 24 h after infusion in plasma versus placebo recipients

Notes

- Preprint publication: 21 November 2020
- Journal articles published: 6 January 2021
- Sponsor/funding: funded by The Bill and Melinda Gates Foundation and The Fundación INFANT Pandemic Fund
- COIs: RL, GPM, DW, Coviello and FPP received fees for serving as investigators for Pfizer; "No other potential conflict of interest relevant to this article was reported."
- Other: early termination due to slow enrolment pace (enrolled 76% of the target population)

Menichetti 2021

Study characteristics

Methods

- Trial design: multicentre, open-label RCT
- Type of publication: journal article
- Setting: inpatient
- Recruitment: 15 July-8 December 2020
- Country: Italy
- Language: English
- Number of centres: 27
- Trial registration number: NCT04716556
- Date of trial registration: 20 January 2020

Participants

- Age (median, IQR; years)
  - CP + SC: 65.0 (55.0 - 74.0)
  - SC: 63.0 (54.0 - 74.0)
- Sex (N, %; female)
  - CP: 82/232 (35.3%)
  - SC: 87/241 (36.1%)
- Ethnicity:

Menichetti 2021 *(Continued)*

- White: CP 95.3; SC 92.8
- Black: CP 2.6; SC 2.9
- Asian: CP 2.2; SC 1.2

- Number of participants (recruited/allocated/evaluated): 492/487/446
- Severity of condition according to study definition: (Pao2/Fio2) ratio between 200 and 350 mm Hg at baseline
- Severity of condition according to WHO score: moderate with WHO levels 4-5
- Comorbidities: hypertension, diabetes, COPD, chronic kidney failure, solid tumours, heart failure
- Inclusion criteria
  - Age ≥ 18 years old
  - Adult patients with positive RT-PCR test for SARS-CoV-2 (nasal swabs or lower respiratory tract sample), diagnosed with pneumonia (≤ 10 days) according to the following definitions:
    - suggestive radiological imaging (CT, X-rays, ultrasound)
    - respiratory failure not fully explained by heart failure or fluid overload
    - PaO_2/FiO_2 200-350 mmHg
    - signed informed consent
- Exclusion criteria
  - Need for non-invasive or IMV at the time of randomisation
  - PaO_2/FiO_2 < 200
  - Patients with hypersensitivity or allergic reaction to blood products or immunoglobulins
  - Patients who expressly refuse to adhere to the clinical study
  - Use of IL-6 receptor inhibitors, IL-1 inhibitors, janus kinase (JAK) inhibitors, tumor necrosis factor (TNF) inhibitors
  - Patients participating in another clinical trial
- Previous treatments: remdesivir, glucocorticoids, LMWH
- Donor eligibility criteria
  - Men or nulliparous women
  - 18-65 years
  - Weighing > 50 kg
  - Previous diagnosis of COVID-19 confirmed by RT-PCR test
  - Asymptomatic for at least 28 days
  - When anti–SARS-CoV-2 microneutralisation test (MNT) showed an antibody titre of at least 1:160
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: CP
  - Volume: 200-300 mL
  - Number of doses: 1-3
  - Antibody-titre: at least 1:160 on microneutralisation test
  - Pathogen inactivated: yes (Intercept or Mirasol)
- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: NA
  - Severity of disease: NR
  - Timing from recovery from disease: NR
  - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): median (IQR) time from onset of symptoms to CP infusion was 7.7 (5.0-9.0) days
- Comparator: SC
- Concomitant therapy: remdesivir, steroids, LMWH
- Duration of follow-up: 30 days from randomisation

Menichetti 2021 *(Continued)*

- Treatment cross-overs: no
- Compliance with assigned treatment: yes

Outcomes	• Primary study outcomes: s a composite of worsening respiratory failure (PaO2/FiO2 ratio < 150 mm Hg) or death within 30 days from randomisation
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: yes (30-day mortality)
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): yes
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: yes
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): grades 3-4 AEs
	  ○ Number of participants with SAEs: NR
	• Secondary study outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participant: NR
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission to the ICU on day 28: NR
	  ○ Duration of hospitalisation: only median
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional study outcomes:

Notes	• Journal article published on 29 November 2021 • Sponsor/funding: Istituto Superiore di Sanità, Gruppo Italiano Malattie EMatologiche dell'Adulto, Agenzia Italiana del Farmaco • CoI: Dr Menichetti: AstraZenecasponsored trial, Toscana Life Science–sponsored trial, speaker honoraria or advisory board or support from Angelini, Menarini, Correvio, MSD, Pfizer, Astellas, Gilead, BMS, Janssen, ViiV, BioMerieux, Biotest, Becton-Dickinson, Pfizer, Shionogi, Roche, GSK, Advanz Pharma, and ThermoFisher; Dr Bartoloni: study grants from MSD, ViiV Healthcare, and Nordic Pharma, fees for presentations from Pfizer and MSD; Dr Puoti: personal fees, grants and/or nonfinancial support from Abbvie, Gilead Science, Merck and Theratechnologies; Dr Marchetti: grants for lectures, advisory board, or conferences by Gilead, ViiV, and Janssen; Dr d'Arminio Monforte: grants for lectures, advisory board, or conferences by Gilead, ViiV, MSD, Angelini, and Janssen; Dr Bonfanti: personal fees from Viiv, Gilead, Jannsen Pharmaceuticals, Merck, and Pfizer; Dr Saracino grants for research and/or educational purposes from Gilead, ViiV, MSD, Abbvie, Janssen, Shionogi, and Pfizer; Dr Castagna: personal fees from ViiV, MSD, Gilead, Janssen, and Theratecnologies; Dr Falcone: grants and speaker honoraria from Angelini, Shionogi, MSD, Pfizer, Gilead, Menarini, and Nordic Pharma; no other disclosures were reported

NCT04421404

Study characteristics

Methods	• Trial design: double-blind, controlled RCT • Type of publication: results from trials registry • Setting: inpatient • Recruitment dates: NR

NCT04421404 *(Continued)*

- Country: USA
- Language: English
- Number of centres: 3
- Trial registration number: NCT04421404
- Date of registration: 9 June 2020

Participants	• Age (median, IQR; years)
	  ○ CP + SC: 52 (40 to 64)
	  ○ SP+ SC: 62 (49 to 74)
	• Sex (N, %; female)
	  ○ CP + SC: 10/16 (62.5%)
	  ○ SP+ SC: 9/18 (50%)
	• Ethnicity
	  ○ Hispanic/Latino: 23/34 (67.6%)
	  ○ Not Hispanic/Latino: 10/34 (29.4%)
	  ○ American Indian or Alaska Native: 1/34 (2.9%)
	  ○ Asian: 4/34 (11.8%)
	  ○ Native Hawaiian or other Pacific Islander: 0%
	  ○ Black or African American: 2 (5.9%
	  ○ White: 8/34 (23.5%)
	  ○ Unknown/not reported: 19/34 (55.9%)
	• Number of participants (recruited/allocated/evaluated): NR/NR/34
	• Severity of condition according to study definition: not clear, but participants are at least hospitalised with COVID-19
	• Severity of condition according to WHO score: moderate to severe with WHO level > 4
	• Comorbidities: NR
	• Inclusion criteria
	  ○ Patients ≥ 18 years of age
	  ○ Hospitalised with COVID-19
	  ○ Enroled within 72 h of hospitalisation or within day 14 from first signs of illness
	  ○ Pulmonary infiltrates on chest imaging
	  ○ Oxygenation of < 95% on room air
	  ○ Laboratory-confirmed COVID-19
	• Exclusion criteria
	  ○ Contraindication to transfusion due to inability to tolerate additional fluid
	  ○ Baseline requirement for oxygen supplementation prior to COVID-19 infection or use of positive pressure therapy for sleep-disordered breathing
	  ○ Currently experiencing severe hypoxaemic failure, as defined in study endpoints
	  ○ Prior receipt of plasma products, IVIG, or hyperimmune globulin within past 3 months
	  ○ Not currently enroled in another interventional clinical trial of COVID-19 treatment
	• Donor eligibility criteria: NR
	• Donor exclusion criteria: NR

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 250 mL
	  ○ Number of doses: 1
	  ○ Antibody test and antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	  ○ RT-PCR tested: NR
	• Details of donors
	  ○ Gender: NR
	  ○ HLA and HNA antibody: NR

NCT04421404 *(Continued)*

- Severity of disease: NR
- Timing from recovery from disease: NR

- Treatment details, including time of plasma therapy (e.g. early stage of disease): enroled within 72 h of hospitalisation or within day 14 from first signs of illness
- Comparator: standard plasma (fresh frozen), AB0 compatible, 250 mL
- Concomitant therapy: standard care
- Duration of follow-up: 90 days
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
  - Mechanical ventilation or death
- Primary review outcomes reported
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: NR
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: yes, day 14 and 28
    - Improvement of clinical status - participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): any AEs
  - Number of participants with SAEs: NR
- Secondary review outcomes reported
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission on the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional outcomes
  - Mortality by day 90

Notes

- Recruitment status: completed
- Sponsor/funding: Priscilla Hsue, MD
- CoI: NR

Ortigoza 2022

Study characteristics

Methods

- Trial design: double-blind, placebo-controlled RCT
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates: 17 April 2020-15 March 2021
- Country: USA
- Language: English
- Number of centres: 2
- Trial registration number: NCT04364737

Ortigoza 2022 *(Continued)*

	• Date of trial registration: 28 April 2020

Participants	• Age (median, IQR; years)
	  ○ CP + SC: 62.0 (51.0-72.0)
	  ○ Placebo + SC: 64.0 (54.0-74.0)
	• Sex (N, %; female):
	  ○ CP + SC: 184/473 (39.3%)
	  ○ Placebo 201/468 (42.5%)
	• Ethnicity (N, %; female):
	  ○ Asian: CP 41 (8.8%), Placebo 30 (6.3%);
	  ○ Hispanic: CP 183 (39.1%), Placebo 190 (40.2%);
	  ○ Non-Hispanic Black: CP 69 (14.7%), Placebo 63 (13.3%)
	  ○ Non-Hispanic White: CP 153 (32.7%), Placebo 165 (34.9%);
	• Number of participants (recruited/allocated/evaluated): 13027/941/926
	• Severity of condition according to study definition: at baseline hospitalised patients with COVID-19 requiring non-invasive supplemental oxygen. Baseline WHO score 5 (n = 660), WHO score, 6 (n = 266)
	• Severity of condition according to WHO score: moderate to severe with WHO levels 5-6
	• Comorbidities: pulmonary, asthma, hypertension, cardiovascular, diabetes, CKD, liver disease, cancer, transplant, HIV
	• Inclusion criteria
	  ○ Patients ≥ 18 years of age
	  ○ Hospitalised with laboratory-confirmed COVID-19
	  ○ ≥ 1 of the following respiratory signs or symptoms: cough, chest pain, shortness of breath, fever, oxygen saturation ≤ 94%, abnormal chest X-ray/CT imaging)
	  ○ Hospitalised for ≤ 72 h or within 3-7 days from first signs of illness
	  ○ On supplemental oxygen, non-invasive ventilation or high-flow oxygen
	  ○ Participants may be on other RCTs of pharmaceuticals for COVID-19 and patients who meet eligibility criteria will not be excluded on this basis
	• Exclusion criteria
	  ○ Receipt of pooled immunoglobulin in past 30 days
	  ○ Contraindication to transfusion or history of prior reactions to transfusion blood products
	  ○ IMV or ECMO
	  ○ Volume overload secondary to congestive heart failure or renal failure
	  ○ Unlikely to survive past 72 h from screening based on the assessment of the investigator
	  ○ Unlikely to be able to assess and follow outcome due to poor functional status
	• Previous treatments: hydroxychloroquine, remdesivir, corticosteroids, therapeutic anticoagulation, antiplatelets, anti-inflammatory agents, antypyretics, antibacterial agents, ACE inhibitors, statins, acid-reducing agents
	• Donor eligibility criteria
	  ○ History of COVID-19 illness
	  ○ A positive COVID-19 test
	  ○ A 2-week period of being asymptomatic post-infection
	  ○ A negative nasopharyngeal swab for SARS-CoV2 by PCR
	• Donor exclusion criteria

Interventions	• Details of CP
	  ○ Type of plasma: CP, ABO-type matched
	  ○ Volume: ~ 250 mL
	  ○ Number of doses: 1
	  ○ Antibody-titre: reactive anti-SARS-CoV-2 antibody test on the SARS-CoV-2 Microsphere Immunoassay; signal-to-cutoff ratio ≥ 12 on the Ortho V platform
	  ○ Pathogen inactivated: yes
	• Details of donors

Ortigoza 2022 *(Continued)*

	○ Sex (N, or %; female): NR ○ Age (median, IQR or mean, SD; years): NR ○ HLA and HNA antibody negative: yes ○ Severity of disease: NR ○ Timing from recovery to disease: at least 2 weeks ○ RT-PCR tested: yes • Treatment details, including time of plasma therapy (e.g. early stage of disease): respiratory symptoms requiring oxygen supplementation within 3-7 days from the onset of illness or within 3 days of hospitalisation • Comparator: sterile saline or lactated Ringer's solution (equivalent volume to CP) • Concomitant therapy: NR • Duration of follow-up: 28 days • Treatment cross-overs: no • Compliance: yes (in CP, only 2 refused transfusion; in placebo, 7 refused transfusion)
Outcomes	• Primary study outcome(s) ○ Percentage of participants reporting each severity rating on the WHO ordinal scale for clinical improvement (time frame: 14 days post-randomisation) • Primary review outcomes ○ All-cause mortality during hospital stay: NR ○ 28 day mortality: yes ○ 60 day mortality: NR ○ Mortality (time-to-event): NR ○ Clinical status ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR ■ Improvement of clinical status: participants discharged from hospital: NR ○ QoL: NR ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes (any AEs) ○ Number of participants with SAEs: NR • Secondary outcomes ○ Improvement of clinical status: ■ weaning or liberation from IMV in surviving participants: NR ■ ventilator-free days: NR ■ liberation from supplemental oxygen in surviving participants: NR ○ Need for dialysis at up to 28 days: NR ○ Admission to the ICU on day 28: NR ○ Duration of hospitalisation: NR ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
Notes	• Journal article published: February 2022 • Sponsor/Funding: NYU Langone Health; Albert Einstein Medical Center • CoI: study authors declared their conflict of interests.

O'Donnell 2021

Study characteristics	
Methods	• Trial design: double-blind RCT • Type of publication: preprint • Setting: inpatient • Recruitment dates: 21 April-27 November 2020

O'Donnell 2021 *(Continued)*

- Country: USA and Brazil
- Language: English
- Number of centres: 5
- Trial registration number: NCT04359810
- Date of trial registration: 24 April 2020

Participants	• Age (median, IQR; years)
	  ○ CP + SC: 60 (48 - 71)
	  ○ SP + SC: 63 (49 - 72)
	• Sex (N, %; female)
	  ○ CP + SC: 54/150 (36%)
	  ○ SP + SC: 22/73 (30%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 630/223/150 (CP) and 73 (SC)
	• Severity of condition according to study definition: adults hospitalised with severe and critical COVID-19, as 57% (126/223) of participants required supplemental oxygen, 25% (55/223) required high-flow oxygen therapy or non-IMV, and 13% (28/223) required IMV or ECMO
	• Severity of condition according to WHO score: moderate to severe with WHO levels 5-9
	• Comorbidities: obesity, diabetes, COPD, hypertension, immunosuppression
	• Inclusion criteria
	  ○ Hospitalised patients aged ≥ 18 years
	  ○ Evidence of SARS-CoV-2 infection by PCR of nasopharyngeal, oropharyngeal swab, or tracheal aspirate sample within 14 days of randomisation
	  ○ Infiltrates on chest imaging
	  ○ Oxygen saturation ≤ 94% on room air or requirement for supplemental oxygen (including non-invasive positive pressure ventilation or high-flow supplemental oxygen), IMV, or ECMO at the time of screening
	• Exclusion criteria
	  ○ Participation in another clinical trial of anti-viral agent(s) for COVID-19
	  ○ Receipt of any anti-viral agent with possible activity against SARS-CoV-2 within 24 h of randomisation
	  ○ Duration of IMV or ECMO ≥ 5 days at time of screening; severe multi-organ failure
	  ○ History of prior reactions to transfusion blood products
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
	• Donor eligibility criteria
	  ○ Recovered from laboratory-confirmed COVID-19
	  ○ Provided informed consent
	  ○ Had a minimum anti-SARS-CoV-2 total IgG antibody titre of ≥ 1:400 by quantitative enzyme linked immunosorbent assay against the spike protein
	  ○ Were at least 14 days asymptomatic following resolution of COVID-19
	  ○ Had a negative PCR test for SARS-CoV-2 from a nasopharyngeal swab
	• Donor exclusion criteria: standard exclusions required for blood donation as per New York Blood Center criteria

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 200-250 mL
	  ○ Number of doses: 1 unit
	  ○ Type of antibody test and antibody-titre:
	  ■ IgG: ELISA, median titre 1:160 (IQR 1:80-1:320; available for 89% of plasma units)
	  ■ neutralising Ab: SARS-CoV-2 strain 2019-nCoV/USA-WA1-2020
	  ○ Pathogen inactivated: NR
	• Details of donors
	  ○ Sex (N, or %; female): NR

O'Donnell 2021 *(Continued)*

- Age (median, IQR or mean, SD; years): NR
- HLA and HNA antibody-negative: NR
- Severity of disease: NR
- Timing from recovery from disease: complete recovery of symptoms for at least 2 weeks prior to donation
- RT-PCR tested: yes (negative)

- Comparator: SP
- Concomitant therapy: during the trial period, 81% (181/223) of participants received corticosteroids and 6% (13/223) received remdesivir, hydroxychloroquine, antibacterial agent
- Duration of follow-up: 28 days
- Treatment cross-overs: no
- Compliance with assigned treatment: 4 participants were randomised but did not receive their assigned treatment: 3 participants (2 randomised to CP and one to SP) had improvements in oxygen saturation to > 94% prior to transfusion, and 1 participant randomised to CP developed a maculopapular rash prior to receipt of plasma for which subsequent transfusion was deferred.

Outcomes

- Primary study outcome
  - Clinical status at day 28 following randomisation, measured using a 7-point ordinal scale based on that recommended by WHO
- Primary review outcomes
  - All-cause mortality during hospital stay: yes
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR (only median and HR)
  - QoL: NR
  - Number of participants with grade 3 and grade 4 AEs: any grade AEs
  - Number of participants with SAEs: yes
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: median only
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional review outcomes
  - Time-to-clinical improvement (defined as improvement in at least 1 point from baseline on the ordinal scale or discharged from hospital, whichever came first)

Notes

- Preprint published 13 March 2021
- Journal article published on 11 May 2021
- Sponsor/funding: Max R. O'Donnell, Columbia University
- CoI: MRO and MJC participated as investigators for clinical trials evaluating the efficacy and safety of remdesivir in hospitalised patients with COVID-19, sponsored by Gilead Sciences. VG is employed by Amazon Care

Pouladzadeh 2021

Study characteristics

Methods	• Trial design: single-blind RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: March-May 2020 • Country: Iran • Language: English • Number of centres: 1 • Trial registration number: IRCT20200310046736N1 • Date of trial registration: 01 April 202

Participants	• Age (mean, SD; years)
	  ○ CP + SC: 53.5 (10.3)
	  ○ SC: 57.2 (17)
	• Sex (N, %; female):
	  ○ CP + SC: 14/30 (46.7 %)
	  ○ SC: 13/30 (43.3%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 62/62/60
	• Severity of condition according to study definition:
	  ○ intervention group: WHO level 5: 66.7%, WHO level 6: 33.3%
	  ○ control group: WHO level 5: 83.3%, WHO level 6: 16.7%
	• Severity of condition according to WHO score: moderate to severe with WHO levels 5 and 6
	• Comorbidities: diabetes mellitus, hypertension, and ischaemic heart disease. In some cases, asthma, rheumatoid arthritis, and hyperlipidaemia
	• Inclusion criteria
	  ○ COVID-19 patients who had specified COVID-19 symptoms (< 7 days since the onset of the symptoms)
	  ○ Positive results for PCR test and CT scan
	  ○ Severity WHO score > 4
	  ○ Blood oxygen saturation (SPO_2) ≤ 93% in room air
	  ○ No hypersensitivity to plasma IV administration
	  ○ Signed informed consent voluntarily
	• Exclusion criteria
	  ○ Pregnant or lactating (based on WHO protocol)
	  ○ People with specific allergic reactions to IV administration
	  ○ History of dangerous underlying diseases such as IgA deficiency
	  ○ History of dangerous diseases such as cardiovascular and or haematological disorders (haemophilia, thalassaemia, leukaemia)
	  ○ History of underlying diseases such as liver and kidney disease
	  ○ Smokers
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
	• Donor eligibility criteria
	  ○ Recovered individuals aged 20–45 years with a recovery asymptomatic period of at least 2 weeks
	  ○ Negative SARS-CoV-2 RT-qPCR test result
	  ○ Negative test result for Hepatitis B, C, AIDS, syphilis, HTLV-1, and influenza
	  ○ No IgA deficiency and or other dangerous underlying diseases
	  ○ Non-smokers
	  ○ Signed the informed consent
	  ○ Prior strong positive results for SARS-CoV-2 IgG/IgM Quick Test (German) for neutralising IgG antibodies and negative results for IgM antibodies

Pouladzadeh 2021 *(Continued)*

- Donor exclusion criteria
  - Pregnant and lactating women

Interventions	• Details of CP
	  ◦ Type of plasma: CP
	  ◦ Volume: 200 mL
	  ◦ Number of doses: in general 1 unit. 5 patients received a 2nd plasma unit
	  ◦ Type of antibody test and antibody-titre: NR
	  ◦ Pathogen inactivated or not: NR
	• Details of donors
	  ◦ Sex (N, or %; female): NR
	  ◦ Age (median, IQR or mean, SD; years): NR
	  ◦ HLA and HNA antibody-negative: NR
	  ◦ Severity of disease: NR
	  ◦ Timing from recovery from disease: NR
	  ◦ RT-PCR tested: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): < 7 days since symptom onset
	• Comparator: SC
	• Concomitant therapy: antiviral therapy, including ritonavir/lopinavir, and chloroquine phosphate
	• Treatment cross-overs: none
	• Compliance with assigned treatment: yes

Outcomes	• Primary study outcome
	  ◦ Improvement in the levels of cytokine storm indices
	• Primary review outcomes
	  ◦ All-cause mortality during hospital stay: NR
	  ◦ 28-day mortality: NR
	  ◦ 60-day mortality: yes
	  ◦ Mortality (time to event): NR
	  ◦ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death):
	  ■ Improvement of clinical status: participants discharged from hospital:
	  ◦ QoL: NR
	  ◦ Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR (frequency of CP therapy-related side effects)
	  ◦ Number of participants with SAEs: NR
	• Secondary review outcomes
	  ◦ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: NR
	  ◦ Need for dialysis at up to 28 days: NR
	  ◦ Admission to the ICU on day 28: NR
	  ◦ Duration of hospital stay: yes (length of in-hospital stay, HR)
	  ◦ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional outcomes
	  ◦ Changes in levels of biomarkers (IL-6, TFN-alpha, IFN-gamma, etc.)
	  ◦ Severity score pre- and post-treatment

Notes	• Journal article published on 10 April 2021 • Sponsor/funding: Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Faculty Research Grants)

Pouladzadeh 2021 *(Continued)*

- CoI: not reported

Ray 2022

Study characteristics

Methods	• Trial design: open-label RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 31 May 2020-12 October 2020 • Country: India • Language: English • Number of centres: 1 • Trial registration number: CTRI/2020/05/025209 • Date of registration: 15 May 2020

Participants	• Age (mean, SD; years):
	  ○ female: 61.43 ± 11.33 years
	  ○ male: 61.36 ± 12.17 years
	• Sex (%; female):
	  ○ 29 % in the intervention and control group together
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 80/80/80
	• Severity of condition according to study definition: severe COVID-19 patients with mild ARDS (defined as patients having PaO_2/FiO_2 ratio of 200-300 mmHg) or moderate ARDS (defined as PaO_2/FiO_2 100-200 mmHg) not on mechanical ventilation
	• Severity of disease according to WHO score: levels 5-6
	• Comorbidities: NR
	• Inclusion criteria
	  ○ Consenting patients admitted with RT-PCR-proven COVID-19 with severe disease (fever or suspected respiratory infection, plus one of the following:
	  ■ respiratory rate > 30 breaths/min
	  ■ severe respiratory distress
	  ■ SpO_2 < 90% at room air
	  ○ Mild ARDS - defined as patients having PaO_2/FiO_2 ratio of 200-300 mmHg - or moderate ARDS, defined as PaO_2/FiO_2 100-200 mmHg, not on mechanical ventilation
	• Exclusion criteria
	  ○ Pregnant or breastfeeding mothers, patients aged < 18 years, patients participating in any other clinical trial, patients having any clinical condition precluding infusion of blood products
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
	• Donor eligibility criteria
	  ○ Age > 18 years
	  ○ Male or nulliparous female convalescent volunteers with history of being positive for SARS-CoV-2 on RT-PCR
	  ○ Weight > 55 kg, complete resolution of symptoms at least 28 days prior to donation, and a negative RT-PCR test for SARS-CoV-2 before plasma donation
	• Donor exclusion criteria: NR

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 200 mL
	  ○ Number of doses: 2

Ray 2022 *(Continued)*

- Antibody test and antibody-titre: anti-SARS-CoV-2 spike protein IgG content via Euroimmun; value of 1.5 for the ratio optical density between the sample and calibrator was taken as a cut-off for inclusion
- Pathogen inactivated or not: NR

- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: NR
  - Severity of disease: between 1 and 5 on the WHO Clinical Progression score, majority mild disease
  - Timing from recovery from disease: complete resolution of symptoms at least 28 days prior to donation
  - RT-PCR-tested: 1 negative RT-PCR test
- Treatment details, including time of plasma therapy: NR
- Comparator: standard therapy
- Concomitant therapy
  - Hydroxychloroquine, azithromycin, ivermectinn, tocilizumab, remdesivir and doxycycline
  - If ARDS: O_2 therapy as per requirement, either IV or oral corticosteroids, for patients with D-dimer 1000 ng/mL FEU therapeutic anticoagulation using either LMWH or unfractionated heparin
  - Awake proning for 6-8 h/day was attempted in all participants with evidence for ARDS.
- Duration of follow-up: 30 days
- Treatment cross-overs: none
- Compliance with assigned treatment: 1 participant died before 2nd transfusion of CP

Outcomes

- Primary study outcome(s): all-cause mortality at 30 days
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): yes
  - Clinical status at day 28, day 60, and up to the longest follow-up, including the following:
    - worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): only transfusion-related AEs
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - wentilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: median only
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
  - Additional study outcomes
    - Immune correlates/cytokines for response to plasma therapy

Notes

- Preprint Ray posted: 29 November 2020
- Preprint Bandopadhyay posted: 7 October 2020
- Journal article published: 19 January 2022

Ray 2022 *(Continued)*

- Sponsor/funding: "DG acknowledges funding for the RCT and associated immune monitoring studies from Council of Scientific Industrial Research (CSIR), Govt. of India (MLP-129); RP acknowledges funding from CSIR (MLP-2005) and Fondation Botnar."
- COIs: "Nil"
- Other: "Nil"

Sekine 2021

Study characteristics

Methods	• Trial design: open-label RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 15 July-10 December 2020 • Country: Brazil • Language: English • Number of centres: 1 • Trial registration number: NCT04547660 • Date of trial registration: 14 September 2020

Participants	• Age (median, IQR; years)
	  ○ CP + SC: 59.0 (48.0 - 68.5)
	  ○ SC: 62.0 (49.5 - 68.0)
	• Sex (N, %; female)
	  ○ CP + SC: 31/80 (38.8%)
	  ○ SC: 36/80 (45.0%)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 443/160/160
	• Severity of condition: 33.7% of participants on medical ward and 66.3% in ICU with severe respiratory disease
	• Severity of condition according to WHO score: moderate to severe with WHO levels 5-7
	• Comorbidities: diabetes, hypertension, cardiovascular disease, COPD, obesity
	• Previous treatments: glucocorticoids, antibacterials
	• Inclusion criteria
	  ○ Age ≥ 18 years
	  ○ Diagnosis of SARS-CoV-2 infection through nasal cavity or oropharynx swab RT-PCR
	  ○ Severe COVID-19 defined by the presence of at least 1 of the following:
	  ■ respiratory rate > 30 breaths per min in room air
	  ■ oxygen saturation (O_2) ≤ 93% in room air
	  ■ PaO_2/FiO_2 ratio ≤ 300
	  ■ need for supplemental O_2 to maintain O_2 saturation > 95%
	  ■ need for therapy with supplemental O_2 by high-flow catheter or non-invasive ventilation or iIMV
	  ○ Onset of symptoms during previous 14 days
	  ○ Attending physician's consent
	  ○ No history of SAEs, such as transfusion anaphylaxis
	  ○ COVID-19 severe pneumonia defined according to WHO criteria: fever and at least 1 of the following: respiratory rate > 30 breaths/min, acute respiratory failure, oxygen saturation < 93%; or oxygen supplementation by nasal catheter; or ICU admission for any reason related to COVID-19 infection
	• Exclusion criteria
	  ○ Failure to perform the first plasma infusion within 14 days of the onset of symptoms

Sekine 2021 *(Continued)*

- Use of immunosuppressants for other underlying diseases, except corticosteroids for the SARS-CoV-2, in the 30 days before enrolment
- Pregnant
- History of SAEs, such as transfusion anaphylaxis
- Participation in another interventional clinical trial
- Disagreement of attending physician
- Decision by patient or legal representative not to participate in the study

- Donor eligibility criteria
  - Age 18-60 years
  - Diagnosis of COVID-19 by RT-PCR according to WHO criteria and/or IgG serology confirmed for SARS-CoV-2 by ELISA or chemiluminescence
  - No symptoms for at least 14 days, preferably < 40 days from symptom onset
  - A 2nd negative RT-PCR result for a nasal swab specimen
  - Haemoglobin > 12.5 g/dL for women (preferably nulliparous) and > 13.0 g/dL for men
  - Blood donation only according to Ministry of Health criteria (Portaria da Consolidação 5 28/9/2018 and RDC 34 11/6/2014)
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: fresh-frozen CP, thawed at 37 °C before infusion
  - Volume: 300 mL
  - Number of doses: 2 doses
  - Type of antibody test and antibody-titre:
    - neutralising antibodies (cytopathic effect-based virus neutralisation test (CPE-based VNT) with SARS-CoV-2/human/BRA/SP02cc/2020 strain virus, median titre 1:320 (IQR, 160 to 1:960)).
  - Pathogen inactivated or not: NR
- Details of donors
  - Sex (N, %; male): 31 (64.9%)
  - Age (median, IQR; years): 37 years (IQR 32.6-46.8)
  - HLA and HNA antibody-negative: NR
  - Severity of disease: NR
  - Timing from recovery from disease: NR
  - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): mean 10 days (SD 3 days) from symptom onset
- Comparator: best supportive care, any form of ventilatory support, ECMO, steroids, antibiotics and other supportive measures except for investigational interventions
- Concomitant therapy: see above
- Duration of follow-up: NR
- Treatment cross-overs: 1 in the SC group to receive CP; 2 in CP group did not receive CP
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome
  - Clinical improvement (time frame: 28 days)
  - Improvement of 2 points from randomisation in a 6-point ordinal severity scale
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: NR

Sekine 2021 *(Continued)*

- Improvement of clinical status: participants discharged from hospital: yes
- QoL: NR
- Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
- Number of participants with SAEs: NR

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes (median and IQR)
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: yes, day 7
- Additional study outcomes
  - 6-point ordinal scale proportion at 14 days
  - 6-point ordinal scale proportion at 28 days
  - Overall mortality (time frame: 14 days)
  - Days alive and free of respiratory support (DAFOR28) (time frame: 28 days)
  - Mechanical ventilation (time frame: 28 days)
  - PaO_2/FiO_2 ratio (time frame: at 7th day from randomisation)
  - Laboratory parameters at day 3, 7 and 14: LDH, troponin I, CRP, D-dimers, fibrinogen, prothrombin time (PT), activated partial thromboplastin time (APTT), tumour necrosis factor alpha (TNF-alpha), IL-6
  - Sequential organ failure assessment (SOFA) score (time frame: at 7th day from randomisation)
  - National Early Warning Score 2 (NEWS) 2 (time frame: at 7th and 14th days from randomisation)

Notes	• Journal article published: 12 August 2021 • Sponsor/funding: Hospital de Clinicas de Porto Alegre, "Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul" (FAPERGS) (grant 16/2551-0000242-8), "Fundação de Amparo à Pesquisa do Estado de São Paulo" (FAPESP) (grants2020/06409-1 and 2016/20045-7) and "Instituto Cultural Floresta" • CoI: RRGM received support from "Fundação de Amparo àPesquisa do Estado de São Paulo (FAPESP)" (2017/24769-2); RGR received research grants from Brazilian Ministry of Health; APZ is a research fellow of the National Council for Scientific and Technological Development (CNPq), Ministry of Science and Technology, Brazil (304226/2018-1), and receives a research grant not related to this work from Pfizer (WI242215 2018); all others have nothing to disclose.

Simonovich 2020

Study characteristics	
Methods	• Trial design: double-blind, multicentre RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: May-September 2020 • Country: Argentina • Language: English • Number of centres: 12 • Trial registration number: NCT04383535 • Date of trial registration: 12 May 2020
Participants	• Age (median, IQR; years)

Simonovich 2020 *(Continued)*

- CP + SC: 62.5 (53-72.5)
- Placebo + SC: 62 (49-71)

- Sex (N, %; female)
  - CP + SC: 67/228 (29.4%)
  - Placebo + SC: 41/105 (39.0%)
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 448/334/333
- Severity of condition according to study definition: all hospitalised; 4.8% in plasma group versus 6.7% in control group receiving high-flow oxygen (WHO = 6), 85.5% versus 81.9% receiving oxygen by mask or nasal prongs (WHO = 5), 9.7% versus 11.4% no oxygen (WHO = 4)
- Severity of condition according to WHO score: moderate with WHO level 4-5
- Comorbidities: BMI > 30, hypertension, diabetes, COPD, asthma, chronic renal failure, haematologic cancer, solid tumours, congestive heart failure, thromboembolic disease
- Inclusion criteria
  - At least 18 years of age
  - Hospitalised adults with an RT-PCR assay of a respiratory tract sample that was positive for SARS-CoV-2
  - Radiologically-confirmed pneumonia
  - No previous directives rejecting advanced life support
  - At least 1 of the following severity criteria: oxygen saturation (SaO_2) < 93% while they were at rest and breathing ambient air, PaO_2: FiO_2 < 300 mmHg, or SOFA or modified SOFA (mSOFA) score of ≥ 2 points above baseline status (scores range from 0-24, with higher scores indicating more severe disease)
  - Provision of informed consent by the participant
- Exclusion criteria
  - Pregnant or lactating, or of reproductive age and not willing to use contraceptive measures for a period of 30 days after enrolment
  - History of blood component allergies, an infectious cause of pneumonia other than SARS-CoV-2, a requirement for mechanical ventilation, multiorgan failure, or any other condition that would impede the provision of informed consent
  - Confirmation of another concomitant microbiological cause of pneumonia other than COVID-19
  - On mechanical ventilation, with multiple organ failure or who for any other reason could not voluntarily give their consent.
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
  - Drugs: ACEI or ARB 2, NSAID, anticoagulation, corticosteroids, immunosuppressants, statins
  - Use of oxygen supplementation devices: low-flow nasal cannula, venturi or non-rebreather mask, high-flow nasal cannula, noninvasive ventilatory support
- Donor eligibility criteria
  - General acceptance criteria for blood donors according to Administrative and Technical Regulations RM 797/13 - 139/14 - 1507/15. Directorate of Blood and Hemoderivatives of the Ministry of Health of the Nation, Argentine Association of Hemotherapy, Immunohematology and Cell Therapy (AAHITC).
  - Age: 18-60 years
  - People who had recovered from SARS-CoV-2 infection and subsequently negative for SARS-CoV-2 and for other respiratory viruses
  - 28 days since complete resolution of symptoms and return a negative result for COVID-19 (quali PCR swab or viral load in blood)
  - Multiparous donors had to be negative for anti-HLA antibodies. If the determination of anti-HLA antibodies could not be carried out, multiparous donors were not accepted.
  - The specific titre of total antibodies had to be > 1/1000
  - Study profile of transfusion transmissible infections (TTI) had to be negative for hepatitis B virus, hepatitis C virus, HIV, syphilis, brucellosis, human T-lymphotropic virus and Chagas disease

Simonovich 2020 *(Continued)*

	○ The donor had to read, understand and voluntarily sign the informed consent for Apheresis Plasma Donation. • Donor exclusion criteria: NR
Interventions	• Details of CP ○ Type of plasma: CP ○ Volume: 5-10 mL/kg with an inferior limit around 400 mL when body weight was < 70 kg, and a superior limit of 600 mL for those > 70 kg. Median volume of infused CP was 500 mL (IQR 415-600) ○ Number of doses: 1 ○ Type of antibody test and antibody-titre: COVIDAR Argentina Consortium ELISA test ○ Pathogen inactivated or not: NR • Details of donors ○ Sex (N, or %; female): NR ○ Age (median, IQR or mean, SD; years): NR ○ HLA and HNA antibody-negative: negative for anti-HLA antibodies in multiparous females, if measurement not available, exclusion ○ Severity of disease: NR ○ Timing from recovery from disease: fully recovered from a clinical perspective and discharged from the hospital for at least 2 weeks ○ RT-PCR tested: yes • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: placebo (saline) • Concomitant therapy: antiviral agents (lopinavir - ritonavier, tocilizumab, hydroxychlorochine), ivermectin, glucocorticoids, • Duration of follow-up: 30 days • Treatment cross-overs: none • Compliance with assigned treatment: good (according to flow-chart)
Outcomes	• Primary study outcome ○ Clinical status 30 days after intervention, as represented by 1 of 6 mutually exclusive ordinal categories on an adapted version of the WHO clinical scale: 1 indicated death, 2 invasive ventilatory support, 3 hospitalised with supplemental oxygen requirement, 4 hospitalised without supplemental oxygen requirement, 5 discharged without full return to baseline physical function, and 6 discharged with full return to baseline physical function. • Primary review outcomes ○ All-cause mortality during hospital stay: NR ○ 28-day mortality: yes ○ 60-day mortality: NR ○ Mortality (time to event): yes ○ Clinical status at day 28, day 60, and up to the longest follow-up, including the following: ■ worsening of clinical status: participants with clinical deterioration (new need for IMV) or death: yes, calculated from mutually exclusive categories (table 2) ■ improvement of clinical status: participants discharged from hospital: yes, calculated from mutually exclusive categories (table 2) ○ QoL: NR ○ Participants with grade 3 and grade 4 AEs: yes ○ Participants with SAEs: yes • Secondary review outcomes ○ Improvement of clinical status: ■ weaning or liberation from IMV in surviving participants: NR ■ ventilator-free days: NR ■ liberation from supplemental oxygen in surviving patients: NR ○ Need for dialysis at up to 28 days: NR ○ Admission to the ICU on day 28: yes

Simonovich 2020 *(Continued)*

- Duration of hospitalisation: NR
- Viral clearance(RT-PCR): NR

- Additional review outcomes
  - Time to improvement in at least 2 categories on the ordinal scale
  - Time to full functional recovery

Notes	• Journal article publication: 24 November 2020 • Sponsor/funding: grant by the Hospital Italiano de Buenos Aires, and the participant institutions which provided their own funding • CoI: disclosure forms not yet available (accessed 28 March 2022)

Sullivan 2022

Study characteristics

Methods	• Trial design: double-blind RCT • Type of publication: full-text article • Setting: outpatient • Recruitment dates: 3 June 2020-1 October 2021 • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04373460 • Date of trial registration: 4 May 2020

Participants	• Age (median, IQR; years)
	  ○ CP + SC: 42 (32-54)
	  ○ SP + SC: 44 (33-55)
	• Sex (N, %; female)
	  ○ CP + SC: 323 (54.6%)
	  ○ SP + SC: 352 (59.8%)
	• Ethnicity
	  ○ Asian: CP 22/592 (3.7%), SP: 22/589 (3.7%)
	  ○ Black: CP 92/592 (15.5%, SP: 71/589 (12.1%)
	  ○ American Indian or Alaska Native: CP 8/592 (1.4%), SP: 9/589 (1.5%)
	  ○ Native Hawaiian or other Pacific Islander: CP: 2/592 (0.3%), 2/589 (0.3%)
	  ○ White: CP 459/592 (77.5%), SP: 475/589 (80.6%)
	  ○ Hispanic/Latino: CP 80/592 (13.5%), SP: 90/598 (15.3%)
	• Number of participants (recruited/allocated/evaluated): 5916/1225/1181
	• Severity of condition according to study definition: mild disease, diagnostic test-positive for SARS-CoV-2 and < 8 days of COVID-19
	• Severity of condition according to WHO score: mild disease with WHO level 1-3
	• Comorbidities: hypertension, diabetes, asthma, HIV infection, pregnancy, coronary artery disease, congestive heart failure, stroke, immunosuppressed CKD, organ transplant, active cancer, cancer any, liver disease
	• Vaccination status: 82.5% unvaccinated, 4.9% partially vaccinated, 12.6% fully vaccinated
	• Inclusion criteria
	  ○ ≥ 18 years of age
	  ○ Competent and capable to provide informed consent, and able and willing to comply with protocol requirements listed in informed consent
	  ○ Positive RNA test for presence of SARS-CoV-2 in fluid collected by oropharyngeal or nasopharyngeal swab

Sullivan 2022 *(Continued)*

- Experiencing any symptoms of COVID-19 including but not limited to fever (T > 100.5° F), cough, or other COVID-associated symptoms like anosmia
- ≤ 8 days since the first symptoms of COVID-19
- ≤ 8 days since first positive SARS-CoV-2 RNA test

- Exclusion criteria
  - Hospitalised or expected to be hospitalised within 24 h of enrolment
  - Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect participant safety and/or compliance
  - History of prior reactions to transfusion blood products
  - Inability to complete therapy with the study product within 24 h after enrolment
  - Receiving any treatment drug for COVID-19 within 14 days prior to screening evaluation (off-label like hydroxychloroquine, compassionate use or study trial related)
- Previous treatments: NR
- Donor eligibility criteria:
  - adult
  - qualified with SARS-CoV-2 antibody (Euroimmun) with minimum titres of ≥ 1:320 as determined using a validated ELISA assay in a CLIA-certified laboratory
  - After qualification, the donor CP was characterised for antibody levels by Euroimmun ratio at 1:101 and endpoint titres
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: ABO-matched FFP or plasma frozen within 24 h of phlebotomy (PF24)
  - Volume: 200-250 mL
  - Number of doses: 1
  - Antibody-titre: titre ≥ 1:320 or current FDA standard titre (80% of all the units had SARS-CoV-2 spike protein antibody titres of at least 1:4860)
  - Pathogen inactivated: NR
- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: NR
  - Severity of disease: NR
  - Timing of recovery from disease: NR
  - RT-PCR tested:
- Treatment details, including time of plasma therapy (e.g. early stage of disease): enrolment within 8 days after symptom onset, infusion within 24 h of enrolment
- Comparator: standard plasma
- Concomitant therapy: NR
- Treatment cross-overs: no
- Compliance: 18/610 in CP and 26/615 in SP group did not receive the assigned intervention, excluded from "mITT" analysis

Outcomes

- Primary study outcome
  - Cumulative incidence of hospitalisation or death prior to hospitalisation (time frame: up to day 28): reported as hospitalisations
  - Cumulative incidence of treatment-related SAEs (time frame: up to day 28)
  - Cumulative incidence of treatment-related grade 3 or higher AEs (time frame: up to day 90)
- Primary review outcomes reported
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Admission to hospital or death within 28 days: yes
  - Symptom resolution:

Sullivan 2022 *(Continued)*

- all initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up: NR
- time to symptom resolution: NR

- QoL: NR
- Number of participants with AEs (any grade, grades 1-2, grades 3-4): grades 3-4 AEs reported as number of AEs, not number of participants
- Number of participants with SAEs: NR

- Secondary outcomes
  - Worsening of clinical status:
    - need for IMV or death: NR
    - need for hospitalisation with oxygen by mask or nasal prongs, or death: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Time to ICU admission, IMV or death in hospital (90 days)
  - Impact of donor antibody titres on hospitalisation rate of CP recipients (time frame: day 0-day 90)

Notes	• Preprint published: 21 December 2021 • Journal article published: March 2022 • Sponsor/funding: principally by the U.S. Department of Defense's (DOD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEOCBRND), in collaboration with the Defense Health Agency (DHA); additional support from Bloomberg Philanthropies, the National Health Institute, National Institute of Allergy and Infectious Diseases, NIH National Center for Advancing Translational Sciences (NCATS), Division of Intramural Research NIAID NIH, Mental Wellness Foundation, Moriah Fund, Octapharma, HealthNetwork Foundation and the Shear Family Foundation • CoI: disclosure forms provided online

Van den Berg 2022

Study characteristics

Methods	• Trial design: double-blinded RCT (with unplanned interim analyses due to variant change) • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 30 September 2020-14 January 2021 • Country: South Africa • Language: English • Number of centres: 4 • Trial registration number: NCT04516811 • Date of trial registration: 24 April 2020

Participants	• Age (median, IQR; in years)
	  ○ CP: 54 (46–62)
	  ○ Placebo: 57 (47–64)
	• Sex (N, %; female):
	  ○ CP: 31/52 (59.6 %)
	  ○ Placebo: 30/51 (58.8 %)
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 109/107/103
	• Severity of condition according to study definition: moderate to severe COVID-19 disease, defined as SpO2 ≤ 93% on room air; plus requiring non-invasive oxygen therapy (WHO R&D BOSCI 4 or 5)
	• Severity of condition according to WHO score: moderate to severe with WHO levels 4-6

Van den Berg 2022 *(Continued)*

- Comorbidities: HIV (25% of those tested), obesity (47.6%), CKD (2.9%), diabetes (38.8%), hypertension (54.4%), cardiovascular disease (2.9%), cancer (1.9%), chronic pulmonary disease (3.9%)
- Inclusion criteria
  - Laboratory-confirmed SARS-CoV-2 by positive RT-PCR on any respiratory sample
  - Age ≥ 18 years
  - Require hospital admission for COVID-19 pneumonia as defined by the presence of pulmonary infiltrates on chest X-ray
  - Moderate to severe COVID-19 disease, defined as: SpO2 ≤ 93% on room air; plus requiring non-invasive oxygen therapy (WHO R&D BOSCI 4 or 5)
  - Signed informed consent
  - Pregnant women allowed to participate
- Exclusion criteria
  - Current participation in another therapeutic clinical trial for COVID-19
  - IMV
  - Expected survival < 24 h based on clinical assessment (however, the study does not exclude critically ill patients who are not, due to resource limitations, candidates for critical care admission and/or mechanical ventilation)
  - Known hypersensitivity to immunoglobulin or any components of the formulation
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
- Donor eligibility criteria
  - Recovered from SARS-CoV-2 infection confirmed by positive nasopharyngeal swab RT-PCR
  - ≥ 14 days after 2 sequential negative nasopharyngeal swab PCR tests performed ≥ 24 hours apart, or ≥ 28 days after last symptoms
  - Age ≥ 18 years
  - Weight ≥ 55kg
  - Healthy lifestyle
  - Males and nulliparous females
- Donor exclusion criteria: NR

Interventions

- Details of CP
  - Type of plasma: CP
  - Volume: 200-250 mL
  - Number of doses: 1
  - Type of antibody test and antibody-titre:
    - ELISA National Institute of Communicable Diseases (NICD); median anti-spike protein IgG optical density (OD450nm) was 2.7 AU/mL (IQR 2.0 to 3.0)
    - neutralising Ab: ID50 of 1:234 AU/mL (IQR 194 to 304; range 71-1245)
  - Pathogen inactivated: pathogen reduced using a riboflavin- or amotosalen-mediated process
- Details of donors
  - Sex (N, or %; female): NR
  - Age (median, IQR or mean, SD; years): NR
  - HLA and HNA antibody-negative: NA
  - Severity of disease: NR
  - Timing from recovery from disease: at least 14 days
  - RT-PCR tested: yes, twice
- Treatment details, including time of plasma therapy (e.g. early stage of disease): median time from symptom onset to infusion: 9 days (IQR 6-11)
- Comparator: 0.9% normal saline placebo (200 mL), with local SC
- Concomitant therapy: antibiotic (24.3%)
- Duration of follow-up: 28 days
- Treatment cross-overs: none
- Compliance with assigned treatment: 4/107 were not transfused

Outcomes

- Primary study outcome:

Van den Berg 2022 *(Continued)*

- Clinical improvement (time frame: day 28): proportion of participants with successful treatment outcome, defined as clinical improvement (≥ 2 points on WHO R&D BOSCI 1)

- Primary review outcomes reported
  - All-cause mortality at hospital discharge: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): yes
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: assessed, but NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): any AE
  - Number of participants with SAEs: NR
- Secondary review outcomes reported
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR

Notes	• Journal article published: 15 February 2022
	• Sponsor/funding:
	  ◦ ELMA South Africa Foundation (20-ESA011)
	  ◦ Allan & Gill Gray Philanthropy LIMITED
	  ◦ Wellcome
	  ◦ South African Medical Research Council with funds received from the Department of Science and Innovation
	  ◦ SW was supported by Wellcome (Grant number 203135/Z/16/Z) andNational Institutes of Health (K43TW011421)South African National Blood Service (SANBS), Karin van den Berg, Dr, South African National Blood Service
	• CoI: "The authors declare no competing interests"

AE: adverse event; **ALT:** alanine transaminase; **ARDS:** acute respiratory distress syndrome; **AST:** aspartate transaminase; **ATS:** American Thoracic Society; **AU:** astronomical unit; **BAL:** bronchoalveolar lavage; **BMI:** body mass index; **CAP:** community-acquired pneumonia; **CKD:** chronic kidney disease; **CoI:** conflict of interest; **COPD:** chronic obstructive pulmonary disease; **CP:** convalescent plasma; **CPK:** creatine phosphokinase; **CRP:** c-reactive protein; **CT:** computed tomography; **ECMO:** extracorporeal membrane oxygenation; **ED:** emergency department; **ELISA:** enzyme-linked immunosorbent assay; **EMA:** European Medicines Agency; **FDA:** US Food and Drug Administration; **FiO_2:** fractional inspired oxygen; **GFR:** glomerular filtration rate; **HBV/HCV:** hepatitis B/C; **HLA:** human leukocyte antigen; **HNA:** human neutrophil antigens; **ICU:** intensive care unit; **IDSA:** Infectious Diseases Society of America; **IgA (B/G/M):** immunoglobulin A (B/G/M);**IL-6:** interleukin-6; **IMV:** invasive mechanical ventilation;**IQR:** interquartile range; **IV:** intravenous; **IVIG:** intravenous immunoglobulin; **LAR:** legal authorised representative; **LDH:** lactate dehydrogenase; **LMWH:** low molecular-weight heparin; **MAP:** mean arterial pressure; **NR:** not reported; **NYHA:** New York Heart Association; **PaO_2:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **PRNT:** plaque reduction neutralisation test; **QoL:** quality of life; **RCT:** randomised controlled trial; **RNA:** ribonucleic acid; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SARS:** severe acute respiratory syndrome; **SC:** subcutaneous; **SD:** standard deviation; **SC:** standard care; **SOFA:** sequential organ failure assessment; **SP:** standard plasma; **SpO_2:** peripheral capillary oxygen saturation; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TB:** tuberculosis; **TRALI:** transfusion-related acute lung injury; **UIP:** usual interstitial pneumonia; **ULN:** upper limit of normal; **WHO:** World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdullah 2020	Single arm study; fewer than 500 participants received convalescent plasma
Abolghasemi 2020	Non-randomised study ; fewer than 500 participants received convalescent plasma
Ahn 2020	Single-arm study; not pre-registered in a clinical study registry
Allahyari 2021	Non-randomised controlled study
Anderson 2020	Single-arm study; not pre-registered in a clinical study registry
Baklaushev 2020	Controlled study, probably not truly randomised
Balcells 2020	Performed another intervention comparison (early vs deferred plasma)
Bao 2020b	Single-arm study; not pre-registered in a clinical study registry
Bobek 2020	Single-arm study; not pre-registered in a clinical study registry
Bradfute 2020	Single arm study; fewer than 500 participants received convalescent plasma
Brasil Ministerio 2020	Standard operating procedure
Budhai 2020	Feasibility of plasma collection only
Cantore 2020	Single-arm study compared to published cases; not pre-registered in a clinical study registry
Cao 2020a	Ineligible intervention
Chen 2020b	Ineligible intervention
Chen 2020c	Ineligible intervention
ChiCTR2000029850	Single arm study; fewer than 500 participants will receive convalescent plasma
ChiCTR2000030039	Single arm study; fewer than 500 participants will receive convalescent plasma
ChiCTR2000030312	Study cancelled before starting recruitment
ChiCTR2000030381	Study cancelled before starting recruitment
ChiCTR2000030442	Study cancelled before starting recruitment
ChiCTR2000031501	Single arm study; fewer than 500 participants will receive convalescent plasma
ChiCTR2000033798	Single arm study; fewer than 500 participants will receive convalescent plasma
Clark 2020	Single-arm study; not pre-registered in a clinical study registry
CTRI/2020/04/024804	Single arm study; fewer than 500 participants will receive convalescent plasma
CTRI/2020/08/027285	Single arm study; fewer than 500 participants will receive convalescent plasma
CTRI/2020/09/027903	Ineligible intervention with hyperimmune immunoglobulin
CTRI/2020/10/028547	Ineligible intervention

Study	Reason for exclusion
de Assis 2020	Ineligible indication
Donato 2020	Single arm study; fewer than 500 participants received convalescent plasma
Duan 2020	Single arm study; fewer than 500 participants received convalescent plasma
Dulipsingh 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Díez 2020	Ineligible intervention
Enzmann 2020	Single-arm study; not pre-registered in a clinical study registry
Erkurt 2020	Single-arm study; not pre-registered in a clinical study registry
EUCTR2020-005979-12-GR	Ineligible intervention: hyperimmune immunoglobulin
Fan 2020	Single-arm study; not pre-registered in a clinical study registry
Figlerowicz 2020	Single-arm study; not pre-registered in a clinical study registry
Franchini 2020	Standard operating procedure
Gaborit 2021	Ineligible intervention: hyperimmune immunoglobulin
Grisolia 2020	Single-arm study; not pre-registered in a clinical study registry
Hashim 2020	Feasibility of plasma collection only
Hu 2020	Ineligible intervention
Ibrahim 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Im 2020	Single-arm study; not pre-registered in a clinical study registry
IRCT20151228025732N53	Single-arm study; fewer than 500 participants will receive convalescent plasma
IRCT20200406046968N2	Single-arm study; fewer than 500 participants will receive convalescent plasma
IRCT20200414047072N1	Single-arm study; fewer than 500 participants will receive convalescent plasma
IRCT20200416047099N1	Single-arm study; fewer than 500 participants will receive convalescent plasma
IRCT20200508047346N1	Ineligible intervention: hyperimmune immunoglobulin
IRCT20200525047562N1	Non-randomised study with fewer than 500 participants receiving convalescent plasma
ISRCTN86534580	Ineligible intervention
Jamous 2020	Single-arm study; not pre-registered in a clinical study registry
Jiang 2020a	Single-arm study; not pre-registered in a clinical study registry
Jiang 2020b	Ineligible intervention
Jin 2020	Single-arm study; fewer than 500 participants received convalescent plasma

Study	Reason for exclusion
Joyner 2020	Expanded-access study
jRCT2031200174	Ineligible intervention with hyperimmune immunoglobulin
Karatas 2020	Single-arm study; not pre-registered in a clinical study registry
Kong 2020	Single-arm study; not pre-registered in a clinical study registry
Lin 2020	Ineligible intervention
Liu 2020a	Single-arm study; fewer than 500 participants received convalescent plasma
Liu 2020b	Single-arm study; not pre-registered in a clinical study registry
Madariaga 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Martinez-Resendez 2020	Single-arm study; not pre-registered in a clinical study registry
McCuddy 2020	Single-arm study; not pre-registered in a clinical study registry
Ministerio de Salud 2020	Standard operating procedure
Mira 2020	Single-arm study; not pre-registered in a clinical study registry
NCT04261426	Ineligible intervention
NCT04264858	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04292340	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04321421	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04323800	Ineligible participant population (participants exposed to COVID-19)
NCT04325672	Study cancelled before starting recruitment
NCT04327349	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04332380	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04333355	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04338360	Expanded-access study
NCT04344015	Feasibility of plasma collection only
NCT04344379	Ineligible intervention
NCT04344977	Feasibility of plasma collection only
NCT04345679	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04346589	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04347681	Controlled, non-randomised study with fewer than 500 participants receiving convalescent plasma

Study	Reason for exclusion
NCT04348877	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04350580	Ineligible intervention
NCT04352751	Single-arm study
NCT04353206	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04354831	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04355897	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04356482	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04358211	Expanded-access study
NCT04360278	Feasibility of plasma collection only
NCT04360486	Expanded-access studies
NCT04363034	Expanded-access studies
NCT04365439	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04366245	Ineligible intervention: hyperimmune immunoglobulin
NCT04368013	Ineligible intervention
NCT04372368	Expanded-access study
NCT04374370	Expanded-access studies
NCT04374565	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04376034	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04377568	This study was withdrawn
NCT04377672	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04383548	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04384497	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04384588	Controlled, non-randomised study with fewer than 500 participants receiving convalescent plasma or hyperimmune immunoglobulin
NCT04388527	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04389710	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04389944	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04390178	Single-arm study; fewer than 500 participants will receive convalescent plasma

Study	Reason for exclusion
NCT04392232	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04393727	Terminated in November 2020 (study was stopped because the sponsor was changed and a new study on convalescent plasma sponsored by the Italian Medicines Agency (AIFA) was started in Italy)
NCT04395170	Ineligible intervention: hyperimmune immunoglobulin
NCT04397523	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04407208	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04408040	Non-randomised study
NCT04408209	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04411602	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04412486	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04418531	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04420988	Expanded-access studies
NCT04432103	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04432272	Non-randomised study with fewer than 500 participants receiving convalescent plasma
NCT04438694	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04445207	Expanded-access studies
NCT04458363	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04462848	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04463823	Prospective case-only study
NCT04467151	Study withdrawn
NCT04468958	Ineligible intervention: hyperimmune immunoglobulin
NCT04469179	Ineligible intervention: hyperimmune immunoglobulin
NCT04471051	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04472572	Expanded-access studies
NCT04474340	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04476888	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04492501	Non-randomised factorial design
NCT04497779	Prospective cohort study

Study	Reason for exclusion
NCT04502472	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04513158	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04514302	Ineligible intervention: hyperimmune immunoglobulin
NCT04516954	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04524507	Ineligible comparison: high vs low titre
NCT04535063	Single-arm study; fewer than 500 participants received convalescent plasma
NCT04545047	Observational study
NCT04546581	Ineligible intervention: hyperimmune immunoglobulin
NCT04554992	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04555109	Study of plasma donors
NCT04555148	Ineligible intervention: hyperimmune immunoblogulin
NCT04565197	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04569188	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04570982	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04573855	Ineligible intervention: hyperimmune immunoglobulin
NCT04593940	Completed platform trial without a convalescent plasma arm
NCT04610502	Ineligible intervention: hyperimmune immunoglobulin
NCT04614012	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04616976	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04622826	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04638634	Study on pharmacokinetics
NCT04642014	Single arm study
NCT04644198	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04661839	Pharmacokinetics study
NCT04669990	Prospective case-only study
NCT04721236	Single-arm hyperimmune immunoglobulin study with fewer than 500 participants
Niu 2020	Single-arm study; not pre-registered in a clinical study registry
Olivares-Gazca 2020	Single-arm study; fewer than 500 participants received convalescent plasma

Study	Reason for exclusion
Pei 2020	Single-arm study; not pre-registered in a clinical study registry
Peng 2020	Single-arm study; not pre-registered in a clinical study registry
PER-031-20	Single-arm study; fewer than 500 participants will receive convalescent plasma
Perotti 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Qiu 2020	No use of convalescent plasma. Reporting on generalised collection of information about COVID-19 infection relating to aetiology, pathology, symptoms, clinical presentation and some generalised pharmacological treatment methods. The papers do not contain patient data that we required. Article translated by Rujan Shrestha and Ya-Ying Wang via Cochrane TaskExchange
Rasheed 2020	Controlled study, probably not truly randomised
RBR-4vm3yy	Single-arm study; fewer than 500 participants will receive convalescent plasma
RBR-5r8gv8p	This study was suspended
Robbiani 2020	Ineligible intervention
RPCEC00000323	Single-arm study; fewer than 500 participants will receive convalescent plasma
Salazar 2020a	Single-arm study; fewer than 500 participants received convalescent plasma
Salazar 2020b	Single-arm study; not pre-registered in a clinical study registry
Shen 2020	Single-arm study; not pre-registered in a clinical study registry
Shi 2020	Ineligible intervention
Soleimani 2020	Single-arm study; not pre-registered in a clinical study registry
Taher 2020	Single-arm study; not pre-registered in a clinical study registry
Tan 2020	Single-arm study; not pre-registered in a clinical study registry
Tu 2020	No use of convalescent plasma. Reporting on generalised collection of information about COVID-19 infection relating to aetiology, pathology, symptoms, clinical presentation and some generalised pharmacological treatment methods. The papers do not contain patient data that we required. Article translated by Rujan Shrestha and Ya-Ying Wang via Cochrane TaskExchange
Wang 2020	Single-arm study; not pre-registered in a clinical study registry
Wright 2020	Single-arm study; not pre-registered in a clinical study registry
Xia 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Xie 2020	Ineligible intervention
Xu 2020b	Single-arm study; not pre-registered in a clinical study registry
Yang 2020	Single-arm study; not pre-registered in a clinical study registry

Study	Reason for exclusion
Ye 2020	Single-arm study; not pre-registered in a clinical study registry
Zeng 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Zhang 2020a	Single-arm study; not pre-registered in a clinical study registry
Zhang 2020b	Single-arm study; not pre-registered in a clinical study registry
Zhang 2020c	Single-arm study; not pre-registered in a clinical study registry
Çınar 2020	Single-arm study; not pre-registered in a clinical study registry

Characteristics of studies awaiting classification *[ordered by study ID]*

CTRI/2020/05/025299

Methods	• Trial design: randomised, parallel-group trial • Sample size: 20 • Setting: inpatient • Country: India • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Men or women aged 18-75 years (both inclusive)
	  ○ Hospitalised with RT-PCR-confirmed COVID-19 illness and had one of either:
	  ■ PaO_2/ FiO_2 < 300
	  ■ respiratory rate > 24/min and SaO_2 < 93% on room air
	  ○ Participant or legal authorised representative agreed to provide a signed written informed consent prior to any study-specific procedures and also agreed to comply with study requirements
	• Exclusion criteria
	  ○ Receipt of pooled immunoglobulin in past 30 days
	  ○ Contraindication to transfusion or history of prior reactions to transfusion blood products
	  ○ Critically ill with:
	  ■ PaO_2/ FiO_2 ratio < 200 (moderate - severe ARDS)
	  ■ shock
	  ○ Participating in any other clinical trial
	  ○ Clinical status precluding infusion of blood products
	  ○ Women with positive pregnancy test, breastfeeding, or planning to become pregnant or breastfeed during the study period

Interventions	• Details of CP
	  ○ Type of plasma: NR
	  ○ Volume: NR
	  ○ Number of doses: 1 dose; additional unit will be given only if required based on participant's clinical status
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): SC

CTRI/2020/05/025299 *(Continued)*

- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes	• Primary study outcome
	  ○ Avoidance of progression to severe ARDS
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: yes
	  ○ 28-day mortality: yes
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
	  ○ Number of participants with SAEs: NR
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: yes
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission to the ICU on day 28: NR
	  ○ Duration of hospitalisation: NR
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: yes
	• Additional study outcomes
	  ○ Improvement in symptoms and radiological findings
	  ○ Change in anti-SARS-CoV-2 titres pre- and post-plasma transfusion
	  ○ Evaluated duration and type (invasive or non-invasive) of ventilation support needed

Notes	• Recruitment status: completed, no results available • Prospective completion date: 28 August 2020 • Sponsor/funding: Wockhardt Limited, Wockhardt Towers, 1st Floor, West Wing, Bandra Kurla Complex Mumbai – 400 051, India

CTRI/2020/05/025328

Methods	• Trial design: randomised, parallel-group, active controlled trial • Sample size: 100 • Setting: inpatient • Country: India • Language: English • Number of centres: 5
Participants	Inclusion criteria • Tested positive for COVID-19 by RT-PCR • Age > 18 years • Written and informed consent • Severe disease, defined as ≥ 1 of: ○ dyspnoea with oxygen saturation 93%

CTRI/2020/05/025328 *(Continued)*

- respiratory frequency 30/min and oxygen saturation 93%
- PaO_2:FiO_2
- infiltrates on chest X-ray > 50% within 24-48 h

- Life-threatening disease, defined as ≥ 1 of:
  - respiratory failure needing invasive support
  - sepsis
  - multiple organ dysfunction or failure
- Exclusion criteria
  - Known hypersensitivity to blood products
  - Receipt of pooled immunoglobulin in last 30 days
  - Participating in any other clinical trial
  - Contraindications to blood products
  - Pregnant or breastfeeding women
  - In the opinion of the site investigator or primary clinical care team, expected to die within 48 h
  - On mechanical ventilation for > 7 days
  - Acute or chronic disease/illness that, in the opinion of the site investigator, had an expected life expectancy of > 28 days unrelated to COVID-19-induced pneumonia (e.g. stage IV malignancy, neurodegenerative disease, anoxic brain injury, etc.)
  - Respiratory failure caused by illness other than SARS-CoV-2
  - Other documented, uncontrolled infection
  - Severe DIC, TTP, or antithrombin III deficiency needing factor replacement, FFP, cryoprecipitate
  - Active intracranial bleeding
  - Clinically significant myocardial ischaemia

Interventions

- Details of CP
  - Type of plasma: NR
  - Volume: 200 mL
  - Number of doses: 2 doses
  - Antibody-titre: NR
  - Pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): SC
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome
  - All-cause mortality at 28 days
  - Improvement of SOFA score post-transfusion
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
  - Number of participants with SAEs: NR

CTRI/2020/05/025328 *(Continued)*

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Time to symptom resolution - fever, shortness of breath, fatigue
  - Change in oxygen requirement post-transfusion
  - Decreased duration of respiratory support required:
    - duration of IMV
    - duration of non-invasive/high-flow nasal cannula
  - Radiological improvement
  - AEs associated with transfusion
  - Levels of bio-markers (CRP, IL-6, ferritin) pre- and post-transfusion
  - Need to use vasopressor

Notes	• Recruitment status: completed • Prospective completion date: 1 December 2020 • Sponsor/funding: Indraprastha Apollo Hospitals (a unit of Apollo Hospitals Enterprise Limited), Mathura Rd, SaritaVihar, New Delhi -110076

CTRI/2020/06/025803

Methods	• Trial design: parallel group, active RCT • Sample size: 400 • Setting: inpatient • Country: India • Language: English • Number of centres: 3

Participants	• Inclusion criteria
	  ◦ Age > 18 years
	  ◦ Patients with severe COVID-19
	  ▪ Severe COVID-19 defined by WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (version 5.0)
	  ▪ Along with confirmation by real-time RT-PCR assay with severe disease i.e. meeting any 2 of the following criteria:
	  ▪ Patients on ventilator (in last 24 hours)
	  ▪ Respiratory distress
	  ▪ Heart rate ≥ 30 beats/min
	  ▪ Oxygen saturation level < 90 % in resting state
	  ▪ PaO_2/FiO_2 ≤ 300 mmHg
	  ▪ Lung infiltrates > 50% within 24-48 h
	• Exclusion criteria
	  ◦ Patient/ family members who do not give consent to participate in the study
	  ◦ Patients aged < 18 years

CTRI/2020/06/025803 *(Continued)*

- Patients presenting with multi-organ failure
- Pregnancy
- Individuals with HIV and viral hepatitis and cancer
- Extremely moribund patients with an expected life expectancy of < 24 h
- Haemodynamic instability requiring vasopressors
- Previous history of allergy to plasma
- Cirrhosis
- Severe renal impairment with GFR < 30 mL/min or recipients of RRT, peritoneal dialysis
- Patients with uncontrolled diabetes mellitus, hypertension, arrhythmias and unstable angina

Interventions	• Details of CP
	  ○ Type of plasma: NR
	  ○ Volume: 250 mL
	  ○ Number of doses: 2 doses
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): 2 doses on consecutive days, start by day 3 of symptom onset (of severe COVID-19 as in inclusion criteria)
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Time to clinical improvement (clinical improvement: reduction of 2 points in ordinal scale or live discharge from the ICU, whichever is earlier)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: yes
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR (proportion of patients on mechanical ventilation)
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
	  ○ Number of participants with SAEs: NR
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: NR
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission to the ICU on day 28: NR
	  ○ Duration of hospitalisation: yes
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional study outcomes
	  ○ Duration of oxygen therapy
	  ○ Proportion of participants on mechanical ventilation
	  ○ Mortality in both groups at day 7 and day 28
	  ○ Incidence of AEs in both groups
	  ○ Cytokines and acute phase reactants

CTRI/2020/06/025803 *(Continued)*

Notes	• Recruitment status: completed, but no results available yet • Prospective completion date: NR • Sponsor/funding: Institute of Liver and Biliary Sciences D-1, Vasant Kunj, New Delhi-110070

EUCTR2020-001860-27-GB

Methods	• Trial design: randomised phase I/II study • Sample size: 250 • Setting: inpatient • Country: UK • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  ○ Adults (≥ 18 years) with laboratory-confirmed SARS-CoV-2 infection (PCR)
	  ○ Ability to provide informed consent signed by study patient or legally acceptable representative
	  ○ Women of childbearing potential (WOCBP) and male patients who are sexually active with WOCBP must agree to use a highly effective method of contraception from the first administration of trial treatment, throughout trial treatment and for the duration outlined in the candidate-specific trial protocol after the last dose of trial treatment
	  ○ Standard additional criteria that may be applied per candidate-specific trial protocol:
	  ■ Group A (severe disease) patients with clinical status of grades 5 (hospitalised, oxygen by mask or nasal prongs), 6 (hospitalised, non-invasive ventilation or high-flow oxygen), 7 (hospitalised, intubation and mechanical ventilation, PaO_2/FiO_2 ≥ 150 or $SpO_2/FiO2$ ≥ 200), 8 (hospitalised mechanical ventilation, PaO^2/FiO^2 < 150 (SpO2/FiO2 < 200)) or vasopressors or 9 (hospitalised, mechanical ventilation pO2/FiO2 < 150 and vasopressors, dialysis or ECMO) as defined by the WHO Clinical Progression Scale.
	  ■ Group B (mild-moderate disease) 4b. ambulant or hospitalised patients with peripheral capillary oxygen saturation (SpO2) >94% RA. Nomacopan candidate-specific trial
	  ○ Additional inclusion criteria specific to this CST
	  ■ Adults (≥ 18 years) with laboratory-confirmed SARS-CoV-2 infection (PCR) who are within 5 days of symptom onset
	  ■ A score of grades 4, 5, 6 or 7 on the 9-point ordinal scale* grades 6 and 7 will only be accepted when 2nd cohort open to recruitment
	  ■ CST-2 (EIDD-2801) additional inclusion criteria: has signs or symptoms of COVID-19 that began within 5 days of the planned first dose of study drug.
	  ■ Is in generally good health (except for current respiratory infection) and is free of uncontrolled chronic conditions
	  ■ Willing and able to comply with all study procedures and attending weekly clinic visits through the 4th week
	  ■ Has someone, aged ≥ 16 living in the same household during the dosing period
	• Exclusion criteria
	  ○ ALT/AST > 5 times ULN
	  ○ Stage 4 severe CKD or requiring dialysis (i.e. estimated GFR < 30 mL/min/1.73 m^2)
	  ○ Pregnant or breastfeeding
	  ○ Anticipated transfer to another hospital, which is not a study site within 72 h
	  ○ Allergy to any study medication
	  ○ Patients taking other prohibited drugs (as outlined in CST protocol) within 30 days or 5 times the half-life (whichever is longer) of enrolment
	  ○ Patients participating in another CTIMP trial Nomacopan Candidate-Specific Trial: for the purpose of the nomacopan candidate-specific trial, appendix exclusion criteria 6 has been amend-

EUCTR2020-001860-27-GB *(Continued)*

ed from the Master protocol as follows, to restrict the population of patients that will be included in the trial: patients taking the following prohibited drugs:
- other complement-inhibiting drug such as eculizumab (Soliris®)
- any other drug which directly inhibits cytokines, chemokines or proinflammatory mediators such as tocilizumab (Actemra®/RoActremra®), anakinra (Kineret®), etanercept (Enbrel®), infliximab (Remicade®) or adalimumab (Humira®).N.B. whilst it is not thought that there is likely to be any adverse interaction between nomacopan and any of these drugs, in the context of a clinical trial, it would be impossible to distinguish the effects of those agents from that of nomacopan. Corticosteroids, antivirals and antibiotics are permitted in conjunction with nomacopan therapy.
- Additional exclusion criteria specific to this candidate-specific appendix are weight < 50 kg or > 100 kg

- CST-2 (EIDD-2801) additional exclusion criteria
  - Has a febrile respiratory illness that includes pneumonia that results in hospitalisation, or requires hospitalisation, oxygenation, mechanical ventilation, or other supportive modalities
  - Has a platelet count < 50 x 10^9/L
  - Is experiencing AEs or laboratory abnormalities that are ≥ grade 3 based on the Common Terminology Criteria for Adverse Events (CTCAE) grading
  - Has clinically significant liver dysfunction or renal impairment
  - Has history of Hepatitis C infection or concurrent bacterial pneumonia
  - Has received an experimental agent (vaccine, drug, biologic, device, blood product, or medication) within 30 days prior to the first dose of study drug
  - In the opinion of the investigator, has significant end-organ disease as a result of relevant comorbidities: CKD, congestive heart failure, peripheral vascular disease including diabetic ulcers
  - Has a SaO_2 < 95% by oximetry or has lung disease that requires supplemental oxygen or maintenance steroids
  - Has any condition that would, in the opinion of the investigator, put the patient at increased risk for participation in a clinical study

Interventions	• Details of CP
	  ○ Type of plasma: NR
	  ○ Volume: NR
	  ○ Number of doses: NR
	  ○ Antibody titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): SC, placebo
	• Concomitant therapy: NR
	• Treatment crossover: NR

Outcomes	• Primary study outcome
	  ○ Phase I - to find the optimal dose of each drug (candidate or combination of candidates)
	  ○ Phase II - to determine the effect each candidate has on improving patients' clinical outcome (using the WHO clinical severity score) and safety of each candidate and recommend whether it should be evaluated further in a large phase II/III trial
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: NR
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes

EUCTR2020-001860-27-GB *(Continued)*

- Improvement of clinical status: participants discharged from hospital: yes
- QoL: NR
- Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
- Number of participants with SAEs: NR

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - The need for (and duration) of oxygen support (including mechanical ventilation)
  - The length of time people remain in hospital (including time in ICU)
  - Clinical improvement at various time points
  - Side effects seen

Notes	• Recruitment status: completed • Prospective completion date: 1 December 2020 • Sponsor/funding: University of Liverpool, Southampton Clinical Trials Unit, Southampton, SO16 6YD

IRCT20120215009014N353

Methods	• Trial design: parallel-arm, phase II RCT • Sample size: 100 • Setting: inpatient and outpatient • Country: Iran • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ◦ Aged 18-65 years
	  ◦ Moderate to severe COVID-19 disease
	• Exclusion criteria
	  ◦ Pregnancy
	  ◦ IGA deficiency

Interventions	• Details of CP
	  ◦ Type of plasma: NR
	  ◦ Volume: 500 IU
	  ◦ Number of doses: every week for at least 3 weeks
	  ◦ Antibody-titre: NR
	  ◦ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): SC, medication
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• Primary study outcome

IRCT20120215009014N353 *(Continued)*

- Dyspnoea
- Fever
- Cough

- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: NR
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - NR

Notes	• Recruitment status: completed • Prospective completion date: NR • Sponsor/funding: Hamedan University of Medical Sciences

IRCT20150808023559N21

Methods	• Trial design: RCT • Sample size: 60 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Blood oxygenation saturation < 90%
	  ○ Abnormal lung CT scan
	  ○ Significant shortness of breath
	  ○ Fever
	  ○ Did not improve within 48 h from enrolment
	  ○ No possibility of discharge in 48 h from enrolment
	  ○ Patient consent
	• Exclusion criteria
	  ○ Connected to a ventilator
	  ○ Did not give consent

IRCT20150808023559N21 *(Continued)*

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 500 mL
	  ○ Number of doses: 1
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: SC
	• Treatment cross-overs: NR

Outcomes	• Primary study outcome
	  ○ Reduction in all-cause mortality
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: yes
	  ○ 28-day mortality: NR
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
	  ○ Number of participants with SAEs: NR
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: NR
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission to the ICU on day 28: NR
	  ○ Duration of hospitalisation: NR
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional study outcomes
	  ○ NR

Notes	• Recruitment status: completed • Prospective completion date: 22 August 2022 • Sponsor/funding: Ardabil University of Medical Sciences

IRCT20200404046948N1

Methods	• Trial design: open-label, RCT • Sample size: 60 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 4

IRCT20200404046948N1 *(Continued)*

Participants	• Inclusion criteria
	  ○ Laboratory-confirmed COVID-19 by PCR
	  ○ Aged 18-70 years
	  ○ Inpatients
	  ○ Clinical severe disease, defined as any of the following:
	  ■ dyspnoea
	  ■ respiratory frequency ≥ 30/min
	  ■ blood oxygen saturation ≤ 93% (in resting state)
	  ■ PaO_2/FiO_2 < 300, and/or lung infiltrates > 50% within 24-48 h
	  ○ Life-threatening disease defined as:
	  ■ respiratory failure and need for mechanical ventilation
	  ■ septic shock and/or multiple organ dysfunction or failure
	  ○ Patient or legal guardian signed informed consent and participated voluntarily
	  ○ Accepted randomised allocation (allocating into any group)
	  ○ Hospitalised before the end of the clinical trial and available for any follow-up
	• Exclusion criteria
	  ○ History of allergy to blood products or plasma components and auxiliary materials (sodium citrate)
	  ○ Critical conditions such as multiple organ failure, and estimated survival time < 3 days
	  ○ Severe congestive heart failure, or any other conditions for which plasma transfusion would be contraindicated (decided by study authors)
	  ○ Any risk factor that might increase the risk of thrombosis
	  ○ Pregnant or breastfeeding women
	  ○ Participation in another clinical trial
	  ○ Taking any other medicine for COVID-19 treatment out of the protocol
	  ○ Doctor believed that the patient was not a suitable participant

Interventions	• Details of CP
	  ○ Type of plasma: NR
	  ○ Volume: 200-500 mL
	  ○ Number of doses: 2 IV infusions during 2 consecutive days
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): conventional therapy and CP or conventional therapy only
	• Concomitant therapy: conventional therapy
	• Treatment cross-overs: NR

Outcomes	• Primary study outcome
	  ○ Clinical improvement within 14 days of admission
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: yes
	  ○ 28-day mortality: NR
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR

IRCT20200404046948N1 *(Continued)*

- Number of participants with SAEs: NR

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: yes
- Additional study outcomes
  - ICU hospitalisation duration
  - ECMO duration
  - Clinical characteristics including, fever, respiratory frequency and PaO2/FiO2

Notes	• Recruitment status: completed • Prospective completion date: 20 June 2020 • Sponsor/funding: Artesh University of Medical Sciences, 1411718541 Tehran, Iran

IRCT20200413047056N1

Methods	• Trial design: randomised, clinical trial • Sample size: 15 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ 18-50 years old
	  ○ RT-PCR
	  ○ Confirmed infection in throat swab or sputum or lower respiratory tract samples
	  ○ Signed informed consent form on a voluntary basis
	  ○ Met any of the following criteria for severe or critically ill conditions:
	  ■ respiratory rate ≥ 30/min; or
	  ■ rest SpO_2 ≤ 90%; or
	  ■ PaO_2/FiO_2 ≤ 300 mmHg; or
	  ■ respiratory failure and needs mechanical ventilation; or
	  ■ multiple organ failure and needed ICU monitoring
	• Exclusion criteria
	  ○ NR

Interventions	• Details of CP
	  ○ Type of plasma: NR
	  ○ Volume: 200 cc each time
	  ○ Number of doses: 2
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

IRCT20200413047056N1 *(Continued)*

- For studies including a control group: comparator (type): 3 arms: CP; IV immunoglobulin (400 mg/kg/d); this group received common national protocol
- Concomitant therapy: common national protocol
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
  - Lung involvement in X-ray and CT-scan
  - SpO_2
  - LDH enzyme
  - Viral load
  - Acute phase protein
  - White blood cell count
  - Erythrocyte sedimentation rate
  - Length of hospital stay
  - Duration of mechanical ventilation
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: NR
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - NR

Notes

- Recruitment status: completed
- Prospective completion date: 15 August 2020
- Sponsor/funding: Birjand University of Medical Sciences, Birjand, Iran

IRCT20200501047258N1

Methods

- Trial design: RCT (3 arms)
- Sample size: 120 (5 samples per participant = 24 participants)
- Setting: inpatient

IRCT20200501047258N1 *(Continued)*

- Country: Iran
- Language: English
- Number of centres: 1

Participants	• Inclusion criteria
	  ○ Positive PCR test
	  ○ Life-threatening disease (defined as respiratory failure, dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, PaO_2:FiO_2 < 300, lung infiltrates > 50% within 24-48 h)
	• Exclusion criteria
	  ○ Pregnancy
	  ○ Hypersensitivity to blood or blood products
	  ○ Uncontrolled bacterial infection
	  ○ Disagreement (no further information available)

Interventions	• Details of CP
	  ○ Type of plasma: NR
	  ○ Volume: 2-5 mL/kg (1st intervention group), 8-10 mL/kg (2nd intervention group)
	  ○ Number of doses: 3 doses (1st intervention group), 1 dose (2nd intervention group)
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): later stage of disease (see inclusion criteria)
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• Primary study outcome
	  ○ Hospitalisation time
	  ○ ICU admission time
	  ○ Mechanical ventilation time
	  ○ Survival rate
	  ○ All outcomes measured on days 0, 1, 3, 7, 14
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 30-day mortality: NR
	• Secondary review outcomes
	  ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8-15 days, 16-30 days: partially (mechanical ventilation until day 14)
	  ○ Mortality (time to event): yes
	  ○ 90-day mortality: NR
	  ○ Time to discharge from hospital: yes
	  ○ Admission to ICU: yes
	  ○ Length of stay on the ICU: NR
	  ○ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes (ELISA on days 0,1,3,7,14)
	  ○ QoL: NR
	  ○ Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and AEs (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  ○ Number of participants with SAEs: NR
	• Additional study outcomes
	  ○ CT scan
	  ○ Haematological markers (flow cytometry)

IRCT20200501047258N1 *(Continued)*

	◦ Clinical findings ◦ All outcomes measured on days 0, 1, 3, 7, 14
Notes	• Recruitment status: completed • Prospective completion date: NR • Sponsor/funding: Oroumia University of Medical Sciences

IRCT20200503047281N1

Methods	• Trial design: RCT • Sample size: 40 • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1
Participants	• Inclusion criteria ◦ Age 20-60 years ◦ People with severe coronavirus disease • Exclusion criteria ◦ People with a history of other immune, genetic or infectious diseases other than coronavirus ◦ Individual suspended, but negative for clinical standard COVID-19 test (no further information available)
Interventions	• Details of CP ◦ Type of plasma: NR ◦ Volume: 200 mL ◦ Number of doses: 2 doses ◦ Antibody-titre: NR ◦ Pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): SC • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	• Primary study outcome ◦ Percentage of participants discharged from the ICU and hospital (timing of measurement: "specific intervals, up to 1 year") • Primary review outcomes ◦ All-cause mortality during hospital stay: NR ◦ 28-day mortality: NR ◦ 60-day mortality: NR ◦ Mortality (time to event): NR ◦ Clinical status ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR ■ Improvement of clinical status: participants discharged from hospital: NR ◦ QoL: NR ◦ Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR ◦ Number of participants with SAEs: NR

IRCT20200503047281N1 *(Continued)*

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Participant mortality rate

Notes	• Recruitment status: completed • Prospective completion date: NR • Sponsor/funding: Yazd University of Medical Sciences

IRCT20201004048922N1

Methods	• Trial design: RCT, 3-arm, parallel, single-centre, phase 3 clinical trial • Sample size: 75 • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ◦ Confirmed or suspected COVID-19 pneumonia based on PCR or pulmonary imaging
	  ◦ Presenting clinical symptoms of COVID-19 (fever, cough, dyspnoea)
	  ◦ O_2 saturation ≤ 93%
	  ◦ Age ≥ 18 years
	  ◦ Provided written consent to participate in the study
	  ◦ < 7 days between the onset of clinical symptoms and the time of enrolment
	  ◦ No participation in another concurrent clinical trial
	• Exclusion criteria
	  ◦ Advanced renal or liver disease
	  ◦ Active cancer
	  ◦ Known hypersensitivity reaction to plasma-derived drugs
	  ◦ Pregnancy
	  ◦ Lactation
	  ◦ Patients could be excluded from the study during the first 48 h

Interventions	• Details of CP
	  ◦ Type of plasma: NR
	  ◦ Volume: 500 mL
	  ◦ Number of doses: 1 dose
	  ◦ Antibody-titre: NR
	  ◦ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): standard of care
	• Concomitant therapy: NR

IRCT20201004048922N1 *(Continued)*

- Treatment cross-overs: NR

Outcomes

- Primary study outcome
  - Length of hospital stay due to COVID-19
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Requirement rate of receiving ICU care
  - The 7-point ordinal scale
  - National Early Warning Score 2 (NEWS2) changes
  - Chest CT-scan score changes

Notes

- Recruitment status: completed
- Prospective completion date: NR
- Sponsor/funding: Tehran University of Medical Sciences

NCT04315948

Methods

- Trial design: RCT (platform trial)
- Sample size: 3100
- Setting: inpatient
- Country: France
- Language English
- Number of centres: NR

Participants

- Inclusion criteria
  - Adults ≥ 18 years of age
  - Hospitalised with any of the following criteria:
    - pulmonary rales/crackles on clinical exam or
    - SpO2 ≤ 94% on room air or

NCT04315948 *(Continued)*

- requirement of supplementary oxygen, including high-flow oxygen devices or non-invasive ventilation
- < 9 days between onset of symptoms and randomisation
- Positive SARS-CoV-2 PCR performed on a NP swab within the 5 days preceding randomisation
- Positive SARS-CoV-2 rapid antigen test performed on a NP swab within the 6 h preceding randomisation
- Contraceptive use (by men and women)
  - Male participants: although contraception was not required, to avoid the transfer of any fluids, all male participants were required to use condoms from Day 1 and agree to continue for 90 days following administration of Investigational Medical Product (IMP)
  - Female participants: women of child-bearing potential required to agree to use contraception for 365 days following administration of Investigational Medical Product (IMP)

- Exclusion criteria
  - Refusal to participate expressed by patient or legally authorised representative
  - Need for IMV and/or ECMO at the time of enrolment
  - Spontaneous blood ALT/AST levels > 5 times the ULN
  - GFR < 15 mL/min or requiring maintenance dialysis
  - Pregnant or breastfeeding
  - Anticipated transfer to another hospital not included in the study within 72 h of randomisation
  - Known history of allergy or reaction to any component of the study drug formulation
  - Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of monoclonal or polyclonal antibodies
  - Any prior receipt of investigational or licensed vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 infection or COVID-19 or expected receipt in the 30 days following hospital discharge, according to current recommendation in each country
  - Any medical condition which, in the judgement of the investigator, could interfere with the interpretation of the trial results or that precluded protocol adherence

Interventions

- Details of CP
  - Type of plasma: NA
  - Volume: NA
  - Number of doses: NA
  - Antibody-titre: NA
  - Pathogen inactivated: NA
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): SC
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
  - Percentage of participants reporting each severity rating on a 7-point ordinal scale (time frame: Day 15)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes (day 29)
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
    - Improvement of clinical status: participants discharged from hospital NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes

NCT04315948 *(Continued)*

- Number of participants with SAEs: yes

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: yes
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Duration of hospitalisation (days)
  - Percentage of participants reporting each severity rating on a 7-point ordinal scale (time frame: Days 3, 5, 8, 11, 15 and 29)
  - The time to discharge or to a NEWS of ≤ 2 and maintained for 24 h, whichever occurs first (time frame: Days 3, 5, 8, 11, 15 and 29)
  - Number of oxygenation-free days in the first 28 days
  - Duration of new oxygen use, non-invasive ventilation or high-flow oxygen devices during the trial
  - Ventilator-free days in the first 28 days
  - Incidence of new mechanical ventilation use during the trial
  - Hospitalisation
  - Number of participants with a discontinuation or temporary suspension of study drugs (for any reason)
  - Changes from baseline in blood white cell count (time frame: 29 days)
  - Changes from baseline in haemoglobin
  - Changes from baseline in platelets
  - Changes from baseline in creatinine
  - Changes from baseline in blood electrolytes (including kalaemia)
  - Changes from baseline in prothrombine time
  - Changes from baseline in international normalised ratio (INR)
  - Changes from baseline in glucose
  - Changes from baseline in total bilirubin
  - Changes from baseline in ALT
  - Changes from baseline in AST
  - Percent of participants with SARS-CoV-2 detectable in nasopharyngeal sample (time frame: Days 3, 5, 8, 11, 15, 29)
  - Quantitative SARS-CoV-2 virus in nasopharyngeal sample (time frame: Days 3, 5, 8, 11, 15, 29)
  - Quantitative SARS-CoV-2 virus in blood (time frame: Days 3, 5, 8 and 11)
  - Plasma concentration of lopinavir (time frame: Days 1, 3, 5, 8 and 11)
  - Plasma concentration of hydroxychloroquine (time frame: Days 1, 3, 5, 8 and 11)

Notes	Recruitment status: active, not recruiting Prospective completion date: March 2023 Sponsor/funding: Institut National de la Santé et de la Recherche Médicale, France

NCT04332835

Methods	• Trial design: randomised, open-label, parallel-controlled trial

NCT04332835 *(Continued)*

- Sample size: 92
- Setting: hospital
- Country: Colombia
- Language: English
- Number of centres: 1

Participants	• Inclusion criteria
	  ◦ Aged 18-100 years, male or female
	  ◦ Hospitalised with diagnosis of COVID-19 by RT-PCR
	  ◦ Moderate cases according to the official guideline 'Pneumonia Diagnosis and Treatment Scheme for Novel Coronavirus Infection (Trial Version 6)'
	  ◦ Confusion, urea, respiratory rate, blood pressure-65 score (CURB-65 score) ≥ 2
	  ◦ SOFA < 6
	  ◦ Ability to understand and the willingness to sign a written informed consent document
	• Exclusion criteria
	  ◦ Pregnant or breastfeeding
	  ◦ Prior allergic reactions to transfusions
	  ◦ Critically ill patients in ICUs
	  ◦ Patients with surgical procedures in the last 30 days
	  ◦ Patients with active treatment for cancer (radiotherapy or chemotherapy)
	  ◦ HIV-diagnosed patients with viral failure (detectable viral load > 1000 copies/mL persistent, 2 consecutive viral load measurements within a 3-month interval, with medication adherence between measurements after at least 6 months of starting a new regimen antiretrovirals)
	  ◦ Suspicion or evidence of co-infections
	  ◦ End-stage CKD (GFR < 15 mL/min /1.73 m2)
	  ◦ Child Pugh C stage liver cirrhosis
	  ◦ High cardiac output diseases
	  ◦ Autoimmune diseases or IgA nephropathy
	  ◦ Any condition that in the judgement of the study authors would make the patient inappropriate for entry into this study

Interventions	• Details of CP
	  ◦ Type of plasma: NR
	  ◦ Volume: 500 mL total (day 1 250 mL, day 2 250 mL)
	  ◦ Number of doses: 2
	  ◦ Antibody-titre: NR
	  ◦ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): azithromycin (500 mg daily) and hydroxychloroquine (400 mg every 12 h) for 10 days
	• Concomitant therapy: azithromycin (500 mg daily) and hydroxychloroquine (400 mg every 12 h) for 10 days
	• Treatment cross-overs: not applicable

Outcomes	• Primary study outcome
	  ◦ Change in viral load
	  ◦ Change in IgM COVID-19 antibodies titres
	  ◦ Change in IgG COVID-19 antibodies titres
	• Primary review outcomes
	  ◦ All-cause mortality during hospital stay: NR
	  ◦ 28-day mortality: yes
	  ◦ 60-day mortality: NR

NCT04332835 *(Continued)*

- Mortality (time to event): NR
- Clinical status
  - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
  - Improvement of clinical status: participants discharged from hospital: NR
- QoL: NR
- Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
- Number of participants with SAEs: NR

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: yes
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Length of ICU stay
  - Duration (days) of mechanical ventilation
  - Clinical status assessed according to the WHO guideline
  - Mortality [time frame: Days 7, 14 and 28]

Notes	• Recruitment status: completed • Prospective completion date: 31 December 2020 • Sponsor/funding: Universidad del RosarioFundación Universitaria de Ciencias de la SaludCES UniversityInstituto Distrital de Ciencia Biotecnología e Innovacion en Salud

NCT04345991

Methods	• Trial design: randomised, parallel-assignment • Sample size: 120 (60 in each arm) • Setting: outpatient • Country: France • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ◦ Patients included in the CORIMUNO-19 cohort
	  ◦ Onset of COVID-19 functional signs < 8 days (plasma transfusion may occur up to day 10 of onset)
	  ◦ Mild severity as described in the WHO scale
	• Exclusion criteria
	  ◦ Pregnancy
	  ◦ Current documented and uncontrolled bacterial infection
	  ◦ Prior severe (grade 3) allergic reactions to plasma transfusion

Interventions	• Details of CP
	  ◦ Type of plasma: details of preparation not described
	  ◦ Volume: 200-220 mL

NCT04345991 *(Continued)*

- Number of doses: 2-4
- Antibody-titre: NR
- Pathogen inactivated or not: NR

- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage (within 10 days of symptom onset)
- For studies including a control group: comparator (type): SC
- Concomitant therapy: SC
- Treatment cross-overs: not applicable

Outcomes	during hospital stay
	• Primary study outcome
	  ○ Survival without need of ventilator utilisation
	  ○ WHO progression scale ≥ 6 at day 4 of randomisation
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: yes
	  ○ 28-day mortality: yes
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death):
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
	  ○ Number of participants with SAEs: yes
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: yes
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission to the ICU on day 28: NR
	  ○ Duration of hospitalisation: NR
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional study outcomes
	  ○ WHO progression scale
	  ○ Time from randomisation to discharge
	  ○ Survival without needs of ventilator utilisation
	  ○ Survival without use of immunomodulatory drugs

Notes	• Recruitment status: completed, but no results yet available • Prospective completion date: NR • Sponsor/funding: Assistance Publique - Hôpitaux de Paris

NCT04358783

Methods	

NCT04358783 *(Continued)*

- Trial design: RCT, double-blind. Phase 2. Parallel assignment. Participants electronically randomised 2:1 (plasma vs best available therapy) in a double-blind fashion. Quadruple masking (participant, care provider, investigator, outcomes assessor)
- Sample size: 20 in 1 arm, 10 in the other (n = 30)
- Setting: inpatient
- Country: Mexico
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
  - Men or women ≥ 18 years. A woman of childbearing age must agree to practice abstinence or to use an effective method of contraception during the study period
  - Vascular access suitable for administration of haemocomponents
  - SARS-CoV-2-positive RT-PCR
  - Negative pregnancy test in case of a woman of reproductive age
  - Signing of evidentiary document of informed consent
  - Hospital admission for SARS-CoV-2 pneumonia with supplemental oxygen requirements
  - Participants who access the storage of biological samples for future examination
- Exclusion criteria
  - Respiratory rate > 30 RPM, SO2 < 93%, PaO_2/FiO_2 < 200 despite intervention with oxygen therapy after 60 min of hospitalisation
  - New alteration of the state of alert that does not revert after interventions 60 min after admission to hospital
  - PAM ≤ 65 mmHg despite initial resuscitation on arrival at the centre
  - Pregnant or breastfeeding patients
  - Patients whom the investigators consider inappropriate to participate in the clinical trial
  - Contraindication to transfusion or history of previous severe reaction to blood products
  - Have received any blood products in the last 120 days

Patients with SARS-CoV-2 PCR-confirmed infection with pulmonary infiltrates and hypoxaemia will be screened and invited to participate

Interventions

- Details of CP
  - Type of plasma: thawed after storage at −80 °C
  - Volume: 200 mL
  - Number of doses: 1
  - Antibody-titre: NR
  - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severely ill and critically ill patients with COVID-19
- For studies including a control group: comparator (type): best available therapy (BAT). Supportive management depending on individual needs. Including but not be limited to, oxygen therapy by means of a nasal cannula; high-flow nasal cannula; IMV or non-IMV; IV hydration; antibiotic therapy; thrombus prophylaxis; pain and fever management
- Concomitant therapy: supportive management depending on individual needs
- Treatment cross-overs: no

Outcomes

- Primary study outcome

NCT04358783 *(Continued)*

- Any-cause mortality during the first 14 days of treatment
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: NR
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: yes, time in days for SARS-CoV-2 RT-PCR negatives
- Additional study outcomes
  - The serum anti-SARS-CoV-2 antibody titres
  - Detection of serum antibodies

Notes	• Recruitment status: completed, but no results available yet • Prospective completion date: NR • Sponsor: Hospital Universitario Dr. Jose E. Gonzalez

NCT04361253

Methods	• Trial design: phase 3 RCT, double-blind (participant, investigator), parallel assignment • Sample size: 110 in each arm (n = 220) • Setting: e.g. inpatient • Country: USA • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  ○ Age > 1 year
	  ○ Active COVID-19 infection confirmed by positive SARS-CoV-2 PCR
	  ○ Meets institutional criteria for admission to hospital for COVID-19
	  ○ Admitted to ICU or non-ICU floor within 5 days of enrolment
	  ○ PaO_2/FiO_2 > 200 mmHg if intubated
	  ○ Patient or legal representative able to provide informed consent
	• Exclusion criteria
	  ○ Previous treatment with CP for COVID-19
	  ○ Current use of investigational antiviral therapy targeting SARS-CoV-2

NCT04361253 *(Continued)*

	○ History of anaphylactic transfusion reaction ○ Clinical diagnosis of acute decompensated heart failure ○ Objection to blood transfusion
Interventions	• Details of CP ○ Type of plasma: apheresis units ○ Volume: 2 x 250 mL units (500 mL) ○ Number of doses: 2 units administered sequentially over not greater than a 24-h period ○ Antibody-titre: high; NR ○ Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients but not yet in moderate or severe ARDS • For studies including a control group: comparator (type): e.g. conventional treatment ○ 2 units of SP (FFP)or FP24 (each 200-275 mL, approximately 500 mL total) administered sequentially • Concomitant therapy: NR • Treatment cross-overs: No
Outcomes	• Primary study outcome ○ Modified WHO Ordinal Scale score • Primary review outcomes ○ All-cause mortality during hospital stay: NR ○ 28-day mortality: NR ○ 60-day mortality: NR ○ Mortality (time to event): NR ○ Clinical status ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR ■ Improvement of clinical status: participants discharged from hospital: NR ○ QoL: NR ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR ○ Number of participants with SAEs: NR • Secondary review outcomes ○ Improvement of clinical status: ■ weaning or liberation from IMV in surviving participants: NR ■ ventilator-free days: NR ■ liberation from supplemental oxygen in surviving participants: NR ○ Need for dialysis at up to 28 days: NR ○ Admission to the ICU on day 28: NR ○ Duration of hospitalisation: NR ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR • Additional study outcomes ○ NR
Notes	• Recruitment status: terminated (futility) • Prospective completion date: NR • Sponsor/Funding: Brigham and Women's Hospital, Boston

NCT04362176

Methods	• Trial design: phase 3 RCT, parallel assignment (1:1). Randomisation completed in permuted blocks and stratified by site, gender, and age. Triple blinding (participant, care provider, outcomes assessor). Study personnel not blinded to the study group assignment • Sample size: 250 in each arm (500) • Setting: inpatient (hospital or ED) • Country: USA • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  ○ All sexes
	  ○ Age ≥ 18 years
	  ○ Currently hospitalised or in an ED with anticipated hospitalisation
	  ○ Symptoms of acute respiratory infection, defined as ≥ 1 of the following: cough, fever (> 37.5 °C/99.5 °F), shortness of breath
	  ○ Laboratory-confirmed SARS-CoV-2 infection within the past 10 days
	• Exclusion criteria
	  ○ Prisoner
	  ○ Unable to randomise within 14 days after onset of acute respiratory infection symptoms
	  ○ Unable to randomise within 48 h after hospital arrival
	  ○ Inability to be contacted on Day 29-36 for clinical outcome assessment
	  ○ Receipt of pooled immunoglobulin in the past 30 days
	  ○ Contraindications to transfusion or history of prior reactions to transfusion blood products
	  ○ Previous enrolment in this trial

Interventions	• Details of CP
	  ○ Type of plasma: SARS-CoV-2 CP
	  ○ Volume: 500 mL/h
	  ○ Number of doses: NR
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated: yes - pathogen reduced
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): require hospitalisation and given within 12 h of randomisation on study Day 0
	• For studies including a control group: comparator (type): 250 mL of lactated Ringer's solution containing multivitamins IV on Day 1 as a placebo
	• Concomitant therapy: NR
	• Treatment cross-overs: no

Outcomes	• Primary study outcome
	  ○ COVID-19 7-point Ordinal Clinical Progression Outcomes Scale [time frame: study Day 15]
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: yes
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes, transfusion-related AEs

NCT04362176 *(Continued)*

- Number of participants with SAEs: NR

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: yes
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - All-location, all-cause 14-day mortality
  - Survival through 28 days
  - Time to hospital discharge through 28 days
  - COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 3, 8, 29
  - Oxygen-free days through Day 28
  - Vasopressor-free days through Day 28
  - ICU-free days through Day 28
  - Hospital-free days through Day 28
  - Acute kidney injury
  - Renal replacement therapy
  - Documented venous thromboembolic disease
  - Documented cardiovascular event

Notes	• Recruitment status: completed, but no results available yet • Prospective completion date: NR • Sponsor/Funding: Vanderbilt University Medical Center

NCT04374526

Methods	• Trial design: randomised phase 2/3 • Sample size: 29 • Setting: inpatient • Country: Italy • Language: translated to English • Number of centres: 3

Participants	• Inclusion criteria
	  ○ Age ≥ 65
	  ○ Pneumonia at CT scan
	  ○ PaO_2/FiO_2 ≥ 300 mmHg
	  ○ Presence of ≥ 1 comorbidities (consider the list provided in Appendix A)
	  ○ Signed informed consent
	• Exclusion criteria
	  ○ Age < 65
	  ○ PaO_2/FiO_2 < 300 mmHg
	  ○ Pending cardiopulmonary arrest
	  ○ Refusal to blood product transfusions
	  ○ Severe IgA deficiency

NCT04374526 *(Continued)*

- Any life-threatening comorbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion

Interventions

- Details of CP
  - Type of plasma: ABO-matched pathogen-inactivated CCP
  - Volume: 200 mL/day
  - Number of doses: 3 (days 1, 2, and 3)
  - Antibody-titre: NR
  - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): SC
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome
  - Proportion of participants without progression in severity of pulmonary disease, defined as worsening of 2 points in the WHO ordinal scale by day 14
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
  - Number of participants with SAEs: yes
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Decreased viral load on NP swab at days 6, 9 and 14
  - Decreased viraemia at days 6 and 9
  - Increased antibody titre against SARS-CoV-2 at days 30 and 60
  - Proportion of participants with negative SARS-CoV-2 NP swab at day 30
  - Total plasma-related AE (day 60)
  - Total non-plasma-related AEs (day 60)

Notes

- Recruitment status: completed
- Prospective completion date: 26 May 2021
- Sponsor/funding: Fondazione Policlinico Universitario Agostino Gemelli IRCCS

NCT04385199

Methods	• Trial design: open, parallel, RCT • Sample size: 30 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Age > 18 with ≥ 1 of the following:
	  ■ dyspnoea respiratory rate ≥ 30 breaths/min
	  ■ oxygen saturation ≤ 93% PaO_2/FiO_2
	  ■ < 300 bilateral airspace opacities on chest radiograph at 24-48 h
	• Exclusion criteria
	  ○ Acute myocardial infarction in past 30 days
	  ○ Acute stroke in past 30 days
	  ○ Venovenous ECMO, venoarterial ECMO

Interventions	• Details of CP
	  ○ Type of plasma: ABO-compatible CP
	  ○ Volume: 200 mL
	  ○ Number of doses: 1
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: NR
	• Treatment cross-overs: no

Outcomes	• Primary study outcome
	  ○ Improvement in respiratory disease (time frame: days 1, 3, 5, 7, 14, 28 post-transfusion)
	  ■ For intubated participants improvement in PaO_2/FiO_2
	  ■ For non-intubated participants time to intubation post-transfusion
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: NR
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
	  ○ Number of participants with SAEs: NR
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: NR

NCT04385199 *(Continued)*

- Need for dialysis at up to 28 days: NR
- Admission to the ICU on day 28: NR
- Duration of hospitalisation: yes
- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR

- Additional study outcomes
  - ICU length of stay
  - Ventilator days
  - Improvement in chest X-ray (days 3, 28)

Notes	• Recruitment status: completed, but no results available yet • Sponsor/funding: Henry Ford Health System

NCT04405310

Methods	• Trial design: RCT, parallel design 3:2:3 • Sample size: 42 • Setting: inpatient • Country: Mexico • Language: English • Number of centres: 2

Participants	• Inclusion criteria
	  ◦ Adults 18-70 years of age
	  ◦ Serious or critically ill patients confirmed with SARS-CoV-2 disease (RT-PCR)
	  ◦ Met criteria for phase II (moderate) and phase III (severe) disease with SARS-CoV-2
	  ◦ Suspected cytokine release syndrome with Hscore 169 points
	  ◦ Presence of severe acute hypoxaemia with SpO_2 < 90% in ambient air and/or PaO_2/FiO_2 < 300 mmHg
	  ◦ Met criteria (plain chest CT or plain chest radiograph) for SARS-CoV-2 disease
	  ◦ Require supplemental oxygen through the facial store plus reservoir bag, high-flow nasal tips or advanced airway management and invasive mechanical ventilation support
	• Exclusion criteria
	  ◦ No interest in participating in the trial
	  ◦ Bilateral pulmonary infiltrate related to heart failure or other cause of water overload
	  ◦ Virus-positive respiratory viral panel other than COVID-19
	  ◦ History of allergy to plasma, sodium citrate, or methylene blue
	  ◦ History of autoimmune diseases or selective IgA insufficiency
	  ◦ Participating in other trial protocols

Interventions	• Details of CP
	  ◦ Type of plasma: NR
	  ◦ Volume: not more than 600 mL
	  ◦ Number of doses: 1-3 depending on response to treatment
	  ◦ Antibody-titre: NR
	  ◦ Pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): people with pneumonia due to SARS-COV-2
	• For studies including a control group: comparator (type): placebo 20% albumin in Hartman solution
	• Concomitant therapy: azithromycin, hydroxychloroquine

NCT04405310 *(Continued)*

- Treatment cross-overs: no

Outcomes

- Primary study outcome
  - All-cause mortality within 15 days
- Primary review outcomes
  - All-cause mortality during hospital stay: yes, to 15 days
  - 28-day mortality: NR
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Length of stay ICU
  - Days of mechanical ventilation
  - Supplemental oxygen support
  - Viral load by RT-PCR
  - Inflammatory biomarkers
  - SOFA

Notes

Recruitment status: completed

Prospective completion date: 20 June 2020

Sponsor/funding: Grupo Mexicano para el Estudio de la Medicina Intensiva, Hospital General Naval de Alta Especialidad - Escuela Medico Naval, National Institute of Pediatrics, Mexico, Instituto Nacional de Enfermedades Respiratorias

NCT04425915

Methods

- Trial design: randomised parallel-assignment
- Sample size: 400
- Setting: severe disease
- Country: India
- Language: English
- Number of centres: 3

NCT04425915 *(Continued)*

Participants	• Inclusion criteria
	  ○ Patients with severe COVID-19 will be considered for randomisation and will be transfused CP within 3 days of symptom onset (severe COVID-19). Severe COVID-19 defined by WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (version 5.0) along with confirmation by real-time RT-PCR assay with severe disease i.e. meeting any 2 of the following criteria:
	  ■ patients on ventilator (in last 24 h)
	  ■ respiratory distress, respiratory rate ≥ 30 breaths/min
	  ■ oxygen saturation level < 90% in resting state
	  ■ $PaO_2)/FiO_2 \leq 300$ mmHg
	  ■ lung infiltrates > 50% within 24-48 h
	• Exclusion criteria
	  ○ Patient/family members who do not give consent to participate in the study
	  ○ Patients aged < 18 years
	  ○ Patients presenting with multi-organ failure
	  ○ Pregnancy
	  ○ Individuals with HIV and viral hepatitis and cancer
	  ○ Extremely moribund patients with an expected life expectancy of < 24 h
	  ○ Haemodynamic instability requiring vasopressors
	  ○ Previous history of allergy to plasma
	  ○ Cirrhosis
	  ○ Severe renal impairment with GFR < 30 mL/min or recipients of renal replacement therapy, peritoneal dialysis
	  ○ Patients with uncontrolled diabetes mellitus, hypertension, arrhythmias and unstable angina

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 250 mL
	  ○ Number of doses: 2
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): within 3 days of severe disease
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: SC
	• Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ Efficacy of CP in severe COVID-19 patients in time to clinical improvement
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: yes
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes, proportion of participants on mechanical ventilation at day 7
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
	  ○ Number of participants with SAEs: NR
	• Secondary review outcomes

NCT04425915 *(Continued)*

- Improvement of clinical status:
  - weaning or liberation from IMV in surviving participants: NR
  - ventilator-free days: NR
  - liberation from supplemental oxygen in surviving participants: NR
- Need for dialysis at up to 28 days: NR
- Admission to the ICU on day 28: NR
- Duration of hospitalisation: NR
- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR

- Additional study outcomes
  - Proportion of participants in each category according to the ordinal scale (48 h, day 7, day 14, day 28)
  - Duration of oxygen therapy in both groups
  - Duration of ICU stay
  - Presence of antibodies against SARS-CoV-2 in serum after plasma administration
  - Change in cytokines in both groups
  - Change in acute phase reactants in both groups
  - Correlation of the titres in COVID-19 CP donors with duration of illness, the severity of symptoms, duration of hospital stay, drugs used in therapy, duration between recovery, and donation

Notes	• Recruitment status: completed, but no results available yet • Sponsor/funding: Institute of Liver and Biliary Sciences, India

NCT04428021

Methods	• Trial design: randomised • Sample size: 180 • Setting: hospitalised patients within 5 days of respiratory failure • Country: Italy • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ◦ Confirmed SARS-CoV-2 diagnosis by RT-PCR on NP swab or on BAL
	  ◦ Respiratory failure onset or progression within 5 days
	  ◦ Signed informed consent
	• Exclusion criteria
	  ◦ Pregnancy
	  ◦ Previous severe reactions to plasma transfusion
	  ◦ Unavailability of blood group-compatible COVID-19 CP

Interventions	• Details of CP
	  ◦ Type of plasma: CP
	  ◦ Volume: 170-300 mL
	  ◦ Number of doses: 3
	  ◦ Antibody-titre: NR
	  ◦ Pathogen inactivated or not: yes (virus inactivated with riboflavin and ultraviolet light illumination technology)
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): within 5 days of respiratory failure

NCT04428021 *(Continued)*

- For studies including a control group: comparator (type): SC, SP
- Concomitant therapy: SC
- Treatment cross-overs: nil

Outcomes

- Primary study outcome
  - 30-day survival
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: NR
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days:v NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: yes
- Additional study outcomes
  - 6-month survival
  - Days in ICU
  - Positivity for IgG to SARS-Cov-2
  - SOFA score
  - Any variation from Standard Therapy Protocol

Notes

- Recruitment status: completed, but no results available yet
- Sponsor/funding: Azienda Ospedaliera Città della Salute e della Scienza di Torino

NCT04442958

Methods

- Trial design: randomised cross-over
- Sample size: 60
- Setting: severe with ARDS
- Country: Turkey
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
  - Clinical diagnosis of COVID-19
  - 18-90 years

NCT04442958 *(Continued)*

- Exclusion criteria
  - < 18
  - Lower plasma IgA levels
  - PaO_2/FiO_2 > 300 mmHg
  - SpO_2 > 90

Interventions	• Details of CP ◦ Type of plasma: CP ◦ Volume: 200 mL ◦ Number of doses: 1 ◦ Antibody -titre: neutralising antibody titres above 1:640 ◦ Pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): severe patients with ARDS • For studies including a control group: comparator (type): SC • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	• Primary study outcome ◦ Plasma ferritin level ◦ Lymphocyte count ◦ D-dimer level ◦ CRP level ◦ Plasma procalcitonin level ◦ Plasma fibrinogen level • Primary review outcomes ◦ All-cause mortality during hospital stay: NR ◦ 28-day mortality: NR ◦ 60-day mortality: NR ◦ Mortality (time to event): NR ◦ Clinical status ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR ■ Improvement of clinical status: participants discharged from hospital: NR ◦ QoL: NR ◦ Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR ◦ Number of participants with SAEs: NR • Secondary review outcomes ◦ Improvement of clinical status: ■ weaning or liberation from IMV in surviving participants: NR ■ ventilator-free days: NR ■ liberation from supplemental oxygen in surviving participants: NR ◦ Need for dialysis at up to 28 days: NR ◦ Admission to the ICU on day 28: NR ◦ Duration of hospitalisation: NR ◦ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR • Additional study outcomes ◦ FiO_2 level ◦ PaO_2 level ◦ Arterial oxygen level

NCT04442958 *(Continued)*

Notes	• Recruitment status: completed • Prospective completion date: 17 June 2020 • Sponsor/funding: Bagcilar Training and Research Hospital

NCT04468009

Methods	• Trial design: randomised sequential assignment • Sample size: 36 • Setting: critically ill requiring mechanical ventilation • Country: Argentina • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Age: ≥ 18 years
	  ○ Patient with COVID-19 confirmed with nuclear acid testing
	  ○ Critically ill patients with COVID-19 on mechanical ventilation. Potentially critically ill patients (with ARDS, septic shock and/or multiple organ failure) with COVID-19
	  ○ Diagnosed with ARDS
	  ○ Informed consent
	• Exclusion criteria
	  ○ No consent
	  ○ Symptoms for a period > 20 days
	  ○ Not detectable by acid nuclear testing within 48 h prior to eligibility
	  ○ Decompensated congestive heart failure, in which receiving 500 mL of IV volume signifies a life risk
	  ○ History of SAEs or anaphylaxis to plasma components

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: NR
	  ○ Number of doses: NR
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill, requiring mechanical ventilation
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: NR
	• Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ ICU mortality (time frame: mortality at 30, 90 days)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: NR
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status

NCT04468009 *(Continued)*

- Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
- Improvement of clinical status: participants discharged from hospital: NR

- QoL: NR
- Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
- Number of participants with SAEs: NR

- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - SOFA score of study days 1, 3, 5, 7, 14 and 28 (time frame: study days 1, 3, 5, 7, 14 and 28)
  - Length of stay in ICU
  - Length of mechanical ventilation
  - Length of hospitalisation after ICU discharge
  - Need for supportive therapy after enrolment (time frame: duration of supportive therapy through study completion, an average of 3 months)
  - Days without ventilation after enrolment
  - Days without vasopressors after enrolment (time frame: days without vasopressors through study completion, an average of 3 months)
  - Changes in chest X-ray (time frame: changes in chest X-ray through study completion, an average of 3 months)

Notes	• Recruitment status: completed, but no results available yet • Sponsor/funding: Hospital de Infecciosas Francisco Javier Muniz

NCT04497324

Methods	• Trial design: multicentre, randomised, open, parallel, controlled trial • Sample size: 100 • Setting: inpatient • Country: Peru • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Hospitalised patient ≥ 18 years with COVID-19 disease, confirmed by a molecular test or a serologic test, along with a typical COVID-19 clinical presentation
	  ○ Severe or critical disease caused by COVID-19. Severe disease is defined as ≥ 2 of the following criteria:
	  ■ respiratory frequency > 22
	  ■ O_2 saturation ≤ 93%
	  ■ PaO_2 50 mmHg
	  ■ PaO_2/FiO_2 < 300
	  ○ Or critical disease with ≥ 1 of the following criteria:

NCT04497324 *(Continued)*

- respiratory insufficiency with requirement of mechanical ventilation within the last 72h
- shock

- Informed consent signed by patient or direct family member

- Exclusion criteria
  - Contraindication for transfusion (history of TRALI or TACO, history of anaphylaxis to blood components)
  - Multi-organ failure, defined by a SOFA score of > 5
  - Haemodynamically unstable, with MAP < 60 mmHg, refractory to vasopressors use
  - Uncontrolled concomitant infection
  - DIC
  - Myocardial infarction
  - Acute coronary disease
  - Patient on dialysis
  - Intracranial bleeding active within the last 7 days
  - Pregnancy

Interventions

- Details of CP
  - Type of plasma: details or NR
  - Volume: 200-250 mL per dose
  - Number of doses: 1-2
  - Antibody-titre: NR
  - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy: within 48 h (possible from admission: unclear) with severe or life-threatening disease
- For studies including a control group: comparator (type): SC
- Concomitant therapy: SC
- Treatment cross-overs: NA

Outcomes

- Primary study outcome
  - Transfusion-related SAEs (time frame: 14 days after randomisation)
  - Incidence of transfusion-related SAEs, according to the Haemovigilance Module Surveillance Protocol v 2.5.2
- Primary review outcomes
  - All-cause mortality during hospital stay: yes
  - 28-day mortality: NR
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): yes
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
  - Number of participants with SAEs: yes
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes

NCT04497324 *(Continued)*

- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Length of ICU stay
  - Duration of mechanical ventilation
  - Clinical Improvement at 14 days

Notes	• Recruitment status: completed, but no results available yet • Sponsor: Universidad Peruana Cayetano Heredia

NCT04501978

Methods	• Trial design: RCT (platform trial) • Sample size: 10,000 • Setting: inpatient • Country: Denmark, USA, India, Poland, Singapore, Spain, Switzerland, UK • Language: English • Number of centres: 88

Participants	• Inclusion criteria
	  ○ Signed informed consent
	  ○ Positive test for COVID-19 and progressive disease suggestive of ongoing COVID-19 infection
	  ○ Symptoms of COVID-19 for ≤ 12 days
	  ○ Require admission to hospital for acute medical care (not for purely public health or quarantine purposes)
	• Exclusion criteria
	  ○ Received plasma from a person who recovered from COVID-19 or who has received neutralising monoclonal antibodies at any time prior to hospitalisation
	  ○ Not willing to abstain from participation in other COVID-19 treatment trials until after Day 5 of the study, although co-enrolment in certain trials that compare recommended SC treatments allowed, based on the opinion of the study leadership team
	  ○ Any condition which, in the opinion of the responsible investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments
	  ○ Considered unable to participate in study procedures
	  ○ Women of child-bearing potential who were not pregnant at study entry and who were unwilling to accept advice to abstain from sexual intercourse with men or practice appropriate contraception during the 18 months of the study
	  ○ Men who were unwilling to accept advice to abstain from sexual intercourse with women of child-bearing potential or to use barrier contraception during the 18 months of the study
	  ○ Presence at study enrolment of any of the following:
	  ■ stroke
	  ■ meningitis
	  ■ encephalitis
	  ■ myelitis
	  ■ myocardial ischaemia
	  ■ myocarditis
	  ■ pericarditis
	  ■ symptomatic congestive heart failure
	  ■ arterial or deep venous thrombosis or pulmonary embolism
	  ○ Current or imminent requirement for any of the following:
	  ■ IMV

NCT04501978 *(Continued)*

- ECMO
- mechanical circulatory support
- vasopressor therapy
- commencement of renal replacement therapy at this admission (i.e. not patients on chronic renal replacement therapy)

Interventions	• Details of CP
	  ○ Drug name: NA
	  ○ Dose: NA
	  ○ Number/frequency of doses: NA
	  ○ Route: NA
	  ○ Source (e.g. human/equine/other): NA
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NA
	• For studies including a control group: NA
	• Concomitant therapy: NA
	• Treatment cross-overs: NA

Outcomes	• Primary study outcome
	  ○ Time from randomisation to sustained recovery (time frame: to Day 90)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: yes
	  ○ 28-day mortality: NR
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
	  ○ Number of participants with SAEs: yes
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: NR
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission to the ICU on day 28: NR
	  ○ Duration of hospitalisation: NR
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional study outcomes
	  ○ All-cause mortality (time frame: to Day 90)
	  ○ Composite of time to sustained recovery and mortality (time frame: to Day 90)
	  ○ Days alive outside short-term acute care hospital (time frame: to Day 90)
	  ○ Pulmonary ordinal outcome (time frame: Days 1-7, 14 and 28)
	  ○ Pulmonary + ordinal outcome (time frame: Days 1-7)
	  ○ Incidence of clinical organ failure (time frame: through Day 28)
	  ○ Composite of death or serious clinical COVID-19-related events (time frame: to Day 90)
	  ○ Composite of cardiovascular events and thromboembolic events (time frame: to Day 90)
	  ○ Composite of grades 3 and 4 clinical AEs, SAEs or death (time frame: to Days 5 and 28)
	  ○ Incidence of infusion reactions (time frame: to Day 0)

NCT04501978 *(Continued)*

- Composite of SAEs or death (time frame: to 18 months)
- Change in SARS-CoV-2 neutralising antibody levels (time frame: baseline to Days 1, 3, 5, 28 and 90)
- Change in overall titres of antibodies (time frame: baseline to Days 1, 3, 5, 28 and 90)
- Change in neutralising antibody levels (time frame: baseline to Days 1, 3, 5, 28 and 90)
- Incidence of home use of supplemental oxygen above pre-morbid oxygen use (time frame: 18 months)
- Incidence of no home use of supplemental oxygen above pre-morbid oxygen use (time frame: 14 days)

Notes	• Recruitment status: active, not recruiting • Planned completion date: July 2022 • Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)

NCT04521309

Methods	• Trial design: RCT, sequential assignment • Sample size: 50 • Setting: inpatient • Country: Pakistan • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  ○ > 18 years of age
	  ○ Positive SARS-CoV-2 PCR on NP and/or oropharyngeal swabs
	  ○ Admitted in isolation ward and ICU of institutes affiliated with DUHS
	  ○ Severe or critical COVID-19 as judged by the treating physician
	  ○ Consent given by the patient or first-degree relative
	• Exclusion criteria
	  ○ Pregnant
	  ○ Previous allergic reaction to immunoglobulin treatment
	  ○ IgA deficiency
	  ○ Requiring 2 inotropic agents to maintain blood pressures
	  ○ Known case of any autoimmune disorder
	  ○ Acute kidney injury or chronic renal failure
	  ○ Known case of thromboembolic disorder
	  ○ Aseptic meningitis

Interventions	• Details of CP
	  ○ Type of plasma: IVIG developed from CP
	  ○ Volume:
	  ■ single dose of 0.20 g/kg anti-COVID-19 IVIG
	  ■ single dose of 0.25 g/kg anti-COVID-19 IVIG
	  ■ single dose of 0.30 g/kg anti-COVID-19 IVIG
	  ■ single dose of 0.35 g/kg anti-COVID-19 IVIG
	  ○ Number of doses: 1
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

NCT04521309 *(Continued)*

	• For studies including a control group: comparator (type): SC only n = 10 participants • Concomitant therapy: airway support, anti-viral medication, antibiotics, fluid resuscitation, haemodynamic support, steroids, painkillers, antipyretics • Treatment cross-overs: none

Outcomes	• Primary study outcomes (time frame: 28 days)
	  ○ Mortality
	  ○ Requirement of supplemental oxygen support
	  ○ Number of days on assisted ventilation
	  ○ Days to step down
	  ○ Days to hospital discharge
	  ○ AEs during hospital stay
	  ○ Change in CRP levels
	  ○ Change in neutrophil lymphocyte ratio
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 30-day mortality: yes, 28-day mortality
	• Secondary review outcomes
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes, TRALI reported
	  ○ Number of participants with SAEs
	  ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
	  ○ Mortality (time to event): NR
	  ○ 90-day mortality: NR
	  ○ Time to discharge from hospital: yes
	  ○ Admission to the ICU: NR
	  ○ Length of stay on the ICU: NR
	  ○ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes, time frame: 28 days
	  ○ QoL: NR
	• Additional study outcomes
	  ○ Change in ferritin levels
	  ○ Change in LDH
	  ○ Change in radiological (X-ray) findings
	  ○ Anti-SARS-CoV-2 antibody
	  ○ Change in sodium levels
	  ○ Change in potassium levels
	  ○ Change in chloride levels
	  ○ Change in bicarbonate levels

Notes	• Recruitment status: completed • Planned completion date: March 2021 • Sponsors: Dow University of Health Sciences Higher Education Commission (Pakistan)

NCT04539275

Methods	• Trial design: double-blind, placebo-controlled RCT • Sample size: 702 • Setting: inpatient

NCT04539275 *(Continued)*

- Country: USA
- Language: English
- Number of centres: 20

Participants	• Inclusion criteria
	  ○ Veterans must meet all the following criteria to be eligible to participate.
	  ■ Admitted to a participating VA clinical site with symptoms suggestive of SARS-CoV-2 infection
	  ■ Participant (or legally authorised representative) provides informed consent prior to initiation of any study procedures
	  ■ Participant (or legally authorised representative) understands and agrees to comply with planned study procedures
	  ■ Veteran ≥ 18 years of age at time of screening
	  ■ Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or antigen test, as documented by either of the following:
	  ■ (1) RT-PCR- or antigen-positive (NP, oropharyngeal, saliva, lower respiratory) in sample collected 72 h prior to screening
	  ■ (2) RT-PCR- or antigen-positive in sample collected > 72 h but 168 hours (i.e. 7 days) prior to screening
	  ■ Documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking > 24 h, etc.), and progressive disease suggestive of ongoing SARS-CoV-2 infection
	  ■ Requiring oxygen by nasal cannula or by face-mask as a new treatment (or if previously on home oxygen, at a litre flow at least 2 L/min greater than home prescription), but not on humidified heated high-flow nasal cannula (HHHFNC) at 15 L/min
	  ■ Can be randomised within 72 h of hospital admission.
	  ■ Agrees not to participate in another therapeutic clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 29 without approval from the investigator(s). Taking part in other research studies, including those unrelated to SARS-CoV-2, without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other study.
	• Exclusion criteria
	  ○ An individual who meets any of the following criteria will be excluded from participation in this study.
	  ■ Respiratory failure requiring mechanical ventilation, non-invasive ventilation including CPAP (for an indication other than previously diagnosed sleep apnoea and maintained on outpatient settings), or ECMO or anticipated to require any of those treatments or to die within 24 h
	  ■ Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 h
	  ■ History of previous transfusion reaction.
	  ■ Previously documented serum IgA deficiency (< 7 mg/dL)
	  ■ Documented to have received CP in the last 60 days.

Interventions	• Details of CP
	  ○ Type of plasma: CP from people recovered from SARS-CoV-2
	  ○ Volume: 200-500 mL
	  ○ Number of doses: 2 doses
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): masked saline placebo
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	

NCT04539275 *(Continued)*

- Primary study outcome
  - Proportion of participants developing acute hypoxaemic respiratory failure or all-cause death (time frame: Day 1 through Day 28)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: yes
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
  - Number of participants with SAEs: NR
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: yes
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Time (in days) to recovery (time frame: Day 1 through Day 28)
  - Time (in days) to death or respiratory failure (time frame: Day 1 through Day 28)
  - Proportion of participants who died from any cause, had respiratory failure, or required humidified heated high-flow nasal cannula (HHHFNC) at 15 L/min (time frame: Day 1 through Day 28)
  - Time (in days) to death or respiratory failure or HHHFNC at 15 L/min (time frame: Day 1 through Day 28)
  - 28-day all-cause mortality (time frame: Day 1 through Day 28)
  - Time to an improvement of 1 category using an ordinal scale: Modified WHO 8-point Ordinal Scale for Clinical Improvement (time frame: up through 28 days)
  - Time to an improvement of 2 categories using an ordinal scale: Modified WHO 8-point Ordinal Scale for Clinical Improvement (time frame: up through 28 days)
  - Participant's clinical status by ordinal scale (time frame: up through 28 days)
  - Mean change in the ordinal scale (time frame: Days 2, 4, 7, 11, 14, 21, and 28)
  - Time to discharge or to a NEWS-2 of = 2 and maintained for 24 h, whichever occurs first (time frame: up through 28 days)
  - Change in NEWS-2 score from Day 1 (baseline) to Days 2, 4, 7, 11, 15, and 29 (time frame: from Day 1 (baseline) to Days 2, 4, 7, 11, 15, and 29)
  - Duration of hospitalisation (time frame: Day 1 through Day 28)
  - Number of hospitalisations related to COVID-19 (time frame: Day 1 through Day 28)
  - Cumulative incidence of SAEs (time frame: Day 1 through Day 29)
  - Cumulative incidence of Grade 3 and 4 clinical and/or laboratory AEs (time frame: Day 1 through Day 29)
  - Incidence of discontinuation or temporary suspension of study product administrations (for any reason) (time frame: Day 1 through Day 29)
  - Change from baseline in haemoglobin (time frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).)
  - Change from baseline in platelets (time frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).)

NCT04539275 *(Continued)*

- Change from baseline in creatinine (time frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).)
- Change from baseline in glucose (time frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).)
- Change from baseline in total bilirubin (time frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised))
- Change from baseline in ALT (time frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised))
- Change from baseline in AST (time frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised))
- Change from baseline in prothrombin time (PT) (time frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).

Notes	• Recruitment status: terminated • Prospective completion date: July 18, 2022 • Sponsor/funding: VA Office of Research and Development

NCT04542967

Methods	• Trial design: double-blind RCT • Sample size: 150 • Setting: inpatient • Country: Mexico • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ O2 saturation < 93%
	  ○ Radiographic evidence of moderate pneumonia according to Rale's classification
	  ○ Acute respiratory distress syndrome ($PaO_2/FiO_2 < 300$ or $SpO_2/FiO_2 \leq 315$)
	  ○ Authorisation to participate in the study and have informed consent letter, signed by the patient or the person responsible for the patient in case of critical patients (intubated)
	• Exclusion criteria
	  ○ Pregnant patients
	  ○ History of transfusion reactions
	  ○ Patients with congestive heart failure
	  ○ Patients with a history of chronic kidney failure on dialysis
	  ○ Patients with multiple organ failure
	  ○ Patients who does not accept or agree with the treatment.

Interventions	• Details of CP
	  ○ Type of plasma: NR
	  ○ Volume: 200 mL
	  ○ Number of doses: 2 doses
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): If a 3rd dose of CP is necessary, it may be used, as long as an evaluation is carried out by the research team
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: NR

NCT04542967 *(Continued)*

	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Disease progression (time frame: up to 30 days after study entry) = change in Ordinal Scale for Clinical Improvement (WHO). The progression of disease, its change in the severity score; a bigger number to the obtained after randomisation
	  ○ Side effects (time frame: up to 30 days after study entry) = side effects associated with the administration of CP
	  ○ Mortality (time frame: up to 30 days after study entry) = any cause of death
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: NR
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): yes
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
	  ○ Number of participants with SAEs: NR
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: NR
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission to the ICU on day 28: NR
	  ○ Duration of hospitalisation: NR
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional study outcomes
	  ○ Respiratory improvement (time frame: 10 days)
	  ○ Clinical improvement (time frame: 10 days)
	  ○ Acute AEs (time frame: after receiving intervention, an average time 1 h, until 24 h after administration) = transfusion reactions during transfusion.
	  ○ Inflammatory biomarkers (D dimer) (time frame: 10 days)
	  ○ Inflammatory biomarkers (ferritin) (time frame: 10 days)
	  ○ Inflammatory biomarkers (CRP) (time frame: 10 days)
	  ○ Inflammatory biomarkers (LDH) (time frame: 10 days)

Notes	• Recruitment status: completed, but no results available yet • Sponsor/funding: Hospital Central Militar

NCT04547127

Methods	• Trial design: multi-centre, randomised, open-label, parallel group pilot study • Sample size: 200 • Setting: inpatient • Country: Spain

NCT04547127 *(Continued)*

- Language: English
- Number of centres: 12

Participants	• Inclusion criteria
	  ○ Hospitalised men and women ≥ 18 years of age
	  ○ Treated in ICU for COVID-19 for < 48 h or for whom it has been decided that severity of COVID-19 disease warrants ICU admission
	  ○ Informed consent provided by participant or representative prior to initiation of any study procedures
	  ○ Laboratory-confirmed novel coronavirus (SARS-CoV-2) infection determined by qualitative RT-PCR, or other commercial or public health assay in any specimen
	  ○ Illness (symptoms) of any duration, and the following:
	  ■ radiographic infiltrates by imaging (chest X-ray, CT scan, etc.), AND
	  ■ requiring mechanical ventilation and/or supplemental oxygen
	  ○ No limitation of therapeutic effort (decision on the status and future of the participant)
	  ○ Negative test for pregnancy blood or urine human chorionic gonadotropin (HCG)-based assay at screening/baseline visit for women of child-bearing potential
	• Exclusion criteria
	  ○ Clinical evidence of any significant acute or chronic disease that, in the opinion of the investigator, may place the participant at undue medical risk
	  ○ Known serious anaphylactic reaction to blood, any blood-derived or plasma product or methylene blue
	  ○ Medical condition in which the infusion of additional fluid is contraindicated
	  ○ Unresponsive to fluid challenge and/or multiple vasopressors and accompanied by multiorgan failure considered by the Principal Investigator not able to be reversed

Interventions	• Details of CP
	  ○ Type of plasma: ABO-compatible CP with each unit of plasma, obtained from the same convalescent donor (FFP)
	  ○ Volume: 200-250 mL
	  ○ Number of doses: 2 doses
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): standard medical treatment
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ All-cause mortality rate (time frame: up to Day 29)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: yes, 29-day mortality
	  ○ 60-day mortality: NR
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
	  ○ Number of participants with SAEs: NR
	• Secondary review outcomes

NCT04547127 *(Continued)*

- Improvement of clinical status:
  - weaning or liberation from IMV in surviving participants: NR
  - ventilator-free days: NR
  - liberation from supplemental oxygen in surviving participants: NR
- Need for dialysis at up to 28 days: NR
- Admission to the ICU on day 28: NR
- Duration of hospitalisation: yes, time to hospital discharge
- Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR

- Additional study outcomes
  - Change from baseline in NEWS
  - Time to clinical response as assessed by NEWS ≤ 2 maintained for 24 h
  - Time to hospital discharge
  - Time to ICU discharge
  - Duration of all oxygen use
  - Duration of mechanical ventilation
  - Absolute value change from baseline in ordinal scale
  - Mean change from baseline in ordinal scale
  - Percentage of participants in each severity category of the 7-point ordinal scale

Notes	• Recruitment status: completed • Prospective completion date: March 2021 • Sponsor/funding: Instituto Grifols, S.A.

NCT04649879

Methods	• Trial design: open-label RCT (2:1) • Sample size: 920 • Setting: inpatient • Country: Sweden • Language: English • Number of centres: 3

Participants	• Inclusion criteria
	  ○ Age ≥ 18
	  ○ Admitted to a study hospital
	  ○ Active COVID-19 defined as symptoms + SARS-CoV-2 identified from upper or lower airway samples and blood
	  ○ Negative pregnancy test taken before inclusion and use of an acceptable effective method of contraception until treatment discontinuation if the participant is a woman of childbearing potential
	  ○ Written informed consent after meeting with a study physician and ability and willingness to complete follow-up
	• Exclusion criteria
	  ○ No matching plasma donor (exact matching in the ABO system is required)
	  ○ Unavailability of plasma
	  ○ Estimated GFR < 30 (kidney failure stage III or more)
	  ○ Pregnancy (urinary-HCG)
	  ○ Breastfeeding
	  ○ Inability to give informed consent

NCT04649879 *(Continued)*

Interventions	• Details of CP
	  ○ Type of plasma: CP
	  ○ Volume: 200 mL over 2 h
	  ○ Number of doses: daily infusion until SARS-CoV-2 is no longer detectable in the blood up to a maximum of 10 CP infusions
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): SC for COVID-19 patients
	• Concomitant therapy: If steroid therapy has not already been initiated, betamethasone 3 mg daily will be given concomitantly with steroid therapy or longer if clinically indicated but for a maximum of 10 days.
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ COVID-19 related mortality within 28 days
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 28-day mortality: yes
	  ○ 60-day mortality: yes
	  ○ Mortality (time to event): NR
	  ○ Clinical status
	  ■ Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
	  ■ Improvement of clinical status: participants discharged from hospital: NR
	  ○ QoL: NR
	  ○ Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
	  ○ Number of participants with SAEs: NR
	• Secondary review outcomes
	  ○ Improvement of clinical status:
	  ■ weaning or liberation from IMV in surviving participants: NR
	  ■ ventilator-free days: NR
	  ■ liberation from supplemental oxygen in surviving participants: NR
	  ○ Need for dialysis at up to 28 days: NR
	  ○ Admission to the ICU on day 28: NR
	  ○ Duration of hospitalisation: NR
	  ○ Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
	• Additional study outcomes
	  ○ COVID-19-related mortality within 60 days
	  ○ Requirement of invasive ventilation or $Pao_2/FiO_2 \leq 70$ for ≥ 12 h in the case of patients not eligible for intensive care
	  ○ Adverse events
	  ○ Dose of plasma needed to clear viraemia
	  ○ Time to clearance of viraemia

Notes	• Recruitment status: completed, but no results available yet • Sponsor/funding: Joakim Dillner

NCT04681430

Methods	• Trial design: 4-arm, multi-centre, randomised, partly double-blind, controlled trial • Sample size: 1094 • Setting: outpatient • Country: Germany • Language: English • Number of centres: 4

Participants	• Inclusion criteria
	  ○ Individuals (female, male, diverse) ≥ 18 years with SARS-CoV-2 infection, confirmed by PCR before study enrolment
	  ○ SARS-CoV-2 positive PCR ≤ 3 days old (date of NP swab)
	  ○ Presence of ≥ 1 SARS-CoV-2 typical symptom (fever, cough, shortness of breath, sore throat, headache, fatigue, smell/and or taste disorder, diarrhoea, abdominal symptoms, exanthema) and symptom duration ≤ 3 days
	  ○ Ability to provide written informed consent
	  ○ Presence of at least one of the following criteria:
	  ■ Patients > 75 years
	  ■ Patients > 65 years with at least 1 other risk factor (BMI > 35 kg/m^2, coronary artery disease, CKD with GFR < 60 mL/min but ≥ 30 mL/min, diabetes mellitus, active tumour disease)
	  ■ Patients with a BMI > 35 kg/m^2 with at least 1 other risk factor (coronary artery disease, CKD with GFR < 60 mL/min but ≥ 30 mL/min, diabetes mellitus, active tumour disease)
	  ■ Patients with a BMI > 40 kg/m^2
	  ■ Patients with COPD and/or pulmonary fibrosis
	• Exclusion criteria
	  ○ Age < 18 years
	  ○ Unable to give informed consent
	  ○ Pregnant women or breastfeeding mothers
	  ○ Previous transfusion reaction or other contraindication to a plasma transfusion
	  ○ Known hypersensitivity to camostat mesylate and/or severe pancreatitis
	  ○ Volume stress due to CP administration would be intolerable
	  ○ Known IgA deficiency
	  ○ Life expectancy < 6 months
	  ○ Duration SARS-CoV-2 typical symptoms > 3 days
	  ○ SARS-CoV-2 PCR detection > 3 days
	  ○ SARS-CoV-2-associated clinical condition ≥ WHO stage 3 (patients hospitalised for other reasons than COVID-19 may be included if they fulfil all inclusion and none of the exclusion criteria)
	  ○ Previously or currently hospitalised due to SARS-CoV-2
	  ○ Previous antiviral therapy for SARS-CoV-2
	  ○ ALT or AST > 5 times ULN at screening
	  ○ Liver cirrhosis > Child A (patients with Child B/C cirrhosis are excluded from the trial)
	  ○ CKD with GFR < 30 mL/min
	  ○ Concurrent or planned anticancer treatment during trial period
	  ○ Accommodation in an institution due to legal orders
	  ○ Any psycho-social condition hampering compliance with the study protocol
	  ○ Evidence of current drug or alcohol abuse
	  ○ Use of other investigational treatment within 5 half-lives of enrolment is prohibited
	  ○ Previous use of CP for COVID-19
	  ○ Concomitant proven influenza A infection
	  ○ Patients with organ or bone marrow transplant in the 3 months prior to screening visit

Interventions	• Details of CP
	  ○ Type of plasma: CP with neutralising antibodies against anti-SARS-CoV-2
	  ○ Volume: NR

NCT04681430 *(Continued)*

- Number of doses: 2 doses
- Antibody-titre: at least 1:160
- Pathogen inactivated or not: NR

- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage of disease (before hospitalisation)
- For studies including a control group: comparator (type): SC, camostat mesylate, placebo camostat
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
  - WHO ordinal COVID-19 scale up to day 28
- Primary review outcomes
  - 28-day mortality: yes
  - 60-day mortality: NR, but 90-day mortality
  - Mortality (time to event): NR
  - Admission to hospital or death within 28 days: NR
  - Symptom resolution:
    - all initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up: NR
    - time to symptom resolution: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): yes
  - Number of participants with SAEs: yes
- Secondary review outcomes
  - Worsening of clinical status
    - Need for invasive mechanical ventilation or death: NR
    - Need for hospitalisation with oxygen by mask or nasal prongs, or death: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - Number of participants with SARS-CoV-2 re-infection up to day 90
  - Number of participants with secondary sclerosis cholangitis at day 90
  - Number of participants with COVID-19-associated COPD
  - The proportion of participants with remdesivir therapy
  - COVID-19 WHO status of participants at start of remdesivir treatment
  - The proportion of participants on dexamethasone therapy
  - COVID-19 WHO status of participants at start of dexamethasone treatment
  - Time to resolution of COVID-19-related symptoms
  - Duration of oxygen therapy (in days)
  - Frequency of occurrence of COVID-19 pneumonia
  - Percentage of participants requiring mechanical ventilation
  - Number of ventilation days per participant up to day 90
  - All-cause mortality at day 28
  - SARS-CoV-2 antibody concentrations (IgA in g/L) in serum on day 8, day 14, day 90
  - SARS-CoV-2 antibody concentrations (IgG in g/l) in serum on day 8, day 14, day 90
  - SARS-CoV-2 neutralising antibody titres in serum on day 8, day 14, day 90
  - Number of screening failures due to the lack of a suitable plasma preparation

Notes

- Recruitment status: completed, but no results yet available
- Sponsor/funding:
  - Heinrich-Heine University, Duesseldorf
  - The Federal Ministry of Health, Germany (Bundesministerium für Gesundheit, BMG)

NCT04801940

Methods	• Trial design: open-label RCT (platform) • Sample size: 2631 • Setting: inpatient • Country: UK • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  ○ ≥ 18 years of age
	  ○ Hospitalised with estimated hospital discharge within 5 days
	  ○ SARS-CoV-2 infection-associated disease (laboratory-confirmed SARS-CoV-2 infection) on this hospital admission
	  ○ Written informed consent obtained from participant or participant's legal representative
	• Exclusion criteria
	  ○ Known hypersensitivity to trial medication (patient will be excluded from specific arm)
	  ○ Long-term pre-hospital administration of trial medication (patient will be excluded from specific arm)
	  ○ Previous medical history of significant complication with trial medication or trial medication drug class
	  ○ Medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial.
	  ○ Participant not expected to survive 14 days from hospital discharge
	  ○ The presence of any of the following will preclude participant inclusion in the Apixaban arm:
	  ■ active clinically significant bleeding
	  ■ Childs-Pugh C, or worse, chronic liver disease
	  ■ known pregnancy or breastfeeding
	  ■ coagulopathy: international normalised ratio > 1.7 or platelet count < 70
	  ■ lesion or condition considered by the investigator as a significant risk factor for major bleeding. This may include recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities.
	  ■ concomitant treatment following discharge with any other anticoagulant agent, including but not limited to unfractionated heparin, low molecular weight heparins (e.g. enoxaparin, dalteparin), heparin derivatives (e.g. fondaparinux), and other oral anticoagulants (e.g. warfarin, rivaroxaban, dabigatran).
	  ○ The presence of any of the following will preclude participant inclusion in the Atorvastatin arm:
	  ■ Childs-Pugh C, or worse, chronic liver disease
	  ■ unexplained persistent elevations of serum transaminases exceeding 5 x ULN
	  ■ known pregnancy or breastfeeding
	  ■ treatment with the hepatitis C antivirals lecaprevir/pibrentasvir, ciclosporin or HIV protease inhibitors
	  ■ serum creatine kinase concentration exceeding 10 x ULN

Interventions	• Details of CP:
	  ○ Type of plasma: anti-SARS-CoV-2 virus inactivated plasma
	  ○ Volume: NR
	  ○ Number of doses: NR
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

NCT04801940 *(Continued)*

- For studies including a control group: comparator (type): SC
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
  - Hospital-free survival (time frame 12 months)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 28-day mortality: NR
  - 60-day mortality: NR
  - Mortality (time to event): NR
  - Clinical status
    - Worsening of clinical status: participants with clinical deterioration (new need for IMV or death): NR
    - Improvement of clinical status: participants discharged from hospital: NR
  - QoL: NR
  - Number of participants with AEs (any grade, grades 1-2, grades 3-4): NR
  - Number of participants with SAEs: yes
- Secondary review outcomes
  - Improvement of clinical status:
    - weaning or liberation from IMV in surviving participants: NR
    - ventilator-free days: NR
    - liberation from supplemental oxygen in surviving participants: NR
  - Need for dialysis at up to 28 days: NR
  - Admission to the ICU on day 28: NR
  - Duration of hospitalisation: NR
  - Viral clearance (RT-PCR) at baseline, up to 3, 7, and 15 days: NR
- Additional study outcomes
  - All-cause mortality (time frame: 12 months)
  - Hospital readmission after discharge from index hospital admission (time frame: 12 months)
  - FACIT-Fatigue
  - Modified MRC Dyspnoea Scale
  - COVID-19 core outcome measure for recovery
  - Patient Health Questionnaire-2 (PHQ-2)
  - Generalized Anxiety Disorder-2 (GAD-2)
  - PTSD Checklist (PCL-2)
  - Quality of life using the EQ5D-5L
  - Intervention tolerability using the FACT-GP5
  - Additional disease specific systemic symptoms
  - Incremental cost-effectiveness

Notes

- Recruitment status: recruiting (platform trial)
- Sponsor/funding: University of Liverpool, Cambridge University Hospitals NHS Foundation Trust (joint Sponsor), The University of Cambridge (joint sponsor)

AE: adverse event; **ALT:** alanine aminotransferase; **ARDS:** acute respiratory distress syndrome; **AST:** aspartate aminotransferase; **BAL:** bronchoalveolar lavage; **CKD:** chronic kidney disease; **COPD:** chronic obstructive pulmonary disease; **CP:** convalescent plasma; **CPAP:** continuous positive airway pressure; **CRP:** C-reactive protein; **CT:** computed tomography; **DIC:** disseminated intravascular coagulation; **ECMO:** extracorporeal membrane oxygenation; **ED:** Emergency Department; **ELISA:** enzyme-linked immunosorbent assay; **FFP:** fresh frozen plasma; **FiO_2:** fractional inspired oxygen; **GFR:** glomerular filtration rate; **ICU:** intensive care unit; **IgA (B/G/M):** immunoglobulin

A (B/G/M); **IL-6:** interleukin-6; **IMV:** invasive mechanical ventilation; **IQR:** interquartile range; **IV:** intravenous;**IVIG:** immunoglobulin; **LDH:** lactate dehydrogenase; **MAP:** mean arterial pressure; **MRC:** Medical Research Council; **NEWS:** National Early Warning Score; **NP:** nasopharyngeal; **NR:** not reported; **PaO_2:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **PTSD:** post-traumatic stress disorder; **QoL:** quality of life; **RCT:** randomised controlled trial; **RRT:** renal replacement therapy; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SaO_2:** oxygen saturation of arterial blook; **SC:** standard care; **SOFA:** sequential organ failure assessment; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TB:** tuberculosis; **TRALI:** transfusion-related acute lung injury; **TTP:** thrombotic thrombocytopenia;**ULN:** upper limit of normal; **VA:** Veterans Association; **WHO:** World Health Organization

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR2000030010

Study name	A randomized, double-blind, parallel-controlled, trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)
Methods	• Trial design: randomised, double-blind, parallel-controlled trial • Sample size: 50 in each arm (100) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Aged 18-70 years old, inpatients, male or female
	  ○ Patients with severe novel coronavirus infection: according to the "Pneumonitis Diagnosis and Treatment Guideline for the Novel Coronavirus Infection (Trial Version 5)", clinically diagnosed cases (suspected cases with pneumonia imaging features) or suspected cases. Severe patients must also meet any of the following: 1) respiratory distress, respiratory rate ≥ 30 times/min; 2) In the resting state, the oxygen saturation is ≤ 93%; 3) PaO_2/FiO_2 ≤ 300 mmHg (1 mm Hg = 0.133 kPa)
	  ○ Participants and/or legal guardians of the participants volunteered to participate in the study and voluntarily signed informed consent
	• Exclusion criteria
	  ○ The clinical classification of patients with severe novel coronavirus infection is to meet any of the following: 1) respiratory failure occurs and requires mechanical ventilation; 2) shock occurs; 3) combined failure of other organs requires ICU monitoring and treatment
	  ○ Those who are allergic to blood products or plasma components and auxiliary materials (sodium citrate)
	  ○ There is multiple organ failure, and the estimated survival time is < 3 days
	  ○ Those who tested positive for HIV antibodies before enrolment
	  ○ Women who are pregnant or breastfeeding or have a birth plan within the past year
	  ○ Participants in other clinical trials within 3 months before screening
	  ○ Poor adherence or other conditions that the study author believes are not suitable for inclusion (such as poor physical condition)

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: anti-SARS-CoV-2 virus inactivated plasma
	• Details of CP
	  ○ Type of plasma: NR
	  ○ Volume: NR
	  ○ Number of doses: NR
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: yes
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): SP
	• Concomitant therapy: NR

ChiCTR2000030010 *(Continued)*

	• Treatment cross-overs: NR

Outcomes	• Primary study outcome: improvement of clinical symptoms (clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital)
	• Primary outcomes
	  ○ All-cause mortality during hospital stay: 14- and 28-day all-cause mortality
	  ○ Time to death: NR
	• Secondary outcomes
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  ○ Number of participants with SAEs: NR
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  ○ 30-day and 90-day mortality: 14- and 28-day all-cause mortality
	  ○ Admission on the ICU
	  ○ Length of stay on the ICU: ICU hospitalisation days
	  ○ Time to discharge from hospital
	  ○ QoL: NR
	• Additional study outcomes
	  ○ Improvement of clinical symptoms (clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital)
	  ○ Main clinical manifestations subsided or significantly improved (fever, dry cough, fatigue, etc.)

Starting date	19 February 2020
Contact information	Liu Ying, Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital), 1 Yintan Road, Dongxihu District, Wuhan, Hubei, China, 430023, whsjytyy_gcp@163.com Zhang Dingyu, 1 Yintan Road, Dongxihu District, Wuhan, Hubei, China, 430023, 1813886398@qq.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31 May 2020 • Sponsor/funding: Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital), Sinopharm Wuhan Blood Products Co., Ltd., Sinopharm Wuhan Blood Products Co., Ltd

ChiCTR2000030179

Study name	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)
Methods	• Trial design:RCT • Sample size: 50 in each arm (100) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Confirmed participant (or legal guardian) agrees to participate in the study and signs the informed consent form
	  ○ Aged 18-65 years

ChiCTR2000030179 *(Continued)*

- Real-time fluorescent RT-PCR of respiratory specimens or blood specimens to detect patients positive for novel coronavirus
- Patients diagnosed as severe and critically ill and with rapid disease progression according to the "Diagnosis and Treatment Program for Pneumonia of New Coronavirus Infection (Trial Version 6)"

- Exclusion criteria
  - Any situation where the solution cannot be carried out safely
  - Allergic constitution, allergic to plasma or drugs
  - Being too old, with severe underlying diseases that affect survival, including uncontrolled clinically significant heart, lung, kidney, digestive, haematological, neuropsychiatric, immune, metabolic, or malignant tumours, severe malnutrition, etc
  - Patients with severe respiratory failure, heart failure, and multiple organ failure
  - Participants in other clinical trials

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: routine treatment + plasma treatment
	• Details of CP
	  ○ Type of plasma: NR
	  ○ Volume: NR
	  ○ Number of doses: NR
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): routine treatment
	• Concomitant therapy: no
	• Treatment cross-overs: no

Outcomes	• Primary study outcomes
	  ○ Cure rate, mortality
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: mortality
	  ○ Time to death: NR
	• Secondary review outcomes
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  ○ Number of participants with SAEs: NR
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  ○ 30-day and 90-day mortality: mortality
	  ○ Admission on the ICU: NR
	  ○ Length of stay on the ICU: NR
	  ○ Time to discharge from hospital: length of stay
	• Additional study outcomes
	  ○ Cure rate

Starting date	24 February 2020
Contact information	Liu Wei, The First Affiliated Hospital of Nanchang University, 17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, cdyfyliuwei@163.com Le Aiping, 17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, leaiping@126.com
Notes	• Recruitment status: recruiting • Prospective completion date: 24 April 2020

ChiCTR2000030179 *(Continued)*

- Sponsor/funding: The First Affiliated Hospital of Nanchang University, raised independently

ChiCTR2000030627

Study name	Study on the application of convalescent plasma therapy in severe COVID-19
Methods	• Trial design: RCT • Sample size: 15 in each arm (30) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  ◦ Patients who were diagnosed with COVID-19 by nucleic acid test and were in accordance with the clinical classification of severe or critical illness. (Refer to the clinical classification criteria in the pneumonia diagnosis and treatment program of novel coronavirus infection, General Office of the National Health Commission (trial version 4))
	• Exclusion criteria
	  ◦ Patients with hypersensitivity to plasma products; patients with severe transfusion reactions in the past; patients with acute pulmonary oedema, congestive heart failure, pulmonary embolism, malignant hypertension, polycythaemia vera, extreme renal failure and other diseases

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP: NR
	  ◦ Type of plasma: NR
	  ◦ Volume: NR
	  ◦ Number of doses: NR
	  ◦ Antibody-titre: NR
	  ◦ Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): routine treatment
	• Concomitant therapy: no
	• Treatment cross-overs: no

Outcomes	• Primary study outcomes: temperature, virus nucleic acid detection
	• Primary review outcomes
	  ◦ All-cause mortality during hospital stay: mortality rate
	  ◦ Time to death
	• Secondary review outcomes
	  ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): incidence of AEs in blood transfusion
	  ◦ Number of participants with SAEs
	  ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  ◦ 30-day and 90-day mortality: yes
	  ◦ Admission on the ICU: NR
	  ◦ Length of stay on the ICU: NR
	  ◦ Time to discharge from hospital: length of admission
	  ◦ QoL: NR
	• Additional study outcomes

ChiCTR2000030627 *(Continued)*

	◦ Laboratory examination
Starting date	1 February 2020
Contact information	Guojun Zhang, The First Affiliated Hospital of Zhengzhou University, 1 Jianshe Road East, Zhengzhou, He'nan, China, zlgj-001@126.com Guojun Zhang, 1 Jianshe Road East, Zhengzhou, He'nan, China, zlgj-001@126.com
Notes	• Recruitment status: recruiting • Prospective completion date: 30 May 2020 • Sponsor/funding: The First Affiliated Hospital of Zhengzhou University, Science and Technology Department of He'nan Province

ChiCTR2000030702

Study name	Convalescent plasma for the treatment of common COVID-19: a prospective RCT
Methods	• Trial design: open-label, RCT • Sample size: 25 in each arm (50) • Setting: inpatient • Country: China • Language: translated to English • Number of Centres: 4
Participants	• Inclusion criteria ◦ Patient signed an informed consent form to participate in the study of CP therapy ◦ Patient aged ≥ 18 years old ◦ COVID-19 patients diagnosed by PCR ◦ Nucleic acid-positive within 72 h before blood transfusion ◦ Pneumonia confirmed by imaging ◦ Hospitalisation for fever (axillary temperature ≥ 36.7 °C, or oral temperature ≥ 38.0 °C, or anal or ear temperature ≥ 38.6 °C) and respiratory rate > 24 breaths/min or cough (at least 1 of the 2) ◦ Severe clinical warning indicators: such as a progressive decrease in peripheral blood lymphocytes, a progressive increase in peripheral blood inflammatory factors, a progressive increase in lactic acid, and rapid progress of lung lesions in the short term, et al ◦ Accept random grouping into any group ◦ Hospitalised before the end of the clinical study ◦ Willing to participate in all necessary research directions and be able to participate in follow-up ◦ During the period of participating in this study, they will no longer participate in clinical trials such as other antiviral drugs • Exclusion criteria ◦ Doctor believes that the patient is not suitable to participate in this trial, including those who may not co-operate, do not comply with the requirements of the procedure, or participating in this trial may put the patient in an unsafe situation ◦ Pregnant or breastfeeding women ◦ Immunoglobulin allergy ◦ IgA deficiency ◦ Clinical symptoms are mild (no pneumonia on imaging) ◦ Clinical symptoms are severe or critical where severe patients meet any of the following: 1) respiratory distress, respiratory rate ≥ 30 breaths/min; 2) in resting state, oxygen saturation ≤ 93%; 3) partial $PaO_2/FiO2 \leq 300$ mmHg (1 mmHg = 0.133 kPa); and critically ill patients meet any

ChiCTR2000030702 *(Continued)*

	of the following: 1) respiratory failure and need mechanical ventilation; 2) shock; 3) patients with other organ failure need ICU monitoring treatment ○ Diseases that may increase the risk of thrombosis, such as cold globulinaemia, severe refractory hypertriglyceridaemia, clinically defined monoclonal gamma globulinaemia, etc ○ Detection of high titre of anti-novel coronavirus antibody RBDIgG (> 1) ○ Received any experimental treatment for novel coronavirus infection within 30 days before screening ○ Researchers judged that the patients had the following life-threatening conditions, including, but not limited to, Phammer F < 100 mmHg, near-death state or expected survival time < 24 h, severe septic shock or DIC), etc ○ Severe congestive heart failure, or other relative contraindications for plasma transfusion determined by study authors
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: conventional treatment and CP therapy • Details of CP: ○ type of plasma: NR ○ volume: NR ○ number of doses: NR ○ antibody-titre: NR ○ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: SC • Concomitant therapy: symptomatic treatment, antiviral treatment, and antibacterial treatment • Treatment cross-overs: NR
Outcomes	• Primary study outcome: time to clinical recovery after randomisation • Primary review outcomes reported ○ All-cause mortality during hospital stay: 28-day mortality ○ Time to death: NR • Secondary review outcomes reported ○ Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (cumulative incidence of AEs (AE), grades 3 and 4 AE): cumulative incidence of severe AEs, incidence of adverse plasma transfusion reactions ○ Number of participants with SAEs: cumulative incidence of SAE ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: IMV during infection; ECMO duration during infection: 28-day assisted oxygen therapy or non-IMV rate ○ 30-day and 90-day mortality: 28-day mortality ○ Admission on the ICU: yes ○ Length of stay on the ICU: yes (ICU hospitalisation) ○ Time to discharge from hospital: yes (hospitalisation time) ○ QoL: NR • Additional study outcomes ○ Incidence of breathing exacerbations ○ Time for conscious cough relief during infection (cough present when enroled) ○ Time to remission of conscious dyspnoea during infection (dyspnoea present upon enrolment) ○ Proportion of viral nucleic acid-negative
Starting date	15 February 2020
Contact information	Liu Zhong, Institute of Blood Transfusion, Chinese Academy of Medical Sciences, 26 Huacai Road, Chenghua District, Chengdu, Sichuan, China, 610000, Liuz@ibt.pumc.edu.cn Cao Bin, 2 Yinghua Street East, Chaoyang District, Beijing, China, 100029, caobin_ben@163.com

ChiCTR2000030702 *(Continued)*

Notes	• Recruitment status: recruiting • Prospective completion date: 15 August 2020 • Sponsor/funding: China-Japan friendship hospital, Beijing, Institute of Blood Transfusion, Chinese Academy of Medical Sciences, Beijing, Government

ChiCTR2000030929

Study name	A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia (COVID-19)
Methods	• Trial design: randomised, double-blind, parallel-controlled trial • Sample size: 30 in each arm (60) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Aged 18-70 years old, inpatients, male or female
	  ○ Patients with severe COVID-19: confirmed cases shall be in compliance with guideline of "Diagnosis and Treatment Plan for COVID-19 (Version 7)" or updated versions
	  ○ Confirmed cases can be defined if suspected cases have characteristic of following pathogeny or serology
	  ■ detect nucleic acid of novel coronavirus positive by real-time fluorescent RT-PCR
	  ■ have highly homologous to known novel coronavirus by sequencing
	  ■ detect sero-specific IgM- and IgG-positive; IgG-specific against new coronavirus positive conversion or the titre of IgG is 4 times higher in convalescent period than in acute period
	  ○ Adult patients with severe COVID-19 shall meet any of the following:
	  ■ respiratory distress, respiratory rate ≥ 30 times/min
	  ■ in the resting state, oxygen saturation is ≤ 93%
	  ■ for lung radiology, the lesion has obtained > 50% obvious improvement within 24-48 h
	  ■ PaO_2/FiO_2 ≤ 300 mmHg (1 mmHg = 0.133 kPa)
	  ○ Patients and/or their legal guardians volunteered to participate in the study and voluntarily signed informed consent
	• Exclusion criteria
	  ○ Clinical classification of patients with severe novel coronavirus infection is to meet any of the following:
	  ■ respiratory failure occurs and requires mechanical ventilation;
	  ■ shock occurs;
	  ■ combined failure of other organs requires ICU monitoring and treatment
	  ○ Those who are allergic to blood products or plasma components and auxiliary materials (sodium citrate)
	  ○ Multiple organ failure, and the estimated survival time is < 3 days
	  ○ Those who tested positive for HIV antibodies before enrolment
	  ○ Women who are pregnant or breastfeeding or have a birth plan within the past year
	  ○ Participants in other clinical trials within 1 month before screening
	  ○ Poor adherence or other conditions that the study author believes are not suitable for inclusion (such as poor physical condition)

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP:

ChiCTR2000030929 *(Continued)*

	◦ type of plasma: anti-SARS CoV virus inactivated plasma ◦ volume: NR ◦ number of doses: NR ◦ antibody-titre: NR ◦ pathogen inactivated or not: yes • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type) - SP • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	• Primary study outcome: improvement of clinical symptoms (clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital) • Primary review outcomes reported: ◦ All-cause mortality during hospital stay: yes (at 14- and 28-day) ◦ Time to death: NR • Secondary review outcomes reported ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: IMV during infection; ECMO duration during infection: NR ◦ 30-day and 90-day mortality: 28-day mortality ◦ Admission on the ICU: yes ◦ Length of stay on the ICU: ICU hospitalisation days ◦ Time to discharge from hospital: NR ◦ QoL: NR • Additional study outcomes ◦ Improving time of main clinical symptoms (wheezing, cough, sputum, etc)
Starting date	17 March 2020
Contact information	Lianghao Zhang, 11443556@qq.com, Sinopharm Wuhan Blood Products Co., Ltd, 1 Golden Industrial Park Road, Zhengdian, Jiangxia District, Wuhan, Hubei, China
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 16 June 2020 • Sponsor/funding: Renmin Hospital of Wuhan University, 99 Zhang-Zhi-Dong Road, Wuchang District, Wuhan, Hubei, China

CTRI/2020/04/024915

Study name	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 associated complications
Methods	• Trial design: open-label, phase II, RCT • Sample size: 100 • Setting: inpatient • Country: India • Language: English

CTRI/2020/04/024915 *(Continued)*

	• Number of centres: 1

Participants	• Inclusion criteria
	  ○ Patients admitted with RT-PCR-confirmed COVID-19 illness
	  ○ Age > 18 years
	  ○ Written informed consent
	  ○ Has any of the 2: PaO_2/ FiO_2 24/min and SaO_2 < 93% on room air
	• Exclusion criteria
	  ○ Pregnant and lactating women
	  ○ Breastfeeding women
	  ○ Known hypersensitivity to blood products
	  ○ Receipt of pooled immunoglobulin in last 30 days
	  ○ Participating in any other clinical trial
	  ○ Clinical status precluding infusion of blood products

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  ○ type of plasma: ABO compatible plasma transfusion
	  ○ volume: 200 mL
	  ○ number of doses: NR
	  ○ antibody-titre: NR
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): SC treatment (guidelines according to The Ministry of Health and Welfare for COVID-19; and ARDSNet and Surviving Sepsis campaign guidelines for ARDS or sepsis)
	• Concomitant therapy: SC for COVID-19 disease
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Progression to severe ARDS (P/F ratio 100)
	  ○ All-cause mortality at 28 days
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 30-day mortality: NR (but 28-day mortality)
	• Secondary review outcomes
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): no, transfusion-related AEs only (and NR, whether number of participants or events)
	  ○ Number of participants with SAEs: NR
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: assessed, but NR ("Duration of respiratory support required")
	  ○ 30-day and 90-day mortality: NR (up to 28 days)
	  ○ Admission on the ICU: NR
	  ○ Length of stay on the ICU: yes
	  ○ Time to discharge from hospital: NR
	  ○ QoL: NR
	• Additional study outcomes
	  ○ Time to symptom resolution: fever, shortness of breath, fatigue
	  ○ Change in SOFA pre- and post-transfusion
	  ○ Radiological improvement
	  ○ To measure the change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR (time frame: Days 0, 1, 3, and 7 after transfusion)

CTRI/2020/04/024915 *(Continued)*

- Levels of bio-markers pre- and post-transfusion
- Need of vasopressor use

Starting date	9 May 2020
Contact information	Corresponding Author: Name: Dr Sangeeta Pathak Affiliation: Blood Bank, Max Super Speciality hospital, Saket (A unit of DevkiDevi Foundation) Full Address: Max Super Speciality Hospital (Devki Devi Foundation), East Block,Blood Bank, 2, Press enclave Road, Saket New DelhiNew DelhiDELHI110017India Email: sangeeta.pathak@maxhealthcare.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 9 May 2021 • Sponsor/funding: Max Super Speciality hospital, Saket (A unit of Devki Devi Foundation)

CTRI/2020/05/025346

Study name	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma in severe COVID-19 patients
Methods	• Trial design: phase II, open-label, RCT • Sample size: 90 • Setting: inpatient • Country: India • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Age > 20 years
	  ○ COVID-positive patients who are under treatment in the COVID acute care facility, and willing to give consent to participate in this study
	  ○ Should be admitted in the acute care facility for the treatment of COVID-19 infection without complications
	  ○ Clinical symptoms suggestive of COVID infection along with confirmed laboratory diagnosis of infection with COVID-19 as per ICMR/FDA guidelines
	  ○ Patients should be classified under severe COVID-19 infection without complications criteria as judged by the qualified treating physician:
	  ■ Dyspnoea
	  ■ Respiratory rate < 30/min
	  ■ Oxygen saturation < 93%
	  ■ Lung infiltrates > 50% within 24-48 h
	• Exclusion criteria
	  ○ Patients with any past history of transfusion reactions to blood products
	  ○ Receipt of ooled Immunoglobulin in last 30 days
	  ○ Critically ill patients: respiratory failure, sepsis, multi-organ failure, shock (requiring vasopressor to maintain a MAP > 65mmHg or MAP < 65 mmHg)
	  ○ Participating in any other clinical trial
	  ○ Pregnant and lactating women
	  ○ Patients infected with COVID-19 not meeting criteria for severe COVID condition

CTRI/2020/05/025346 *(Continued)*

	○ Patients with any chronic history of coronary artery disease, coronary bypass surgery, acute pulmonary oedema, pulmonary embolism, congestive heart failure, malignant hypertension, polycythaemia vera, severe renal failure, cirrhosis and with any implants
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: ○ type of plasma: ABO compatible convalescent plasma ○ volume: 200 mL ○ number of doses: 2 doses ○ antibody-titre: yes (titration of anti-covid-19 (both IgG and IgM) antibodies and SARS-CoV-2 neutralising antibodies may be done depending on availability of facilities at the time of testing. (Desired titres for IgG antibodies > 1024 or neutralising antibodies > 40) doubling dilution of donor serum will be done and titration will be done using CLIA. If not done at the time of plasma collection the donor samples will be stored in aliquots at −80 °C to be tested at a later date) ○ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): severe (see inclusion criteria), initially first dose and subsequent dose after 24 h of the initial dose • For studies including a control group: comparator (type): standard acute care • Concomitant therapy: standard acute care • Treatment cross-overs: none
Outcomes	• Primary study outcome ○ Prevent progression to severe ARDS (P/F ratio 100) ○ All-cause mortality at 30 days • Primary review outcomes ○ All-cause mortality during hospital stay: yes ○ Time to death: no • Secondary review outcomes ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): unclear whether only transfusion-related AEs are recorded ("After the CCP transfusion, serious adverse events will be noted") ○ Number of participants with SAEs: NR ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR ○ 30-day and 90-day mortality: 30-day mortality only ○ Admission on the ICU: NA ○ Length of stay on the ICU: NA ○ Time to discharge from hospital: yes (length of hospital stay) ○ QoL: NR • Additional study outcomes ○ Duration(days) of ICU stay/hospital stay from symptom onset ○ Duration of IMV/non-IMV ○ Incidence of transfusion reactions, ARDS and sepsis ○ Duration of clinical symptoms and radiological improvement post-transfusion ○ Levels of IgG antibody, neutralising antibody titres
Starting date	1 June 2020
Contact information	Corresponding author Name: Dr S Anbuselvi Mattuvar Kuzhali Affiliation: Madras Medical College

CTRI/2020/05/025346 *(Continued)*

	Full Address: Institute of Physiology and Experimental Medicine, Madras MedicalCollege, Chennai 4B, third floor, KGEYES HYACINTH, LB road, Kamaraj Nagar, Thiruvanmiyur, Chennai, Chennai, TAMIL NADU 600003 India Email: dranbuselvimk@gmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 1 June 2022 • Sponsor/funding: Secretariat, Government of Tamilnadu, Namakkal Kavignar Maaligai, Fort St. George, Chennai 600 009

CTRI/2020/06/026123

Study name	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma in severe COVID-19
Methods	• Trial design: randomised, parallel group, active controlled trial • Sample size: 472 • Setting: inpatient • Country: India • Language: English • Number of centres: 21

Participants	• Inclusion criteria
	  ○ Age > 18 years
	  ○ Hospitalised COVID-19 patients
	  ○ Fever, cough, breathlessness plus ≥ 1 of the following: respiratory rate > 30/min, O_2 saturation < 90%, PaO_2 by FiO_2 < 300
	  ○ Patients with comorbidities: e.g. diabetes mellitus, COPD, hypertension, asthma
	• Exclusion criteria
	  ○ Pregnant and breastfeeding women
	  ○ Critically ill patients e.g. with severe ARDS, sepsis, septic shock, multiple organ dysfunction syndrome, coronary artery disease, arrhythmia, heart failure

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  ○ type of plasma: anti-SARS-CoV-2 convalescent plasma viral neutralising antibodies blood product
	  ○ volume: 200 mL
	  ○ number of doses: 2 doses
	  ○ antibody-titre: NR
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): 2 doses, 24 h apart
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ All-cause mortality at 28 days
	  ○ Proportion of participants showing at least 2 points' clinical improvement on WHO ordinal scale at 28 days post randomisation.
	• Primary review outcomes

CTRI/2020/06/026123 *(Continued)*

- All-cause mortality during hospital stay: NR
- 30-day mortality: NR (28 days)

- Secondary review outcomes
  - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (see primary study outcomes)
  - Mortality (time to event): NR
  - 90-day mortality: NR
  - Time to discharge from hospital: length of hospital stay
  - Admission to the ICU: NR
  - Length of stay on the ICU: NR
  - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
  - QoL: NR
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, TACO, TAD, acute transfusion reactions): NR
  - Number of participants with SAEs: NR
- Additional study outcomes
  - Time to clinical improvement
  - Change in SOFA score
  - Duration of oxygen support
  - Duration of respiratory support required
  - Levels of biomarkers CRP, ferritin, D-dimer pre-and post-transfusion
  - Radiological improvement

Starting date	25 June 2020
Contact information	Corresponding Author Name: Dr Sushant Meshram Affiliation: Government Medical College and Hospital, Nagpur Full Address: Dept of Pulmonary Medicine, 4th floor, Super Specialty Hospital, Government Medical College Hospital, Nagpur. Nagpur, MAHARASHTRA 440009 India Email: drsushant.in@gmail.com
Notes	Recruitment status: not yet recruiting • Prospective completion date: 25 December 2020 • Sponsor/funding: Dr Sanjay Mukherjee Secretary Medical Education and Drug Department 9th floor G T Hospital campus, new Mantralya, Mumbai Government of Maharashtra

EUCTR2020-001632-10

Study name	A randomized open label phase-II clinical trial with or without infusion of plasma from subjects after convalescence of SARS-CoV-2 infection in high-risk patients with confirmed severe SARS-CoV-2 disease
Methods	• Trial design: randomised, open, cross-over, parallel-arm, multi-centre, phase II • Sample size: 174 • Setting: inpatient • Country: Germany • Language: English

EUCTR2020-001632-10 *(Continued)*

	• Number of centres: 15
Participants	• Inclusion criteria ○ PCR-confirmed SARS-CoV-2 infection in a respiratory tract sample ○ Oxygen saturation (SaO_2) of ≤ 94% while breathing ambient air or a ratio of PaO_2:FiO_2 of < 300 mmHg ○ High risk due to either pre-existing or concurrent haematologic malignancy and/or active cancer therapy (including chemotherapy, radiotherapy, surgery) within the last 24 months or less (group 1) ○ And/or chronic immunosuppression not meeting the criteria of group 1 (group 2) ○ And/or age ≥ 50-75 years meeting neither the criteria of group 1 nor group 2 (group 3) ○ And at least 1 of these criteria: ■ Lymphopenia < 0.8 x g/L ■ D-dimer > 1µg/mL ■ Age ≥ 75 years meeting neither the criteria of group 1 nor group 2 (group 4) ○ Blood haemoglobin concentration ≥ 8 g/dL ○ Provision of written informed consent ○ Patient is able to understand and comply with the protocol for the duration of the study, including treatment and scheduled visits and examinations ○ Male or female patient aged ≥ 18 years ○ Postmenopausal or evidence of non-childbearing status. For women of childbearing potential: negative urine or serum pregnancy test within 14 days prior to study treatment • Exclusion criteria ○ Dementia, psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the Principal Investigator, would affect participant safety and/or compliance ○ Contraindication to transfusion or history of prior reactions to transfusion blood products ○ Patients with known selective IgA deficiency ○ Patients with mechanical ventilation and/or ECMO at time of initial inclusion into the trial ○ Participation in another trial with an investigational medicinal product ○ Treatment with SARS-CoV-2 CPin the past
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: ○ type of plasma: anti-SARS-CoV-2 CP with SARS-CoV-2 antibodies obtained from people following recovery of a SARS-CoV-2 infection ○ volume: 238-337 mL ○ number of doses: 2 doses ○ antibody-titre: NR ○ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): doses given on day 1, 2 • For studies including a control group: comparator (type): SC • Concomitant therapy: NR • Treatment cross-overs: possible ("A cross over from the standard arm into the experimental arm is possible after day 10 in case of not improving or worsening clinical condition.")
Outcomes	• Primary study outcome ○ Time from randomisation until improvement (within 84 days), defined as 2 points on a 7-point ordinal scale or live discharge from the hospital • Primary review outcomes ○ All-cause mortality during hospital stay: NR ○ 30-day mortality: NR (28-day mortality) • Secondary review outcomes ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8-15

EUCTR2020-001632-10 *(Continued)*

	days, 16-30 days: possibly ("Time from randomisation until improvement (within 84 days), defined as 2 points on a 7-point ordinal scale or live discharge from the hospital") ○ Mortality (time to event): NR ○ 90-day mortality: NR (84 days) ○ Time to discharge from hospital: yes ○ Admission to the ICU: NR ○ Length of stay on the ICU: NR ○ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes, but timing of measurement NR ("SARS-CoV-2 viral clearance and load, cytokine changes over time, as well as antiviral antibody titres") ○ QoL: NR ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): NR ○ Number of participants with SAEs: NR • Additional study outcomes ○ Overall survival ○ Overall survival rate at 28, 56 and 84 days ○ Percentage of patients who required mechanical ventilation
Starting date	04 May 2020
Contact information	Corresponding author Name: Prof. Dr. Carsten Müller-Tidow Affiliation: University Hospital Heidelberg; Dpt. of Internal Medicine V Hematology, Oncology and Rheumatology Full Address: Im Neuenheimer Feld 410, 69120 Heidelberg, Germany Email: Carsten.Mueller-Tidow@med.uni-heidelberg.de
Notes	• Trial status: ongoing • Prospective completion date: NR • Sponsor/funding: Ruprecht-Karls-Universität Heidelberg, Medical Faculty, University Hospital Heidelberg • Abbreviation of title: RECOVER

EUCTR2020-001936-86

Study name	A prospective, randomized, open label phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19
Methods	• Trial design: randomised, open-label, parallel-arm, phase 2 • Sample size: 340 • Setting: inpatient • Country: Germany • Language: English • Number of centres: 10
Participants	• Inclusion criteria ○ Patients infected with SARS-CoV-2 virus and ○ Age ≥ 18 years and ≤ 75 years

EUCTR2020-001936-86 *(Continued)*

- Fulfils RKI case definition including a positive verification of a SARS-CoV-2 infection from any specimen (e.g. respiratory, blood, other bodily fluid)
  - confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swap)
- Mild disease defined by the following criteria:
  - hospitalised (score 3 or 4 of WHO R&D Blueprint ordinal scale for clinical improvement)
- Signed written informed consent and willingness to comply with treatment and follow-up procedures
- Men
- Women without childbearing potential defined as follows:
  - at least 6 weeks after surgical sterilisation by bilateral tubal ligation or bilateral oophorectomy,
  - hysterectomy or uterine agenesis,
  - ≥ 50 years and in postmenopausal state > 1 year, or
  - < 50 years and in postmenopausal state > 1 year with serum FSH > 40 IU/l and serum oestrogen < 30 ng/L or a negative oestrogen test, both at screening
- Women with childbearing potential:
  - who have sexual relationship with female partners only and/or with sterile male partners, or
  - who are sexually active with fertile male partner, have a negative pregnancy test during screening and agree to use reliable methods of contraception from the time of screening until end of the clinical trial

- Exclusion criteria
  - Accompanying diseases other than COVID-19 with an expected survival time of < 12 months
  - In the opinion of the clinical team, progression to death is imminent and inevitable with-in the next 24 h, irrespective of the provision of treatment
  - COPD, stage 4
  - Lung fibrosis with UIP pattern in CT and severe emphysema
  - Chronic heart failure NYHA ≥ 3 and/or pre-existing reduction of left ventricular ejection fraction to ≤ 30%
  - Liver cirrhosis Child C
  - Liver failure: bilirubin > 5 x ULN and elevation of ALT /AST (at least 1 > 10 x ULN)
  - End stage renal failure requiring haemodialysis
  - Organ or bone marrow transplant in the 3 months prior to screening
  - History of adverse reactions to plasma proteins
  - Known deficiency of IgA
  - Pregnant and breastfeeding women
  - Volume overload until sufficiently treated
  - Pulmonary oedema
  - BMI > 40 kg/m2
  - Participation in another clinical trial, especially for treatment of COVID-19
  - Allergy or other contraindication to one of the investigational products
  - Previous treatment with SARS-CoV-2 CP

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  ○ type of plasma: FFP (Gefrorenes Apherese-COVID-19-RKP Leukozytendepletiert)
	  ○ volume: 230-270 mL
	  ○ number of doses: NR
	  ○ antibody-titre: NR
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage (patients: WHO R&D Blueprint Ordinal Scale for Clinical Improvement = 3 or 4)
	• For studies including a control group: comparator (type): sC
	• Concomitant therapy: NR

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	• Treatment cross-overs: no

Outcomes	• Primary study outcome
	  ○ Proportion of participants with treatment failure on day 14 (defined as progression of COVID-19 disease, defined as score 5, 6, 7 or 8 of WHO R&D Blueprint ordinal scale for clinical improvement)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 30-day mortality: NR (28-day mortality)
	• Secondary review outcomes
	  ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8-15 days, 16-30 days: possibly ("Time to clinical improvement (defined as time from randomization to an improvement of two points on the WHO R&D Blueprint ordinal scale for clinical improvement")
	  ○ Mortality (time to event): NR
	  ○ 90-day mortality: NR (4 months)
	  ○ Time to discharge from hospital: "Length of hospital stay"
	  ○ Admission to ICU: NR
	  ○ Length of stay on the ICU: NR
	  ○ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes, but other timing of measurement (day 0, 2, 4 and 6 and every week thereafter up to day 28)
	  ○ QoL: NR
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): NR in detail (only "adverse events")
	  ○ Number of participants with SAEs: NR in detail (only "adverse events")
	• Additional study outcomes
	  ○ Failure rates at day 7, day 21, day 28
	  ○ All-cause mortality on day 7, day 14, day 21, day 28, 4 months
	  ○ Deterioration in health (progressive disease)
	  ○ Need of ventilation support/additional organ support, e.g. ECMO
	  ○ Predictive value of comorbidities and inflammation and coagulation markers on clinical improvement, mortality, length of hospital stay and necessity of transfer to ICU
	  ○ Feasibility of collection of plasma units from donors who recovered from a SARS-CoV-2 infection
	  ○ Level of identity of kinetics of anti-SARS-CoV-2 antibodies in plasma of patients compared to plasma of donors (kinetics of antibodies detectable in the patient after CP treatment, pharmacokinetic parameters. The maximum observed anti-SARS-CoV-2 (Cmax), and the time to Cmax (tmax) will be determined directly from the anti-SARS-CoV-2 vs time data. The observed titre at the end of a dosing interval (Ctrough) will also be determined directly from the anti-SARS-CoV-2 vs time data. Calculated parameters (apparent terminal phase elimination rate constant (b), terminal phase elimination half-life (t1/2), and the area under the curve (AUC)) will be estimated using non-compartmental analysis with PK-Sim software. Accumulation ratios will be calculated based on the AUC values of the consecutive dosing intervals and the Cmax values of the consecutive dosing intervals)
	  ○ Titre of neutralising anti-SARS-CoV-2 in transfused plasma units
	  ○ Impact of donor characteristics on humoral response against anti-SARS-CoV-2 (age; gender; severity of COVID-19; interval between resolution of symptoms and plasmaphaeresis)
	  ○ Course of anti-SARS-CoV-2 titre in participants (prior to transfusion of CP, on days 1 and 2 and after transfusion (days 3 and 7) as well as every week thereafter up to day 28)

Starting date	19 October 2020

EUCTR2020-001936-86 *(Continued)*

Contact information	Corresponding author/contact Name: Institute of Transfusion Medicine, Hannover Medical School Affiliation: - Full Address: Carl-Neuberg-Str. 1, Hannover, 30625, Germany Email: NR
Notes	• Trial status: ongoing • Prospective completion date: NR • Sponsor/funding: Hannover Medical School, Germany and German Federal Ministry of Health

EUCTR2020-002122-82

Study name	Prospective open-label randomized controlled phase 2b clinical study in parallel groups for the assessment of efficacy and safety of immune therapy with COVID-19 convalescent plasma plus standard treatment vs. standard treatment alone of subjects with severe COVID-19
Methods	• Trial design: open-label, parallel-arm, multicentre, RCT • Sample size: 58 • Setting: inpatient • Country: Germany • Language: English • Number of centres: 4

Participants	• Inclusion criteria
	  ○ Male or female aged ≥ 18 years
	  ○ Estimated BMI ≥ 19 kg/m² to ≤ 40 kg/m²
	  ○ Florid SARS-CoV-2 infection confirmed by RT-PCR in tracheo-bronchial secretion sample or pharyngeal swab sample
	  ○ ARDS with Horovitz index < 300 mmHg
	  ○ Necessity of IMV
	  ○ Written informed consent obtained from the patient's legal representative or under such arrangement as is legally acceptable in Germany
	  ○ Participant's assent if obtainable
	• Exclusion criteria
	  ○ Adverse reaction to plasma proteins in medical history
	  ○ Interval > 72 h since endotracheal intubation
	  ○ Current or imminent necessity of ECMO treatment
	  ○ Pre-existing COPD, based on The Global Initiative for Chronic Obstructive Lung Disease definition, stage 4
	  ○ Chronic congestive heart failure NYHA ≥ 3
	  ○ Pre-existing left ventricular ejection fraction < 30%
	  ○ Liver cirrhosis Child-Pugh class C
	  ○ Acute liver failure with bilirubin > 5 x ULN and either ALT or AST > 10 x ULN
	  ○ Known deficiency of IgA
	  ○ Cardiovascular resuscitation in the 14 days prior to screening visit [V1]
	  ○ Organ or bone marrow transplant in the 3 months prior to screening visit [V1]
	  ○ Pregnancy
	  ○ Breastfeeding woman
	  ○ Previous exposure to COVID-19 CP

EUCTR2020-002122-82 *(Continued)*

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  ○ type of plasma: NR
	  ○ volume: 870 to 910 µl/ml
	  ○ number of doses: NR
	  ○ antibody-titre: NR
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): severe disease/later stage (see inclusion criteria)
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Change in SOFA score from Baseline Visit (Day 1, Visit 2) to Day 8 (Visit 9)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 30-day mortality: yes (day 29)
	• Secondary review outcomes
	  ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8-15 days, 16-30 days: NR
	  ○ Mortality (time to event): NR
	  ○ 90-day mortality: NR
	  ○ Time to discharge from hospital: NR
	  ○ Admission to the ICU: NR
	  ○ Length of stay on the ICU: NR
	  ○ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
	  ○ QoL: NR
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, TACO, TAD, acute transfusion reactions): NR
	  ○ Number of participants with SAEs: NR
	• Additional study outcomes
	  ○ SOFA score: mean change from baseline visit (Day 1, visit 2) to all subsequent visits until and including Day 29 (visit 15) or until extubation, whichever comes first
	  ○ Rescue therapy: number and proportion of participants without rescue therapy until and including Day 8 (visit 9)
	  ○ ECMO: mean number of days without ECMO during the period from baseline visit (Day 1, Visit 2) until and including Day 8 (visit 9), Day 15 (visit 13), and Day 29 (visit 15), per treatment group and per participant
	  ○ IMV parameters and endotracheal Intubation: mean number of days without IMV during the period from baseline visit (Day 1, visit 2) until and including Day 8 (visit 9), Day 15 (visit 13), and Day 29 (visit 15), per treatment group and per participant
	  ○ Safety: cumulated number and proportion of participants with AE, adverse reaction, SAE, serious adverse reaction, and suspected unexpected serious adverse reaction from baseline visit (Day 1, Visit 2) until and including Day 11 (visit 12)

Starting date	12 June 2020
Contact information	Corresponding Author Name: Holger Hackstein Affiliation: Universitätsklinikum Erlangen

EUCTR2020-002122-82 *(Continued)*

	Full Address: Universitätsklinikum Erlangen, Transfusionsmedizinische Abteilung, Krankenhausstr. 12, Erlangen 91054, Germany Email: holger.hackstein@uk-erlangen.de
Notes	• Recruitment status: ongoing • Prospective completion date: NR • Sponsor/funding: Universitätsklinikum Erlangen, Germany

EUCTR2020-005410-18

Study name	Multicentre, randomized, double-blind, placebo-controlled, non-commercial clinical trial to evaluate the efficacy and safety of specific anti-SARS-CoV-2 immunoglobulin in the treatment of COVID-19
Methods	• Trial design: multicentre, randomised, double-blind, placebo-controlled, non-commercial clinical trial • Sample size: 480 • Setting: inpatient • Country: Poland • Language: English • Number of centres: 5

Participants	• Inclusion criteria
	  ○ Age > 18 years
	  ○ Sign informed consent in order to participate in the study
	  ○ SARS-CoV-2 infection (positive RT-PCR test for SARS-CoV-2)
	  ○ Indication for hospitalisation due to the course of COVID-19
	  ○ The patient's clinical condition is assessed at 3-5 on the ordinal scale:
	  ■ 3 - hospitalisation without oxygen therapy
	  ■ 4 - hospitalisation with low-flow oxygen support on a nasal mask or moustache
	  ■ 5 - hospitalisation with high-flow oxygen therapy > 15 L/min without mechanical ventilation
	  ○ There are no contraindications to the use of standard symptomatic treatment in accordance with the guidelines of the Polish Association of Epidemiologists and Infectiologists (Polskie Towarzystwo Epidemiologów i Lekarzy Chorób Zakaźnych)
	• Exclusion criteria
	  ○ The patient's inability to comply with the protocol in opinion of the Investigator
	  ○ Intake of any experimental anti-COVID-19 study drugs
	  ○ Intake of any plasma therapy, in particular plasma therapy with COVID-19 convalescents
	  ○ Infection with HIV
	  ○ Pregnancy or breastfeeding
	  ○ All conditions that the doctor qualifying for the study considers harmful to the patient participating in this study, including any clinically significant deviations from normal clinical laboratory values or concurrent medical events or situations that prevent the proper performance of the study (e.g. insufficient knowledge of the Polish language by the patient in the opinion of the researcher)
	  ○ Participation in another interventional clinical trial in the last 30 days

Interventions	• Details of therapy:
	  ○ drug name: anti SARS-CoV-2 human immunoglobulin
	  ○ dose: 60 AU/mL
	  ○ number of doses: NR
	  ○ route: intramuscular

EUCTR2020-005410-18 *(Continued)*

	○ source: human • Treatment details, including time of plasma therapy (e.g. early stage of disease) • For studies including a control group: comparator (type): placebo • Concomitant therapy: none • Treatment cross-overs: none
Outcomes	• Primary study outcome: ○ No oxygen supplementation required on Day 7 and 14 from the start of the therapy • Primary review outcomes ○ All-cause mortality during hospital stay: NR ○ 30-day mortality: NR • Secondary review outcomes ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8-15 days, 16-30 days: probably yes ○ Mortality (time to event): NR ○ 90-day mortality: NR ○ Time to discharge from hospital: yes ○ Admission to the ICU: NR ○ Length of stay on the ICU: NR ○ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: probably yes ○ QoL: NR ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, TACO, TAD, acute transfusion reactions): yes ○ Number of participants with SAEs: yes • Additional study outcomes ○ Occurrence of SAEs up to day 28 from the start of study therapy ○ The need for mechanical ventilation in the patient ○ Time of using oxygen therapy ○ The need to use tocilizumab or other anti-cytokine drugs ○ Time to discharge from hospital ○ Time to negative PCR test for SARS-CoV-2 virus RNA ○ Occurrence of any COVID-19-related symptoms on day 28 ○ Changes in inflammatory parameters and coagulation parameters at successive time points ○ Presence of lung tissue pathology after completion of therapy ○ Generation of a specific humoral response: Presence and titre of anti-SARS-CoV-2 antibodies during the therapy and after the observation period (on day 28 from the start of study therapy)
Starting date	16 November 2020
Contact information	Samodzielny Publiczny Szpital Kliniczny Nr 1 w Lublinie Samodzielny Publiczny Zakład Opieki Zdrowotnej Krzysztof Tomasiewicz ul. Stanisława Staszica 16 Lublin20-081 Poland 00488153 49 414564 00488153 49 410 krzysztoftomasiewicz@umlub.pl

EUCTR2020-005410-18 *(Continued)*

Notes	• Recruitment status: ongoing • Prospective completion date: NR • Sponsor/funding: Samodzielny Publiczny Szpital Kliniczny Nr 1 w Lublinie Samodzielny Publiczny Zakład Opieki Zdrowotnej

ISRCTN49832318

Study name	SURCOVID trial: a randomized controlled trial using convalescent plasma early during moderate COVID-19 disease course in Suriname
Methods	• Trial design: open-label randomised prospective clinical trial • Sample size: 210 • Setting: inpatient • Country: Suriname • Language: English • Number of centre: 1

Participants	• Inclusion criteria
	  ○ COVID-19-positive patients who have understood and signed the informed consent
	  ○ Aged ≥ 18 years
	  ○ Hospital admitted patients with moderate COVID-19 to the non-ICU ward: laboratory-confirmed infection with COVID-19
	• Exclusion criteria
	  ○ Severe or life-threatening respiratory disease upon admission
	  ○ Viral pneumonia with other viruses besides COVID-19
	  ○ Ineligible for CP therapy
	  ○ Participation in other studies
	  ○ Other circumstances in which the investigator determined that the patient is not suitable for the clinical trial
	  ○ Refusal of informed consent study participation by donor and/or patient
	  ○ Known IgA deficiency
	  ○ Medical conditions in which receipt of 220 mL volume may be detrimental to the patient (e.g.decompensated congestive heart failure)
	  ○ Women who are pregnant or breastfeeding

Interventions	• After referral to the non-ICU COVID-19 ward, the participants were treated with dexamethasone standard therapy. After being randomised by sealed envelope the participants receive CP or placebo treatment added to the standard therapy. An interim-analysis for efficacy and harm will be performed on the primary endpoint when 50% of participants have been included and have been followed up for at least 30 days, and follow-up will continue until discharge or death before day 60
	• Details of CP:
	  ○ type of plasma: NR
	  ○ volume: 220 ml
	  ○ number of doses: NR
	  ○ antibody titre: NR
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease: NR
	• For studies including a control group: comparator (type): control group receives volume of NaCl 0.9%
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

ISRCTN49832318 *(Continued)*

Outcomes	• Primary outcomes
	  ○ Development of severe respiratory disease, defined as a respiratory rate of ≥ 30 breaths/min, an oxygen saturation of < 93% while the patient was breathing ambient air, or both, measured for up to 60 days from baseline
	• Secondary outcomes
	  ○ Measured using patient records
	  ○ Clinical status assessed by the ordinal scale on days 0, 3, 7, and 15 (time frame: up to 15 days)
	  ○ The differences in oxygen intake methods (time frame: up to 15 days)
	  ■ No need for supplemental oxygenation
	  ■ Nasal catheter oxygen inhalation
	  ■ Mask oxygen inhalation
	  ■ Non-invasive ventilator oxygen supply
	  ■ Invasive ventilator oxygen supply
	  ○ Duration (days) of supplemental oxygenation (time frame: up to 15 days)
	  ○ Duration (days) of mechanical ventilation (time frame: up to 15 days)
	  ○ The mean PaO2/FiO2 (time frame: up to 15 days) if applicable
	  ○ The detection frequency could be increased according to the clinician's decision
	  ○ Time to COVID-19 negativity in respiratory tract specimens (every 3 days) (time frame: up to 15 days)
	  ○ Dynamic changes of COVID-19 antibody titre in blood (time frame: up to 15 days). The antibody titre is detected on days 0, 3, 7 and 15
	  ○ Dynamic changes of IL-6 levels in blood (time frame: up to 15 days). The titre is detected on days 0, 3, 7 and 15
	  ○ MCU/ICU admission
	  ○ Length of MCU/ICU (days) (time frame: up to 28 days)
	  ○ Length of hospital stay (days) (time frame: up to 28 days)
	  ○ All-cause mortality (time frame: up to 28 days)
	• Additional study outcomes

Starting date	1 June 2021
Contact information	Name: Rosita Bihariesingh-Sanchit Address: Kwattaweg 639 - Wanica Suriname Telephone:+596 8753150 Email:rbihariesingh@azp.sr
Notes	• Overall trial end date: 1 April 2022 • Recruitment start date: 1 Sepetmber 2021 • Recruitment status: recruiting • Expected recruitment end date: 1 February 2022 • Intention to publish date: 1 October 2022 • Sponsor: Hospital/treatment Center, Academisch Ziekenhuis Paramaribo (Academic Hospital Paramaribo)

jRCTs031200374

Study name	An open-label, randomized, controlled trial to evaluate the efficacy of convalescent plasma therapy for COVID-19 (COVIPLA-RCT)
Methods	• Trial design: open-label RCT

jRCTs031200374 *(Continued)*

- Sample size: 200
- Setting: probably inpatient
- Country: Japan
- Language: Japanese, English
- Number of centres: single-centre

Participants	• Inclusion criteria
	  ○ Written consent to participate in the study
	  ○ Hospitalised patients with a confirmed diagnosis of COVID-19 by PCR or LAMP, antigen testing, or other methods.
	  ○ Within 5 days of onset
	  ○ Oxygen saturation ≥ 95%
	  ○ Aged ≥ 60 years or have 1 of the following underlying diseases:
	  ■ renal dysfunction, COPD, cardiac disease, cerebrovascular disease, malignancy, obesity, diabetes, hypertension, immunosuppressed state
	  ○ ≥ 20 years of age
	  ○ First-time infection
	• Exclusion criteria
	  ○ Pregnant or breastfeeding
	  ○ Religious beliefs do not support the administration of blood transfusions
	  ○ Participating in another interventional study that provides therapeutic intervention for COVID-19
	  ○ Vaccinated against SARS-CoV-2
	  ○ Patients who have already received CP
	  ○ History of allergy to blood products
	  ○ Plasma protein deficiency, such as IgA
	  ○ NYHA class III or IV heart failure
	  ○ Others who are judged inappropriate for inclusion in the study by the principal investigator, principal investigator, or sub-investigator

Interventions	• Details of intervention:
	  ○ dose: NR
	  ○ route of administration: NR
	• For studies including a control group: comparator (type): SC
	• Treatment details of control group (e.g dose, route of administration): NR
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	Primary study outcome: time-weighted mean change in the amount of SARS-CoV-2 virus in NP swabs from (days 0, 3, 5) Secondary study outcomes • Avoidance of ventilation or death • Death • Time to need for oxygen • Time to clinical improvement • Clinical improvement in participants receiving CP • Time to clinical improvement in CP recipients • Time to improvement in the National Early Warning Score (NEWS) in the UK • Viral load in the CP group at each assessment date • Safety endpoints
Starting date	25 February 2021

jRCTs031200374 *(Continued)*

Contact information	Corresponding author • Name: Sho Saito • Affiliation: Centor Hospital of the National Center for Global Health and Medicine • Full Address: 1-21-1, Toyama, Shinjuku-ku,Tokyo • Email: ssaito@hosp.ncgm.go.jp
Notes	• Recruitment status: recruiting started • Prospective completion date: NR • Sponsor/funding: Health and Labor Sciences Research Grants, The National Center for Global Health and Medicine, Japan Agency for Medical Research and Development

NCT04333251

Study name	Evaluating convalescent plasma to decrease coronavirus associated complications. A phase I study comparing the efficacy and safety of high-titer anti-SARS-CoV-2 plasma versus best supportive care in hospitalized patients with interstitial pneumonia due to COVID-19
Methods	• Trial design: open-label, phase I, parallel-RCT • Sample size: 115 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ ≥ 18 years
	  ○ Must have been hospitalised with COVID-19 respiratory symptoms within 3-7 days from the beginning of illness
	  ○ Patient and/or LAR willing to provide informed consent
	  ○ Patient agrees to storage of specimens for future testing
	• Exclusion criteria
	  ○ ≤ 18 years
	  ○ Receipt of pooled immunoglobulin in past 30 days
	  ○ Contraindication to transfusion or history or prior reactions to transfusion blood products
	  ○ Women who are identified as donors must not be pregnant
	• Donor eligibility criteria
	  ○ ≥ 18 years
	  ○ Must have been hospitalised with COVID-19 respiratory symptoms and confirmation via COVID-19 SARS-CoV-2 RT-PCR testing but are now PCR-negative by 2 NP tests
	  ○ Women of child-bearing potential must have a negative serum pregnancy test
	  ○ Donor and/or LAR willing to provide informed consent
	  ○ Donor agrees to storage of specimens for future testing

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  ○ type of plasma: NR
	  ○ volume: NR
	  ○ number of doses: 1-2 units
	  ○ antibody-titre > 1:64
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

NCT04333251 *(Continued)*

	• For studies including a control group: comparator (type): best supportive care • Concomitant therapy: oxygen therapy • Treatment cross-overs: not applicable

Outcomes	• Primary study outcome: reduction in oxygen and ventilation support (time frame: through study completion, an average of 4 weeks)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ Time to death: NR
	• Secondary review outcomes
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  ○ Number of participants with SAEs: NR
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  ○ 30-day and 90-day mortality: NR
	  ○ Admission on the ICU: NR
	  ○ Length of stay on the ICU: NR
	  ○ Time to discharge from hospital: NR
	  ○ QoL: NR
	• Additional outcomes: NR

Starting date	1 April 2020
Contact information	NR
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31 December 2022 • Sponsor/funding: NR

NCT04345289

Study name	Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia (CCAP)
Methods	• Trial design: investigator-initiated, multicentre, randomised, double-blinded, placebo-controlled, multi-stage trial (Phase 3) • Sample size: 1500 • Setting: multicentre sites • Country: Denmark • Language: English • Number of centres: 12

Participants	• Inclusion criteria
	  ○ ≥ 18 years of age
	  ○ Confirmed COVID-19 infection by presence of SARS-CoV-2 nucleic acid by PCR
	  ○ Evidence of pneumonia given by at least 1 of the following: $SpO_2 \leq 93\%$ on ambient air or $PaO_2/FiO_2 < 300$ mmHg/40 kPa or radiographic findings compatible with COVID-19 pneumonia
	  ○ Onset of first experienced symptom, defined as 1 respiratory symptom or fever, not > 10 days before admission
	  ○ For women of childbearing potential: negative pregnancy test and willingness to use contraceptive (consistent with local regulations) during study period

NCT04345289 *(Continued)*

- Signed informed consent form by any participant capable of giving consent, or, when the participant is not capable of giving consent, by his or her LAR

- Exclusion criteria
  - In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 h, irrespective of the provision of treatment
  - History of allergic reaction to study drug (as judged by the site investigator)
  - Participating in other drug clinical trials (participation in COVID-19 antiviral trials may be permitted if approved by sponsor)
  - Pregnant or breastfeeding, positive pregnancy test in a pre-dose examination or patient's family planning within 3 months after receiving study agent
  - Estimated GFR < 30 mL/min
  - Severe liver dysfunction (Child Pugh score C)
  - Known history of the following medical conditions: active or latent TB or history of incompletely treated TB; chronic hepatitis B or C infection; retinopathy or maculopathy; neurogenic hearing impairment
  - Presence of any of the following abnormal laboratory values at screening: absolute neutrophil count (ANC) < 1000 mm3 (= 1.0 x 10^9 /L); ALT > 5 x ULN; platelet count < 50,000 per mm^3 (= 50 x 10^9 /L)
  - Immunosuppression, defined as following: treatment with immunosuppressive agents, chemotherapy or immunomodulatory drugs within 30 days prior to inclusion; use of chronic oral corticosteroids for a non-COVID-19-related condition in a dose > prednisolone 20 mg or equivalent per day for 4 weeks; ongoing chemotherapy
  - Any serious medical condition or abnormality of clinical laboratory tests that, in the study author's judgement, precludes the patient's safe participation in and completion of the study

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: randomised 1:1:1:1:1:1 to parallel treatment arms: CP, sarilumab, hydroxychloroquine, baricitinib, IV and subcutaneous placebo, or oral placebo
	• Details of CP:
	  ◦ type of plasma: preparation method NR
	  ◦ volume: 600 mL
	  ◦ number of doses: 2 x 300 mL given in single infusion
	  ◦ antibody-titre: NR
	  ◦ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): sarilumab, hydroxychloroquine, baricitinib, IV and subcutaneous placebo, or oral placebo
	• Concomitant therapy: placebo treatment with saline 0.9% (1.14 mL) as a single subcutaneous injection, in addition to SC
	• Treatment cross-overs

Outcomes	• Primary study outcome:
	• Primary review outcomes
	  ◦ All-cause mortality during hospital stay: yes (up to 90 days)
	  ◦ Time to death: yes
	• Secondary review outcomes:
	  ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
	  ◦ Number of participants with SAEs: yes
	  ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  ◦ 30-day and 90-day mortality: yes
	  ◦ Admission on the ICU
	  ◦ Length of stay on the ICU

NCT04345289 *(Continued)*

- Time to discharge from hospital: yes
- QoL: NR

- Additional outcomes
  - Composite endpoint of all-cause mortality or need of IMV (up to 28 days)
  - Ventilator-free days (time frame: 28 days)
  - Organ failure-free days (time frame: 28 days)
  - Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status (time frame: 90 days)
    - number of days to improvement of at least 2 categories relative to baseline on the ordinal scale. Categories are as follows: death; hospitalised, in ICU requiring ECMO or mechanical ventilation; hospitalised, on non-IMV or high-flow oxygen device; hospitalised, requiring supplemental oxygen; hospitalised, not requiring supplemental oxygen; not hospitalised, limitation on activities and/or requiring home oxygen; not hospitalised, no limitations on activities

Starting date	20 April 2020
Contact information	Thomas Benfield, MD, DMSc: thomas.lars.benfield@regionh.dk
Notes	• Recruitment status: recruiting • Prospective completion date: 15 June 2021 • Sponsor/funding: Thomas Benfield

NCT04372979

Study name	Evaluation of efficacy of COVID-19 convalescent plasma versus standard plasma in the early care of COVID-19 patients hospitalized outside intensive care units
Methods	• Trial design: triple-blinded, parallel, clinical RCT • Sample size: 80 • Setting: inpatient • Country: France • Language: translated to English • Number of centres: at least 4

Participants	Inclusion criteria
	• Age 18-80 years
	• COVID-19-confirmed case
	• Cases showing respiratory symptoms, checking at least 1 of the following criteria:
	  ◦ cough, dyspnoea, respiratory rate > 24 breaths/min
	  ◦ oxygen saturation < 95% at rest in ambient air
	  ◦ PaO_2 < 70 mmHg
	  ◦ pulmonary scan compatible with COVID in the absence of any other aetiology
	• Risk of deterioration, checking at least 1 of the following comorbidity criteria:
	  ◦ chronic respiratory pathology
	  ◦ diabetes
	  ◦ cancer pathology
	  ◦ cardiovascular disease
	  ◦ chronic kidney failure
	  ◦ congenital or acquired immunodeficiency
	  ◦ cirrhosis at stage B
	  ◦ major sickle cell syndrome

NCT04372979 *(Continued)*

- BMI > 30 kg/m^2
- Or 1 of the biological criteria:
  - D-dimer 1 µg/mL
  - lymphocytes < 0.8 G/L
  - ferritin > 300 µg/L
  - troponin I > 11 pg/mL

Exclusion criteria

- Patients admitted in ICU within the first 6 h of hospital care
- Patients after 10 days from the start of symptoms
- Age < 18 years and > 80 years
- Long-term oxygen-dependent patients (at home)
- Decompensated chronic cardiac, respiratory, urological pathology
- Patient refusing administration of blood products
- Allergic reaction to plasma products
- IgA deficiency
- Contraindication to transfusion
- Ig transfusion within 30 days
- Patient currently participating in another clinical trial
- Pregnant women
- Not affiliated to social security
- Person deprived of liberty by a legal or administrative decision, person under guardianship

Interventions	• Intervention(s): transfusion of SARS-CoV-2 CP
	  ◦ Details of CP: SARS-CoV-2 CP
	  ◦ Type of plasma:
	  ◦ Volume: 200-230 mL
	  ◦ Number of doses: 2 infusions be administered with 24-72 h in between
	  ◦ Antibody-titre: NR
	  ◦ Pathogen inactivated: by amotosalen
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• Comparator: SP
	• Concomitant therapy: NR
	• Treatment cross-overs: no

Outcomes	• Primary study outcome: survival time without need of a ventilator (time frame: day 30)
	• Primary review outcomes reported
	  ◦ All-cause mortality during hospital stay: 30-day mortality without need of a ventilator
	  ◦ Time to death: NR
	• Secondary review outcomes reported
	  ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  ◦ Number of participants with SAEs: NR
	  ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  ◦ 30-day and 90-day mortality: NR
	  ◦ Admission on the ICU: NR
	  ◦ Length of stay on the ICU: NR
	  ◦ Time to discharge from hospital: yes (length of stay (time frame: day 30)
	  ◦ QoL: NR
	• Additional study outcomes
	  ◦ Morbidity (time frame: Day 15)

NCT04372979 *(Continued)*

- Morbidity (time frame: Day 30)
- Effect on viral pharyngeal specimen clearance (time frame: at inclusion and Day 7)
- Effect on viral blood specimen clearance (time frame: at inclusion and Day 7)
- Effect on haemostasis disorders (time frame: at inclusion, Day 1 and every 48 h)
- Kinetics of appearance of neutralising antibodies (time frame: at inclusion, Day 7)
- Transfusion endotheliopathy effect (time frame: at inclusion, Day 1, Day 7)
- Transfusion biological inflammation effect (time frame: at inclusion, Day 1, Day 7)
- Transfusion haemovigilance (time frame: 30 days)
- Decrease in the consumption of antibiotics (time frame: 30 days)

Starting date	May 2020
Contact information	• Contact: Christophe MARTINAUD, PU PH: +33 141467241; christophe.martinaud@intradef.gouv.fr • Contact: Christophe RENARD: +33 140514103; christophe1.renard@intradef.gouv.fr
Notes	• Recruitment status: recruiting • Prospective completion date: May 2021 • Sponsor/funding: Direction Centrale du Service de Santé des Armées, University Hospital, Grenoble; Investigators Study Director:Hervé FOEHRENBACHDirection Centrale du Service de Santé des Armées (DCSSA), Study Director:Catherine VERRETService de Santé des Armées-Direction de la Formation de la Recherche et de l'Innovation, Principal Investigator:Christophe MARTINAUDCentre de Transfusion Sanguine des Armées, Principal Investigator:Jean-Luc BOSSONStatistical and methodological investigator - Laboratoire TIMC UMR 5525 CNRS Equipe Themas

NCT04374487

Study name	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 associated complications
Methods	• Trial design: phase II, open-label, RCT • Sample size: 100 (50 each group) • Setting: inpatient • Country: India • Language: English • Number of centres: 1

Participants	Inclusion criteria
	• Patients admitted with RT-PCR-confirmed COVID-19 illness
	• Age > 18 years
	• Written informed consent
	• Has any of the 2
	  ○ PaO_2/ FiO_2 < 300
	  ○ respiratory rate > 24/min and SaO_2 < 93% on room air
	Or in case of severe or immediately life-threatening COVID-19, for example:
	• severe disease is defined as:
	  ○ dyspnoea
	  ○ respiratory frequency ≥ 30/min
	  ○ blood oxygen saturation ≤ 93%
	  ○ PaO_2:FiO_2 < 300
	  ○ lung infiltrates > 50% within 24-48 h

NCT04374487 *(Continued)*

- life-threatening disease is defined as:
  - respiratory failure
  - septic shock
  - multiple organ dysfunction or failure

Exclusion criteria

- Pregnant women
- Breastfeeding women
- Known hypersensitivity to blood products
- Receipt of pooled immunoglobulin in last 30 days
- Participating in any other clinical trial
- Clinical status precluding infusion of blood products

Interventions	• Intervention(s): CP
	• Details of CP:
	  ○ Type of plasma: ABO-compatible plasma transfusion
	  ○ Volume: 200 mL
	  ○ Number of doses: NR
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• Comparator: standard care treatment according to institutional protocols
	• Concomitant therapy: NR
	• Treatment cross-overs: no

Outcomes	• Primary study outcome:
	  ○ The primary outcome is a composite measure of the avoidance of
	  ■ progression to severe ARDS (P/F ratio 100) and
	  ■ all-cause mortality at 28 days (time frame: depends on the total treatment time of the participants within 1-year period of the trial)
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: all-cause mortality at 28 days (time frame: depends on the total treatment time of the participants within 1-year period of the trial)
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  ○ Number of participants with SAEs: NR
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: IMV during infection; ECMO duration during infection: yes (duration of respiratory support required; duration of IMV; duration of non-IMV (time frame: 1 year)
	  ○ 30-day and 90-day mortality: yes (28-day mortality)
	  ○ Admission on the ICU: NR
	  ○ Length of stay on the ICU: NR
	  ○ Time to discharge from hospital: NR
	  ○ QoL: NR
	• Additional study outcomes
	  ○ Progression to severe ARDS (P/F ratio 100)
	  ○ Time to symptom resolution - fever, shortness of breath, fatigue (time frame: 1 year)
	  ○ Change in SOFA pre- and post-transfusion (time frame: 1 year)
	  ○ Radiological improvement (time frame: 1 year)
	  ○ AEs associated with transfusion (time frame: 1 year)

NCT04374487 *(Continued)*

	○ To measure the change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR (time frame: days 0, 1, 3, and 7 after transfusion) (time frame: 1 year) ○ Levels of bio-markers pre- and post-transfusion (time frame: 1 year) ○ Need of vasopressor use (time frame: 1 year)
Starting date	9 May 2020
Contact information	• Principal Investigator: Sangeeta Pathak, MBBS, Diploma; Max Super Speciality Hospital, Saket (DDF), New Delhi, India
Notes	• Recruitment status: active, not recruiting • Prospective completion date: 9 August 2021 • Sponsor/funding: Max Healthcare Institute Limited

NCT04376788

Study name	Exchange transfusion versus plasma from convalescent patients with methylene blue in patients with COVID-19
Methods	• Trial design: randomised, parallel-assigned, open-label, phase 2 • Sample size: 15 (5 each group) • Setting: inpatient • Country: Egypt • Language: translated to English • Number of centres: 1
Participants	Inclusion criteria • Adult patients are ≥ 18 years • Inpatients diagnosed as severe COVID-19 disease according to WHO criteria • CT chest with extensive lung disease (ground-glass and consolidative pulmonary opacities) • O_2 saturation < 93% resting • Respiratory rate ≥ 30/min Exclusion criteria • Patients with pregnancy and lactation • Renal failure and heart failure • Contraindication for plasma or blood transfusion
Interventions	• Intervention(s): CP • Details of CP (group I) ○ Type of plasma: will receive exchange transfusion by venesection of 500 cc blood with good replacement of 1 unit packed washed red blood cells daily for 3 days according to daily clinical and investigational follow-up ○ Volume: 500 cc blood ○ Number of doses: ○ Antibody-titre: NR ○ Pathogen inactivated: NR ○ Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Details of CP (group II) ○ Type of plasma: will receive IV methylene blue 1 mg/kg IV over 30 min with 200 cc plasma from convalescent matching single patient by plasma extractor machine for 3 days according to daily clinical and investigational follow-up

NCT04376788 *(Continued)*

- Volume: IV methylene blue 1 mg/kg IV over 30 min with 200 cc plasma
- Number of doses:
- Antibody-titre: NR
- Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

- Details of CP (group III)
  - Type of plasma: will receive exchange transfusion by venesection of 500 cc blood with good replacement of 1 unit packed washed red blood cells and IV methylene blue 1 mg/kg IV over 30 min with 200 cc plasma from convalescent matching single patient by plasma extractor machine for 3 days according to daily clinical and investigational follow-up
  - Volume: venesection of 500 cc blood
  - Number of doses: 1
  - Antibody-titre: NR
  - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes	• Primary study outcome
	  ◦ Improvement of condition (time frame: 3-5 days) (improvement of general condition of the participants as the ventilator parameters and serum level of ferritin, D dimer, complete blood count, oxygen level in blood and patient O_2 saturation)
	• Primary review outcomes reported
	  ◦ All-cause mortality during hospital stay: NR
	  ◦ Time to death: NR
	• Secondary review outcomes reported
	  ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  ◦ Number of participants with SAEs: NR
	  ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  ◦ 30-day and 90-day mortality: NR
	  ◦ Admission to the ICU: NR
	  ◦ Length of stay on the ICU: NR
	  ◦ Time to discharge from hospital: NR
	  ◦ QoL: NR
	• Additional study outcomes
	  ◦ Improvement of condition (time frame: 3-5 days) (improvement of general condition of the participants as the ventilator parameters and serum level of ferritin, D-dimer, complete blood count, oxygen level in blood and patient O_2 saturation)
	  ◦ Change in organ function with progression-free survival and overall survival (time frame: 1 month) change in the liver, kidney function and change in ferritin level with normal D Dimer

Starting date	6 May 2020
Contact information	• Contact: Mohamed M Moussa, MD: +201001553744; drmohamed_metwali1@med.asu.edu.eg • Contact: Essam A Hassan, MD: +201001839394; essam.abdelwahed@yahoo.com
Notes	• Recruitment status: recruiting • Prospective completion date: 1 July 2020 • Sponsor/funding: Ain Shams University • Principal Investigator: Mohamed M Moussa, Ain Shams University

NCT04380935

Study name	Effectiveness and safety of convalescent plasma therapy on COVID-19 patients with acute respiratory distress syndrome
Methods	• Trial design: multicentre, open-label RCT • Sample size: 60 • Setting: inpatients • Country: Indonesia • Language English • Number of centres: 3
Participants	Inclusion criteria • Patients aged ≥ 18 years • COVID-19 confirmed by RT-PCR • Having severe pneumonia • PAO_2 / FIO_2 < 300 • Using mechanical ventilation Exclusion criteria • Contraindication to blood transfusions (fluid overload, history of anaphylaxis of blood products) • Multiple and severe organ failure, haemodynamically unstable • Other uncontrolled infections • DIC, which requires a replacement factor/FFP • Haemodialysis patients or CRRT (continuous renal replacement therapy) • Active intracranial bleeding • Significant myocardial ischaemia • Receiving tocilizumab treatment

Interventions	• Intervention(s): standard of care and CP
	• Details of CP:
	  ○ Type of plasma: NR
	  ○ Volume: NR
	  ○ Number of doses: NR
	  ○ Antibody-titre: NR
	  ○ Pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• Comparator: standard therapy
	• Concomitant therapy: NR
	• Treatment cross-overs: no

Outcomes	• Primary study outcome: all-cause mortality at 28 days
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: 28-day mortality
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): allergic reactions, haemolytic transfusion reaction, TRALI, TACO
	  ○ Number of participants with SAEs: NR
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: only duration of mechanical ventilation

NCT04380935 *(Continued)*

	○ 30-day and 90-day mortality: yes (28-day mortality) ○ Admission on the ICU: yes ○ Length of stay on the ICU: yes ○ Time to discharge from hospital: NR ○ QoL: NR • Additional outcomes: NR
Starting date	8 May 2020
Contact information	Robert Sinto, MD: +628158835432, rsinto@yahoo.com
Notes	• Recruitment status: recruiting • Prospective completion date: 31 October 2020 • Sponsor/funding: Indonesia University/NR

NCT04385043

Study name	Phase 2b/3 trial to evaluate the safety and efficacy of plasma transfusion from convalescent patients with SARS-CoV-2 infection on severity and mortality of COVID-19 in hospitalized patients
Methods	• Trial design: randomised, parallel, open-label clinical trial • Sample size: 200 in each arm (400) • Setting: inpatient • Country: Italy • Language: translated to English • Number of centres: 5
Participants	Inclusion criteria • Inclusion criteria for donors: null-gravid, with a negative history of transfusion of blood components; possibility to sign the informed consent • Inclusion criteria for COVID-19-infected patients: serious COVID-19 infection, possibility to sign the informed consent (also through the legal tutor) Exclusion criteria: • Exclusion criteria for donors: presence of pregnancy, recent history of transfusion of blood components, < 18 years • Exclusion criteria for COVID-19-infected patients: non-serious COVID-19 infection, impossibility to sign the informed consent (also through the legal tutor)
Interventions	• Intervention(s): plasma-hyperimmune add-on to the SC • Details of CP: ○ Type of plasma: NR ○ Volume: NR ○ Number of doses: NR ○ Antibody-titre: NR ○ Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: SC • Concomitant therapy: NR • Treatment cross-overs: no

NCT04385043 *(Continued)*

Outcomes	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: 30-day mortality
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  ○ Number of participants with SAEs: NR
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: IMV during infection; ECMO duration during infection: NR
	  ○ 30-day and 90-day mortality: yes (30-day mortality)
	  ○ Admission on the ICU: NR
	  ○ Length of stay on the ICU: NR
	  ○ Time to discharge from hospital: NR
	  ○ QoL: NR
	• Additional study outcomes
	  ○ Lymphocytes (time frame: 7 and 14 days)
	  ○ PCR levels vs control (time frame: 7 and 14 days)
	  ○ PCR levels vs before treatment (time frame: 7 and 14 days)
	  ○ AB levels and clinical improvement (time frame: 30 days)
	  ○ Inflammatory cytokines vs controls (time frame: 7 and 14 days)
	  ○ Inflammatory cytokines vs before treatment (time frame: 7 and 14 days)

Starting date	1 May 2020
Contact information	Gabriella Talarico, MD0961883111, trasfusionale@aocz.it
Notes	• Recruitment status: recruiting • Prospective completion date: 15 October 2020 (primary), 15 May 2021 (study) • Sponsor/funding: University of Catanzaro; Azienda Ospedaliera Policlinico "Mater Domini", Azienda Sanitaria Provinciale Di Catanzaro, Annunziata Hospital, Cosenza, Italy, Azienda Ospedaliera Bianchi-Melacrino-Morelli

NCT04385186

Study name	Inactivated convalescent plasma as a therapeutic alternative in hospitalized patients COVID-19
Methods	• Trial design: multicentre, single-blind, clinical RCT • Sample size: 60 • Setting: inpatient • Country: Colombia • Language: translated to English • Number of centres: 10
Participants	Inclusion criteria • > 18 years • Confirmed laboratory diagnosis for qRT-PCR to SARS-CoV-2 • Meet any of the following medical criteria (defined by WHO): be currently hospitalised with: pneumonia, severe pneumonia, ARDS (moderate or severe), sepsis or septic shock • The patient, or his representative, must sign an informed consent Exclusion criteria

NCT04385186 *(Continued)*

	• Participate in another clinical trial for COVID-19 • History of acute allergic transfusion reactions due to transfusion of blood or other components, especially plasma components (FFP, cryoprecipitate and platelets) • History of allergic reaction due to IgA deficiency • Allergic reaction to sodium citrate or riboflavin (vitamin B2) • History of immunosuppression

Interventions	• Intervention(s): inactivated CP SARS-CoV-2 + support treatment under medical decision (day 0)
	• Details of CP:
	  ○ type of plasma: ABO-Rh compatible inactivated CP SARS-CoV-2
	  ○ volume: 200 mL
	  ○ number of doses: 2, day 0 and day 1
	  ○ antibody-titre: NR
	  ○ pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): transfusion day 0 and day 1
	• Comparator: support treatment, Day 0: start of support treatment selected by medical staff according to each institutional protocol
	• Concomitant therapy: NR
	• Treatment cross-overs: no

Outcomes	• Primary study outcome: mortality reduction in COVID-19 patients treated with inactivated CP + support treatment
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: 28-day mortality (mortality reduction in COVID-19 patients treated with inactivated CP + support treatment (time frame: over a period of 28 days)
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (incidence of AEs (time frame: up to 28 days)
	  ○ Number of participants with SAEs: NR
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  ○ 30-day and 90-day mortality: NR
	  ○ Admission on the ICU: NR
	  ○ Length of stay on the ICU: yes (ICU-free days through Day 28 (time frame: until hospital discharge or a maximum of 28 days whichever comes first)
	  ○ Time to discharge from hospital: yes (hospital-free days through Day 60 (time frame: until hospital discharge or a maximum of 60 days whichever comes first)
	  ○ QoL: NR
	• Additional study outcomes
	  ○ Clinical evolution (time frame: over a period of 28 days)
	  ○ Clinical evolution by 7-parameter ordinal scale (time frame: 3, 7, 14 and 28 days)
	  ○ Multi-organ failure progression (time frame: 3, 7, 14 and 28 days)
	  ○ Change in haemoglobin concentration (time frame: 3, 7, 14 and 28 days)
	  ○ Change in blood cell count (time frame: 3, 7, 14 and 28 days)
	  ○ Change in serum creatinine level (time frame: 3, 7, 14 and 28 days)
	  ○ Change in AST level (time frame: 3, 7, 14 and 28 days)
	  ○ Change in ALT level (time frame: 3, 7, 14 and 28 days)
	  ○ Change in bilirubin level (time frame: 3, 7, 14 and 28 days)
	  ○ Change in LDH level (time frame: 3, 7, 14 and 28 days)
	  ○ Change in creatine kinase level (time frame: 3, 7, 14 and 28 days)
	  ○ Change in creatine kinase MB level (time frame: 3, 7, 14 and 28 days)

NCT04385186 *(Continued)*

- Change in CRP concentration (time frame: 3, 7, 14 and 28 days)
- Change in D Dimer concentration (time frame: 3, 7, 14 and 28 days)
- Change in procalcitonin concentration (time frame: 3, 7, 14 and 28 days)
- Change in IL6 level (time frame: 3, 7, 14 and 28 days)
- Radiography imaging (time frame: over a period of 60 days)
- Tomography imaging (time frame: over a period of 60 days)
- Assessment of oxygenation (time frame: 3, 7, 14 and 28 days)
- Viral load (time frame: 0, 3, 7 days and until hospital discharge or a maximum of 60 days whichever comes first)

Starting date	20 June 2020
Contact information	• Andrés F Zuluaga, MD, MSc, MeH 3014020291, andres.zuluaga@udea.edu.co • Ana L Muñoz, MSc, PhD, ana.munoz@hemolifeamerica.org
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 30 December 2020 estimated study completion date; 30 November 2020 (final data collection date for primary outcome measure) • Sponsor/funding: National Blood Center Foundation, Hemolife, Principal Investigator: Andrés F Zuluaga, MD, MSc, MeH, Universidad de Antioquia

NCT04388410

Study name	Phase 2b/3 trial to evaluate the safety and efficacy of plasma transfusion from convalescent patients with SARS-CoV-2 infection on severity and mortality of COVID-19 in hospitalized patients.
Methods	• Trial design: RCT, double-blinded, multicentre, placebo-controlled • Sample size: 410 • Setting: inpatient • Country: Mexico • Language: English • Number of centres: at least 6

Participants	• Inclusion criteria
	  ◦ Adults ≥ 18 years
	  ◦ Confirmed SARS-CoV-2 infection
	  ◦ Hospitalised for COVID-19
	  ◦ Severe disease or risk for severe disease
	  ◦ Informed consent from patient or responsible person
	• Exclusion criteria
	  ◦ History of allergic reactions to blood products
	  ◦ SOFA scale > 12 points
	  ◦ Absolute contraindication for administration of plasma
	  ◦ Participation in other blinded clinical trial
	  ◦ Projected life expectancy < 3 months
	  ◦ Any condition perceived by the investigator as not appropriate for participation of the patient in the trial

Interventions	• Intervention(s): normal saline and CP therapy
	• Details of CP:
	  ◦ type of plasma: NR
	  ◦ volume: 200 mL

NCT04388410 *(Continued)*

	◦ number of doses: 2 separated by 24-72 h ◦ antibody-titre: NR ◦ pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator: normal saline • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	• Primary study outcomes ◦ Severity and death (time frame: 28 days) ◦ AEs that require study treatment interruption (time frame: 28 days) • Primary review outcomes reported ◦ All-cause mortality during hospital stay: mortality (time frame: 28 days) ◦ Time to death: yes (time frame: 28 days) • Secondary review outcomes reported ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes ◦ Number of participants with SAEs: yes ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes by ordinal 8-point severity outcome scale (time frame: Days 1, 3, 5, 7, 12, 14, 21, 28) ◦ 30-day and 90-day mortality: yes (28-day mortality) ◦ Admission on the ICU: yes ◦ Length of stay on the ICU: yes (ICU hospitalisation) ◦ Time to discharge from hospital: yes (hospitalisation time) ◦ QoL: NR • Additional study outcomes ◦ Antibodies against SARS-CoV-2 (time frame: Days 0, 3, 7, 14, 21, 28) ◦ Time on mechanical ventilation (time frame: 28 days) ◦ Number of days with fever (time frame: 28 days)
Starting date	1 June 2020
Contact information	• Juan G Sierra-Madero, MD+52556559675, jsmadero@yahoo.com
Notes	• Recruitment status: recruiting • Prospective completion date: 30 November 2020 • Sponsor/funding: Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran

NCT04390503

Study name	A phase 2 randomized, double-blinded trial to evaluate the efficacy and safety of human anti-SARS-CoV-2 plasma in close contacts of COVID-19 cases
Methods	• Trial design: double-blinded RCT • Sample size: 150 • Setting: outpatient, close contacts of COVID-19 cases • Country: USA • Language: English • Number of centres: 1

NCT04390503 *(Continued)*

Participants	• Inclusion criteria
	  ○ Participants must be ≥ 18 years
	  ○ Recent close contact with a person with COVID-19, i.e. last close contact occurred within 7 days of anticipated infusion of study product. It is anticipated that most contacts will be household contacts with extensive interaction. All must meet the CDC criteria for close contacts. This includes healthcare workers at higher risk of developing severe disease, or
	  ○ Recent self-reported or documented evidence of infection by nasal swab PCR that is positive for SARS-CoV-2, i.e., nasal sample was collected within 7 days or 10 days of anticipated infusion of study product for those who are asymptomatic or symptomatic, respectively
	  ○ Evidence of infection by nasal swab PCR that is positive for SARS-CoV-2 at screening visit
	  ○ May or may not be hospitalised
	  ○ No symptoms or no more than 5 days of mild symptoms at the time of screening. Mild symptoms (rated by participant as mild and not interfering with normal daily activities) may include:
	  ■ mild rhinorrhea
	  ■ mild sore throat or throat irritation
	  ■ mild nonproductive cough
	  ■ mild fatigue (able to perform ADLs)
	  ○ Risk for severe COVID-19 based on a risk score of ≥ 1 Calculated Risk Score of ≥ 1 point, with risk factors based on CDC description
	  ■ Age 65-74: 1 point
	  ■ Age ≥ 75: 2 points
	  ■ Known cardiovascular disease (including hypertension): 1 point
	  ■ Diabetes mellitus: 1 point
	  ■ Pulmonary disease (COPD, moderate to severe asthma, current smoking or other): 1 point
	  ■ Morbid obesity: 1 point
	  ■ Immunocompromised state: 1 point Received a bone marrow or solid organ transplant at any time, received chemotherapy for a malignancy within the past 6 months, has an acquired or congenital immunodeficiency, currently receiving immunosuppressive or immune modulating medications, HIV with non-suppressed viral load and/or cluster of differentiation 4 (CD4+) T cell count < 200 cells/mL).
	• Exclusion criteria
	  ○ Receipt of any blood product in past 120 days
	  ○ Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect participant safety and/or compliance.
	  ○ Confirmed or self-reported presumed COVID-19, with symptoms that began > 5 days prior to enrolment, and SARS-CoV-2 PCR-positive sample that was collected more than 7 days prior to anticipated infusion for an asymptomatic participant or > 10 days prior to anticipated infusion for a patient with mild symptoms at screening
	  ○ Symptoms consistent with COVID-19 infection that are more than mild (as defined above) at time of screening
	  ○ Symptoms consistent with COVID-19 infection that are more than mild at time of screening.
	  ○ History of allergic reaction to transfusion blood products
	  ○ Inability to complete infusion of the product within 48 h after randomisation.
	  ○ Resident of a long-term or skilled nursing facility
	  ○ Known prior diagnosis of immunoglobulin A (IgA) deficiency
	  ○ Oxygen saturation that is < 95% at the screening visit
	  ○ On supplemental oxygen at time of enrolment
	  ○ Participation in another clinical trial of anti-viral agent(s) for COVID-19
	  ○ Receipt of any COVID-19 vaccine, either as part of a clinical research trial or through routine service delivery

Interventions	• Intervention(s): CP therapy • Details of CP: ○ type of plasma: NR

NCT04390503 *(Continued)*

	○ volume: 200-250 mL ○ number of doses: 1 ○ antibody-titre: NR ○ pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): close contacts of COVID-19 cases without symptoms or with mild symptoms • Comparator: 250 mL of albumin (human) 5% infusion • Concomitant therapy: NR • Treatment cross-overs: not applicable
Outcomes	• Primary study outcome ○ Efficacy of treatment, determined by rating disease severity on day 28, on 7-category severity scale • Primary review outcomes reported ○ All-cause mortality: NR ○ Admission to hospital: NR • Secondary review outcomes reported ○ Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR ○ Time to symptom onset: NR ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8-15 days, 16-30 days: NR ○ Mortality (time to event): NR ○ 90-day mortality: NR ○ Length of hospital stay, for hospitalised patients: NR ○ Admission to ICU: NR ○ Viral clearance, assessed with RT-PCR test: NR ○ QoL: NR ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, TACO, TAD, acute transfusion reactions): NR ○ Number of participants with SAEs: NR • Additional study outcomes ○ Rate of measurable anti-SARS-CoV-2 titres (up to 90 days) ○ Rate of SARS-CoV-2 PCR positivity (up to 28 days) ○ Duration of SARS-CoV-2 PCR positivity (up to 28 days) ○ Levels of SARS-CoV-2 RNA (up to 28 days)
Starting date	March 2021 (estimated)
Contact information	• Jessica Justman, MD 212-342-0537, jj2158@cumc.columbia.edu • Jennifer Zech, MSc 212-304-5506, jz2973@cumc.columbia.edu
Notes	• Recruitment status: recruiting • Prospective completion date: April 2022 • Sponsor/funding: Columbia University

NCT04391101

Study name	Efficacy of convalescent plasma for the treatment of severe SARS-CoV-2 infection: a randomized, open label clinical trial

NCT04391101 *(Continued)*

Methods	• Trial design: open-label, RCT • Sample size: 231 • Setting: ICU • Country: Colombia • Language: English • Number of centres: 8

Participants	• Inclusion criteria
	  ○ > 18 years of age
	  ○ SARS-CoV-2 infection confirmed by PCR in any sample
	  ○ Hospitalised in the ICU due to shock or respiratory failure, with < 24 h after entering the ICU
	• Exclusion criteria
	  ○ Serious volume overload or other condition that contraindicates plasma transfusion
	  ○ History of anaphylaxis or serious adverse reaction to plasma
	  ○ Previous diagnosis of IgA deficiency
	• Donor eligibility criteria
	  ○ > 18 years of age
	  ○ Men or nulliparous women with no history of recent abortions or transfusions SARS-CoV-2 infection by PCR in any sample or serological test with a maximum of 60 days from resolution of symptoms
	  ○ If donation is done within 14-28 days after resolution of symptoms, the patient must have a negative PCR test for SARS-CoV-2. If donation is done after 28 days of resolving symptoms, no negative control test will be required
	• Donor exclusion criteria
	  ○ Severe SARS-CoV-2 infections with an ICU requirement or those with asymptomatic infections will not be accepted as donors
	  ○ Nor will a person who has received CP as part of the COVID-19 treatment

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: NR
	  ○ volume: 400-500 mL total
	  ○ number of doses: 2
	  ○ antibody-titre: NR
	  ○ pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): ICU patients within 24 h of entering ICU
	• Comparator: standard management
	• Concomitant therapy: NR
	• Treatment cross-overs: not applicable

Outcomes	• Primary study outcome
	  ○ In-hospital mortality from any cause (up to 28 days)
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: 28-day mortality
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
	  ○ Number of participants with SAEs: yes
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  ○ 30-day and 90-day mortality: yes (28-day and 60-day mortality)

NCT04391101 *(Continued)*

- Admission on the ICU: no (only ICU patients included)
- Length of stay on the ICU: NR
- Time to discharge from hospital: yes (up to 60 days)
- QoL: NR

- Additional study outcomes: none

Starting date	June 2020
Contact information	• Oliver G Perilla Suarez, Hematologist +573136395608 gerardoperilla@gmail.com • Fabian A Jaimes Barragan, Epidemiologist +5742192420 fabian.jaimes@udea.edu.co
Notes	• Recruitment status: not yet recruiting • Prospective completion date: December 2021 • Sponsor/funding: Hospital San Vicente Fundación, Clínica León XIII, Grupo de Inmunodeficiencias primarias Universidad de Antioquia, Clínica Universitaria Bolivariana, Hospital Pablo Tobón Uribe, Clínica Rosario El Tesoro, Clínica Las Américas, Clínica Cardiovid

NCT04403477

Study name	Convalescent plasma transfusion therapy in severe COVID-19 patients - a tolerability, efficacy and dose-response phase II RCT
Methods	• Trial design: RCT • Sample size: 60 in 3 arms of 20 each • Setting: inpatient • Country: Bangladesh • Language: English • Number of centres: 3

Participants	• Inclusion criteria
	  ◦ Respiratory rate > 30 breaths/min; plus
	  ◦ Severe respiratory distress; or SpO2 ≤ 88% on room air or PaO_2/FiO_2 ≤ 300 mm of Hg, plus
	  ◦ Radiological evidence of bilateral lung infiltrate, and/or
	  ◦ Systolic BP < 90 mm of Hg or diastolic BP < 60 mm of Hg and/or
	  ◦ Criteria 1-4 and/or patient on ventilator support
	• Exclusion criteria
	  ◦ Patients < 18 years
	  ◦ Pregnant women and breastfeeding mothers
	  ◦ Previous history of allergic reaction to plasma
	  ◦ Those who will not give consent
	• Donor eligibility criteria
	  ◦ Between day 22 and day 35 of recovery
	  ◦ 2 consecutive negative RT-PCR samples
	  ◦ Antibody titre > 1:320
	• Donor exclusion criteria NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ◦ type of plasma: NR
	  ◦ volume: 200 mL (Arm-B); 400 mL (Arm-C)
	  ◦ number of doses: 1
	  ◦ antibody-titre: determined by endpoint dilution

NCT04403477 *(Continued)*

	◦ pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with RT-PCR-confirmed diagnosis • Comparator: SC (Arm-A) • Concomitant therapy: enoxaparin, antibiotic, fluid, immune modulator (steroid) and or antiviral (favipiravir or ramdesivir or lopinavir + ritonavir) • Treatment cross-overs: no
Outcomes	• Primary study outcome ◦ Proportion of in-hospital mortality ◦ Time to death • Primary review outcomes reported ◦ All-cause mortality during hospital stay: yes ◦ Time to death: yes • Secondary review outcomes reported ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: yes ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes, to 14 days ◦ 30-day and 90-day mortality: yes to 7 days ◦ Admission on the ICU: yes to 14 days ◦ Length of stay on the ICU: yes to 14 days ◦ Time to discharge from hospital: yes to 14 days ◦ QoL: NR • Additional outcomes ◦ Fever (time frame: 7 days); temperature in degrees Fahrenheit at Day 0, 1, 3, 7 ◦ Respiratory distress (time frame: 7 days); respiratory rate/min at Day 0, 1, 3, 7 ◦ Saturation of oxygen (time frame: 7 days); saturation of oxygen in % at Day 0, 1, 3, 7 ◦ BP (time frame: 7 days); BP in mm of Hg at Day 0, 1, 3, 7 ◦ CRP (time frame: Day 0, 3 and 7); CRP level in mg/L ◦ Ferritin (time frame: Day 0, 3 and 7); serum ferritin level in ng/mL ◦ Serum glutamic-pyruvic transaminase (SGPT) (time frame: Day 0, 3 and 7); serum SGPT level in I/U ◦ Serum glutamic-oxaloacetic transaminase (SGOT) (time frame: Day 0, 3 and 7); serum SGOT level in I/U
Starting date	20 May 2020
Contact information	• Contact: Mohammad S Rahman, MPhil,FCPS+88 01971840757, srkhasru@gmail.com • Contact: Fazle R Chowdhury, FCPS; PhD+88 01916578699, mastershakil@hotmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 20 July 2020 • Sponsor/funding: Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; Dhaka Medical College

NCT04415086

Study name	Treatment of patients with COVID-19 with convalescent plasma transfusion: a multicenter, open-labeled, randomized and controlled study

NCT04415086 *(Continued)*

Methods	• Trial design: randomised • Sample size: 120 • Setting: hospitalised patients • Country: Brazil • Language: English • Number of centres: 1 • Trial registration number: NCT04415086 • Date of registration: 4 June 2020

Participants	• Inclusion criteria
	  ○ Age ≥ 18 years
	  ○ Laboratory-proven COVID-19 infection by RT-PCR in any clinical sample
	  ○ Time since symptom onset < 10 days at the time of screening
	  ○ Presence of COVID-19 pneumonia, with a typical, indeterminate or atypical compatible image in a chest tomography exam (see definition below)
	  ○ Presence of 1 of the following criteria:
	  ■ need for > 3L of O2 in the catheter/mask or > 25% in the Venturi mask to maintain O2 saturation > 92%
	  ■ presence of respiratory distress syndrome with PaO_2/FiO_2 < 300 mmHg If intubated, within 48 h of orotracheal intubation
	  ■ absence of a history of serious adverse reactions to transfusion, for example, anaphylaxis
	  ■ participation approval by the research clinician
	• Exclusion criteria:
	  ○ Already enroled in another clinical trial evaluating antiviral or immunobiological therapy for the treatment of COVID-19
	  ○ IgA deficiency
	  ○ Presence of a clinical condition that does not allow infusion of 400 mL of volume at clinical discretion
	  ○ Pregnancy or breastfeeding
	  ○ Receipt of immunoglobulin in the last 30 days
	  ○ Presence of significant risk of death within the next 48 h at clinical discretion
	• Donor eligibility criteria: NR
	• Donor exclusion criteria: NR

Interventions	• Intervention(s): CP therapy (3 arms, randomised 1:1:1 into 3 treatment groups: A- standard (control); B- standard and CP in a volume of 200 mL (150-300 mL); C- standard and CP in a volume of 400 mL (300-600 mL)
	• Details of CP:
	  ○ Type of plasma: CP
	  ○ Volume: 200 mL or 400 mL
	  ○ Number of doses: NR
	  ○ Antibody test and antibody-titre: NR
	  ○ Pathogen inactivated or not: NR
	  ○ RT-PCR tested: NR
	• Details of donors:
	  ○ Gender: NR
	  ○ HLA and HNA antibody: NR
	  ○ Severity of disease: NR
	  ○ Timing from recovery from disease: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
	• Comparator: nil
	• Concomitant therapy: SC

NCT04415086 *(Continued)*

	• Duration of follow-up: 28 days • Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ Time elapsed until clinical improvement or hospital discharge
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: reported
	  ○ Time to death: reported
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
	  ○ Number of participants with SAEs: reported
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
	  ○ WHO ordinal scale: reported
	  ○ 30-day and 90-day mortality: reported
	  ○ Admission on the ICU: NR
	  ○ Length of stay on the ICU: NR
	  ○ Time to discharge from hospital: reported
	  ○ QoL: NR
	  ○ Virological response:
	  ■ SARS-CoV-2 in NP swab (time frame: Days 0, 1, 3, 7, 14 and 28 after transfusion and control groups)
	  ■ IgG, IgM and IgA titres for SARS-CoV-2 (time frame: Days 0, 1, 3, 5, 7, 14 and 28 after transfusion and control groups)
	  ■ neutralising antibodies (time frame: 0,1,7 14 and 28 days after transfusion and control groups)
	• Additional outcomes: nil

Starting date	1 June 2020
Contact information	• Contact: Zelinda B Nakagawa, MsC55-11-2661-7214, zelinda.bartolomei@gmail.com • Contact: Natália B Cerqueira55-112661-2277, natalia.b.cerqueira@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 20 April 2022 • Sponsor/funding: University of Sao Paulo General Hospital

NCT04418518

Study name	CONCOR-1: a randomized open-label trial of convalescent plasma for hospitalized adults with acute COVID-19 respiratory illness
Methods	• Trial design: randomised • Sample size: 1200 • Setting: hospitalised patients • Country: USA • Language: English • Number of centres: 3 • Trial registration number: NCT04418518 • Date of registration: 5 June 2020

NCT04418518 *(Continued)*

Participants	• Inclusion criteria
	  ○ ≥ 18 years old
	  ○ Admitted to hospital with confirmed COVID-19 respiratory illness
	  ○ Receiving supplemental oxygen
	  ○ 500 mL of ABO-compatible CP is available
	• Exclusion criteria
	  ○ Onset of symptoms > 12 days prior to randomisation
	  ○ Intubated or plan for intubation in place
	  ○ Plasma is contraindicated (e.g. history of anaphylaxis from transfusion)
	  ○ Decision in place for no active treatment
	• Donor eligibility criteria: NR
	• Donor exclusion criteria: NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: 500 mL
	  ○ number of doses: 1 (or 2 x 250 ml)
	  ○ antibody test and antibody-titre: NR
	  ○ pathogen inactivated or not: NR
	  ○ RT-PCR tested: NR
	• Details of donors:
	  ○ gender: NR
	  ○ HLA and HNA antibody: NR
	  ○ Severity of disease: NR
	  ○ Timing from recovery from disease: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
	• Comparator: nil
	• Concomitant therapy: SC
	• Duration of follow-up: 90 days
	• Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ Intubation or death in hospital
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: reported
	  ○ Time to death: reported
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
	  ○ Number of participants with SAEs: reported
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
	  ○ WHO ordinal scale: NR
	  ○ 30-day and 90-day mortality: reported
	  ○ Admission on the ICU: reported
	  ○ Length of stay on the ICU: reported
	  ○ Time to discharge from hospital: reported
	  ○ QoL: NR
	  ○ Virological response: NR

NCT04418518 *(Continued)*

	• Additional outcomes: need for intubation, time of intubation, need for renal replacement therapy, development of myocarditis
Starting date	24 June 2020
Contact information	Celine Arar: 212-746-4177; cea4002@med.cornell.edu
Notes	• Recruitment status: recruiting • Prospective completion date: December 2021 • Sponsor/funding: Weill Medical College of Cornell University

NCT04425837

Study name	Effectiveness and safety of convalescent plasma in patients with high-risk COVID-19: a randomized, controlled study CRI-CP (Coronavirus Investigation - Convalescent Plasma)
Methods	• Trial design: randomised • Sample size: 236 • Setting: critically ill or high risk of progression • Country: Colombia • Language: English • Number of centres: 1 • Trial registration number: NCT04425837 • Date of registration: 11 June 2020

Participants	• Inclusion criteria
	  ○ Patients diagnosed with COVID-19 infection by RT-PCR technique
	  ○ Patients ≥ 18 years of age
	  ○ Patients in SC according to the national guide
	  ○ Onset of symptoms ≤ 14 days
	  ○ Signature of informed consent report
	  ○ Patients at high risk of progression, defined by all of the following:
	  ■ score > 9 on the CALL scale
	  ■ Pao_2/Fio_2 ≤ 200 (parameters adjusted to the elevation of Bogotá, Colombia)
	  ■ X-ray or CT compatible with pneumonia
	  ■ hospitalised patients
	  ○ Critically ill patients, defined by any of the following:
	  ■ mechanical ventilation requirement
	  ■ patients in IICU or Intermediate Care Unit
	  ■ ventilatory failure, septic shock, dysfunction or multi-organ failure
	• Exclusion criteria
	  ○ Negative RT-PCR result from secretion 48 h prior to study recruitment
	  ○ History of allergic reaction to blood or plasma in patients with a known history of IgA deficiency
	  ○ Patients participating in other clinical trial
	  ○ History of allergy to blood products
	  ○ History of confirmed infection and that required antibiotic or antifungal treatment 30 days prior to recruitment
	  ○ Pregnant women
	• Donor eligibility criteria: NR
	• Donor exclusion criteria: NR

Interventions	• Intervention(s): CP therapy

NCT04425837 *(Continued)*

- Details of CP:
  - type of plasma: CP
  - volume: 400 mL
  - number of doses: 2
  - antibody test and antibody-titre: titre ≥ 1:160
  - pathogen inactivated or not: NR
  - RT-PCR tested: NR
- Details of donors:
  - gender: NR
  - HLA and HNA antibody: NR
  - severity of disease: NR
  - timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill/high risk of progression
- Comparator: SC
- Concomitant therapy: SC
- Duration of follow-up: 30 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome
  - Mortality
  - Safety: presence of AEs
  - ICU admission
  - Mechanical ventilation
- Primary review outcomes reported
  - All-cause mortality during hospital stay: reported
  - Time to death: reported
- Secondary review outcomes reported
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
  - Number of participants with SAEs: reported
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
  - WHO ordinal scale: reported
  - 30-day and 90-day mortality: reported
  - Admission on the ICU: reported
  - Length of stay on the ICU: reported
  - Time to discharge from hospital: NR
  - QoL: NR
  - Virological response:
- Additional outcomes: laboratory parameters (CRP, ferritin, procalcitonin, lymphocyte count, LDH), SOFA score, increase in PaO2/Fio2, lung infiltration

Starting date: July 2020

Contact information

- Contact: Guillermo E Quintero, Hematologist, 5716030303 ext 1221, quiquequintero@yahoo.com.mx
- Contact: José A De la Hoz, Epidemiologist, 5716030303 ext 1127, jose.delahoz@fsfb.org.co

Notes

- Recruitment status: not yet recruiting
- Prospective completion date: February 2021
- Sponsor/funding: Fundación Santa Fe de Bogota

NCT04438057

Study name	Evaluating the efficacy of convalescent plasma in symptomatic outpatients infected with COVID-19
Methods	• Trial design: randomised 2:1 (CP:SC) • Sample size: 150 • Setting: mild to moderate symptoms • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04438057 • Date of registration: 18 June 2020

Participants	• Inclusion criteria
	  ○ Laboratory-confirmed diagnosis of infection with SARS-CoV-2
	  ○ Symptoms of COVID -19 - cough, fever, sore throat, shortness of breath, anosmia, diarrhoea, myalgia
	  ○ Symptoms < 14 days
	  ○ ID physician determination that the patient does not need hospitalisation
	  ○ O2 saturation of > 93%
	  ○ Informed consent provided by the patient or healthcare proxy
	  ○ Age ≥ 18 years
	  ○ Ambulatory outpatient when informed consent obtained and study drug is administered
	• Exclusion criteria
	  ○ Age < 18 years
	  ○ Patients currently receiving IVIG
	  ○ Hypercoagulable state - neoplasia, collagen vascular disease, myelodysplastic syndrome, chronic anticoagulation treatment, etc
	  ○ Need to be hospitalised
	  ○ O2 sat < 93%
	  ○ D-Dimer > 2 x normal
	  ○ Chronic oxygen therapy
	  ○ Renal insufficiency with creatinine clearance < 30
	  ○ Long-term care or assisted living facility resident
	  ○ Ongoing usage of hydroxychloroquine for any indication
	  ○ History of blood or plasma transfusion-related complications
	  ○ Enrolment into any other investigational drug or device study within the previous 30 days
	  ○ Any drug, chemical or alcohol dependency as determined by the investigator through history that may affect study procedures and follow-up
	  ○ Pregnant or breastfeeding
	  ○ Any acute or chronic medical comorbidity, psychiatric, social or other circumstance that, in the opinion of the investigator, may interfere with study compliance, completion, or accurate assessment of the study outcomes/safety
	  ○ Admitted to or expected to be admitted to a medical facility
	• Donor eligibility criteria: NR
	• Donor exclusion criteria: NR

Interventions	• Intervention(s): CP therapy (arm 1: 1 dose, arm 2: 2 doses)
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: NR
	  ○ number of doses: 1
	  ○ antibody test and antibody-titre: NR

NCT04438057 *(Continued)*

	○ pathogen inactivated or not: NR ○ RT-PCR tested: NR • Details of donors: ○ gender: NR ○ HLA and HNA antibody: NR ○ severity of disease: NR ○ timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): mild to moderate symptoms • Comparator: SC • Concomitant therapy: SC • Duration of follow-up: 28 days • Treatment cross-overs: nil
Outcomes	• Primary study outcome ○ Time to resolution of symptoms (time frame: 28 days) ○ SAEs within 24 h of plasma infusion (time frame: 28 days) • Primary review outcomes reported ○ All-cause mortality: NR ○ Admission to hospital: yes (28 days) • Secondary review outcomes reported ○ Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR ○ Time to symptom onset: NR ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8-15 days, 16-30 days: NR ○ Mortality (time to event): NR ○ 90-day mortality: NR ○ Length of hospital stay, for hospitalised patients: NR ○ Admission to ICU: NR ○ Viral clearance, assessed with RT-PCR test: NR ○ QoL: NR ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, TACO, TAD, acute transfusion reactions): NR ○ Number of participants with SAEs: NR (severe adverse effects of CP only, 24 h after infusion) • Additional outcomes ○ Laboratory parameters (CRP, D-dimer, LDH, Ferritin, LDH)
Starting date	6 July 2020
Contact information	• Contact: Nicholas Van Hise, PharmD 630-655-6952 nvanhise@midcusa.com • Contact: Nathan Skorodin, PharmD nskorodin@midcusa.com
Notes	• Recruitment status: recruiting • Prospective completion date: 12 August 2021 • Sponsor/funding: Metro Infectious Disease Consultants

NCT04442191

Study name	Infusion of convalescent plasma for the treatment of patients infected with severe acute respiratory syndrome-coronavirus-2 (COVID-19): a double-blinded, placebo-controlled, proof-of-concept study
Methods	• Trial design: randomised • Sample size: 50 • Setting: hospitalised patients requiring supplemental oxygen • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04442191 • Date of registration: 22 June 2020

Participants	• Inclusion criteria
	  ○ Patients ≥ 40 years who are admitted to the University of Illinois Hospital (UIC) due to COVID-19
	  ○ Positive oropharyngeal and/or NP swab test for SARS-CoV-2 by RT-PCR within the preceding 72 h (performed by University of Illinois Hospital Laboratories or, if performed elsewhere, documented in the patient's UIC medical record)
	  ○ Symptomatic infection with any of the following: fever, cough, dyspnoea, or tachypnoea > 22 breaths/min
	  ○ Need for supplemental oxygen, between 1-5 L/min by nasal canula, to maintain O2 saturations > 92%
	  ○ Consents to comply with all protocol requirements
	  ○ Agrees to storage of specimens for future testing
	• Exclusion criteria
	  ○ Patients with known IgA deficiency (high risk of severe or fatal anaphylactic reactions)
	  ○ Patients who are on a ventilator
	  ○ Patients with past history of severe transfusion reaction including TRALI or anaphylaxis
	  ○ Patients with a baseline requirement for supplemental oxygen due to chronic lung disease or with known history of either moderate-to-severe asthma or emphysema
	  ○ Women who report that they are pregnant or breastfeeding
	  ○ Receipt of pooled immunoglobulin in the past 30 days
	  ○ Patients must be willing to not take any another alternative experimental treatment for COVID-19 from the time they undergo enrolment until the 28-day follow-up phone call
	  ○ Participants who are being treated with remdesivir and have had their first dose of remdesivir > 24 h prior to the time they will receive their first dose of CP
	  ○ Patients with severe disease due to COVID-19, as manifested by a need for vasopressors, and/or diagnosis of ARDS
	• Donor eligibility criteria: NR
	• Donor exclusion criteria: NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: NR
	  ○ number of doses: NR
	  ○ antibody test and antibody-titre: neutralising antibody titres > 1:64
	  ○ pathogen inactivated or not: NR
	  ○ RT-PCR tested: NR
	• Details of donors:
	  ○ gender: NR
	  ○ HLA and HNA antibody: NR
	  ○ severity of disease: NR
	  ○ timing from recovery from disease: NR

NCT04442191 *(Continued)*

	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients requiring supplemental oxygen • Comparator: standard FFP • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: NR

Outcomes	• Primary study outcome
	  ○ The primary endpoint will be clinical response at 8 days, defined as no need for oxygen supplementation for the previous 24 h
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: NR (up to 28 days)
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
	  ○ Number of participants with SAEs: reported
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
	  ○ WHO ordinal scale: NR
	  ○ 30-day and 90-day mortality: NR
	  ○ Admission on the ICU: reported
	  ○ Length of stay on the ICU: NR
	  ○ Time to discharge from hospital: reported
	  ○ QoL: NR
	  ○ Virological response: NR
	• Additional outcomes
	  ○ CRP (time frame: 28 days)
	  ○ Lymphocyte count (time frame: 28 days)
	  ○ Change in LDH following treatment
	  ○ LDH (time frame: 28 days)
	  ○ Ferritin (time frame: 28 days)
	  ○ D-Dimer (time frame: 28 days)
	  ○ WBC count (time frame: 28 days)

Starting date	5 May 2020
Contact information	Jessica Herrick, Assistant Professor of Clinical Medicine, University of Illinois at Chicago
Notes	• Recruitment status: recruiting • Prospective completion date: 5 May 2021 • Sponsor/funding: University of Illinois at Chicago

NCT04452812

Study name	Pilot clinical, statistical and epidemiological study on efficacy and safety of convalescent plasma for the management of patients with COVID-19
Methods	• Trial design: pilot, experimental, randomised, prospective, longitudinal, clinical study • Sample size: 15 • Setting: hospitalised patients in ICU

NCT04452812 *(Continued)*

- Country: Mexico
- Language: English
- Number of centres: 1
- Trial registration number: NCT04452812
- Date of registration: 30 June 2020

Participants	• Inclusion criteria
	  ○ Signed informed consent provided by the patient, legal guardian or the health provider if not available
	  ○ Patients hospitalised in an ICU dedicated to the treatment of COVID-19 patients
	  ○ At least positive for 1 q-PCR test for SARS-CoV-2
	  ○ Patients with COVID-19 defined as severe or critically ill:
	  ■ severe: respiratory rate > 30 breaths/min, oxygen saturation < 94%, Pa/FiO_2 < 301, bilateral lung infiltrates that extends in > 50% (by chest radiograph or CT scan) in 24-48 h
	  ■ critically ill: RF (PaO_2 < 60 mmHg or $SatO_2$ < 90% with FiO_2 > 60%) and septic shock (MAP < 65 mmHg with vasoactive requirement, lactate > 2 mmol/L and SOFA score > 1)
	• Exclusion criteria
	  ○ Positive pregnancy test
	  ○ Patients in lactation
	  ○ Informed consent not signed
	  ○ Patients involved in other treatment protocols
	  ○ Patients on immunomodulatory drugs (DMARDs, monoclonal antibodies or small molecule drugs)
	• Donor eligibility criteria
	  ○ Signed informed consent
	  ○ At least positive for 1 q-PCR test for SARS-CoV-2
	  ○ 14 days of COVID-19 clinical remission
	  ○ Positive serologic test for SARS-CoV-2
	  ○ Requirements to donate according to NOM-253-SSA1-2012
	  ○ To accept sample storing for future study
	• Donor exclusion criteria: NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: 200 mL
	  ○ number of doses: 2
	  ○ antibody test and antibody-titre: yes
	  ○ pathogen inactivated or not: NR
	  ○ RT-PCR tested: yes
	• Details of donors:
	  ○ gender: NR
	  ○ HLA and HNA antibody: NR
	  ○ severity of disease: NR
	  ○ timing from recovery from disease: at least 14 days from resolution of COVID-19-associated symptoms including fevers
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients in ICU
	• Comparator: placebo
	• Concomitant therapy: NR
	• Duration of follow-up: NR
	• Treatment cross-overs: nil

Outcomes	• Primary study outcome

NCT04452812 *(Continued)*

- All-cause mortality (time frame: 30 days)
- Side effects (time frame: 30 days)

- Primary review outcomes reported
  - All-cause mortality during hospital stay: reported
  - Time to death: reported
- Secondary review outcomes reported
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
  - Number of participants with SAEs: reported
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
  - WHO ordinal scale: NR
  - 30-day and 90-day mortality: reported (30 days)
  - Admission on the ICU: reported (inclusion criteria)
  - Length of stay on the ICU: reported
  - Time to discharge from hospital: reported
  - QoL: NR
  - Virological response: NR
- Additional outcomes
  - Inflammatory biomarkers (D-dimer) (time frame: 21 days)
  - Inflammatory biomarkers (CRP) (time frame: 21 days)
  - Inflammatory biomarkers (LDH) (time frame: 21 days)
  - Inflammatory biomarkers (ferritin) (time frame: 21 days)

Starting date	6 July 2020
Contact information	• Contact: Julio César Martínez Gallegos, MD, MMSc8113852249, juliomartinez.18@hotmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 1 March 2021 • Sponsor/funding: Universidad Autonoma de Coahuila

NCT04456413

Study name	Phase II randomized study of convalescent plasma from recovered COVID-19 donors collected by plasmapheresis as treatment for subjects with early COVID-19 infection
Methods	• Trial design: randomised • Sample size: 306 • Setting: outpatient, early stage, high-risk for hospitalisation • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04456413 • Date of registration: 2 July 2020

Participants	• Inclusion criteria
	  ◦ Patient age > 30 years old, newly diagnosed with a COVID-19 infection with onset of first symptoms < 96 h
	  ◦ And least 1 other high-risk feature:
	  ■ age > 65

NCT04456413 *(Continued)*

- BMI ≥ 3
- hypertension, defined as systolic BP > 140 or diastolic BP > 90, or requiring medication for control
- Coronary artery disease (history, not ECG changes only)
- Congestive heart failure
- Peripheral vascular disease (includes aortic aneurysm ≥ 6 cm)
- Cerebrovascular disease
- Dementia
- Chronic pulmonary disease
- Liver disease (such as portal hypertension, chronic hepatitis)
- Diabetes (excludes diet-controlled alone)
- Moderate or severe renal disease defined as having a GFR < 60 mL/min
- Cancer (exclude if > 5 years in remission)
- AIDS (not just HIV-positive)

- Exclusion criteria
  - History of severe transfusion reaction to plasma products
  - Need for oxygen supplementation
  - Positive test for COVID-19 antibodies
  - Chemotherapy-induced neutropenia (ANC < 0.5 x 103/mcL)
  - Immunosuppressive medications except for prednisone (or steroid equivalent) > 10 mg daily
  - Performance status < 50 by Karnofsky Performance Scale (KPS) scale
  - Pneumonia by radiographic evaluation
- Donor eligibility criteria
  - Age 18-60
  - A history of a positive NP swab for COVID-19 or a history of positive antibody titre test
  - At least 14 days from resolution of COVID-19-associated symptoms including fevers
  - A negative NP swab (or similar test) for COVID-19
  - Anti-SARS-CoV2 titres > 1:500
  - Adequate venous access for apheresis
  - Meets donor eligibility criteria in accordance to Hackensack University Medical Center (HUMC) Collection Facility at the John Theurer Cancer Center (JTCC) if collecting at the JTCC, and all regulatory agencies as described in SOP 800 01
  - Required testing of the donor and product must be performed in accordance to FDA regulations (21 CFR 610.40), and the donation must be found suitable (21 CFR 630.30)
- Donor exclusion criteria: NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: NR
	  ○ number of doses: NR
	  ○ antibody test and antibody-titre: > 1:500
	  ○ pathogen inactivated or not: NR
	  ○ RT-PCR tested: yes
	• Details of donors:
	  ○ gender: both
	  ○ HLA and HNA antibody: NR
	  ○ severity of disease: NR
	  ○ timing from recovery from disease: at least 14 days from resolution of COVID-19-associated symptoms including fevers
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
	• Comparator: nil

NCT04456413 *(Continued)*

	• Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ Hospitalisation rate (up to 10 days)
	• Primary review outcomes reported
	  ○ All-cause mortality: yes (60 days)
	  ○ Admission to hospital: yes
	• Secondary review outcomes reported
	  ○ Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
	  ○ Time to symptom onset: NR
	  ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8-15 days, 16-30 days: NR
	  ○ Mortality (time to event): NR
	  ○ 90-day mortality: NR
	  ○ Length of hospital stay, for hospitalised patients: NR
	  ○ Admission to ICU: NR
	  ○ Viral clearance, assessed with RT-PCR test: yes (day 14, 28)
	  ○ QoL: NR
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, TACO, TAD, acute transfusion reactions): NR
	  ○ Number of participants with SAEs: NR
	• Additional outcomes
	  ○ Time to symptom resolution
	  ○ Rate of NP swab positivity in donors
	  ○ Rate of donor titres level
	  ○ Impact of donor titres level on efficacy
	  ○ Participants' anti-SARS-CoV2 titre assessment pre-infusion for the treatment group, at 2 weeks, 4 weeks and 2 months
	  ○ Participants' cytokine levels assessment at +2 and +4 weeks post-randomisation (time frame: 2 weeks and 4 weeks)
	  ○ Participants' chemokines levels assessment at +2 and +4 weeks post-randomisation (time frame: 2 weeks and 4 weeks)
	  ○ Rates of AEs (adverse effects) associated with CP infusion (days 3, 7, 14, 28)

Starting date	6 November 2020
Contact information	• Contact: Mariefel Vendivil: 551-996-5828; Mariefel.Vendivil@HackensackMeridian.org • Contact: Marlo Kemp: 551-996-4464; Marlo.Kemp@HackensackMeridian.org
Notes	• Recruitment status: recruiting • Prospective completion date: November 2021 • Sponsor/funding: University of California, Los Angeles

NCT04483960

Study name	An international multi-centre randomised clinical trial to assess the clinical, virological and immunological outcomes in patients diagnosed with SARS-CoV-2 infection (COVID-19)

NCT04483960 *(Continued)*

Methods	• Trial design: RCT (randomised factorial design, participants enroled into the study have the option of deciding whether to be randomised in one or both (if available) treatment domains concurrently, if they meet the eligibility criteria) • Sample size: 2400 • Setting: hospitalised patients • Country: Australia • Language: English • Number of centres: 77 • Trial registration number: NCT04483960 • Date of registration: 23 July 2020

Participants	• Inclusion criteria
	  ○ Age ≥ 18 years
	  ○ Confirmed SARS-CoV-2 by nucleic acid testing in the past 12 days
	  ○ Able to be randomised within 12 days of symptom onset
	  ○ Expected to remain an inpatient for at least 48 h from the time of randomisation
	• Exclusion criteria
	  ○ Overall exclusions
	  ■ Currently receiving acute intensive respiratory support (IMV or non-IMV) or vasopressor/inotropic support. Note, participants already on non-invasive ventilation (either CPAP or BiPAP) in the community can still be recruited if they are continuing on their usual degree of non-invasive ventilation. Humidified high-flow nasal oxygen will not be considered an exclusion criterion
	  ■ Previous participation in the trial
	  ■ Known pregnancy
	  ■ Treating team deems enrolment in the study is not in the best interests of the patient
	  ■ Death is deemed to be imminent and inevitable within the next 24 h
	  ■ Enrolment to other study protocols that do not allow co-enrolment in ASCOT
	  ○ Domain 2 (CP) specific exclusions
	  ■ CP not available at trial site
	  ■ Participant has already received treatment with non-trial-prescribed SARS-CoV-2-specific immunoglobulin therapy (CP, hyperimmune globulin or monoclonal antibody)
	  ■ Known previous history of TRALI
	  ■ Known previous history of serious allergic reaction to blood product transfusion
	  ■ Known religious objection to receiving blood products
	  ■ Treating team deems enrolment in antibody interventions is not in the best interests of the patient
	• Donor eligibility criteria: NR
	• Donor exclusion criteria: NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: C)
	  ○ volume: NR
	  ○ number of doses: 2 (days 1, 2)
	  ○ antibody test and antibody-titre: NR
	  ○ pathogen inactivated or not: NR
	  ○ RT-PCR tested: NR
	• Details of donors:
	  ○ gender: NR
	  ○ HLA and HNA antibody: NR
	  ○ severity of disease: NR
	  ○ timing from recovery from disease: NR

NCT04483960 *(Continued)*

	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients currently not receiving invasive/noninvasive ventilation • Comparator: no CP, also antiviral domain (antiviral - standard of care, lopinavir/ritonavir, lopinavir and ritonavir + hydroxychloroquine) • Concomitant therapy: SC, antiviral domain • Duration of follow-up: 90 days • Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ Proportion of participants alive and not having required new intensive respiratory support (invasive or non-invasive ventilation) or vasopressors/inotropic support in the 28 days after randomisation (time frame: 28 days)
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: yes
	  ○ Time to death: yes
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
	  ○ Number of participants with SAEs: reported
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
	  ○ WHO ordinal scale: reported
	  ○ 30-day and 90-day mortality: reported
	  ○ Admission on the ICU: reported
	  ○ Length of stay on the ICU: reported
	  ○ Time to discharge from hospital: reported
	  ○ QoL: NR
	  ○ Virological response: viral clearance (at 3 and 7 days)
	• Additional outcomes
	  ○ Presence of chest infiltrates on chest X-ray or CT (time frame: 3 and 7 days)
	  ○ Time to defervescence from randomisation (time frame: 28 days)
	  ○ Biomarker levels (time frame: 28 days)
	  ○ Antibiotic use (time frame: 10 days)
	  ○ AEs (time frame: 10 days)
	  ○ Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital (time frame: 28 days)
	  ○ Acute kidney injury (time frame: 28 days)
	  ○ Thrombotic events (-time frame: 28 days)

Starting date	21 July 2020
Contact information	• Contact: Naomi Perry+61 3 83442647 naomi.perry@unimelb.edu.au • Contact: Jocelyn Mora+61 3 8344 0770 jocelyn.mora@unimelb.edu.au
Notes	• Recruitment status: recruiting • Prospective completion date: 31 December 2021 • Sponsor/funding: University of Melbourne

NCT04521036

Study name	Convalescent plasma for COVID-19 patients (CPCP)

NCT04521036 *(Continued)*

Methods	• Trial design: RCT, parallel assignment • Sample size: 44 • Setting: inpatient • Country: Vietnam • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  ○ Age 18-75 years
	  ○ SARS-CoV-19 PCR-positive
	  ○ Moderate stage and above
	  ○ Time from onset to screening ≤ 21 days, the SARS-CoV-2 test is still positive
	• Exclusion criteria
	  ○ Patients with a history of autoimmune disease or IgA deficiency
	  ○ Patients with a history of allergy
	  ○ Multi-organ/system failure
	  ○ Pregnant or breastfeeding at the time of study
	  ○ Cancer, history of heart failure, stroke, bronchial asthma
	  ○ Multi-organ/system failure with indications for dialysis, severe hypoxia, failure with conventional treatment methods, indications for ECMO
	  ○ The patient is infected with multidrug-resistant bacteria
	  ○ The patient is participating in another study
	  ○ Time from onset to screening > 21 days

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: 500 mL
	  ○ number of doses: 1
	  ○ antibody-titre: neutralising antibody titres of at least 1:80
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: (supportive care, oxygen, antibiotics, no CP)
	• Treatment cross-overs: none

Outcomes	• Primary study outcome: change in mortality (time frame: until hospital discharge or a maximum of 60 days whichever comes first)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 30-day mortality: yes (time frame: until hospital discharge or a maximum of 60 days, whichever comes first)
	• Secondary review outcomes
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): incidence of treatment-emergent AEs
	  ○ Number of participants with SAEs: NR
	  ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8-15 days, 16-30 days: NR
	  ○ Mortality (time to event): NR
	  ○ 90-day mortality: NR

NCT04521036 *(Continued)*

- Time to discharge from hospital: NR
- Admission to ICU: NR
- Length of stay on the ICU: NR
- Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
- QoL: NR

- Additional study outcomes
  - Change in requirement for mechanical ventilation (time frame: until hospital discharge or a maximum of 60 days whichever comes first)
  - Change in the time a participant will remain on the ventilator

Starting date	1 December 2020
Contact information	• Contact: Phuong Hoang Nguyen, MPH, (+84) 39756885 ext 2321, v.phuongnh9@vinmec.com • Contact: Liem Thanh Nguyen, PhD, (+84) 39756885 ext 2308, v.liemnt@vinmec.com

Notes	• Recruitment status: not yet recruiting
	• Planned completion date: 30 June 2021
	• Sponsors:
	  ○ Vinmec Research Institute of Stem Cell and Gene
	  ○ TechnologyNational Institute of Hygiene and Epidemiology, Vietnam
	  ○ National Hospital for Tropical Diseases, Hanoi, Vietnam
	  ○ National Institute of Hematology and Blood Transfusion, Vietnam

NCT04528368

Study name	Convalescent plasma for treating patients with COVID-19 pneumonia without indication of ventilatory support
Methods	• Trial design: RCT, parallel assignment • Sample size: 60 • Setting: • Country: Brazil • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  ○ Confirmed diagnosis of COVID-19 by RT-PCR
	  ○ Time between symptom onset and inclusion ≤ 7 days
	  ○ Chest tomography with < 50% involvement of the lung parenchyma
	  ○ No indication of ventilatory support at the time of randomisation
	  ○ Signed the consent form
	• Exclusion criteria
	  ○ Contraindication to transfusion or history of previous reactions to blood products for transfusion
	  ○ Pregnant women
	  ○ Limiting comorbidity for administering the therapies provided for in this protocol in the opinion of the investigator

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: 400 mL

NCT04528368 *(Continued)*

	○ number of doses: 1 ○ antibody-titre: SARS-CoV-2 antispike antibody titre with a dilution ≥ 1: 320 ○ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): SC • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	• Primary study outcome: area under the curve of SARS-COV-2 viral load obtained from NP and /or oropharyngeal swabs. (time frame: 0, 3, 6, 9, 12, 15, 18 and 21 days) • Primary review outcomes ○ All-cause mortality during hospital stay: NR ○ 30-day mortality: yes at 28 days • Secondary review outcomes ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): yes, rate of transfusion reactions to CP infusion ○ Number of participants with SAEs: NR ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8-15 days, 16-30 days: yes, assessment of clinical improvement using an Ordinal Severity Scale (time frame: 0, 7, 10, 14, 21 and 28 days) ○ Mortality (time to event): NR ○ 90-day mortality: NR ○ Time to discharge from hospital: yes ○ Admission to ICU: NR ○ Length of stay on the ICU: yes ○ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR ○ QoL: NR • Additional study outcomes ○ Evaluate oxygen saturation (time frame: 0, 3, 6, 9, 12, 15, 18 and 21 days) ○ Evaluate oxygen supplementation (time frame: 0, 3, 6, 9, 12, 15, 18 and 21 days) ○ Assess respiratory rate ○ Evaluate the PaO_2/FiO_2 ratio (for patients on mechanical mechanisms) ○ Assess the rate of orotracheal intubation ○ Change in the profile of cytokines/chemokines in both groups ○ Presence of antibodies against SARS-CoV-2 in serum after convalescent plasma administration
Starting date	18 August 2020
Contact information	Contact: Eduardo M Rego, MD, PhD: edumrego@hotmail.com
Notes	• Recruitment status: recruiting • Planned completion date: 30 April 2021 • Sponsors: D'Or Institute for Research and Education Hospital do Coracao

NCT04558476

Study name	A multicenter randomized trial to assess the efficacy of convalescent plasma therapy in patients with invasive COVID-19 and acute respiratory failure treated with mechanical ventilation: the CONFIDENT trial
Methods	• Trial design: phase II, multi-centre, open-label RCT • Sample size: 500 (250 with plasma, 250 without plasma) • Setting: inpatient • Country: Belgium • Language: English • Number of centres: 16

Participants	• Inclusion criteria
	  ○ Age at least 18 years
	  ○ Hospitalisation in an ICU participating in the study
	  ○ Medical diagnosis with SARS-CoV-2 pneumonia as defined by both:
	  ■ extended interstitial pneumonia on CT scan or a chest X-ray, consistent with viral pneumonia, within 10 days prior to inclusion
	  ■ positive result of SARS-CoV-2 PCR test, or any emerging and validated diagnostic laboratory test for COVID-19, within 15 days prior to inclusion
	  ○ Under mechanical ventilation administered through an endotracheal tube, for < 5 days
	  ○ Prior Clinical Frailty Scale < 6
	  ○ Written consent of the patient, or - if impossible - of a relative acting as the legal representative, or - if impossible - of a physician from a non-participating department of the same hospital acting as an impartial witness
	• Exclusion criteria
	  ○ Pregnancy
	  ○ Prior episode of transfusion-related side effect
	  ○ Medical decision to limit therapy
	  ○ Current participation in another trial testing a COVID-19 therapy

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  ○ type of plasma: plasma from 2 different donors
	  ○ volume: 400-500 mL
	  ○ number of doses: 2 units
	  ○ antibody-titre: NR
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): under medical ventilation
	• For studies including a control group: comparator (type): SC according to the latest gold standard
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Vital status (dead or alive) at day 28
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 30-day mortality: probably reported
	• Secondary review outcomes
	  ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8-15 days, 16-30 days: NR
	  ○ Mortality (time to event): NR
	  ○ 90-day mortality: reported

NCT04558476 *(Continued)*

- Time to discharge from hospital: length of hospital stay
- Admission to ICU: NR
- Length of stay on the ICU: NR
- Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: probably reported
- QoL: reported
- Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): NR
- Number of participants with SAEs: NR

- Additional study outcomes
  - Day 90 mortality (time frame: at day 90)
  - Number of ventilator-free days at day 28 (time frame: at day 28)
  - Number of renal replacement therapy-free days at day 28 (time frame: at day 28)
  - Number of vasopressor-free days at day 28 (time frame: at day 28)
  - Use of ECMO before day 28 (time frame: till day 28)
  - Value of the SOFA score at days 7, 14 and 28 (time frame: Day 1, 7, 14, 28)
  - Changes in SOFA scores (delta SOFA) over 7, 14 and 28 days (time frame: Day 7, 14 and 28 days)
  - Assessment of the SARS-CoV-2 viral load (time frame: Days 7, 14 and 28)
  - Blood CRP concentration (time frame: Days 7, 14 and 28)
  - Ferritin concentration (time frame: Days 7, 14 and 28)
  - Lymphocyte count (time frame: Days 7, 14 and 28)
  - Length of stay in the acute care hospital (time frame: through study completion, 1 year)
  - Location of the patient (time frame: Day 90)
  - Katz Index of independence in Activity Day Living functional score (time frame: Day 90 and 365)
  - Hospital Anxiety and Depression Scale (HADS) (time frame: Day 90 and 365)
  - QoL scale EQ-5D-5L (time frame: Day 90 and 365)
  - Transfusion-related AEs (time frame: till 28 days)

Starting date	1 September 2020
Contact information	Benoit Misset, MD,PhD: benoit.misset@chuliege.be
Notes	• Recruitment status: recruiting • Prospective completion date: 1 September 2022 • Sponsor/funding: University of Liege

NCT04567173

Study name	A randomized, open-label, single center clinical trial to assess the efficacy and safety of convalescent plasma to hospitalized adult COVID-19 patients as adjunctive therapy to reduce the need for ICU admission: Co-CLARITY trial
Methods	• Trial design: phase 3, randomised, non-placebo controlled, open-label, non-blinded, single-centre clinical trial • Sample size: 136 • Setting: inpatient • Country: Philippines • Language: English • Number of centres: 1

NCT04567173 *(Continued)*

Participants	• Inclusion criteria
	  ○ Patient must be ≥ 19 years of age
	  ○ Hospitalised with COVID-19 and confirmed via SARS-CoV-2 RT-PCR testing
	  ○ Patient is willing and able to provide written consent and comply with all protocol requirements
	  ○ Patient agrees to storage of specimens for future testing
	• Exclusion criteria
	  ○ Women with positive pregnancy test, are breastfeeding or planning to become pregnant/breastfeed during the study period
	  ○ Symptomatic illness exceeding 14 days from onset of illness at time of enrolment
	  ○ ICU admission on initial presentation at the hospital (includes patients with clinical indications for ICU admission as follows:Haemodynamic
	  ■ respiratory distress with requirement of O_2 > 6 L/min to maintain O_2 sat > 92%
	  ■ rapid escalation of O_2 requirement/significant work of breathing
	  ■ haemodynamic instability: systolic BP < 90, MAP < 65
	  ○ Receipt of any blood products including pooled immunoglobulin or IVIg in the past 30 days prior to enrolment
	  ○ Known IgA deficiency
	  ○ Presence of any contraindication to transfusion (or history of prior severe reactions to transfusion of blood products)

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  ○ type of plasma: type-specific anti-SARS-CoV-2 CP
	  ○ volume: 500 mL
	  ○ number of doses: 2 doses
	  ○ antibody-titre: NR
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): 3rd to 14th day of illness after the onset of symptoms in preventing ICU admission
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Incidence of SAEs (time frame: 28 days from enrolment)
	  ○ Cumulative incidence of SAEs (TRALI, TACO, transfusion-related infection and anaphylaxis/severe allergic reactions) during the study period
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 30-day mortality: probably reported
	• Secondary review outcomes
	  ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8-15 days, 16-30 days: partially (see primary study outcomes)
	  ○ Mortality (time to event): NR
	  ○ 90-day mortality: NR
	  ○ Time to discharge from hospital: length of hospital stay
	  ○ Admission to ICU: NR
	  ○ Length of stay on the ICU: reported
	  ○ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
	  ○ QoL: NR

NCT04567173 *(Continued)*

- Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
- Number of participants with SAE: reported

- Additional study outcomes
  - Quick SOFA (qSOFA) score (time frame: 28 days from enrolment)
  - Cardiopulmonary arrest (time frame: 28 days from enrolment)
  - ICU mortality (time frame: 28 days from enrolment)
  - ICU length of stay (time frame: 28 days from enrolment)
  - Hospital mortality (time frame: 28 days from enrolment)
  - Hospital length of stay (time frame: 28 days from enrolment)
  - Dialysis-free days (time frame: 28 days from enrolment)
  - Vasopressor-free days (time frame: 28 days from enrolment)
  - ICU-free days (time frame: 28 days from enrolment)
  - 28-day mortality (time frame: 28 days from enrolment)
  - Anti-SARS-CoV-2 antibody titres (time frame: days 0, 1, 7 and 14 from enrolment)
  - SARS-CoV-2 RNA by RT-PCR (time frame: days 0, 1, 7 and 14 from enrolment)

Starting date	28 September 2020
Contact information	Deonne Thaddeus V Gauiran, MD: +639088150248.; dvgauiran@up.edu.ph
Notes	• Recruitment status: recruiting • Prospective completion date: 30 June 2021 • Sponsor/funding: University of the Philippines

NCT04634422

Study name	Plasma exchange (PLEX) and convalescent plasma (CCP) in COVID-19 patients with multiorgan failure - the COVID PLEX+CCP Trial
Methods	• Trial design: multi-centre, parallel-grouped, stratified, centrally RCT • Sample size: 220 • Setting: inpatient • Country: Denmark • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  ◦ Confirmed SARS-CoV-2 (COVID-19) requiring intensive care and use of advanced respiratory support as IMV or non-invasive ventilation or continuous use of CPAP for hypoxia or oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system and RRT (continuous or intermittent) OR ECMO
	• Exclusion criteria
	  ◦ Received CP for COVID-19
	  ◦ Have known hypersensitivity to plasma
	  ◦ Pregnant
	  ◦ The clinical team has decided not to escalate therapy (except that for cardiac arrest; patients who are not for cardio-pulmonary-resuscitation may be enroled)
	  ◦ Received RRT for > 72 h
	  ◦ Received mechanical ventilation for > 14 days

NCT04634422 *(Continued)*

	◦ We will not exclude patients enroled in other interventional trials unless the protocols of the two trials collide (e.g. use of CP by protocol). Co-enrolment agreements will be established with the sponsor/investigator to maintain an updated list of trials approved for co-enrolment
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: ◦ type of plasma: NR ◦ volume: 300 mL ◦ number of doses: 2 doses ◦ antibody-titre: NR ◦ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): also full plasma exchange therapy tested • For studies including a control group: comparator (type): SC • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	• Primary study outcome ◦ Alive at day 90 • Primary review outcomes ◦ All-cause mortality: probably reported ◦ Admission to hospital: NR • Secondary review outcomes ◦ Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR ◦ Time to symptom onset: NR ◦ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8-15 days, 16-30 days: NR ◦ Mortality (time to event): NR ◦ 90-day mortality: probably reported ◦ Length of hospital stay, for hospitalised patients: NR ◦ Admission to ICU: NR ◦ Viral clearance, assessed with RT-PCR test: NR ◦ QoL: NR ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, TACO, TAD, acute transfusion reactions): NR ◦ Number of participants with SAEs: reported (day 8) • Additional study outcomes ◦ Day 8 SAEs ◦ Day 28 all-cause mortality ◦ Days alive without life support at day 90
Starting date	18 November 2020
Contact information	Wladimir M Szpirt, MD: 4535451767; mail@covid-plex.com
Notes	• Recruitment status: recruiting • Prospective completion date: 30 June 2021 • Sponsor/funding: Wladimir Szpirt

NCT04712344

Study name	Assessment of efficacy and safety of therapy with COVID-19 convalescent plasma in subjects with severe COVID-19 (IPCO)
Methods	• Trial design: RCT • Sample size: 58 • Setting: inpatient • Country: Germany • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  ○ Male or female patients aged ≥ 18 years
	  ○ Estimated BMI ≥ 19 kg/m² to ≤ 40kg/m²
	  ○ Florid1 SARS-CoV-2 infection confirmed by RT-PCR in tracheo-bronchial secretion sample or pharyngeal swab sample
	  ○ ARDS with Horovitz index < 300 mmHg
	  ○ Necessity of IMV
	  ○ Written informed consent obtained from the patient's legal representative or under such arrangement as is legally acceptable in Germany
	  ○ Participant's assent if obtainable
	• Exclusion criteria
	  ○ Previous exposure to COVID-19 CP
	  ○ Adverse reaction to plasma proteins in medical history
	  ○ Interval > 72 h since endotracheal intubation
	  ○ Current or imminent necessity of ECMO treatment
	  ○ Pre-existing COPD GOLD stage 4
	  ○ Chronic congestive heart failure NYHA ≥ 3
	  ○ Pre-existing left ventricular ejection fraction < 30%

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  ○ type of plasma: convalescent plasma
	  ○ volume: NR
	  ○ number of doses: 2-3
	  ○ antibody-titre: NR
	  ○ pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): SC
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary study outcome
	  ○ Change in SOFA score from baseline visit (time frame: (Day 1, visit 2) to Day 8 (visit 9)
	• Primary review outcomes
	  ○ All-cause mortality during hospital stay: NR
	  ○ 30-day mortality: yes, day 29
	• Secondary review outcomes
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  ○ Number of participants with SAEs
	  ○ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8-15 days, 16-30 days: NR

NCT04712344 *(Continued)*

- Mortality (time to event): NR
- 90-day mortality: NR
- Time to discharge from hospital: NR
- Admission to ICU: NR
- Length of stay on the ICU: NR
- Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
- QoL: NR

- Additional study outcomes
  - Mean number of days without IMV during the period from baseline visit (Day 1, visit 2) until and including Day 8 (visit 9), Day 15 (visit 13), and Day 29 (visit 15), per treatment group and per participant
  - Number of participants without supplemental oxygen on Day 8 (visit 9), on Day 15 (visit 13), and on Day 29 (visit 15)
  - Proportion of participants without supplemental oxygen on Day 8 (visit 9), on Day 15 (visit 13), and on Day 29 (visit 15)
  - Mean number of days without supplemental oxygen during the period from baseline visit (Day 1, visit 2) until and including Day 8 (visit 9), Day 15 (visit 13), and Day 29 (visit 15), per treatment group and per participant
  - Mean relative change of positive end-expiratory pressure from baseline visit (Day 1, visit 2) to all subsequent visits until and including Day 29 (visit 15) or until stop of IMV, whichever comes first.
  - Mean relative change of FiO2 from baseline visit (Day 1, visit 2) to all subsequent visits until and including Day 29 (visit 15) or until stop of IMV, whichever comes first
  - Mean relative change of driving pressure from baseline visit (Day 1, visit 2) to all subsequent visits until and including Day 29 (visit 15) or until stop of IMV, whichever comes first.
  - Time from baseline visit (Day 1, visit 2) to stop of IMV

Starting date	18 January 2021
Contact information	Contact: Mario Schiffer, MD: +49913185 ext 39002; mario.schiffer@uk-erlangen.de
Notes	• Recruitment status: recruiting • Prospective completion date: September 2021 • Sponsor/funding: University of Erlangen-Nürnberg Medical School

NCT04730401

Study name	Convalescent plasma in the treatment of COVID-19 (CP_COVID-19)
Methods	• Trial design: double-blind, randomised, placebo-controlled trial • Sample size: 390 • Setting: inpatient • Country: Finland • Language: English • Number of centres: NR
Participants	Inclusion criteria • Acute COVID-19 disease at the time of recruitment, laboratory-confirmed by upper respiratory tract PCR • Patient recently (0-4 days earlier) admitted to hospital due to COVID-19 infection • The day should be recorded from the duration of the COVID-19 symptoms/positive test result • The dose of low-molecular-weight heparin thromboprophylaxis should be recorded

NCT04730401 *(Continued)*

- Written informed consent
- Availability for all visits scheduled in this study

Exclusion criteria

- Chronic (> 14 days) administration of immunosuppressants or other immune-modifying drugs within 6 months before the first dose; oral corticosteroids in dosages of ≥ 0.5 mg/kg/d prednisolone or equivalent are excluded (inhaled or topical steroids allowed)
- Regular (daily), systemic administration of corticosteroids at the time on inclusion (inhaled or topical corticosteroids are allowed)
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection
- Pregnancy or lactation
- Alcohol or drug abuse
- Suspected non-compliance
- Presence of venous thromboembolism, including pulmonary embolism or other manifestations of thrombosis
- Use of any investigational drug (other than hydroxychloroquine) or vaccine within 30 days prior to first dose of study vaccine or planned use during study period
- Any clinically significant history of known or suspected anaphylaxis or hypersensitivity reaction as judged by investigator
- Known IgA deficiency
- Existing treatment limitations: do-not-resuscitate (DNR) order or withholding treatment in ICU
- Any other criteria which, as judged by investigator, might compromise a patient's well-being or ability to participate in the study or its outcome

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
  - type of plasma: convalescent plasma
  - volume: 200 mL
  - number of doses: 2-3
  - antibody-titre: low titre and high titre
  - pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): 200 mL saline
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome
  - Safety (SAE) (time frame: SAEs will be reviewed, recorded and reported up to 6 h after administration of CP or placebo)
  - Safety (SAE) (time frame: SAEs will be recorded and reported up to 7 days after administration of CP or placebo)
  - Rate of intubation (time frame: through study completion, up to 6 months)
  - Number of participants initiating systemic corticosteroids (time frame: through study completion, up to 6 months)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 30-day mortality: yes, up to 1 year
- Secondary review outcomes
  - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8-15 days, 16-30 days: NR
  - Mortality (time-to-event): NR
  - 90-day mortality: yes, up to 1 year

NCT04730401 *(Continued)*

- Time to discharge from hospital: yes
- Admission to ICU: NR
- Length of stay on the ICU: yes
- Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
- QoL: NR
- Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
- Number of participants with SAEs: yes

- Additional study outcomes
  - Ventilator days
  - Number of participants developing ARDS
  - Viral load, up to 1 year
  - Antibody measurements
  - Development of a thrombotic complication, including venous thromboembolism or arterial thrombosis
  - The rate of participants presenting with coagulopathy disorders
  - Number of participants with oxygenation change
  - Change in inflammatory (CRP, ferritin) and coagulopathy markers during the COVID-19 infection hospital period
  - CP (high- or low-titre) efficacy versus placebo: rate of intubation or initiating systemic corticosteroids during the COVID-19 infection hospital period

Starting date	27 January 2021
Contact information	• Contact: Sari Pakkanen: 0405166165; anu.kantele@hus.fi
Notes	• Recruitment status: recruiting • Prospective completion date: 31 December 2021 • Sponsor/funding: Helsinki University Central Hospital; Finnish Red Cross

NCT04803370

Study name	Efficacy of reinforcing standard therapy in COVID-19 patients with repeated transfusion of convalescent plasma
Methods	• Trial design: open-label RCT • Sample size: 100 • Setting: inpatient • Country: • Language: • Number of centres:
Participants	Inclusion criteria • Ability to give informed consent and willing to sign consent form • Male or female ≥ 18 years • Patient hospitalised with a COVID-19 diagnosis by PCR on NP swabs or any other biological sample • Presence of respiratory symptoms and/or fever associated with COVID-19, with clinical evolution time for COVID-19 ≤ 7 days • Presence of pneumonia on chest X-ray and/or SatO2 < 94% aa • SOFA score ≤ 6

NCT04803370 *(Continued)*

- Accept the condition of complying with the procedures established in the protocol

Exclusion criteria

- Patients with a previous history of allergic transfusion reaction
- Lactating or pregnant women and a positive pregnancy test
- Patients who have been treated with plasma in the 21 days prior to the screening/baseline visit
- Patients who are at the time of study, participating in another clinical trial
- Patients who haven't completed all study procedures

Interventions

- Details of CP:
  - type of plasma: CP
  - volume: 300 ml given in 2 consecutive days
  - number of doses: days 1 and 2
  - antibody-titre: NR
  - pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease):
- For studies including a control group: comparator (type): SC for COVID-19
- Concomitant therapy:
- Treatment cross-overs:

Outcomes

- Primary study outcome: WHO clinical progression scale (day 21)
- Primary review outcomes
  - All-cause mortality during hospital stay: NR
  - 30-day mortality: yes
- Secondary review outcomes
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
  - Number of participants with SAEs: NR
  - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8-15 days, 16-30 days: yes day 21
  - Mortality (time to death): NR
  - 90-day mortality: NR
  - Time to discharge from hospital: NR
  - Admission on the ICU: yes
  - Length of stay on the ICU: yes
  - Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: yes
  - QoL: NR
- Additional study outcomes
  - Lung X-ray
  - Concomitant medication assessment
  - Hematimetry
  - Activated partial thromboplastin time
  - Fibrinogen level
  - Fragment D-dimer assessment
  - GFR assessment
  - Ferritin blood assessment
  - CRP assessment
  - LDH
  - Troponin I assessment
  - Procalcitonin assessment

NCT04803370 *(Continued)*

	○ IL-6 assessment ○ PaO_2 assessment ○ Quantitative determination of antibodies ○ SARS-Cov-2 viral quantification in a NP specimen ○ Time to negativisation of RT-PCR ○ Pneumonia Severity Index (PSI) score
Starting date	17 March 2021
Contact information	Maria Arrizabalaga Asenjo, 0034871202000, email: marrizab@hsll.es
Notes	• Recruitment status: recruiting • Prospective completion date: 1 September 2021 • Sponsor/funding: Hospital Son Llatzer

NCT05077930

Study name	Convalescent plasma therapy for hospitalized patients with COVID-19
Methods	• Trial design: open-label RCT (1:1) • Sample size: 200 • Setting: inpatient • Country: Brazil • Language: English • Number of centres: 1
Participants	• Inclusion criteria ○ Hospitalised patients aged ≥ 18 years ○ Confirmed diagnosis of COVID-19 by RT-PCR or antigen test in respiratory samples ○ Time between symptom onset and inclusion ≤ 7 days ○ Enroled within 5 days of hospitalisation ○ Sign the consent form • Exclusion criteria ○ Contraindication to transfusion due to inability to tolerate additional fluid, such as due to de-compensated congestive heart failure ○ History of previous severe allergic reactions to transfused blood products ○ Limiting comorbidity for administering the therapies provided for in this protocol in the opinion of the investigator ○ Not currently enroled another interventional clinical trial of COVID-19 treatment ○ Critically ill patient with COVID-19 being treated in ICU
Interventions	• Details of CP: ○ type of plasma: anti-SARS-CoV-2 convalescent plasma ○ volume: 200ml or 400ml ○ number of doses: NR ○ antibody-titre: NR ○ pathogen inactivated or not: ○ Treatment details, including time of plasma therapy(e.g.) early stage of disease): NR ○ For studies including a control group: comparator (type): SC ○ Concomitant therapy: NR ○ Therapy cross-overs: NR

NCT05077930 *(Continued)*

Outcomes

- Primary outcome: proportion of participants with clinical improvement at day 14 following randomisation
- Primary outcomes
  - Clinical status on a 7-point ordinal scale (time frame: from randomisation to end of study at Day 14)
  - Participants' clinical status over time assessed by a 7-point ordinal scale from WHO. Lower scores are seen with better clinical outcomes. The scale categories are as follows:
    - (1) not hospitalised with resumption of normal activities
    - (2), not hospitalised, but unable to resume normal activities
    - (3), hospitalised, not requiring supplemental oxygen
    - (4), hospitalised, requiring supplemental oxygen
    - (5), hospitalised, requiring high-flow oxygen therapy or non-IMV
    - (6), hospitalised, requiring ECMO, intermittent mandatory ventilation, or both
    - (7), death.
  - Proportion of participants with clinical improvement, defined by an increase of 2 points in the ordinal scale of 7 WHO categories
- Secondary outcomes
  - Percentage of participants at each clinical status on a 7-point ordinal scale (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - Measure of participants' clinical status using an ordinal scale for clinical improvement created by WHO and based on 7-point scale categories (see above under primary outcomes.)
  - Oxygen saturation (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - Prevalence of oxygen-intake methods (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - Percentage of participants using oxygen by mask or nasal prongs, oxygen by non-IMV or high flow, intubation and mechanical ventilation and ECMO
  - Respiratory rate (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - The PaO2/FiO2 ratio (for participants on mechanical mechanisms) (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - Number and/or extension of affected lung areas on chest CT (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - Length of hospital stay (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - Length of stay in ICU (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - Time until independence from oxygen therapy in days (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - Ventilator-free days (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - In patients who needed mechanical ventilation, time to initiate mechanical ventilation (calculated in days, from entry into the protocol until orotracheal intubation) (time frame: Day 1, Day 3, Day 7, and Day 14 after randomisation)
  - Rate of transfusion reactions to CP infusion (time frame: Daily, until Day 14 after randomisation)
  - Percentage of participants who develop SAEs and AEs considered as definitely or probably associated with plasma transfusion (time frame: Daily, until Day 14 after randomisation)
  - AEs (worsening anemia, urticaria, skin rash, TACO, and others) assessed during hospitalisation.
- Additonal outcomes
  - Association between the presence of comorbidities at baseline and clinical status on a 7-point ordinal scale (time frame: Day 1 and Day 14 after randomisation)
  - Association between the volume of CP transfused and clinical status on a 7-point ordinal scale (time frame: Day 1 and Day 14 after randomisation)
  - Changes from baseline in inflammatory surrogate markers: WBC counts, lymphocyte counts, CRP and D-dimer levels (time frame: Day 1 and Day 14 after randomisation)
  - Association between the concentration of inflammatory surrogate markers and clinical status on a 7-point ordinal scale (time frame: Day 14 after randomisation)

NCT05077930 *(Continued)*

Starting date	October 2021
Contact information	Contact: Tânia P Costa, Master+55 41 3136-2515tania.p@hospitaldorocio.com.br Contact: Leandro B Agati, PhD+55 11 4040-8670agati@svriglobal.com
Notes	• Recruitment status: recruiting • Prospective completion date: January 2022 • Sponsor/funding: Tânia Portella Costa

NL8633

Study name	A randomized, double blinded clinical trial of convalescent plasma compared to standard plasma for treatment of hospitalized non-ICU patients with COVID-19 infections (COV-PLAS)
Methods	• Trial design: randomised, prospective, multi-centre, double-blinded phase 2/3 trial • Sample size: 215 each arm (430) • Setting: inpatient • Country: The Netherlands • Language: English • Number of centres: multi-centre • Trial registration number: prospective - NL8633 • Date of registration: 13 May 2020

Participants	• Inclusion criteria
	  ◦ Maximal 3 days hospitalised at plasma infusion
	  ◦ Age ≥ 18 years and ≤ 85 years
	  ◦ SARS-CoV-2 infection: confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swap) < 7 days before
	  ◦ Symptoms not expected to lead to ICU transfer within 6 h of study plasma administration
	  ◦ Written informed consent including storing of specimen for future testing
	• Exclusion criteria
	  ◦ A potential participant who meets any of the following criteria will be excluded from participation in this study:
	  ■ accompanying diseases other than COVID-19 with an expected survival time of < 6 months
	  ■ chronic severe pulmonary dysfunction like COPD, GOLD stage 4; severe emphysema; or lung fibrosis with usual interstitial pneumonia pattern
	  ■ chronic heart failure NYHA ≥ 3 and/or pre-existing reduction of left ventricular ejection fraction to ≤ 30% for which among others e.g. strict fluid restriction is needed
	  ■ clinical diagnosis of circulatory overload for which active therapy (like increased doses of diuretics) is initiated
	  ■ clinical judgement of deterioration in oxygenation (e.g. > 2 L increase in additional O2 by nose tube), respiratory rates (e.g. > 5 / min increase) in the 2 h before the planned randomisation/plasma infusion
	  ■ signs of severe coagulopathy: thrombocytopenia by consumption (< 100 x 10e9/L) or prolongation of the PT (+3 sec), PTT (+ 5 sec)
	  ■ any history of severe adverse reactions to plasma proteins
	  ■ Known deficiency of IgA
	  ■ Pregnancy
	  ■ Breastfeeding women
	  ■ Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect participant safety and/or compliance

NL8633 *(Continued)*

Interventions	• Intervention(s): CP therapy vs SP
	• Details of CP:
	  ○ type of plasma: convalescent thawed FFP
	  ○ volume: 1 unit (250-325 mL)
	  ○ number of doses: 1 unit
	  ○ antibody-titre: NR
	  ○ pathogen inactivated: NR
	• Treatment details, including time of plasma therapy
	  ○ Early. Maximally 3 days hospitalised COVID-19 patients that are not at or bound to be referred to the ICU or expected to go to the ICU within 6 h of first plasma administration. Patients with COVID-19 that are sick enough to warrant hospitalisation but have not (yet) experienced overwhelming disease including a systemic inflammatory response, sepsis, and/or ARDS warranting ventilation and (imminent) ICU referral
	• Comparator: standard thawed FFP 1 unit (250-325 mL)
	• Concomitant therapy: NR
	• Treatment cross-overs: no - parallel

Outcomes	• Primary study outcome(s)
	  ○ Ordinal outcome at day 14 of all-cause mortality, mechanical ventilation, ICU admission and long duration of hospital stay (≥ 6 days), with < 6 hospitalised days as reference category
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: ordinal outcome of all-cause mortality at day 6, 14, 21, 18 and 56
	  ○ Length of ICU mortality (no further results provided for this outcome)
	  ○ Time to death: ordinal outcome of all-cause mortality at day 14, 21, 18 and 56
	  ○ ICU mortality
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction: yes. Deterioration of respiratory, circulatory or otherwise the clinical status during transfusion; transfusion-transmitted infections
	  ○ Number of participants with SAEs: numbers not mentioned: "The following safety parameters will be assessed during this trial: deterioration of respiratory, circulatory or otherwise the clinical status during transfusion; transfusion transmitted infections."
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: maybe. Ordinal outcome includes mechanical ventilation, ICU admission and long duration of hospital stay day 6, 14, 21, 28
	  ○ 30-day and 90-day mortality: yes. Ordinal outcome of all-cause mortality, mechanical ventilation, ICU admission and long duration of hospital stay day 21, 28 and 56
	  ○ Admission on ICU: yes within ordinal outcome of all-cause mortality, mechanical ventilation, ICU admission and long duration of hospital stay day 6, 14, 21, 28 and 56
	  ○ Length of stay on the ICU: Yes. "Length of stay in ICU."
	  ○ Time to discharge from hospital: yes. "duration of hospitalisation in days"
	• Additional outcomes
	  ○ e.g. proportion of viral nucleic acid negatives (3 days after transfusion): yes. "The time until negative SARS-CoV-2 PCR (nasal/ pharyngeal swab)"
	  ○ e.g. results of lab tests and vital signs: NR

Starting date	13 May 2020
Contact information	Name: Jaap Jan Zwaginga Email: j.j.zwaginga@lumc.nl Phone: 0715264006
Notes	• Recruitment status: open for patient inclusion • Prospective completion date: 1 May 2021

NL8633 *(Continued)*

- Sponsor: Leiden University Medical Center
- www.trialregister.nl/trial/8633

PACTR202006760881890

Study name	Lagos COVID-19 convalescent plasma trial (LACCPT)
Methods	• Trial design: RCT • Sample size: 100 • Setting: Inpatient • Country: Nigeria • Language: English • Number of centres: 6 • Trial registration number: PACTR202006760881890 • Date of registration: 24 June 2020

Participants	• Inclusion criteria
	  ○ Adults > 18 years
	  ○ Moderate to severe COVID-19 disease confirmed by PCR
	  ○ Agrees to the collection of NP and oropharyngeal swabs, sputum and venous blood per protocol
	  ○ Illness of any duration, and at least 1 of the following:
	  ■ > 50% radiographic infiltrates by imaging (chest x-ray, CT scan, etc)
	  ■ clinical assessment (evidence of rales/crackles on exam) and $SpO_2 \leq 94\%$ on room air
	  ■ requiring mechanical ventilation and/or supplemental oxygen
	  ○ If female of childbearing age, should agree to use at least one primary form of contraception for the duration of the study (acceptable methods will be determined by the site)
	• Exclusion criteria
	  ○ ALT/AST > 5 x ULN
	  ○ Stage 4 severe CKD or requiring dialysis (i.e. eGFR < 30)
	  ○ Pregnancy or lactation
	  ○ Anticipated transfer to another hospital which is not a study site within 72 h
	  ○ Allergy to any study medication
	• Donor eligibility criteria NR
	• Donor exclusion criteria NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: 200 ml
	  ○ number of doses: 2
	  ○ antibody-titre: NR
	  ○ pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• Comparator: saline with multivitamin
	• Concomitant therapy: SC
	• Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ SARS-CoV-2 detectable in NP, orophangyeal or sputum samples at days 1, 3, 5, 7, 9, & 11
	  ○ Clinical status at day 11 (7-point ordinal scale)
	• Primary review outcomes reported

PACTR202006760881890 *(Continued)*

- All-cause mortality during hospital stay: yes
- Time to death: NR

- Secondary review outcomes reported
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: yes
  - Number of participants with SAEs: yes
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
  - 30-day and 90-day mortality: NR
  - Admission on the ICU: NR
  - Length of stay on the ICU: NR
  - Time to discharge from hospital: NR
  - QoL: NR
  - Virological response: yes
- Additional outcomes
  - Changes in laboratory safety indices assessed on Days 1, 5 and 11 (except for D-dimer, which will be assessed on days 1, 3, 5, 7 and 11)

Starting date	24 September 2020
Contact information	• **Full Name:** Akin Abayomi • **Zip Code:** NR • **City:** Ikeja • **Address:** Block 4, State Secretariat, Alausa • **Telephone:** +2349031101982 • **Email:** profakinabayomi@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 30 November 2020 • Sponsor/funding: Lagos State Government

PACTR202007653923168

Study name	A clinical trial comparing use of convalescent plasma therapy plus standard treatment to standard treatment alone in patients with severe COVID-19 infection
Methods	• Trial design: RCT • Sample size: 206 • Setting: Inpatient • Country: Kenya • Language: English • Number of centres: 1 • Trial registration number: PACTR202007653923168 • Date of registration: 16 July 2020

Participants	• Inclusion criteria
	  ◦ Adults > 18 years with confirmed diagnosis of COVID-19
	  ◦ Severe disease defined as oxygen saturation ≤ 93 in resting state and PaO_2/FiO_2 ≤ 300 mmHg
	• Exclusion criteria
	  ◦ History of allergic reaction to blood or blood products
	  ◦ Participation in other clinical trials

PACTR202007653923168 *(Continued)*

- Known IgA deficiency
- Medical conditions in which receipt of 350 mL volume may be detrimental to the patient (e.g. decompensated congestive heart failure, renal failure)
- Pregnancy or lactation

- Donor eligibility criteria
  - Confirmation of previous infection with SARS-CoV-2 by a record of RT-PCR test result
  - At least 2 negative RT-PCR tests after recovery
  - An interval of at least 14 days after initial illness which is assumed to be the day when the patient had a positive RT-PCR test for SARS-COV-2
  - Age (> 18 years)
  - Weight (> 50 kg)
  - At least 3 months since last donation
  - Vital signs within normal ranges
  - Non-reactivity of blood samples for transfusion-transmitted infections including HIV, HBV, HCV, syphilis (for whole blood) and malaria
  - To avoid the risk of TRALI, preference will be given to use of plasma from male donors or from female donors who have never been pregnant including abortions
- Donor exclusion criteria
  - Patients aged < 18 years of age
  - Symptomatic patients with COVID-19
  - Fever of unknown origin
  - Anaemic patients, underweight (< 50 kg), chronic diseases such as HIV, hepatitis B and C, cancers, uncontrolled hypertension
  - Women who have given birth or had an abortion

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: 350 ml
	  ○ number of doses: 1
	  ○ antibody-titre: NR
	  ○ pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): transfused over 4 h
	• Comparator: SC
	• Concomitant therapy: SC
	• Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ Safety of CP therapy
	  ○ Time to clinical improvement: time to decline 2 categories on WHO score (28 days)
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: yes, mortality up to 28 days
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: yes
	  ○ Number of participants with SAEs: yes
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  ○ 30-day and 90-day mortality: NR (28 days)
	  ○ Admission on the ICU: yes
	  ○ Length of stay on the ICU: yes

PACTR202007653923168 *(Continued)*

- Time to discharge from hospital: yes
- QoL: NR
- Virological response: yes, time to negative SARS-COV-2 RT-PCR

- Additional outcomes: duration of severe illness based on SOFA score

Starting date	1 August 2020
Contact information	• **Full Name:** Isaac Adembesa • **Zip Code:** 00100 • **City:** Nairobi • **Address:** Kenyatta University Teaching Referral and Research Hospital, 7674, Nairobi • **Telephone:** +254720949430 • **Email:** kadembesa@yahoo.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31 December 2020 • Sponsor/funding: Kenyatta University Teaching Referral and Research Hospital

PER-013-20

Study name	Convalescent plasma as treatment for COVID-19
Methods	• Trial design: RCT • Sample size: 192 • Setting: Inpatient • Country: Peru • Language: English • Number of centres: 1 • Trial registration number: PER-013-20 • Date of registration: 25 June 2020

Participants	• Inclusion criteria
	  ◦ Adults > 18 years with confirmed diagnosis of COVID-19
	  ◦ Patients at risk of progression with ≥ 2 of the following:
	  ■ ferritin > 500 ng/mL
	  ■ D-dimer > 1 mg/L
	  ■ CRP > 15 mg/L
	  ■ total lymphocytes < 1000/mm3
	  ■ neutrophil/lymphocyte ratio > 3.13
	  ◦ Admission to ICU for management of COVID-19 or ≥ 2 of the following:
	  ■ dyspnoea
	  ■ respiratory rate ≥ 30/min
	  ■ oxygen saturation < 93%
	  ■ $PO_2/FioO_2$ < 300
	  ■ lung infiltrates > 50% in chest X-ray or
	  ■ Chest CT scan with increasing compromise in a 24-48-h period
	• Exclusion criteria
	  ◦ Previous transfusion of any haemoderivate in the 120 days prior to CP administration
	  ◦ Pregnancy
	• Donor eligibility criteria NR
	• Donor exclusion criteria NR

PER-013-20 *(Continued)*

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: NR
	  ○ number of doses: NR
	  ○ antibody-titre: NR
	  ○ pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): Day 1 after randomisation
	• Comparator: SC
	• Concomitant therapy: SC
	• Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ Oxygen requirement (14 days, 28 days)
	  ○ Ventilation requirement (14 days, 28 days)
	  ○ Mortality (14 days, 28 days, 56 days)
	  ○ AEs (28 days)
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: yes
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
	  ○ Number of participants with SAEs: yes
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  ○ 30-day and 90-day mortality: 30 days yes; 90 days NR
	  ○ Admission on the ICU: NR
	  ○ Length of stay on the ICU: NR
	  ○ Time to discharge from hospital: NR
	  ○ QoL: NR
	  ○ Virological response: NR
	• Additional outcomes: time to ventilation

Starting date	19 September 2020
Contact information	• **Full Name:** Martin Oyanguren Miranda • **Zip Code:** • **City:** Lima • **Address:** Hospital Nacional Edgardo Rebagliati Martins, Caminos del Inca, Jesus María • **Telephone:** 952393544 • **Email:** Bettochunga17@hotmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: NR • Sponsor/funding: Seguro Social De Salud- Essalud

PER-060-20

Study name	Randomized phase 2 clinical trial to evaluate safety and efficacy of the use of plasma from convalescent patients with the new coronavirus disease (COVID-19) for the experimental treatment of patients hospitalized in the Centro Médico Naval 'Cirujano Mayor Santiago Távara'
Methods	• Trial design: RCT • Sample size: 100 • Setting: hospitalised patients • Country: Peru • Language: English • Number of centres: 1 • Trial registration number: PER-060-20 • Date of registration: 21 September 2020

Participants	• Inclusion criteria
	  ○ Adults > 18 years with diagnosis of COVID-19
	  ○ Diagnosis of moderate to severe ARDS according to the definition of the Berlin criteria < 10 days
	  ○ Mechanical ventilation or continuous oxygenation at positive pressure
	• Exclusion criteria
	  ○ Diagnosis of mild ARDS according to the definition of the Berlin criteria
	  ○ Diagnosis of moderate to severe ARDS, > 10 days
	  ○ Demonstrated hypersensitivity or history of allergy to blood products or immunoglobulins
	  ○ Pregnancy or lactation
	• Donor eligibility criteria NR
	• Donor exclusion criteria NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ○ type of plasma: CP
	  ○ volume: 200 ml
	  ○ number of doses: up to 2
	  ○ antibody-titre: NR
	  ○ pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): repeat dose given after 24 h, if required
	• Comparator: SC
	• Concomitant therapy: SC
	• Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ Mortality (60 days)
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: NR
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: yes
	  ○ Number of participants with SAEs: yes
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  ○ 30-day and 90-day mortality: NR
	  ○ Admission on the ICU: NR
	  ○ Length of stay on the ICU: NR

PER-060-20 *(Continued)*

- Time to discharge from hospital: yes
- QoL: NR
- Virological response: NR

- Additional outcomes: NR

Starting date	19 October 2020
Contact information	• **Full Name:** Mario Ortiz Mondragón • **Zip Code:** 20153408191 • **City:** Lima • **Address:** Marina de Guerra del Perú, Av. La Marina Cdra 36 Nro. S/N Cuartel La Perla (Av. La Marina Cdra. 36 Esq. Insurgentes) • **Telephone:** 2078900 Anx 1400 / 1401 • **Email:** ortiz60marina51@hotmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: NR • Sponsor/funding: Marina De Guerra Del Perú

RBR-7jqpnw

Study name	Therapeutic effectiveness of COVID-19 convalescent plasma produced by HEMOPE: a multicenter, randomized and controlled clinical trial
Methods	• Trial design: RCT • Sample size: 220 • Setting: hospitalised patients • Country: Brazil • Language: Portuguese/English • Number of centres: 77 • Trial registration number: U1111-1254-0612 • Date of registration: 22 June 2020

Participants	• Inclusion criteria
	  ◦ Adults > 18 years with diagnosis of COVID-19, who are hospitalised; and considered as having a condition that increases the risk of a worse prognosis: obesity; diabetes mellitus; systemic arterial hypertension; chronic lung disease, obesity, diseases that alter immunity (AIDS, neoplasms or autoimmune diseases in immunosuppressive therapy), chronic liver disease
	• Exclusion criteria
	  ◦ History of anaphylactic reaction related to blood transfusion
	• Donor eligibility criteria NR
	• Donor exclusion criteria NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  ◦ type of plasma: CP
	  ◦ volume: NR
	  ◦ number of doses: NR
	  ◦ antibody-titre: NR
	  ◦ pathogen inactivated: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• Comparator: SC

RBR-7jqpnw *(Continued)*

	• Concomitant therapy: SC • Treatment cross-overs: nil

Outcomes	• Primary study outcome
	  ○ Mortality
	• Primary review outcomes reported
	  ○ All-cause mortality during hospital stay: yes
	  ○ Time to death: NR
	• Secondary review outcomes reported
	  ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
	  ○ Number of participants with SAEs: NR
	  ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  ○ 30-day and 90-day mortality: yes
	  ○ Admission on the ICU: yes
	  ○ Length of stay on the ICU: yes
	  ○ Time to discharge from hospital: yes
	  ○ QoL: NR
	  ○ Virological response: NR
	• Additional outcomes: NR

Starting date	1 July 2020
Contact information	• **Full Name:** Democritus of Barros Miranda Filho • **Zip Code:** 55100-130 • **City:** Recife / Brazil • **Address:** Rua Arnóbio Marques, 310, Santo Amaro • **Telephone:** +55 081 999764712 • **Email:** demofilho@gmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: NR • Sponsor/funding: University of Pernambuco

ADL: activities of daily living; **AE**: adverse event; **ALT**: alanine transaminase; **ANC:** absolute neutrophil count; **ARDS**: acute respiratory distress syndrome; **AST**: aspartate transaminase; **BAL**: bronchoalveolar lavage; **BAT**: best available therapy; **B(i)PAP:** bi-level positive airway pressure; **BMI**: body mass index; **BP:** blood pressure; **CDC**: Centers for Disease Control and Prevention; **COI**: conflict of interest; **COPD**: chronic obstructive pulmonary disease; **CAP**: community-acquired pneumonia; **CLIA:** chemiluminescent immunoassay; **CP**: convalescent plasma; **CPAP**: continuous positive airway pressure; **CPK**: creatine phosphokinase; **CRP**: C-reactive protein; **CT**: computed tomography; **DBP:** diastolic blood pressure; **DIC:** disseminated intravascular coagulation; **DFPP**: double-filtration plasmapheresis; **DIC**: disseminated intravascular coagulation; **DMARD:** disease-modifying anti-rheumatic drug; **DVT**: deep vein thrombosis; **ECG:** electrocardiogram; **ECMO**: extracorporeal membrane oxygenation; **ED**: emergency department; **FDA**: US Food and Drug Administration; **FFP**: fresh frozen plasma; **FiO_2**: fractional inspired oxygen; **GFR**: glomerular filtration rate; **HBV/HCV**: hepatitis B/C; **HCPOA**: healthcare power of attorney; **HLA**: human leukocyte antigen; **HNA:** human neutrophil antigens; **ICU**: intensive care unit; **IgA (B/G/M)**: immunoglobulin A (B/G/M); **IL-6**: interleukin-6; **IMV:** invasive mechanical ventilation; **IV**: intravenous; **IVIG**: intravenous immunoglobulin; **LAMP:** loop-mediated isothermal amplification; **LAR**: legal authorised representative; **LDH**: lactate dehydrogenase; **MAP:** mean arterial pressure; **MCU:** medium care unit; **NR**: not reported; **NYHA**: New York Heart Association; **PaO_2**: arterial blood oxygen partial pressure; **PCR**: polymerase chain reaction; **PE**: pulmonary embolism; **QoL**: quality of life; **RCT**: randomised controlled trial; **RF:** respiratory failure; **RNA**: ribonucleic acid; **RRT:** renal replacement therapy; **RT-PCR**: reverse transcription polymerase chain reaction; **SAE**: serious adverse event; **SARS**: severe acute respiratory syndrome; **SBP:** systolic blood pressure; **SC**: standard care; **SOFA**: Sequential Organ Failure Assessment; **SP:** standard plasma; **SpO_2**: peripheral capillary oxygen saturation; **SRD**: severe respiratory disease; **TACO**: transfusion-associated circulatory overload; **TAD**: transfusion-associated dyspnoea; **TB**: tuberculosis; **TRALI**: transfusion-related acute lung injury;

TTP: thrombotic thrombocytopenic purpura; **UIP**: usual interstitial pneumonia; **ULN**: upper limit of normal; **WBC**: white blood cell; **WHO**: World Health Organization

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Individuals with moderate disease						
AlQahtani 2021	✓	✓	✓	✓	~	~
Simonovich 2020	✓	✓	✓	✓	✓	✓
Avendano-Sola 2021	✓	✓	✓	✓	✓	✓
Holm 2021	✓	✓	✓	✓	~	~
Menichetti 2021	✓	✓	✓	✓	✓	✓
Agarwal 2020	✓	~	✓	✓	✓	~
Korley 2021	✗	✓	✓	✓	✓	✗
Kirenga 2021	✓	✓	✓	✓	✓	✓
Subgroup 1.1.2 Individuals with severe disease						
Li 2020	✓	✓	✓	✓	✓	✓
Estcourt 2021	✓	✓	✓	✓	✓	✓
Bar 2021	~	✓	✓	✓	✓	~
De Santis 2022	~	✓	✓	✓	✓	~
Subgroup 1.1.3 Individuals with moderate to severe disease						
Ray 2022	~	✓	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Van den Berg 2022	✓	✓	✓	✓	✓	✓
Horby 2021b	✓	✓	✓	✓	✓	✓
Begin 2021	✓	✓	✓	✓	✓	✓
Sekine 2021	✓	✓	✓	✓	✓	✓
Koerper 2021	✓	✓	✓	✓	✓	✓
Ortigoza 2022	✓	✓	✓	✓	✓	✓
Devos 2021	✓	✓	✓	✓	✓	✓
Gharbharan 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.2 All-cause mortality at up to day 60

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.2.1 Individuals with moderate to severe disease						
Koerper 2021	✓	✓	✓	✓	✓	✓
Pouladzadeh 2021	✓	✓	✓	✓	~	~
Subgroup 1.2.2 Individuals with severe disease						
De Santis 2022	~	✓	✓	✓	✓	~

Risk of bias for analysis 1.3 All-cause mortality (time to event)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.3.1 Individuals with moderate disease						
Avendano-Sola 2021	✓	✓	✓	✓	✓	✓
Kirenga 2021	✓	✓	✓	✓	✓	✓
Menichetti 2021	✓	✓	✓	✓	✓	✓
Simonovich 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.3.2 Individuals with severe disease						
Bar 2021	~	✓	✓	✓	✓	~
De Santis 2022	~	✓	✓	✓	✓	~
Estcourt 2021	✓	✓	✓	✓	✓	✓
Li 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.3.3 Individuals with moderate to severe disease						
Begin 2021	✓	✓	✓	✓	✓	✓
Devos 2021	✓	✓	✓	✓	✓	✓
Gharbharan 2021	✓	~	✓	✓	✓	~
Horby 2021b	✓	✓	✓	✓	✓	✓
Koerper 2021	✓	✓	✓	✓	✓	✓
Ray 2022	~	✓	✓	✓	~	~
Sekine 2021	✓	✓	✓	✓	✓	✓
Van den Berg 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 All-cause mortality during hospital stay

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.4.1 Individuals with moderate disease						
Agarwal 2020	✓	~	✓	✓	✓	~
AlQahtani 2021	✓	✓	✓	✓	✓	✓
Subgroup 1.4.2 Individuals with severe disease						
Estcourt 2021	✓	✓	✓	✓	✓	✓
Gharbharan 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.5 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.5.1 Individuals with moderate disease						
Agarwal 2020	✓	~	✓	✓	✓	~
Korley 2021	✗	✓	✓	✓	✓	✗
Simonovich 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.5.2 Individuals with severe disease						
Estcourt 2021	✓	✓	✓	✓	✓	✓
Subgroup 1.5.3 Individuals with moderate to severe disease						
Begin 2021	✓	✓	✓	✓	✓	✓
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.6 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.6.1 Individuals with moderate disease						
Simonovich 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.6.2 Individuals with severe disease						
Li 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.6.3 Individuals with moderate to severe disease						
Devos 2021	✓	✓	✓	✓	✓	✓
Gharbharan 2021	✓	~	✓	✓	~	~
Horby 2021b	✓	✓	✓	✓	✓	✓
Sekine 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.7 Quality of life, assessed with standardised scales at day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Devos 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.8 Any grade adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Holm 2021	✓	✓	✓	~	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Kirenga 2021	✓	✓	~	~	✓	~
Koerper 2021	✓	✓	✓	~	✓	~
Ortigoza 2022	✓	✓	✓	✓	✓	✓
Sekine 2021	✓	✓	✓	~	✓	~
Simonovich 2020	✓	✓	✓	✓	✓	✓
Van den Berg 2022	✓	✓	✓	~	~	~

Risk of bias for analysis 1.9 Grades 1-2 adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sekine 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.10 Grades 3 and 4 adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.10.1 Individuals with moderate disease						
Agarwal 2020	✓	~	✓	~	✓	~
AlQahtani 2021	✓	✓	✓	~	✓	~
Menichetti 2021	✓	✓	✓	~	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Simonovich 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.10.2 Individuals with moderate to severe disease						
Begin 2021	✓	✓	✓	~	✓	~
Sekine 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.11 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.11.1 Individuals with moderate disease						
Simonovich 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.11.2 Individuals with moderate to severe disease						
Bar 2021	~	✓	✓	~	✓	~
Begin 2021	✓	✓	✓	~	✓	~
Devos 2021	✓	✓	✓	~	✓	~
Estcourt 2021	✓	✓	✓	~	✓	~
Koerper 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.12 Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving participants, for subgroups of participants requiring invasive mechanical ventilation at baseline

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gharbharan 2021	✓	~	✓	✓	✓	~
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.13 Clinical improvement: ventilator-free days by day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Begin 2021	✓	✓	✓	✓	✓	✓
De Santis 2022	~	✓	✓	✓	✓	~

Risk of bias for analysis 1.14 Clinical improvement: liberation from supplemental oxygen in surviving participants, for subgroup of participants requiring any supplemental oxygen or ventilator support at baseline

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Devos 2021	✓	✓	✓	✓	✓	✓
Gharbharan 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.16 Admission to the intensive care unit (ICU)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Devos 2021	✓	✓	✓	✓	✓	✓
Simonovich 2020	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.18 Viral clearance at up to day 3

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Agarwal 2020	✓	~	~	✗	✓	✗
Hamdy Salman 2020	✓	✓	✓	✓	~	~
Kirenga 2021	✓	✓	✓	✓	✓	✓
Li 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.19 Viral clearance at up to day 7

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Agarwal 2020	✓	~	~	✗	✓	✗
Kirenga 2021	✓	✓	✓	✓	✓	✓
Li 2020	✓	✓	✓	✓	✓	✓
Sekine 2021	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.20 Viral clearance at up to day 14

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Kirenga 2021	✓	✓	✓	✓	✓	✓
Li 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.1.1 Individuals with moderate disease						
Baldeon 2022	~	✓	✓	✓	✓	~
Subgroup 2.1.2 Individuals with moderate to severe disease						
Bajpai 2020	✓	✓	✓	✓	✓	✓
Bennett-Guerrero 2021	✓	✓	✓	✓	✓	✓
O'Donnell 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.2 All-cause mortality (time to event)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Bajpai 2020	✓	✓	✓	✓	✓	✓
Baldeon 2022	~	✓	✓	✓	✓	~
Bennett-Guerrero 2021	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
O'Donnell 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.3 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
NCT04421404	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.4 Duration of hospitalisation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Bajpai 2020	✓	✓	✓	✓	✓	✓
Baldeon 2022	~	✓	✓	✓	✓	~

Risk of bias for analysis 2.5 Any grade adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
NCT04421404	✓	✓	✓	✓	✓	✓
O'Donnell 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.6 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.6.1 Individuals with moderate to severe disease						
Bennett-Guerrero 2021	✓	✓	✓	~	~	~
NCT04421404	✓	✓	✓	✓	✓	✓
O'Donnell 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beltran Gonzalez 2021	~	✓	✓	✓	✓	~

Risk of bias for analysis 3.2 All-cause mortality (time to event)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beltran Gonzalez 2021	~	✓	✓	✓	✓	~

Risk of bias for analysis 3.3 All-cause mortality during hospital stay

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beltran Gonzalez 2021	~	✓	✓	✓	✓	~

Risk of bias for analysis 4.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alemany 2022	✓	✓	✓	✓	✓	✓
Libster 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.2 All-cause mortality at up to day 60

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alemany 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.3 Admission to hospital or death within 28 days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alemany 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.4 Time to symptom resolution

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alemany 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.5 Clinical worsening: need for hospitalisation with at least need of oxygen by mask or nasal prongs, or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alemany 2022	✓	✓	✓	✓	✓	✓
Libster 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.6 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alemany 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.7 Clinical worsening: need for invasive mechanical ventilation or death at up to day 60

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alemany 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.8 Grades 3 and 4 adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alemany 2022	✓	✓	✓	~	✓	~

Risk of bias for analysis 4.9 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alemany 2022	✓	✓	✓	~	✓	~

Risk of bias for analysis 5.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
CoV-Early	~	✓	~	✓	✓	~
Sullivan 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.2 Admission to hospital or death within 28 days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
CoV-Early	~	✓	~	~	✓	~
Sullivan 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.3 All initial symptoms resolved (asymptomatic) at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
CoV-Early	~	✓	~	~	✓	~

Risk of bias for analysis 5.4 All initial symptoms resolved (asymptomatic) at up to day 14

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
CoV-Early	~	✓	~	~	✓	~

Risk of bias for analysis 5.5 Clinical worsening: need for hospitalisation with need of at least oxygen by mask or nasal prongs, or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sullivan 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.6 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
CoV-Early	~	✓	~	~	✓	~

Risk of bias for analysis 6.1 All-cause mortality at up to day 28 (random-effects analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 6.1.1 Antibodies detected at baseline						
Avendano-Sola 2021	✓	✓	✓	✓	✓	✓
Bar 2021	~	✓	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Estcourt 2021	✓	✓	✓	✓	✓	✓
Horby 2021b	✓	✓	✓	✓	✓	✓
Ortigoza 2022	✓	✓	✓	✓	✓	✓
Subgroup 6.1.2 No antibodies detected at baseline						
Avendano-Sola 2021	✓	✓	✓	✓	✓	✓
Bar 2021	~	✓	✓	✓	✓	~
Estcourt 2021	✓	✓	✓	✓	✓	✓
Horby 2021b	✓	✓	✓	✓	✓	✓
Ortigoza 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.3 Clinical worsening: need for invasive mechanical ventilation or death (random-effects model)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 6.3.1 Antibodies detected at baseline						
Agarwal 2020	✓	~	✓	✓	✓	~
Horby 2021b	✓	✓	✓	✓	✓	✓
Subgroup 6.3.2 No antibodies detected at baseline						
Agarwal 2020	✓	~	✓	✓	✓	~
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.4 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 6.4.1 Antibodies detected at baseline						
Horby 2021b	✓	✓	✓	✓	✓	✓
Subgroup 6.4.2 No antibodies detected at baseline						
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.1 All-cause mortality at up to day 28 (random-effects model)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 7.1.1 Duration of symptom onset up to and including 7 days						
Gharbharan 2021	✓	~	✓	✓	✓	~
Horby 2021b	✓	✓	✓	✓	✓	✓
Korley 2021	✗	✓	✓	✓	✓	✗
Subgroup 7.1.2 Duration of symptom onset more than 7 days						
De Santis 2022	~	✓	✓	✓	~	~
Gharbharan 2021	✓	~	✓	✓	✓	~
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.2 All-cause mortality (time to event) (random-effects model)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 7.2.1 Duration of symptom onset more than 7 days						
De Santis 2022	~	✓	✓	✓	✓	~

Risk of bias for analysis 7.3 Clinical worsening: need for invasive mechanical ventilation or death (random-effects model)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 7.3.1 Duration of symptom onset up to and including 7 days						
Horby 2021b	✓	✓	✓	✓	✓	✓
Korley 2021	✗	✓	✓	✓	✓	✗
Subgroup 7.3.2 Duration of symptom onset more than 7 days						
Begin 2021	✓	✓	✓	✓	✓	✓
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.4 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 7.4.1 Duration of symptom onset up to 7 days						
Gharbharan 2021	✓	~	✓	✓	~	~
Horby 2021b	✓	✓	✓	✓	✓	✓
Subgroup 7.4.2 Duration of symptom onset more than 7 days						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gharbharan 2021	✓	~	✓	✓	~	~
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 8.1 All-cause mortality at up to day 28 (random-effects analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 8.1.1 Duration of symptom onset up to and including 7 days						
O'Donnell 2021	✓	✓	✓	✓	✓	✓
Subgroup 8.1.2 Duration of symptom onset more than 7 days						
O'Donnell 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 9.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 9.1.1 Duration of symptom onset up to and including 7 days						
CoV-Early	~	✓	~	✓	✓	~
Subgroup 9.1.2 Duration of symptom onset more than 7 days						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 9.2 Admission to hospital or death within 28 days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 9.2.1 Duration of symptom onset up to and including 7 days						
CoV-Early	~	✓	~	~	✓	~
Subgroup 9.2.2 Duration of symptom onset more than 7 days						
CoV-Early	~	✓	~	~	✓	~

Risk of bias for analysis 9.3 All initial symptoms resolved (asymptomatic) at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 9.3.1 Duration of symptom onset up to and including 7 days						
CoV-Early	~	✓	~	✓	✓	~
Subgroup 9.3.2 Duration of symptom onset more than 7 days						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 10.1 All-cause mortality at up to day 28 (random-effects model)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 10.1.1 Immunosuppression (immune deficiency and cancer)						
Bar 2021	~	✓	✓	✓	✓	~
Estcourt 2021	✓	✓	✓	✓	✓	✓
Gharbharan 2021	✓	~	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 10.1.2 No immunosuppression (immune deficiency and cancer)						
Bar 2021	~	✓	✓	✓	✓	~
Estcourt 2021	✓	✓	✓	✓	✓	✓
Gharbharan 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 10.2 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 10.2.1 Immunosuppression (immune deficiency and cancer)						
Gharbharan 2021	✓	~	✓	✓	~	~
Subgroup 10.2.2 No immunosuppression (immune deficiency and cancer)						
Gharbharan 2021	✓	~	✓	✓	~	~

Risk of bias for analysis 11.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 11.1.1 No immunosuppression (immune deficiency and cancer)						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 11.2 Admission to hospital or death within 28 days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 11.2.1 No immunosuppression (immune deficiency and cancer)						
CoV-Early	~	✓	~	~	✓	~

Risk of bias for analysis 11.3 All initial symptoms resolved (asymptomatic) at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 11.3.1 No immunosuppression (immune deficiency and cancer)						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 12.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 12.1.1 Diabetes						
Bar 2021	~	✓	✓	✓	✓	~
Gharbharan 2021	✓	~	✓	✓	✓	~
Subgroup 12.1.2 No diabetes						
Bar 2021	~	✓	✓	✓	✓	~
Gharbharan 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 12.2 Clinical worsening: need for invasive mechanical ventilation or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 12.2.1 Diabetes						
Begin 2021	✓	✓	✓	✓	✓	✓
Subgroup 12.2.2 No diabetes						
Begin 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 12.3 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 12.3.1 Diabetes						
Gharbharan 2021	✓	~	✓	✓	~	~
Subgroup 12.3.2 No diabetes						
Gharbharan 2021	✓	~	✓	✓	~	~

Risk of bias for analysis 13.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 13.1.1 Diabetes						
CoV-Early	~	✓	~	✓	✓	~
Subgroup 13.1.2 No diabetes						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 13.2 Admission to hospital or death within 28 days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 13.2.1 Diabetes						
CoV-Early	~	✓	~	~	✓	~
Sullivan 2022	✓	✓	✓	✓	✓	✓
Subgroup 13.2.2 No diabetes						
CoV-Early	~	✓	~	~	✓	~
Sullivan 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 13.3 All initial symptoms resolved (asymptomatic) at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 13.3.1 Diabetes						
CoV-Early	~	✓	~	✓	✓	~
Subgroup 13.3.2 No diabetes						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 14.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 14.1.1 Pulmonary disease						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gharbharan 2021	✓	~	✓	✓	✓	✓
Subgroup 14.1.2 No pulmonary disease						
Gharbharan 2021	✓	~	✓	✓	✓	✓

Risk of bias for analysis 14.2 Clinical worsening: need for invasive mechanical ventilation or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 14.2.1 Respiratory disease						
Begin 2021	✓	✓	✓	✓	✓	✓
Subgroup 14.2.2 No respiratory disease						
Begin 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 14.3 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 14.3.1 Pulmonary disease						
Gharbharan 2021	✓	~	✓	✓	~	~
Subgroup 14.3.2 No pulmonary disease						
Gharbharan 2021	✓	~	✓	✓	~	~

Risk of bias for analysis 15.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 15.1.1 Hypertension						
Bar 2021	~	✓	✓	✓	✓	~
Gharbharan 2021	✓	~	✓	✓	✓	~
Subgroup 15.1.2 No hypertension						
Bar 2021	~	✓	✓	✓	✓	~
Gharbharan 2021	✓	~	✓	✓	✓	~

Risk of bias for analysis 15.2 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 15.2.1 Hypertension						
Gharbharan 2021	✓	~	✓	✓	~	~
Subgroup 15.2.2 No hypertension						
Gharbharan 2021	✓	~	✓	✓	~	~

Risk of bias for analysis 16.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 16.1.1 < 65 years						
Gharbharan 2021	✓	~	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 16.1.2 ≥ 65 years						
Gharbharan 2021	✓	~	✓	✓	✓	~
Subgroup 16.1.3 ≤ 60 years						
Bar 2021	~	✓	✓	✓	✓	~
Subgroup 16.1.4 > 60 years						
Bar 2021	~	✓	✓	✓	✓	~

Risk of bias for analysis 16.2 Clinical worsening: need for invasive mechanical ventilation, or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 16.2.1 < 60 years						
Begin 2021	✓	✓	✓	✓	✓	✓
Subgroup 16.2.2 ≥ 60 years						
Begin 2021	✓	✓	✓	✓	✓	✓
Subgroup 16.2.3 < 70 years						
Horby 2021b	✓	✓	✓	✓	✓	✓
Subgroup 16.2.4 ≥ 70 years						
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 16.3 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 16.3.1 < 65 years						
Gharbharan 2021	✓	~	✓	✓	~	~
Subgroup 16.3.2 ≥ 65 years						
Gharbharan 2021	✓	~	✓	✓	~	~
Subgroup 16.3.3 < 70 years						
Horby 2021b	✓	✓	✓	✓	✓	✓
Subgroup 16.3.4 > 70 years						
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 17.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 17.1.1 < 65 years						
CoV-Early	~	✓	~	✓	✓	~
Subgroup 17.1.2 ≥ 65 years						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 17.2 Admission to hospital or death within 28 days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 17.2.1 < 65 years						
CoV-Early	~	✓	~	~	✓	~
Sullivan 2022	✓	✓	✓	✓	✓	✓
Subgroup 17.2.2 ≥ 65 years						
CoV-Early	~	✓	~	~	✓	~
Sullivan 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 17.3 All initial symptoms resolved (asymptomatic) at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 17.3.1 < 65 years						
CoV-Early	~	✓	~	✓	✓	~
Subgroup 17.3.2 ≥ 65 years						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 18.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 18.1.1 Female						
Bar 2021	~	✓	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gharbharan 2021	✓	~	✓	✓	✓	~
Subgroup 18.1.2 Male						
Bar 2021	~	✓	✓	✓	✓	~
Gharbharan 2021	✓	~	✓	✓	✓	~
Kirenga 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 18.2 Clinical worsening: need for invasive mechanical ventilation or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 18.2.1 Female						
Begin 2021	✓	✓	✓	✓	✓	✓
Horby 2021b	✓	✓	✓	✓	✓	✓
Menichetti 2021	✓	✓	✓	✓	✓	✓
Subgroup 18.2.2 Male						
Begin 2021	✓	✓	✓	✓	✓	✓
Horby 2021b	✓	✓	✓	✓	✓	✓
Menichetti 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 18.3 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 18.3.1 Female						
Gharbharan 2021	✓	~	✓	✓	~	~
Horby 2021b	✓	✓	✓	✓	✓	✓
Subgroup 18.3.2 Male						
Gharbharan 2021	✓	~	✓	✓	~	~
Horby 2021b	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 19.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 19.1.1 Female						
CoV-Early	~	✓	~	✓	✓	~
Subgroup 19.1.2 Male						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 19.2 Admission to hospital or death within 28 days

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 19.2.1 Female						
CoV-Early	~	✓	~	~	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sullivan 2022	✓	✓	✓	✓	✓	✓
Subgroup 19.2.2 Male						
CoV-Early	~	✓	~	~	✓	~
Sullivan 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 19.3 All initial symptoms resolved (asymptomatic) at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 19.3.1 Female						
CoV-Early	~	✓	~	✓	✓	~
Subgroup 19.3.2 Male						
CoV-Early	~	✓	~	✓	✓	~

Risk of bias for analysis 20.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 20.1.1 High-income countries						
Menichetti 2021	✓	✓	✓	✓	✓	✓
Estcourt 2021	✓	✓	✓	✓	✓	✓
Bar 2021	~	✓	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Horby 2021b	✓	✓	✓	✓	✓	✓
Koerper 2021	✓	✓	✓	✓	✓	✓
Ortigoza 2022	✓	✓	✓	✓	✓	✓
Devos 2021	✓	✓	✓	✓	✓	✓
Avendano-Sola 2021	✓	✓	✓	✓	✓	✓
AlQahtani 2021	✓	✓	✓	✓	~	~
Holm 2021	✓	✓	✓	✓	~	~
Korley 2021	✗	✓	✓	✓	✓	✗
Subgroup 20.1.2 Low- to middle-income countries						
Li 2020	✓	✓	✓	✓	✓	✓
De Santis 2022	~	✓	✓	✓	✓	~
Ray 2022	~	✓	✓	✓	✓	~
Sekine 2021	✓	✓	✓	✓	✓	✓
Van den Berg 2022	✓	✓	✓	✓	✓	✓
Gharbharan 2021	✓	~	✓	✓	✓	~
Simonovich 2020	✓	✓	✓	✓	✓	✓
Agarwal 2020	✓	~	✓	✓	✓	~
Kirenga 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 20.2 Clinical worsening: need for invasive mechanical ventilation, or death at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 20.2.1 High-income countries						
Estcourt 2021	✓	✓	✓	✓	✓	✓
Horby 2021b	✓	✓	✓	✓	✓	✓
Korley 2021	✗	✓	✓	✓	✓	✗
Subgroup 20.2.2 Low- to middle-income countries						
Agarwal 2020	✓	~	✓	✓	✓	~
Simonovich 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 20.3 Clinical improvement: participants discharged from hospital

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 20.3.1 High-income countries						
Devos 2021	✓	✓	✓	✓	✓	✓
Horby 2021b	✓	✓	✓	✓	✓	✓
Subgroup 20.3.2 Low- to middle-income countries						
Gharbharan 2021	✓	~	✓	✓	~	~
Li 2020	✓	✓	✓	✓	✓	✓
Sekine 2021	✓	✓	✓	✓	✓	✓
Simonovich 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 20.4 Grades 3 and 4 adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 20.4.1 High-income countries						
AlQahtani 2021	✓	✓	✓	~	✓	~
Menichetti 2021	✓	✓	✓	~	✓	~
Subgroup 20.4.2 Low- to middle-income countries						
Agarwal 2020	✓	~	✓	~	✓	~
Sekine 2021	✓	✓	✓	~	✓	~
Simonovich 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 20.5 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 20.5.1 High-income countries						
Bar 2021	~	✓	✓	~	✓	~
Devos 2021	✓	✓	✓	~	✓	~
Estcourt 2021	✓	✓	✓	~	✓	~
Koerper 2021	✓	✓	✓	~	✓	~
Subgroup 20.5.2 Low- to middle-income countries						
Simonovich 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 21.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 21.1.1 High-income countries						
Bennett-Guerrero 2021	✓	✓	✓	✓	✓	✓
Subgroup 21.1.2 Low- to middle-income countries						
Bajpai 2020	✓	✓	✓	✓	✓	✓
Baldeon 2022	~	✓	✓	✓	✓	~

Risk of bias for analysis 21.2 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 21.2.1 High-income countries						
NCT04421404	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 21.3 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 21.3.1 High-income countries						
Bennett-Guerrero 2021	✓	✓	✓	~	~	~
NCT04421404	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 22.1 All-cause mortality at up tp day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 22.1.1 High-income countries						
Alemany 2022	✓	✓	✓	✓	✓	✓
Subgroup 22.1.2 Low- to middle-income countries						
Libster 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 22.2 Grades 3 and 4 adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 22.2.1 High-income countries						
Alemany 2022	✓	✓	✓	~	✓	~

Risk of bias for analysis 22.3 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 22.3.1 High-income countries						
Alemany 2022	✓	✓	✓	~	✓	~

Risk of bias for analysis 23.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 23.1.1 High-income countries						
CoV-Early	~	✓	~	✓	✓	~
Sullivan 2022	✓	✓	✓	✓	✓	✓

DATA AND ANALYSES

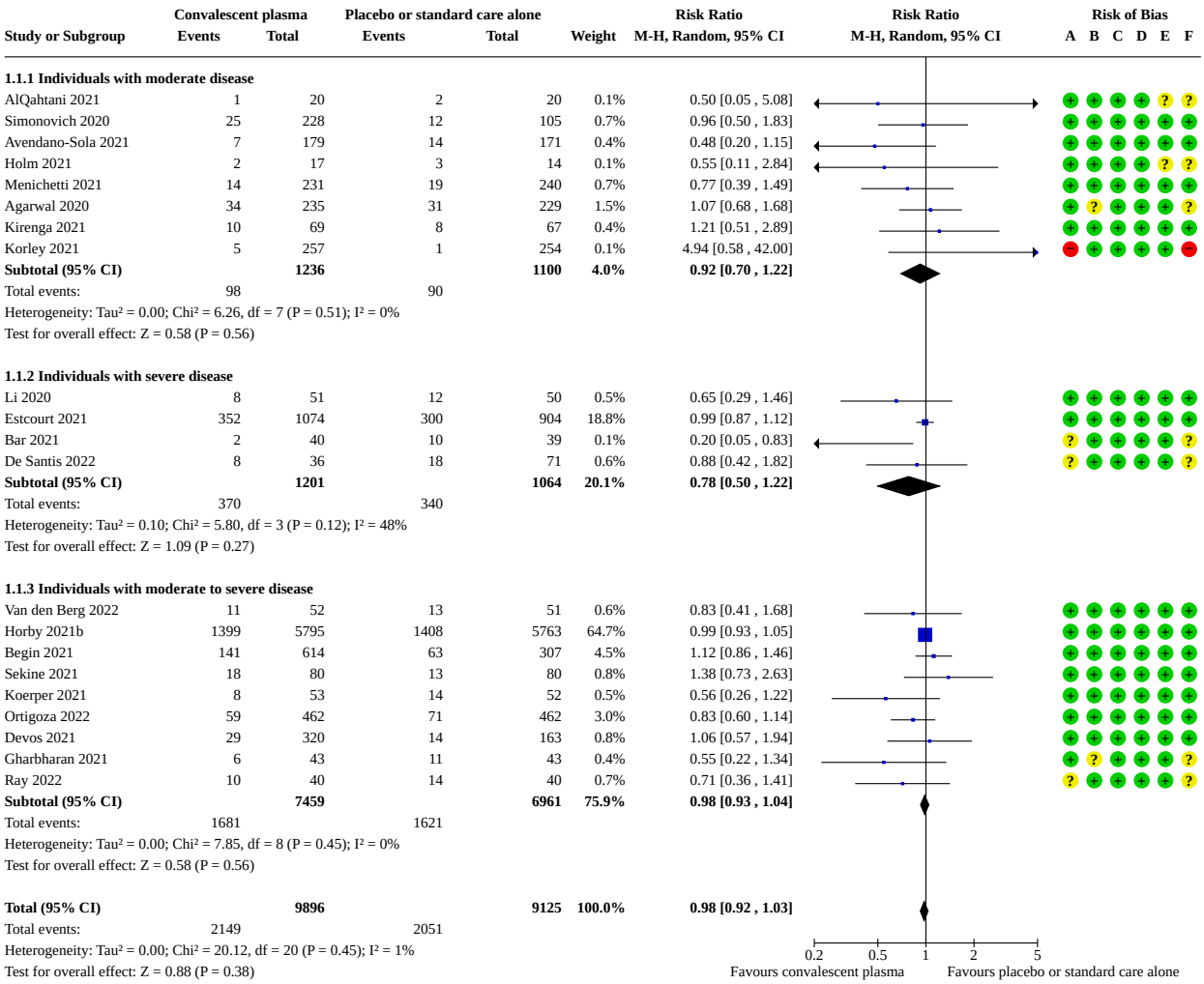
Comparison 1. Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality at up to day 28	21	19021	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.03]
1.1.1 Individuals with moderate disease	8	2336	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.70, 1.22]
1.1.2 Individuals with severe disease	4	2265	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.50, 1.22]
1.1.3 Individuals with moderate to severe disease	9	14420	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.04]
1.2 All-cause mortality at up to day 60	3	272	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.49, 1.12]
1.2.1 Individuals with moderate to severe disease	2	165	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.35, 1.13]
1.2.2 Individuals with severe disease	1	107	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.48, 1.56]
1.3 All-cause mortality (time to event)	16	17070	Hazard Ratio (IV, Random, 95% CI)	0.98 [0.92, 1.04]
1.3.1 Individuals with moderate disease	4	1290	Hazard Ratio (IV, Random, 95% CI)	0.81 [0.55, 1.19]
1.3.2 Individuals with severe disease	4	2267	Hazard Ratio (IV, Random, 95% CI)	0.77 [0.48, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.3 Individuals with moderate to severe disease	8	13513	Hazard Ratio (IV, Random, 95% CI)	0.99 [0.93, 1.07]
1.4 All-cause mortality during hospital stay	4	2556	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.08]
1.4.1 Individuals with moderate disease	2	491	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.71, 1.76]
1.4.2 Individuals with severe disease	2	2065	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.56, 1.36]
1.5 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28	6	14477	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.97, 1.11]
1.5.1 Individuals with moderate disease	3	1308	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.77, 1.43]
1.5.2 Individuals with severe disease	1	1307	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.97, 1.22]
1.5.3 Individuals with moderate to severe disease	2	11862	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.90, 1.18]
1.6 Clinical improvement: participants discharged from hospital	6	12721	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.02]
1.6.1 Individuals with moderate disease	1	333	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.12]
1.6.2 Individuals with severe disease	1	101	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.90, 2.24]
1.6.3 Individuals with moderate to severe disease	4	12287	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.02]
1.7 Quality of life, assessed with standardised scales at day 28	1	483	Mean Difference (IV, Random, 95% CI)	1.00 [-2.14, 4.14]
1.8 Any grade adverse events	7	1809	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.95, 1.17]
1.9 Grades 1-2 adverse events	1	160	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.87, 1.41]
1.10 Grades 3 and 4 adverse events	6	2392	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.96, 1.42]
1.10.1 Individuals with moderate disease	4	1311	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.43, 5.02]
1.10.2 Individuals with moderate to severe disease	2	1081	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.02, 1.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11 Serious adverse events	6	3901	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.91, 1.44]
1.11.1 Individuals with moderate disease	1	333	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.82, 2.09]
1.11.2 Individuals with moderate to severe disease	5	3568	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.85, 1.46]
1.12 Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving participants, for subgroups of participants requiring invasive mechanical ventilation at baseline	2	630	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.57, 1.93]
1.13 Clinical improvement: ventilator-free days by day 28	2	1028	Mean Difference (IV, Random, 95% CI)	-0.53 [-1.90, 0.84]
1.14 Clinical improvement: liberation from supplemental oxygen in surviving participants, for subgroup of participants requiring any supplemental oxygen or ventilator support at baseline	2	560	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.08]
1.15 Need for dialysis at up to 28 days	2	12325	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.86, 1.23]
1.16 Admission to the intensive care unit (ICU)	2	816	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.77, 1.11]
1.17 Duration of hospitalisation	2	97	Mean Difference (IV, Random, 95% CI)	-1.04 [-6.87, 4.79]
1.18 Viral clearance at up to day 3	4	619	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.76, 2.18]
1.19 Viral clearance at up to day 7	4	674	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.85, 1.79]
1.20 Viral clearance at up to day 14	2	212	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.58, 3.68]

Analysis 1.1. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



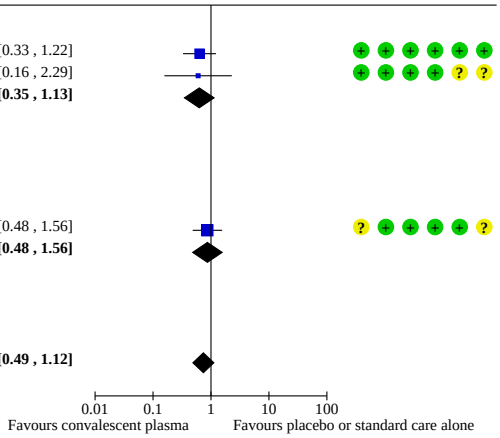
Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.1.1 Individuals with moderate disease							
AlQahtani 2021	1	20	2	20	0.1%	0.50 [0.05 , 5.08]	+ + + + ? ?
Simonovich 2020	25	228	12	105	0.7%	0.96 [0.50 , 1.83]	+ + + + + +
Avendano-Sola 2021	7	179	14	171	0.4%	0.48 [0.20 , 1.15]	+ + + + + +
Holm 2021	2	17	3	14	0.1%	0.55 [0.11 , 2.84]	+ + + + ? ?
Menichetti 2021	14	231	19	240	0.7%	0.77 [0.39 , 1.49]	+ + + + + +
Agarwal 2020	34	235	31	229	1.5%	1.07 [0.68 , 1.68]	+ ? + + + ?
Kirenga 2021	10	69	8	67	0.4%	1.21 [0.51 , 2.89]	+ + + + + +
Korley 2021	5	257	1	254	0.1%	4.94 [0.58 , 42.00]	− + + + + −
Subtotal (95% CI)		**1236**		**1100**	**4.0%**	**0.92 [0.70 , 1.22]**	
Total events:	98		90				
Heterogeneity: Tau² = 0.00; Chi² = 6.26, df = 7 (P = 0.51); I² = 0%							
Test for overall effect: Z = 0.58 (P = 0.56)							
1.1.2 Individuals with severe disease							
Li 2020	8	51	12	50	0.5%	0.65 [0.29 , 1.46]	+ + + + + +
Estcourt 2021	352	1074	300	904	18.8%	0.99 [0.87 , 1.12]	+ + + + + +
Bar 2021	2	40	10	39	0.1%	0.20 [0.05 , 0.83]	? + + + + ?
De Santis 2022	8	36	18	71	0.6%	0.88 [0.42 , 1.82]	? + + + + ?
Subtotal (95% CI)		**1201**		**1064**	**20.1%**	**0.78 [0.50 , 1.22]**	
Total events:	370		340				
Heterogeneity: Tau² = 0.10; Chi² = 5.80, df = 3 (P = 0.12); I² = 48%							
Test for overall effect: Z = 1.09 (P = 0.27)							
1.1.3 Individuals with moderate to severe disease							
Van den Berg 2022	11	52	13	51	0.6%	0.83 [0.41 , 1.68]	+ + + + + +
Horby 2021b	1399	5795	1408	5763	64.7%	0.99 [0.93 , 1.05]	+ + + + + +
Begin 2021	141	614	63	307	4.5%	1.12 [0.86 , 1.46]	+ + + + + +
Sekine 2021	18	80	13	80	0.8%	1.38 [0.73 , 2.63]	+ + + + + +
Koerper 2021	8	53	14	52	0.5%	0.56 [0.26 , 1.22]	+ + + + + +
Ortigoza 2022	59	462	71	462	3.0%	0.83 [0.60 , 1.14]	+ + + + + +
Devos 2021	29	320	14	163	0.8%	1.06 [0.57 , 1.94]	+ + + + + +
Gharbharan 2021	6	43	11	43	0.4%	0.55 [0.22 , 1.34]	+ ? + + + ?
Ray 2022	10	40	14	40	0.7%	0.71 [0.36 , 1.41]	? + + + + ?
Subtotal (95% CI)		**7459**		**6961**	**75.9%**	**0.98 [0.93 , 1.04]**	
Total events:	1681		1621				
Heterogeneity: Tau² = 0.00; Chi² = 7.85, df = 8 (P = 0.45); I² = 0%							
Test for overall effect: Z = 0.58 (P = 0.56)							
Total (95% CI)		**9896**		**9125**	**100.0%**	**0.98 [0.92 , 1.03]**	
Total events:	2149		2051				
Heterogeneity: Tau² = 0.00; Chi² = 20.12, df = 20 (P = 0.45); I² = 1%							
Test for overall effect: Z = 0.88 (P = 0.38)							
Test for subgroup differences: Chi² = 1.18, df = 2 (P = 0.55), I² = 0%							

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

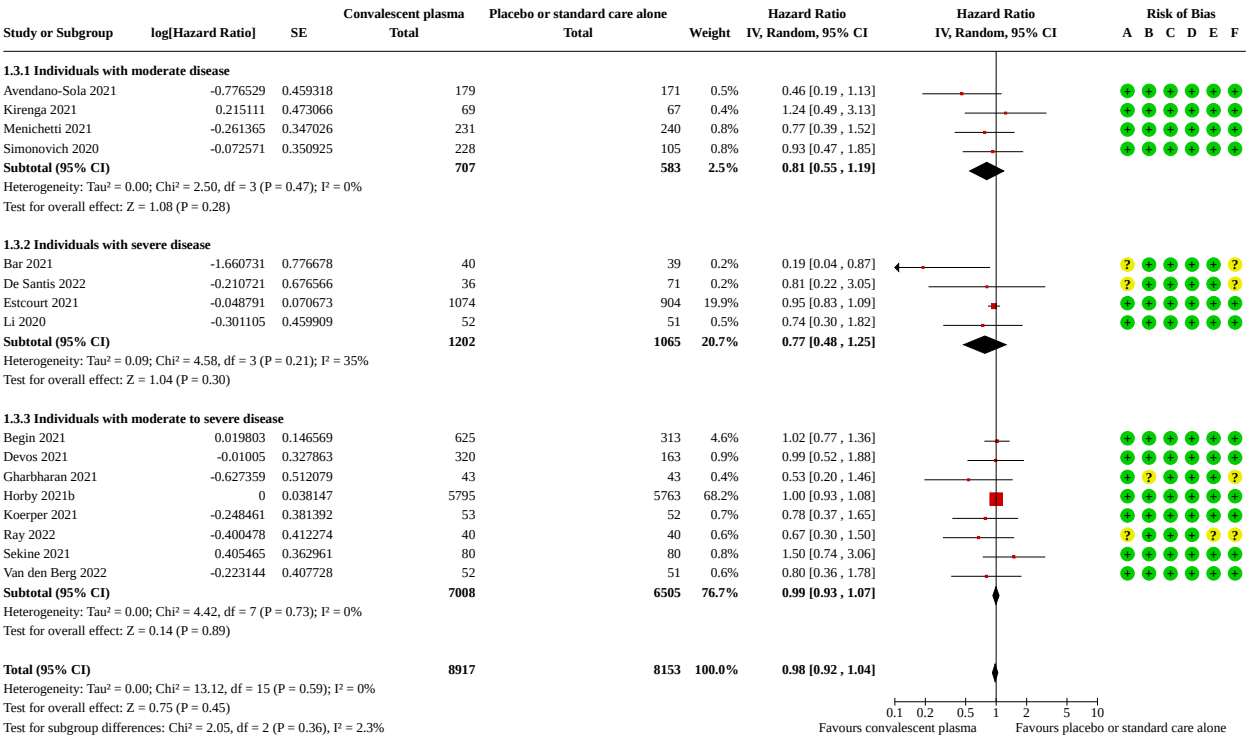
Analysis 1.2. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: All-cause mortality at up to day 60

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Individuals with moderate to severe disease						
Koerper 2021	11	53	17	52	40.1%	0.63 [0.33 , 1.22]
Pouladzadeh 2021	3	30	5	30	9.6%	0.60 [0.16 , 2.29]
Subtotal (95% CI)		**83**		**82**	**49.7%**	**0.63 [0.35 , 1.13]**
Total events:	14		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.55 (P = 0.12)						
1.2.2 Individuals with severe disease						
De Santis 2022	11	36	25	71	50.3%	0.87 [0.48 , 1.56]
Subtotal (95% CI)		**36**		**71**	**50.3%**	**0.87 [0.48 , 1.56]**
Total events:	11		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		**119**		**153**	**100.0%**	**0.74 [0.49 , 1.12]**
Total events:	25		47			
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Test for subgroup differences: Chi² = 0.58, df = 1 (P = 0.44), I² = 0%						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: All-cause mortality (time to event)

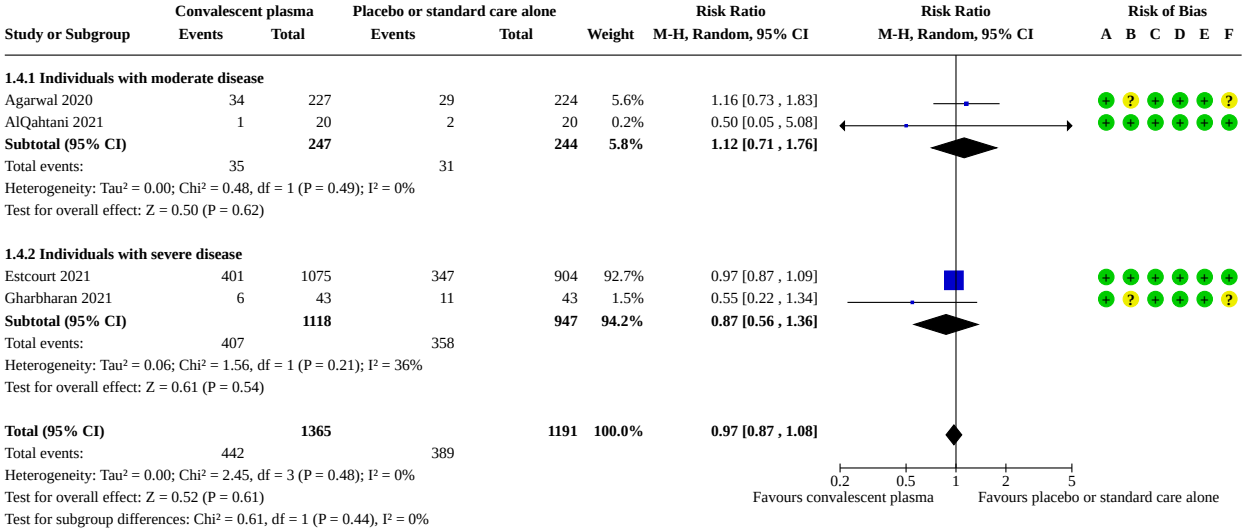


Study or Subgroup	log[Hazard Ratio]	SE	Convalescent plasma Total	Placebo or standard care alone Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
1.3.1 Individuals with moderate disease							
Avendano-Sola 2021	-0.776529	0.459318	179	171	0.5%	0.46 [0.19 , 1.13]	+ + + + + +
Kirenga 2021	0.215111	0.473066	69	67	0.4%	1.24 [0.49 , 3.13]	+ + + + + +
Menichetti 2021	-0.261365	0.347026	231	240	0.8%	0.77 [0.39 , 1.52]	+ + + + + +
Simonovich 2020	-0.072571	0.350925	228	105	0.8%	0.93 [0.47 , 1.85]	+ + + + + +
Subtotal (95% CI)			**707**	**583**	**2.5%**	**0.81 [0.55 , 1.19]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.50, df = 3 (P = 0.47); I² = 0%							
Test for overall effect: Z = 1.08 (P = 0.28)							
1.3.2 Individuals with severe disease							
Bar 2021	-1.660731	0.776678	40	39	0.2%	0.19 [0.04 , 0.87]	? + + + + ?
De Santis 2022	-0.210721	0.676566	36	71	0.2%	0.81 [0.22 , 3.05]	? + + + + ?
Estcourt 2021	-0.048791	0.070673	1074	904	19.9%	0.95 [0.83 , 1.09]	+ + + + + +
Li 2020	-0.301105	0.459909	52	51	0.5%	0.74 [0.30 , 1.82]	+ + + + + +
Subtotal (95% CI)			**1202**	**1065**	**20.7%**	**0.77 [0.48 , 1.25]**	
Heterogeneity: Tau² = 0.09; Chi² = 4.58, df = 3 (P = 0.21); I² = 35%							
Test for overall effect: Z = 1.04 (P = 0.30)							
1.3.3 Individuals with moderate to severe disease							
Begin 2021	0.019803	0.146569	625	313	4.6%	1.02 [0.77 , 1.36]	+ + + + + +
Devos 2021	-0.01005	0.327863	320	163	0.9%	0.99 [0.52 , 1.88]	+ + + + + +
Ghabrharan 2021	-0.627359	0.512079	43	43	0.4%	0.53 [0.20 , 1.46]	+ ? + + + ?
Horby 2021b	0	0.038147	5795	5763	68.2%	1.00 [0.93 , 1.08]	+ + + + + +
Koerper 2021	-0.248461	0.381392	53	52	0.7%	0.78 [0.37 , 1.65]	+ + + + + +
Ray 2022	-0.400478	0.412274	40	40	0.6%	0.67 [0.30 , 1.50]	? + + + ? ?
Sekine 2021	0.405465	0.362961	80	80	0.8%	1.50 [0.74 , 3.06]	+ + + + + +
Van den Berg 2022	-0.223144	0.407728	52	51	0.6%	0.80 [0.36 , 1.78]	+ + + + + +
Subtotal (95% CI)			**7008**	**6505**	**76.7%**	**0.99 [0.93 , 1.07]**	
Heterogeneity: Tau² = 0.00; Chi² = 4.42, df = 7 (P = 0.73); I² = 0%							
Test for overall effect: Z = 0.14 (P = 0.89)							
Total (95% CI)			**8917**	**8153**	**100.0%**	**0.98 [0.92 , 1.04]**	
Heterogeneity: Tau² = 0.00; Chi² = 13.12, df = 15 (P = 0.59); I² = 0%							
Test for overall effect: Z = 0.75 (P = 0.45)							
Test for subgroup differences: Chi² = 2.05, df = 2 (P = 0.36), I² = 2.3%							

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 4: All-cause mortality during hospital stay



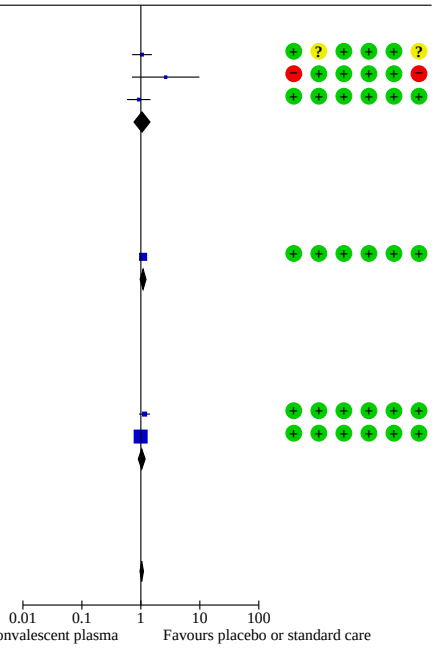
Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.4.1 Individuals with moderate disease							
Agarwal 2020	34	227	29	224	5.6%	1.16 [0.73 , 1.83]	+ ? + + + ?
AlQahtani 2021	1	20	2	20	0.2%	0.50 [0.05 , 5.08]	+ + + + + +
Subtotal (95% CI)		**247**		**244**	**5.8%**	**1.12 [0.71 , 1.76]**	
Total events:	35		31				
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%							
Test for overall effect: Z = 0.50 (P = 0.62)							
1.4.2 Individuals with severe disease							
Estcourt 2021	401	1075	347	904	92.7%	0.97 [0.87 , 1.09]	+ + + + + +
Gharbharan 2021	6	43	11	43	1.5%	0.55 [0.22 , 1.34]	+ ? + + + ?
Subtotal (95% CI)		**1118**		**947**	**94.2%**	**0.87 [0.56 , 1.36]**	
Total events:	407		358				
Heterogeneity: Tau² = 0.06; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%							
Test for overall effect: Z = 0.61 (P = 0.54)							
Total (95% CI)		**1365**		**1191**	**100.0%**	**0.97 [0.87 , 1.08]**	
Total events:	442		389				
Heterogeneity: Tau² = 0.00; Chi² = 2.45, df = 3 (P = 0.48); I² = 0%							
Test for overall effect: Z = 0.52 (P = 0.61)							
Test for subgroup differences: Chi² = 0.61, df = 1 (P = 0.44), I² = 0%							

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 5: Clinical worsening: need for invasive mechanical ventilation or death at up to day 28

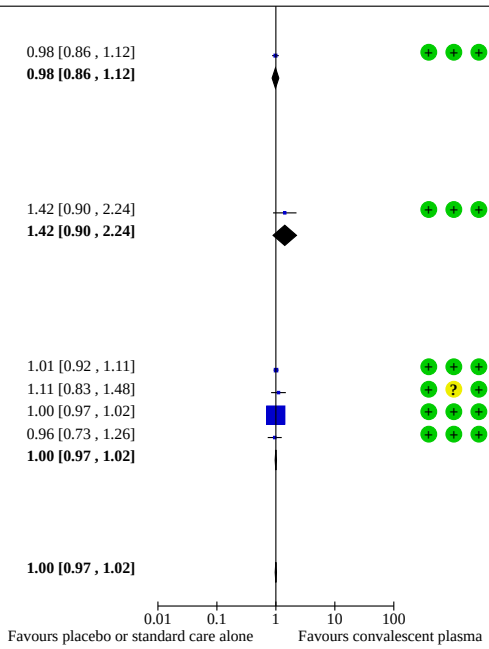
Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Individuals with moderate disease						
Agarwal 2020	44	235	41	229	3.0%	1.05 [0.71 , 1.54]
Korley 2021	8	257	3	254	0.3%	2.64 [0.71 , 9.82]
Simonovich 2020	44	228	22	105	2.2%	0.92 [0.58 , 1.45]
Subtotal (95% CI)		**720**		**588**	**5.4%**	**1.05 [0.77 , 1.43]**
Total events:	96		66			
Heterogeneity: Tau² = 0.01; Chi² = 2.21, df = 2 (P = 0.33); I² = 9%						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.5.2 Individuals with severe disease						
Estcourt 2021	347	701	275	606	26.2%	1.09 [0.97 , 1.22]
Subtotal (95% CI)		**701**		**606**	**26.2%**	**1.09 [0.97 , 1.22]**
Total events:	347		275			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
1.5.3 Individuals with moderate to severe disease						
Begin 2021	199	614	86	307	9.3%	1.16 [0.94 , 1.43]
Horby 2021b	1568	5493	1568	5448	59.1%	0.99 [0.93 , 1.05]
Subtotal (95% CI)		**6107**		**5755**	**68.3%**	**1.03 [0.90 , 1.18]**
Total events:	1767		1654			
Heterogeneity: Tau² = 0.01; Chi² = 1.87, df = 1 (P = 0.17); I² = 47%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Total (95% CI)		**7528**		**6949**	**100.0%**	**1.03 [0.97 , 1.11]**
Total events:	2210		1995			
Heterogeneity: Tau² = 0.00; Chi² = 5.74, df = 5 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.36, df = 2 (P = 0.83), I² = 0%						

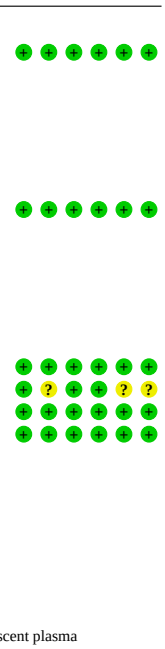


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 6: Clinical improvement: participants discharged from hospital

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Individuals with moderate disease						
Simonovich 2020	171	228	80	105	3.5%	0.98 [0.86 , 1.12]
Subtotal (95% CI)		**228**		**105**	**3.5%**	**0.98 [0.86 , 1.12]**
Total events:	171		80			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.6.2 Individuals with severe disease						
Li 2020	26	51	18	50	0.3%	1.42 [0.90 , 2.24]
Subtotal (95% CI)		**51**		**50**	**0.3%**	**1.42 [0.90 , 2.24]**
Total events:	26		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.6.3 Individuals with moderate to severe disease						
Devos 2021	257	320	130	163	6.7%	1.01 [0.92 , 1.11]
Gharbharan 2021	31	43	28	43	0.7%	1.11 [0.83 , 1.48]
Horby 2021b	3832	5795	3822	5763	88.0%	1.00 [0.97 , 1.02]
Sekine 2021	44	80	46	80	0.8%	0.96 [0.73 , 1.26]
Subtotal (95% CI)		**6238**		**6049**	**96.2%**	**1.00 [0.97 , 1.02]**
Total events:	4164		4026			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.63$, df = 3 (P = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 0.14 (P = 0.89)						
Total (95% CI)		**6517**		**6204**	**100.0%**	**1.00 [0.97 , 1.02]**
Total events:	4361		4124			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.93$, df = 5 (P = 0.71); $I^2 = 0\%$						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: $Chi^2 = 2.29$, df = 2 (P = 0.32), $I^2 = 12.7\%$						

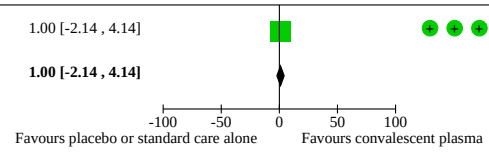


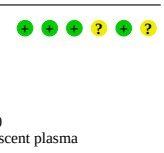


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.7. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 7: Quality of life, assessed with standardised scales at day 28

Study or Subgroup	Convalescent plasma Mean	SD	Total	Placebo or standard care alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Devos 2021	73	16	320	72	17	163	100.0%	1.00 [-2.14 , 4.14]
Total (95% CI)			**320**			**163**	**100.0%**	**1.00 [-2.14 , 4.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.53)								
Test for subgroup differences: Not applicable								



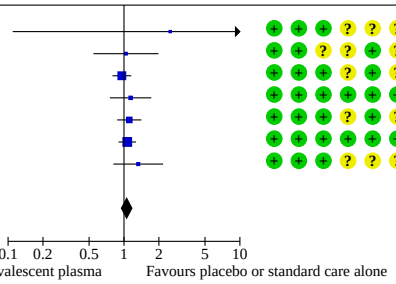


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 8: Any grade adverse events

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Holm 2021	1	17	0	14	0.1%	2.50 [0.11 , 56.98]
Kirenga 2021	15	69	14	67	2.6%	1.04 [0.55 , 1.99]
Koerper 2021	42	53	43	52	31.5%	0.96 [0.80 , 1.15]
Ortigoza 2022	44	468	39	473	6.4%	1.14 [0.76 , 1.72]
Sekine 2021	52	79	48	81	18.7%	1.11 [0.87 , 1.41]
Simonovich 2020	153	228	66	105	36.3%	1.07 [0.90 , 1.27]
Van den Berg 2022	23	52	17	51	4.4%	1.33 [0.81 , 2.17]
Total (95% CI)		**966**		**843**	**100.0%**	**1.05 [0.95 , 1.17]**
Total events:	330		227			

Heterogeneity: Tau² = 0.00; Chi² = 2.82, df = 6 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable

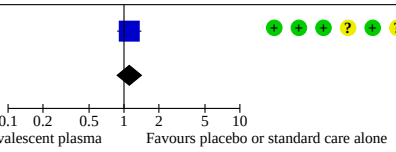


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.9. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 9: Grades 1-2 adverse events

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Sekine 2021	52	79	48	81	100.0%	1.11 [0.87 , 1.41]
Total (95% CI)		**79**		**81**	**100.0%**	**1.11 [0.87 , 1.41]**
Total events:	52		48			

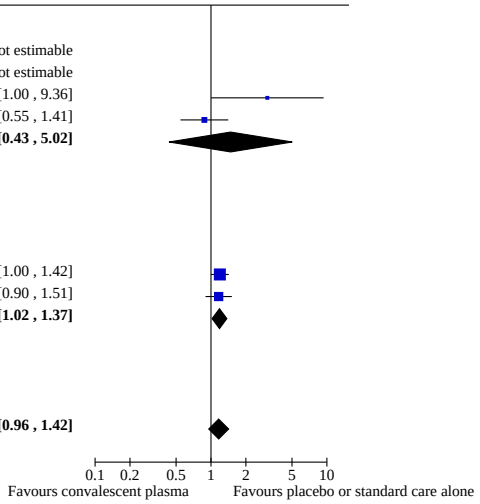
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.10. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 10: Grades 3 and 4 adverse events

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Individuals with moderate disease						
Agarwal 2020	0	227	0	224		Not estimable
AlQahtani 2021	0	20	0	20		Not estimable
Menichetti 2021 (1)	12	241	4	246	3.0%	3.06 [1.00 , 9.36]
Simonovich 2020	40	228	21	105	14.2%	0.88 [0.55 , 1.41]
Subtotal (95% CI)		**716**		**595**	**17.2%**	**1.48 [0.43 , 5.02]**
Total events:	52		25			
Heterogeneity: Tau² = 0.61; Chi² = 4.18, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.10.2 Individuals with moderate to severe disease						
Begin 2021	260	614	109	307	49.2%	1.19 [1.00 , 1.42]
Sekine 2021	50	79	44	81	33.6%	1.17 [0.90 , 1.51]
Subtotal (95% CI)		**693**		**388**	**82.8%**	**1.18 [1.02 , 1.37]**
Total events:	310		153			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.26 (P = 0.02)						
Total (95% CI)		**1409**		**983**	**100.0%**	**1.17 [0.96 , 1.42]**
Total events:	362		178			
Heterogeneity: Tau² = 0.01; Chi² = 4.32, df = 3 (P = 0.23); I² = 31%						
Test for overall effect: Z = 1.52 (P = 0.13)						
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.72), I² = 0%						

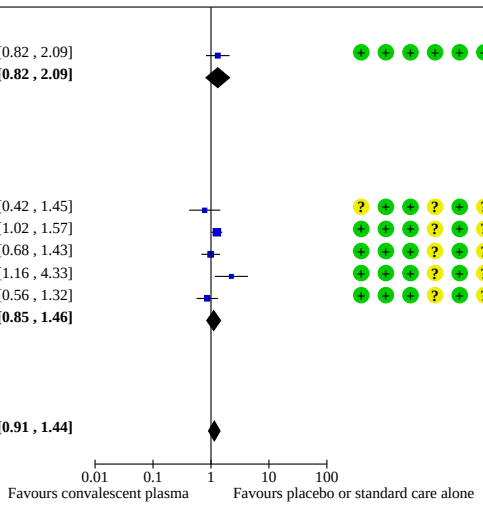


Footnotes

(1) This outlier has been double-checked.

Analysis 1.11. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 11: Serious adverse events

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
1.11.1 Individuals with moderate disease							
Simonovich 2020	54	228	19	105	14.9%	1.31 [0.82 , 2.09]	+ + + + + +
Subtotal (95% CI)		**228**		**105**	**14.9%**	**1.31 [0.82 , 2.09]**	
Total events:	54		19				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.13 (P = 0.26)							
1.11.2 Individuals with moderate to severe disease							
Bar 2021	12	40	15	39	10.2%	0.78 [0.42 , 1.45]	? + + ? + ?
Begin 2021	205	614	81	307	29.2%	1.27 [1.02 , 1.57]	+ + + ? + ?
Devos 2021	66	320	34	163	19.6%	0.99 [0.68 , 1.43]	+ + + ? + ?
Estcourt 2021 (1)	32	1075	12	905	9.3%	2.24 [1.16 , 4.33]	+ + + ? + ?
Koerper 2021	22	53	25	52	16.7%	0.86 [0.56 , 1.32]	+ + + ? + ?
Subtotal (95% CI)		**2102**		**1466**	**85.1%**	**1.11 [0.85 , 1.46]**	
Total events:	337		167				
Heterogeneity: Tau² = 0.05; Chi² = 8.76, df = 4 (P = 0.07); I² = 54%							
Test for overall effect: Z = 0.77 (P = 0.44)							
Total (95% CI)		**2330**		**1571**	**100.0%**	**1.14 [0.91 , 1.44]**	
Total events:	391		186				
Heterogeneity: Tau² = 0.03; Chi² = 9.03, df = 5 (P = 0.11); I² = 45%							
Test for overall effect: Z = 1.13 (P = 0.26)							
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%							



Footnotes

(1) This outlier has been double-checked.

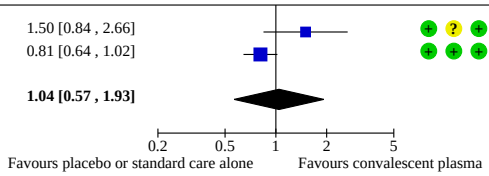
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.12. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 12: Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving participants, for subgroups of participants requiring invasive mechanical ventilation at baseline

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Gharbharan 2021	5	5	5	8	41.1%	1.50 [0.84 , 2.66]		+ ? + + + ?
Horby 2021b	87	302	112	315	58.9%	0.81 [0.64 , 1.02]		+ + + + + +
Total (95% CI)		**307**		**323**	**100.0%**	**1.04 [0.57 , 1.93]**		
Total events:	92		117					

Heterogeneity: Tau² = 0.15; Chi² = 4.04, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable

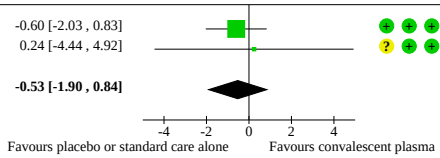


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.13. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 13: Clinical improvement: ventilator-free days by day 28

Study or Subgroup	Convalescent plasma Mean [days]	SD [days]	Total	Placebo or standard care alone Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Random, 95% CI [days]	Mean Difference IV, Random, 95% CI [days]	Risk of Bias A B C D E F
Begin 2021	23.4	10.4	614	24	10.5	307	91.4%	-0.60 [-2.03 , 0.83]		+ + + + + +
De Santis 2022	13.58	11.65	36	13.34	11.74	71	8.6%	0.24 [-4.44 , 4.92]		? + + + + ?
Total (95% CI)			**650**			**378**	**100.0%**	**-0.53 [-1.90 , 0.84]**		

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable

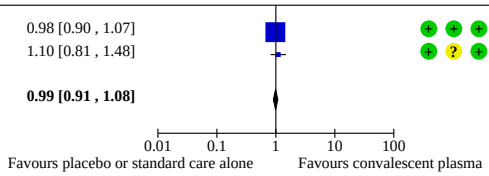


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.14. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 14: Clinical improvement: liberation from supplemental oxygen in surviving participants, for subgroup of participants requiring any supplemental oxygen or ventilator support at baseline

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Devos 2021	258	320	134	163	91.8%	0.98 [0.90 , 1.07]
Gharbharan 2021	26	36	27	41	8.2%	1.10 [0.81 , 1.48]
Total (95% CI)		**356**		**204**	**100.0%**	**0.99 [0.91 , 1.08]**
Total events:	284		161			

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable

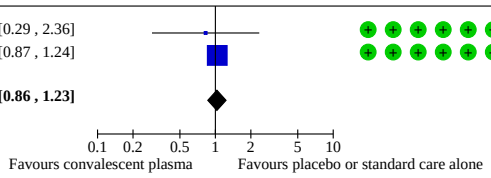


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.15. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 15: Need for dialysis at up to 28 days

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Begin 2021	10	614	6	307	2.9%	0.83 [0.29 , 2.36]
Horby 2021b	250	5707	241	5697	97.1%	1.04 [0.87 , 1.24]
Total (95% CI)		**6321**		**6004**	**100.0%**	**1.03 [0.86 , 1.23]**
Total events:	260		247			

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable

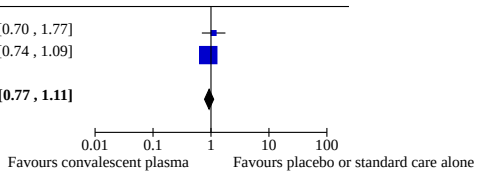


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.16. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 16: Admission to the intensive care unit (ICU)

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Devos 2021	48	320	22	163	15.0%	1.11 [0.70 , 1.77]
Simonovich 2020	123	228	63	105	85.0%	0.90 [0.74 , 1.09]
Total (95% CI)		**548**		**268**	**100.0%**	**0.93 [0.77 , 1.11]**
Total events:	171		85			

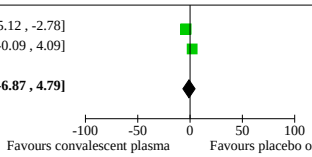
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 17: Duration of hospitalisation

Study or Subgroup	Convalescent plasma Mean [days]	SD [days]	Total	Placebo or standard care alone Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Random, 95% CI [days]	Mean Difference IV, Random, 95% CI [days]	Risk of Bias A B C D E F
AlQahtani 2021	14.1	1.24	19	18.05	2.22	18	51.1%	-3.95 [-5.12 , -2.78]		+ + + ? ? ?
Pouladzadeh 2021	8.66	3.94	30	6.66	4.3	30	48.9%	2.00 [-0.09 , 4.09]		+ + + + ? ?
Total (95% CI)			**49**			**48**	**100.0%**	**-1.04 [-6.87 , 4.79]**		

Heterogeneity: Tau² = 16.96; Chi² = 23.78, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable

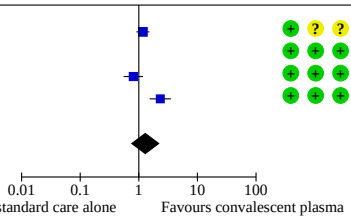


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.18. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 18: Viral clearance at up to day 3

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Agarwal 2020	79	184	67	183	35.9%	1.17 [0.91 , 1.51]		+ ? ? − + −
Hamdy Salman 2020	0	15	0	15		Not estimable		+ + + + ? ?
Kirenga 2021	27	68	33	67	32.5%	0.81 [0.55 , 1.18]		+ + + + + +
Li 2020 (1)	41	47	15	40	31.5%	2.33 [1.54 , 3.52]		+ + + + + +
Total (95% CI)		**314**		**305**	**100.0%**	**1.29 [0.76 , 2.18]**		
Total events:	147		115					

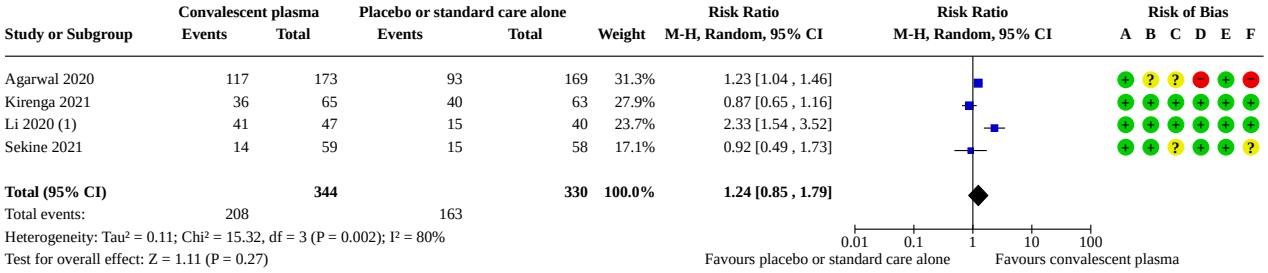
Heterogeneity: Tau² = 0.18; Chi² = 13.94, df = 2 (P = 0.0009); I² = 86%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Footnotes
(1) This outlier has been double-checked.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.19. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 19: Viral clearance at up to day 7



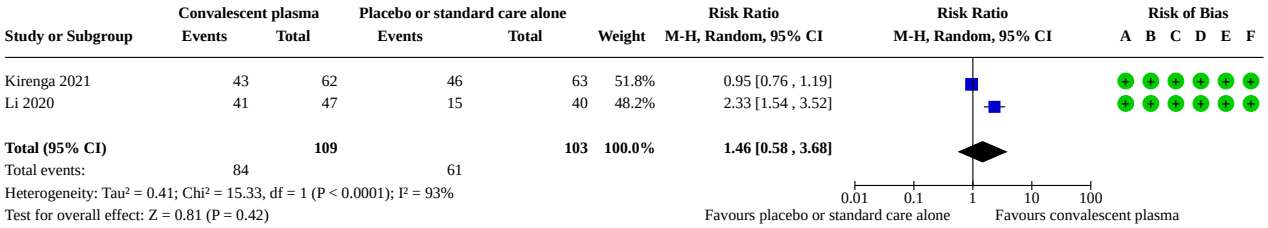
Footnotes

(1) This outlier has been double-checked.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.20. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 20: Viral clearance at up to day 14



Risk of bias legend

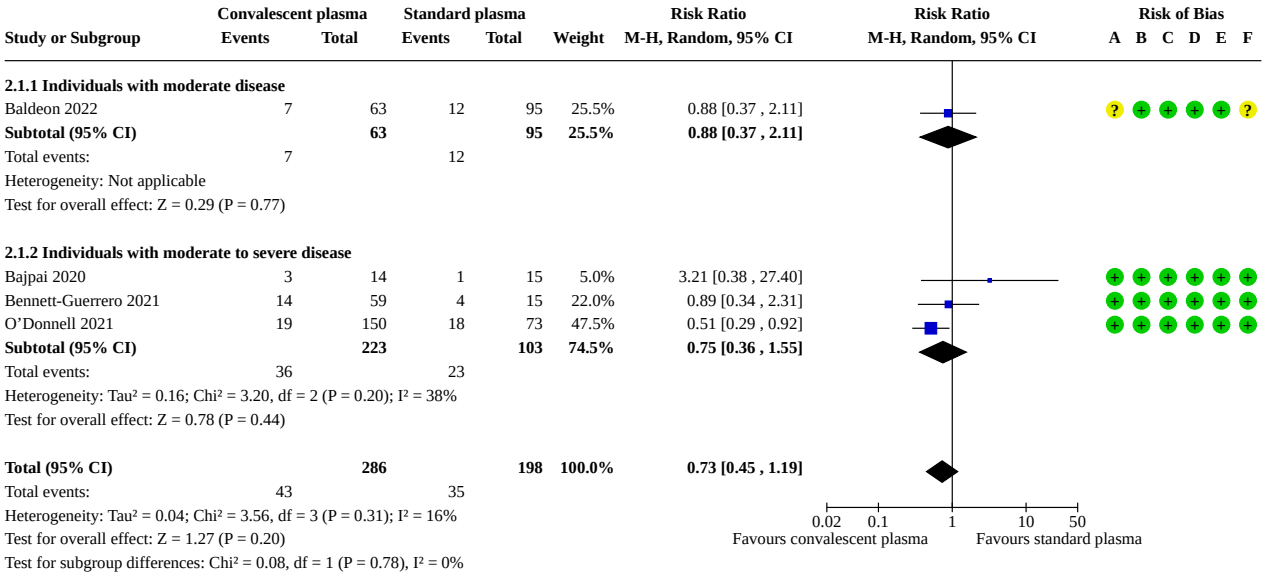
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2. Convalescent plasma versus standard plasma for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality at up to day 28	4	484	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.45, 1.19]
2.1.1 Individuals with moderate disease	1	158	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.37, 2.11]
2.1.2 Individuals with moderate to severe disease	3	326	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.36, 1.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 All-cause mortality (time to event)	4	484	Hazard Ratio (IV, Random, 95% CI)	0.94 [0.41, 2.14]
2.3 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28	1	34	Risk Ratio (M-H, Random, 95% CI)	5.59 [0.29, 108.38]
2.4 Duration of hospitalisation	2	187	Mean Difference (IV, Random, 95% CI)	-2.14 [-5.24, 0.95]
2.5 Any grade adverse events	2	253	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.93, 1.50]
2.6 Serious adverse events	3	327	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.15]
2.6.1 Individuals with moderate to severe disease	3	327	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.15]

Analysis 2.1. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28

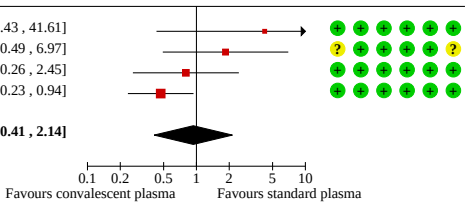


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 2: All-cause mortality (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Convalescent plasma Total	Standard plasma Total	Weight	Hazard Ratio IV, Random, 95% CI
Bajpai 2020	1.442202	1.166366	14	15	10.6%	4.23 [0.43 , 41.61]
Baldeon 2022	0.615186	0.676566	63	95	22.7%	1.85 [0.49 , 6.97]
Bennett-Guerrero 2021	-0.223144	0.571202	59	15	27.3%	0.80 [0.26 , 2.45]
O'Donnell 2021	-0.755023	0.353653	150	73	39.4%	0.47 [0.23 , 0.94]
Total (95% CI)			**286**	**198**	**100.0%**	**0.94 [0.41 , 2.14]**

Heterogeneity: Tau² = 0.33; Chi² = 5.73, df = 3 (P = 0.13); I² = 48%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable

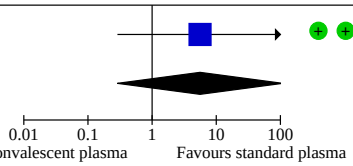


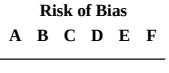
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 3: Clinical worsening: need for invasive mechanical ventilation or death at up to day 28

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
NCT04421404	2	16	0	18	100.0%	5.59 [0.29 , 108.38]
Total (95% CI)		**16**		**18**	**100.0%**	**5.59 [0.29 , 108.38]**
Total events:	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.26)
Test for subgroup differences: Not applicable



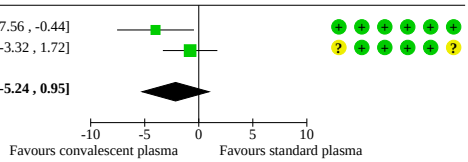


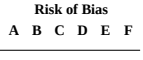
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 4: Duration of hospitalisation

Study or Subgroup	Convalescent plasma Mean [days]	SD [days]	Total	Standard plasma Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Random, 95% CI [days]
Bajpai 2020	12.1	4.1	14	16.1	5.6	15	42.0%	-4.00 [-7.56 , -0.44]
Baldeon 2022	11.9	7.5	63	12.7	8.5	95	58.0%	-0.80 [-3.32 , 1.72]
Total (95% CI)			**77**			**110**	**100.0%**	**-2.14 [-5.24 , 0.95]**

Heterogeneity: Tau² = 2.65; Chi² = 2.07, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 1.36 (P = 0.17)
Test for subgroup differences: Not applicable



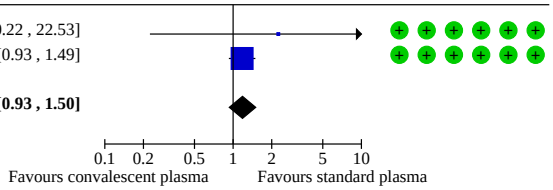


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.5. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 5: Any grade adverse events

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
NCT04421404	2	16	1	18	1.1%	2.25 [0.22 , 22.53]
O'Donnell 2021	96	147	40	72	98.9%	1.18 [0.93 , 1.49]
Total (95% CI)		**163**		**90**	**100.0%**	**1.18 [0.93 , 1.50]**
Total events:	98		41			

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

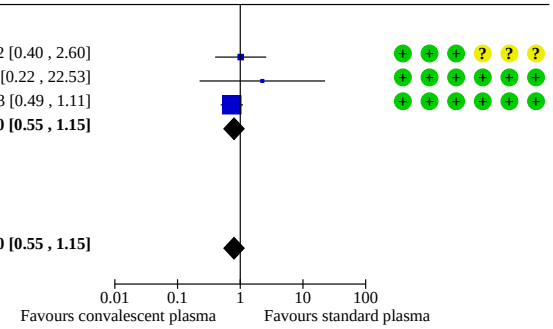
Analysis 2.6. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 6: Serious adverse events

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Individuals with moderate to severe disease						
Bennett-Guerrero 2021	16	59	4	15	15.5%	1.02 [0.40 , 2.60]
NCT04421404	2	16	1	18	2.6%	2.25 [0.22 , 22.53]
O'Donnell 2021	39	147	26	72	81.9%	0.73 [0.49 , 1.11]
Subtotal (95% CI)		**222**		**105**	**100.0%**	**0.80 [0.55 , 1.15]**
Total events:	57		31			

Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.22)

Total (95% CI)		**222**		**105**	**100.0%**	**0.80 [0.55 , 1.15]**
Total events:	57		31			

Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.22)
Test for subgroup differences: Not applicable



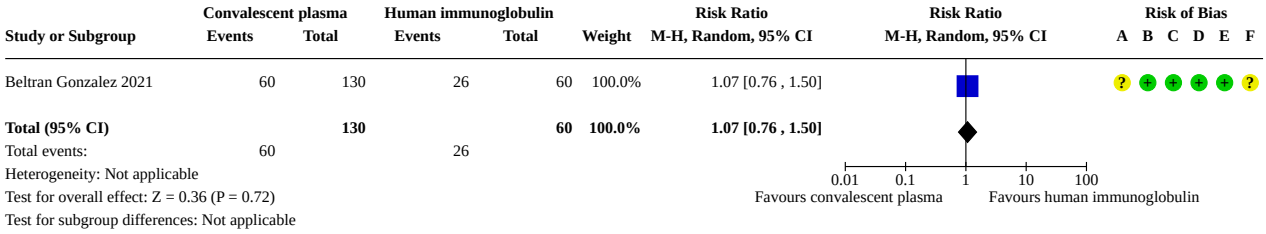
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 3. Convalescent plasma versus human immunoglobulin for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality at up to day 28	1	190	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.76, 1.50]
3.2 All-cause mortality (time to event)	1	190	Hazard Ratio (IV, Random, 95% CI)	1.14 [0.84, 1.54]

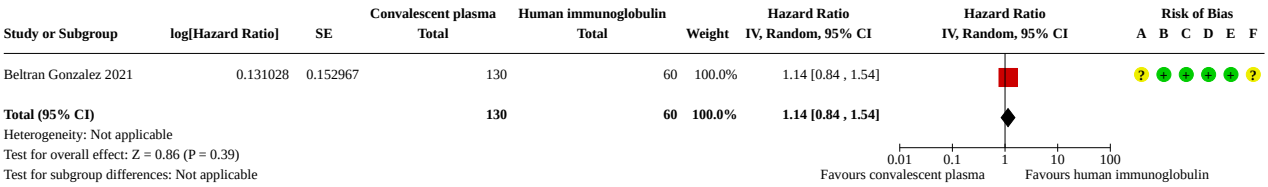
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 All-cause mortality during hospital stay	1	190	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.76, 1.34]

Analysis 3.1. Comparison 3: Convalescent plasma versus human immunoglobulin for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



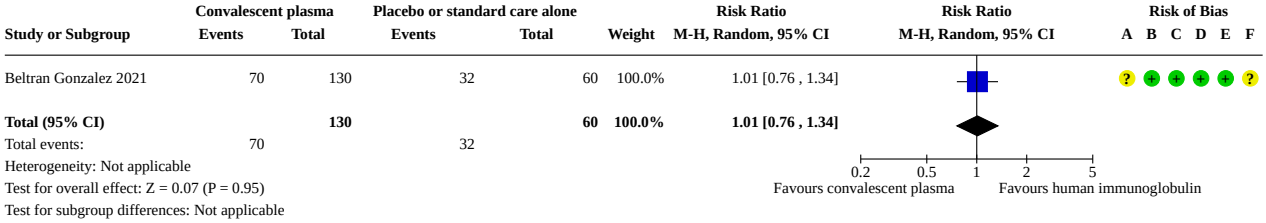
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.2. Comparison 3: Convalescent plasma versus human immunoglobulin for individuals with moderate to severe disease, Outcome 2: All-cause mortality (time to event)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.3. Comparison 3: Convalescent plasma versus human immunoglobulin for individuals with moderate to severe disease, Outcome 3: All-cause mortality during hospital stay



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

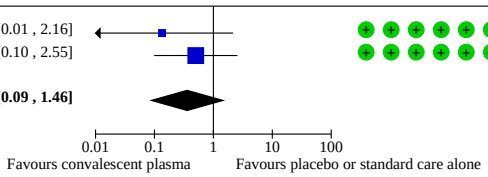
Comparison 4. Convalescent plasma versus placebo or standard care alone for outpatients with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality at up to day 28	2	536	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.09, 1.46]
4.2 All-cause mortality at up to day 60	1	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.16]
4.3 Admission to hospital or death within 28 days	1	376	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.60, 1.84]
4.4 Time to symptom resolution	1	376	Hazard Ratio (IV, Random, 95% CI)	1.05 [0.85, 1.30]
4.5 Clinical worsening: need for hospitalisation with at least need of oxygen by mask or nasal prongs, or death	2	536	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.36, 1.59]
4.6 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28	1	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.10, 2.55]
4.7 Clinical worsening: need for invasive mechanical ventilation or death at up to day 60	1	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.10, 2.55]
4.8 Grades 3 and 4 adverse events	1	376	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.75, 2.19]
4.9 Serious adverse events	1	376	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.66, 1.94]

Analysis 4.1. Comparison 4: Convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 1: All-cause mortality at up to day 28

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F
Alemany 2022	0	188	2	188	25.6%	0.13 [0.01 , 2.16]	+ + + + + +
Libster 2020	2	80	4	80	74.4%	0.50 [0.10 , 2.55]	+ + + + + +
Total (95% CI)		**268**		**268**	**100.0%**	**0.36 [0.09 , 1.46]**	
Total events:	2		6				

Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.43 (P = 0.15)
Test for subgroup differences: Not applicable

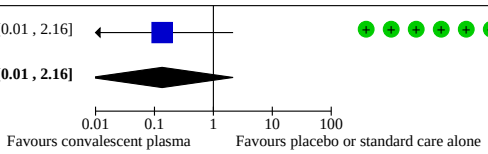


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.2. Comparison 4: Convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 2: All-cause mortality at up to day 60

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F
Alemany 2022	0	188	2	188	100.0%	0.13 [0.01 , 2.16]	+ + + + + +
Total (95% CI)		**188**		**188**	**100.0%**	**0.13 [0.01 , 2.16]**	
Total events:	0		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable

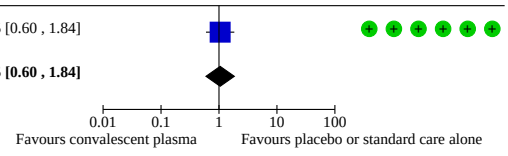


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.3. Comparison 4: Convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 3: Admission to hospital or death within 28 days

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alemany 2022	22	188	21	188	100.0%	1.05 [0.60 , 1.84]	+ + + + + +
Total (95% CI)		**188**		**188**	**100.0%**	**1.05 [0.60 , 1.84]**	
Total events:	22		21				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable

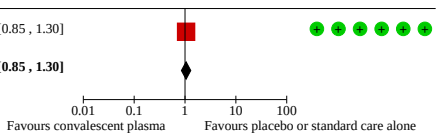


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.4. Comparison 4: Convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 4: Time to symptom resolution

Study or Subgroup	log[Hazard Ratio]	SE	Convalescent plasma Total	Placebo or standard care alone Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Alemany 2022	0.04879	0.108391	188	188	100.0%	1.05 [0.85 , 1.30]		+ + + + + +
Total (95% CI)			**188**	**188**	**100.0%**	**1.05 [0.85 , 1.30]**		

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable

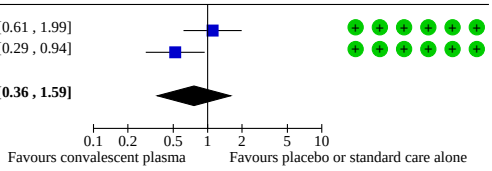


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.5. Comparison 4: Convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 5: Clinical worsening: need for hospitalisation with at least need of oxygen by mask or nasal prongs, or death

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard or care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alemany 2022	21	188	19	188	50.2%	1.11 [0.61 , 1.99]		+ + + + + +
Libster 2020	13	80	25	80	49.8%	0.52 [0.29 , 0.94]		+ + + + + +
Total (95% CI)		**268**		**268**	**100.0%**	**0.76 [0.36 , 1.59]**		
Total events:	34		44					

Heterogeneity: Tau² = 0.19; Chi² = 3.14, df = 1 (P = 0.08); I² = 68%
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable

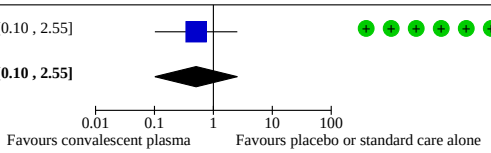


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.6. Comparison 4: Convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 6: Clinical worsening: need for invasive mechanical ventilation or death at up to day 28

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F
Alemany 2022	2	188	4	188	100.0%	0.51 [0.10 , 2.55]		+ + + + + +
Total (95% CI)		**188**		**188**	**100.0%**	**0.51 [0.10 , 2.55]**		
Total events:	2		4					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable

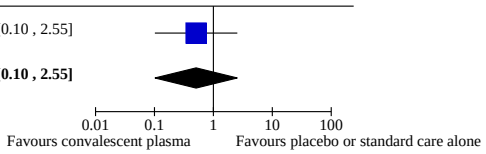


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.7. Comparison 4: Convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 7: Clinical worsening: need for invasive mechanical ventilation or death at up to day 60

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Alemany 2022	2	188	4	188	100.0%	0.51 [0.10 , 2.55]
Total (95% CI)		**188**		**188**	**100.0%**	**0.51 [0.10 , 2.55]**
Total events:	2		4			

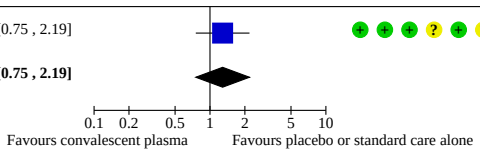
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 4.8. Comparison 4: Convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 8: Grades 3 and 4 adverse events

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alemany 2022	27	188	21	188	100.0%	1.29 [0.75 , 2.19]	+ + + ? + ?
Total (95% CI)		**188**		**188**	**100.0%**	**1.29 [0.75 , 2.19]**	
Total events:	27		21				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable

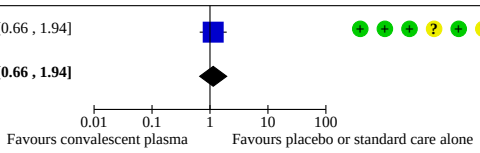


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.9. Comparison 4: Convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 9: Serious adverse events

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alemany 2022	25	188	22	188	100.0%	1.14 [0.66 , 1.94]	+ + + ? + ?
Total (95% CI)		**188**		**188**	**100.0%**	**1.14 [0.66 , 1.94]**	
Total events:	25		22				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable



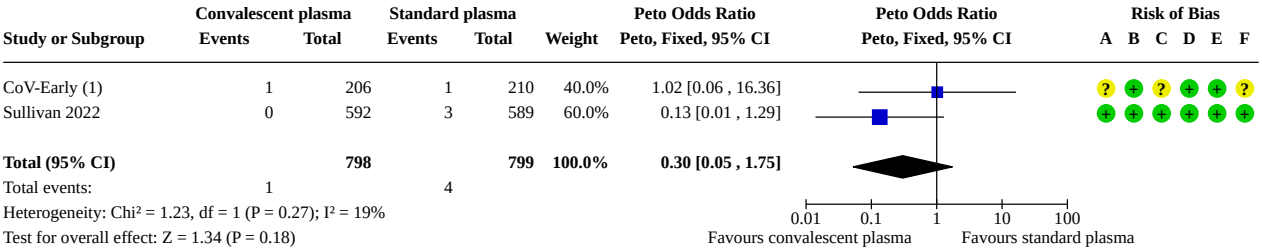
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 5. Convalescent plasma versus standard plasma for outpatients with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 All-cause mortality at up to day 28	2	1597	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.05, 1.75]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Admission to hospital or death within 28 days	2	1595	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.31, 0.75]
5.3 All initial symptoms resolved (asymptomatic) at up to day 28	1	416	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.27]
5.4 All initial symptoms resolved (asymptomatic) at up to day 14	1	417	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.83, 1.21]
5.5 Clinical worsening: need for hospitalisation with need of at least oxygen by mask or nasal prongs, or death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.6 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28	1	414	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.05, 1.77]

Analysis 5.1. Comparison 5: Convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 1: All-cause mortality at up to day 28



Footnotes

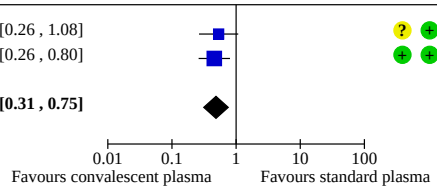
(1) Study is not published yet, data obtained from study investigator

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.2. Comparison 5: Convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 2: Admission to hospital or death within 28 days

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
CoV-Early (1)	11	205	21	209	39.0%	0.53 [0.26 , 1.08]	? + ? ? + ?
Sullivan 2022	17	592	37	589	61.0%	0.46 [0.26 , 0.80]	+ + + + + +
Total (95% CI)		**797**		**798**	**100.0%**	**0.49 [0.31 , 0.75]**	
Total events:	28		58				



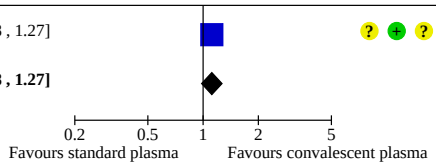
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.22 (P = 0.001)
Test for subgroup differences: Not applicable

Footnotes
(1) Study is not published yet, data obtained from study investigator

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.3. Comparison 5: Convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 3: All initial symptoms resolved (asymptomatic) at up to day 28

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
CoV-Early (1)	151	206	138	210	100.0%	1.12 [0.98 , 1.27]	? + ? ? + ?
Total (95% CI)		**206**		**210**	**100.0%**	**1.12 [0.98 , 1.27]**	
Total events:	151		138				



Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable

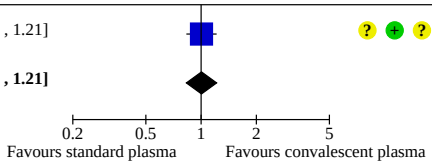
Footnotes
(1) Study is not published yet, data obtained from study investigator

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.4. Comparison 5: Convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 4: All initial symptoms resolved (asymptomatic) at up to day 14

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
CoV-Early (1)	105	207	106	210	100.0%	1.00 [0.83 , 1.21]	? + ? ? + ?
Total (95% CI)		**207**		**210**	**100.0%**	**1.00 [0.83 , 1.21]**	
Total events:	105		106				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



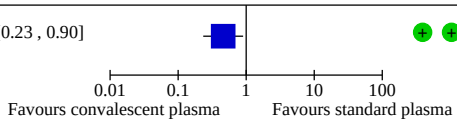
Footnotes
(1) Study is not published yet, data obtained from study investigator

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.5. Comparison 5: Convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 5: Clinical worsening: need for hospitalisation with need of at least oxygen by mask or nasal prongs, or death

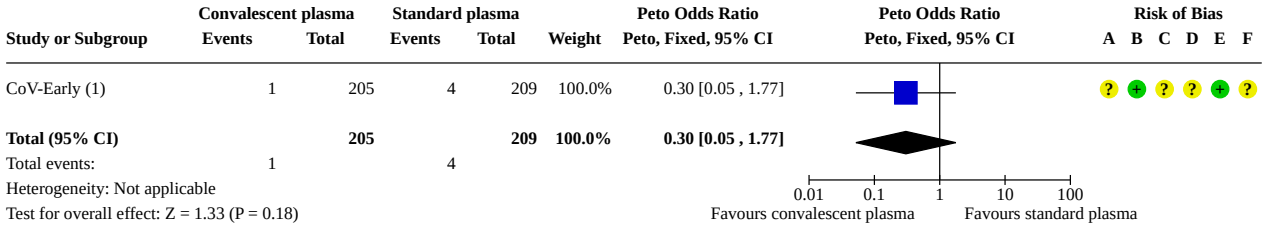
Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Sullivan 2022	12	592	26	589	0.46 [0.23 , 0.90]	+ + + + + +

Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.6. Comparison 5: Convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 6: Clinical worsening: need for invasive mechanical ventilation or death at up to day 28



Footnotes

(1) Study is not published yet, data obtained from study investigator

Risk of bias legend

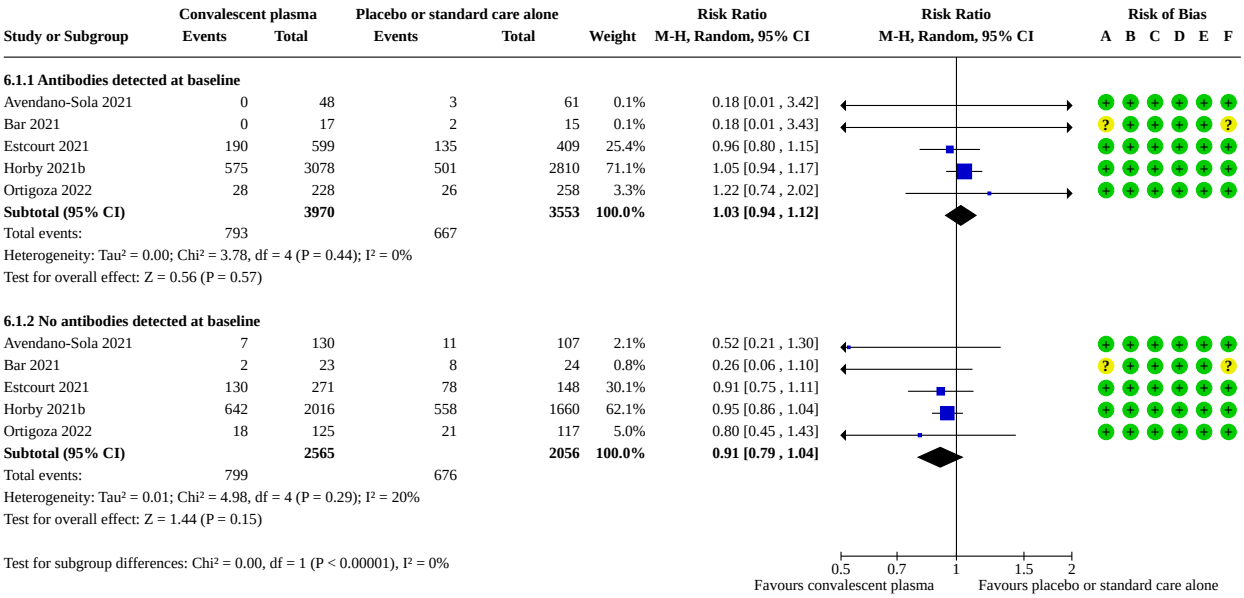
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 6. Subgroup analysis: antibodies in recipients detected at baseline for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 All-cause mortality at up to day 28 (random-effects analysis)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1.1 Antibodies detected at baseline	5	7523	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.12]
6.1.2 No antibodies detected at baseline	5	4621	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.79, 1.04]
6.2 All-cause mortality (time to event)	2		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
6.2.1 Antibodies detected at baseline	2	5997	Hazard Ratio (IV, Random, 95% CI)	1.06 [0.94, 1.19]
6.2.2 No antibodies detected at baseline	2	3913	Hazard Ratio (IV, Random, 95% CI)	0.83 [0.50, 1.40]
6.3 Clinical worsening: need for invasive mechanical ventilation or death (random-effects model)	2	9472	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.12]
6.3.1 Antibodies detected at baseline	2	5816	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.96, 1.17]
6.3.2 No antibodies detected at baseline	2	3656	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.84, 0.98]

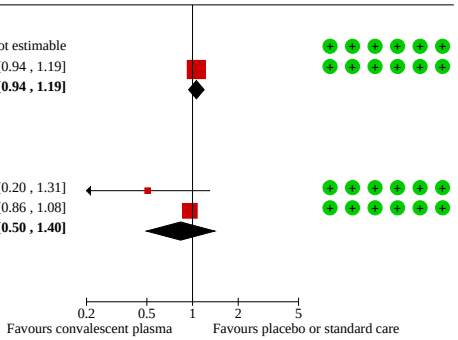
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.4 Clinical improvement: participants discharged from hospital	1	9564	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.08]
6.4.1 Antibodies detected at baseline	1	5888	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]
6.4.2 No antibodies detected at baseline	1	3676	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.99, 1.11]

Analysis 6.1. Comparison 6: Subgroup analysis: antibodies in recipients detected at baseline for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28 (random-effects analysis)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

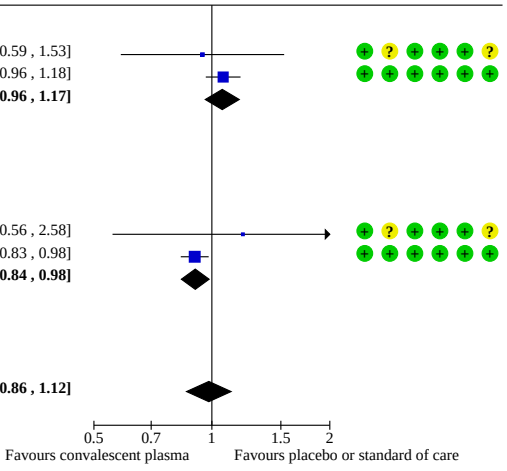
Analysis 6.2. Comparison 6: Subgroup analysis: antibodies in recipients detected at baseline for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: All-cause mortality (time to event)



Study or Subgroup	log[Hazard Ratio]	SE	Convalescent plasma Total	Placebo or standard care Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
6.2.1 Antibodies detected at baseline							
Avendano-Sola 2021	0.1212	0	48	61		Not estimable	+ + + + + +
Horby 2021b	0.058269	0.060161	3078	2810	100.0%	1.06 [0.94 , 1.19]	+ + + + + +
Subtotal (95% CI)			**3126**	**2871**	**100.0%**	**1.06 [0.94 , 1.19]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.97 (P = 0.33)							
6.2.2 No antibodies detected at baseline							
Avendano-Sola 2021	-0.681219	0.483838	130	107	21.9%	0.51 [0.20 , 1.31]	+ + + + + +
Horby 2021b	-0.040822	0.05872	2016	1660	78.1%	0.96 [0.86 , 1.08]	+ + + + + +
Subtotal (95% CI)			**2146**	**1767**	**100.0%**	**0.83 [0.50 , 1.40]**	
Heterogeneity: Tau² = 0.09; Chi² = 1.73, df = 1 (P = 0.19); I² = 42%							
Test for overall effect: Z = 0.68 (P = 0.49)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%							

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

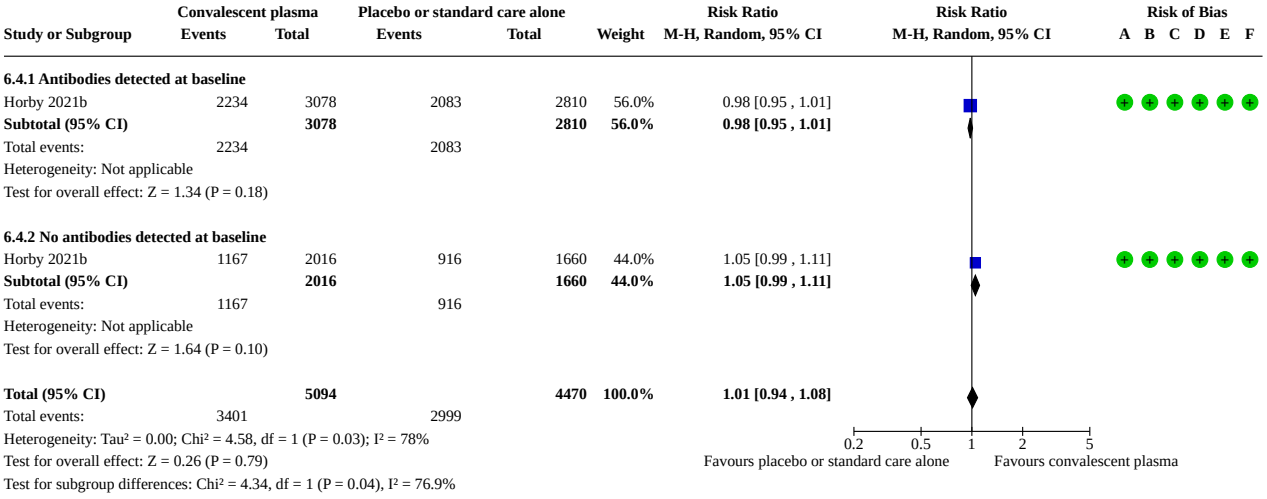
Analysis 6.3. Comparison 6: Subgroup analysis: antibodies in recipients detected at baseline for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: Clinical worsening: need for invasive mechanical ventilation or death (random-effects model)



Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
6.3.1 Antibodies detected at baseline							
Agarwal 2020	29	185	27	163	6.6%	0.95 [0.59 , 1.53]	+ ? + + + ?
Horby 2021b	630	2859	538	2609	43.1%	1.07 [0.96 , 1.18]	+ + + + + +
Subtotal (95% CI)		**3044**		**2772**	**49.7%**	**1.06 [0.96 , 1.17]**	
Total events:	659		565				
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%							
Test for overall effect: Z = 1.20 (P = 0.23)							
6.3.2 No antibodies detected at baseline							
Agarwal 2020	9	30	10	40	2.8%	1.20 [0.56 , 2.58]	+ ? + + + ?
Horby 2021b	731	1969	664	1617	47.5%	0.90 [0.83 , 0.98]	+ + + + + +
Subtotal (95% CI)		**1999**		**1657**	**50.3%**	**0.91 [0.84 , 0.98]**	
Total events:	740		674				
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%							
Test for overall effect: Z = 2.35 (P = 0.02)							
Total (95% CI)		**5043**		**4429**	**100.0%**	**0.98 [0.86 , 1.12]**	
Total events:	1399		1239				
Heterogeneity: Tau² = 0.01; Chi² = 6.69, df = 3 (P = 0.08); I² = 55%							
Test for overall effect: Z = 0.27 (P = 0.79)							
Test for subgroup differences: Chi² = 5.83, df = 1 (P = 0.02), I² = 82.8%							

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.4. Comparison 6: Subgroup analysis: antibodies in recipients detected at baseline for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 4: Clinical improvement: participants discharged from hospital



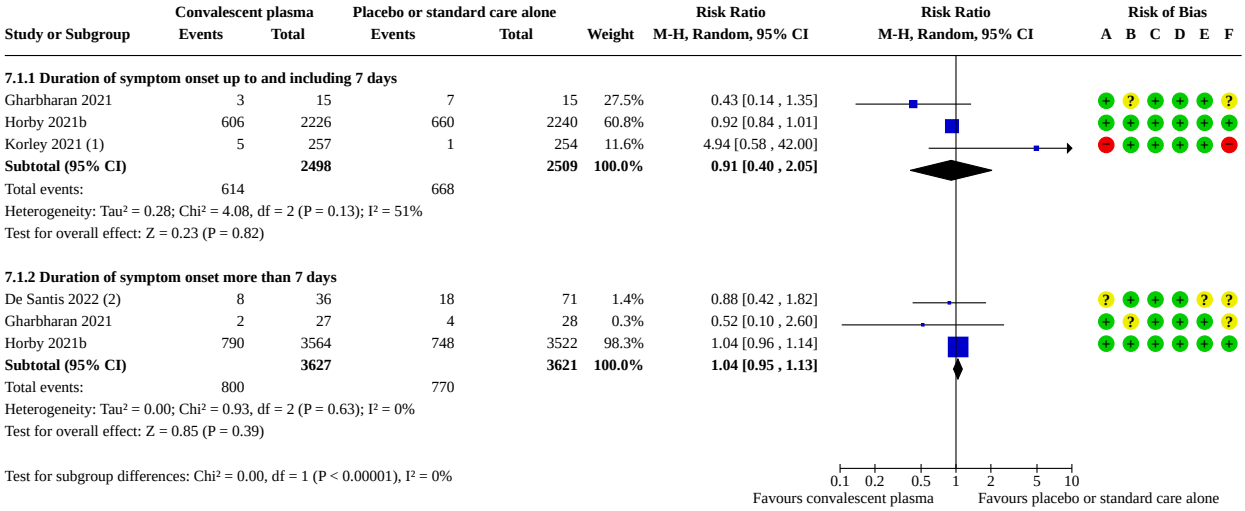
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 7. Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 All-cause mortality at up to day 28 (random-effects model)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1.1 Duration of symptom onset up to and including 7 days	3	5007	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.40, 2.05]
7.1.2 Duration of symptom onset more than 7 days	3	7248	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.95, 1.13]
7.2 All-cause mortality (time to event) (random-effects model)	1	107	Hazard Ratio (IV, Random, 95% CI)	0.81 [0.42, 1.55]
7.2.1 Duration of symptom onset more than 7 days	1	107	Hazard Ratio (IV, Random, 95% CI)	0.81 [0.42, 1.55]
7.3 Clinical worsening: need for invasive mechanical ventilation or death (random-effects model)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.3.1 Duration of symptom onset up to and including 7 days	2	4816	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.50, 3.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3.2 Duration of symptom onset more than 7 days	2	6686	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.96, 1.14]
7.4 Clinical improvement: participants discharged from hospital	2	11637	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.96, 1.04]
7.4.1 Duration of symptom onset up to 7 days	2	4496	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.98, 1.08]
7.4.2 Duration of symptom onset more than 7 days	2	7141	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]

Analysis 7.1. Comparison 7: Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28 (random-effects model)



Footnotes

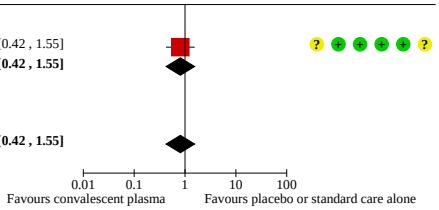
(1) For Korley 2021, the subgroup included the whole population and is defined as "onset of symptoms within 7 days before enrollment"; Korley may not be fully comparable to other inpatient studies
(2) De Santis 2022 includes the whole population, as first infusion was "administered on day 9 (range 8–10) for both groups".

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.2. Comparison 7: Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: All-cause mortality (time to event) (random-effects model)

Study or Subgroup	log[Hazard Ratio]	SE	Convalescent plasma Total	Placebo or standard care alone Total	Weight	Hazard Ratio IV, Random, 95% CI
7.2.1 Duration of symptom onset more than 7 days						
De Santis 2022 (1)	-0.210721	0.330375	36	71	100.0%	0.81 [0.42 , 1.55]
Subtotal (95% CI)			**36**	**71**	**100.0%**	**0.81 [0.42 , 1.55]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)			**36**	**71**	**100.0%**	**0.81 [0.42 , 1.55]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Not applicable						

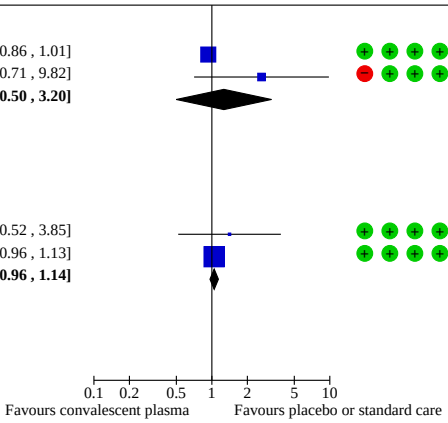


Footnotes
(1) The whole study population had a duration of symptom onset more than 7 days; HR recalculated from log-rank p-value and number of events

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.3. Comparison 7: Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: Clinical worsening: need for invasive mechanical ventilation or death (random-effects model)

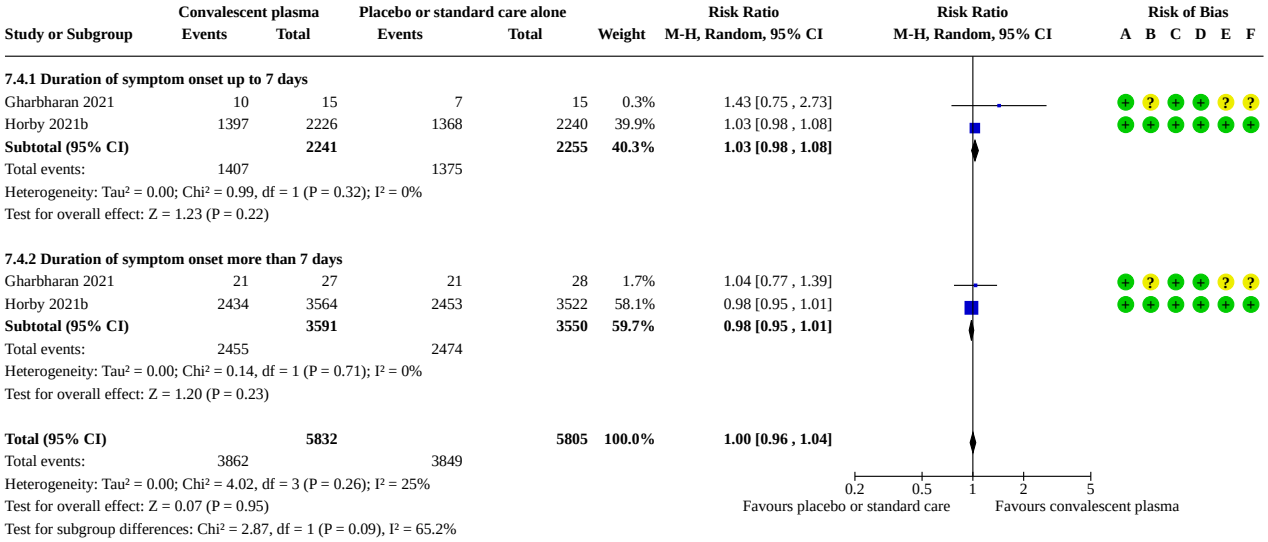
Study or Subgroup	Convalescent plasma Events	Convalescent plasma Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI
7.3.1 Duration of symptom onset up to and including 7 days						
Horby 2021b	693	2149	746	2156	70.7%	0.93 [0.86 , 1.01]
Korley 2021 (1)	8	257	3	254	29.3%	2.64 [0.71 , 9.82]
Subtotal (95% CI)		**2406**		**2410**	**100.0%**	**1.26 [0.50 , 3.20]**
Total events:	701		749			
Heterogeneity: Tau² = 0.32; Chi² = 2.39, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 0.49 (P = 0.62)						
7.3.2 Duration of symptom onset more than 7 days						
Begin 2021 (2)	11	37	4	19	0.7%	1.41 [0.52 , 3.85]
Horby 2021b	871	3339	822	3291	99.3%	1.04 [0.96 , 1.13]
Subtotal (95% CI)		**3376**		**3310**	**100.0%**	**1.05 [0.96 , 1.14]**
Total events:	882		826			
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.09 (P = 0.28)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



Footnotes
(1) For Korley 2021, the subgroup included the whole population and is defined as "onset of symptoms within 7 days before enrollment"; Korley may not be fully comparable to other inpatient studies
(2) For Begin 2021, the subgroup is defined as "duration of symptom onset more than 12 days", so day 8, 9, 10, 11 and 12 are not included and assessed here.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.4. Comparison 7: Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 4: Clinical improvement: participants discharged from hospital

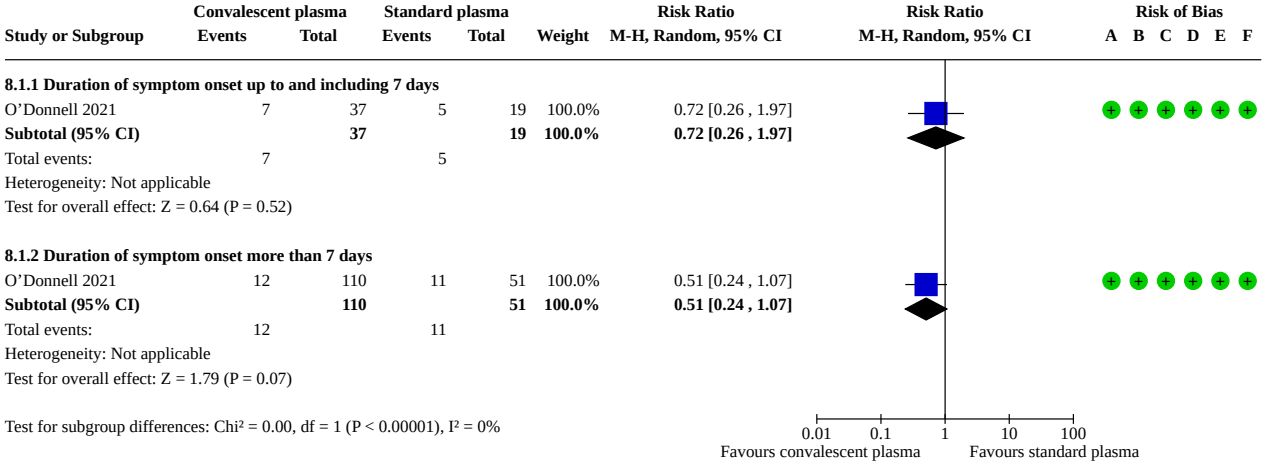


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 8. Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus standard plasma for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 All-cause mortality at up to day 28 (random-effects analysis)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1.1 Duration of symptom onset up to and including 7 days	1	56	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.26, 1.97]
8.1.2 Duration of symptom onset more than 7 days	1	161	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.24, 1.07]

Analysis 8.1. Comparison 8: Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28 (random-effects analysis)



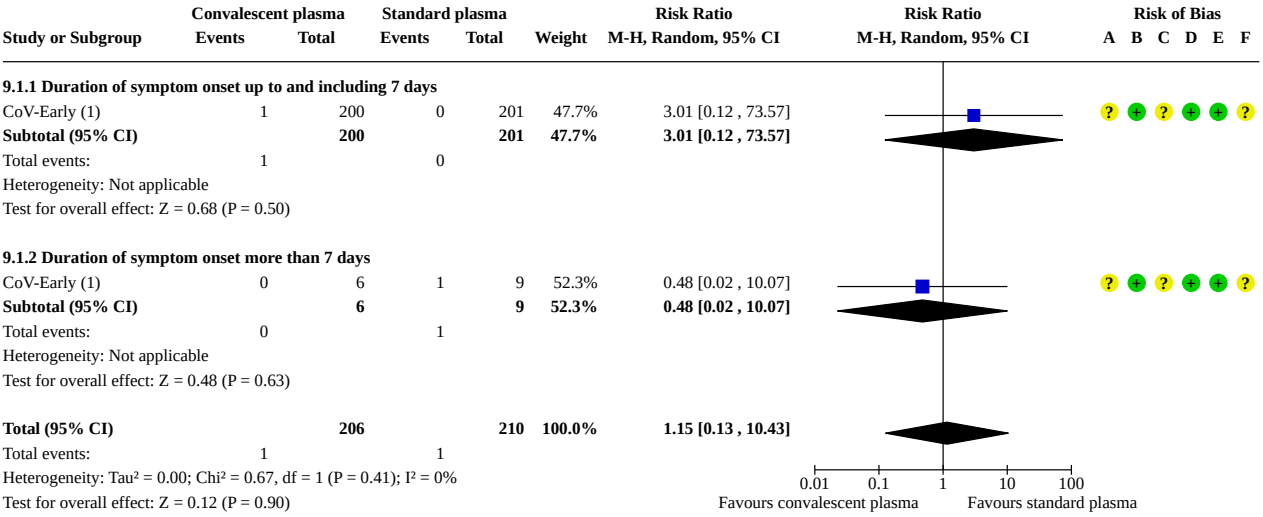
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 9. Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 All-cause mortality at up to day 28	1	416	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.13, 10.43]
9.1.1 Duration of symptom onset up to and including 7 days	1	401	Risk Ratio (M-H, Random, 95% CI)	3.01 [0.12, 73.57]
9.1.2 Duration of symptom onset more than 7 days	1	15	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.02, 10.07]
9.2 Admission to hospital or death within 28 days	1	414	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.27, 1.12]
9.2.1 Duration of symptom onset up to and including 7 days	1	400	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.24, 1.04]
9.2.2 Duration of symptom onset more than 7 days	1	14	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.14, 22.99]
9.3 All initial symptoms resolved (asymptomatic) at up to day 28	1	416	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.65, 1.59]
9.3.1 Duration of symptom onset up to and including 7 days	1	401	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.00, 1.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3.2 Duration of symptom onset more than 7 days	1	15	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.27, 1.54]

Analysis 9.1. Comparison 9: Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 1: All-cause mortality at up to day 28



Footnotes

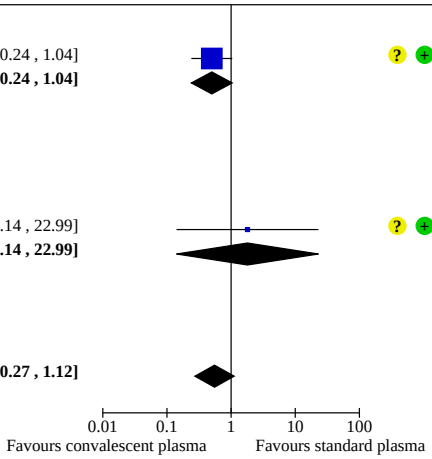
(1) Study is not published yet, data obtained from study investigator

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.2. Comparison 9: Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 2: Admission to hospital or death within 28 days

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
9.2.1 Duration of symptom onset up to and including 7 days							
CoV-Early (1)	10	200	20	200	92.3%	0.50 [0.24 , 1.04]	? + ? ? + ?
Subtotal (95% CI)		**200**		**200**	**92.3%**	**0.50 [0.24 , 1.04]**	
Total events:	10		20				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.85 (P = 0.06)							
9.2.2 Duration of symptom onset more than 7 days							
CoV-Early (1)	1	5	1	9	7.7%	1.80 [0.14 , 22.99]	? + ? ? + ?
Subtotal (95% CI)		**5**		**9**	**7.7%**	**1.80 [0.14 , 22.99]**	
Total events:	1		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.45 (P = 0.65)							
Total (95% CI)		**205**		**209**	**100.0%**	**0.55 [0.27 , 1.12]**	
Total events:	11		21				
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%							
Test for overall effect: Z = 1.66 (P = 0.10)							
Test for subgroup differences: Chi² = 0.90, df = 1 (P = 0.34), I² = 0%							



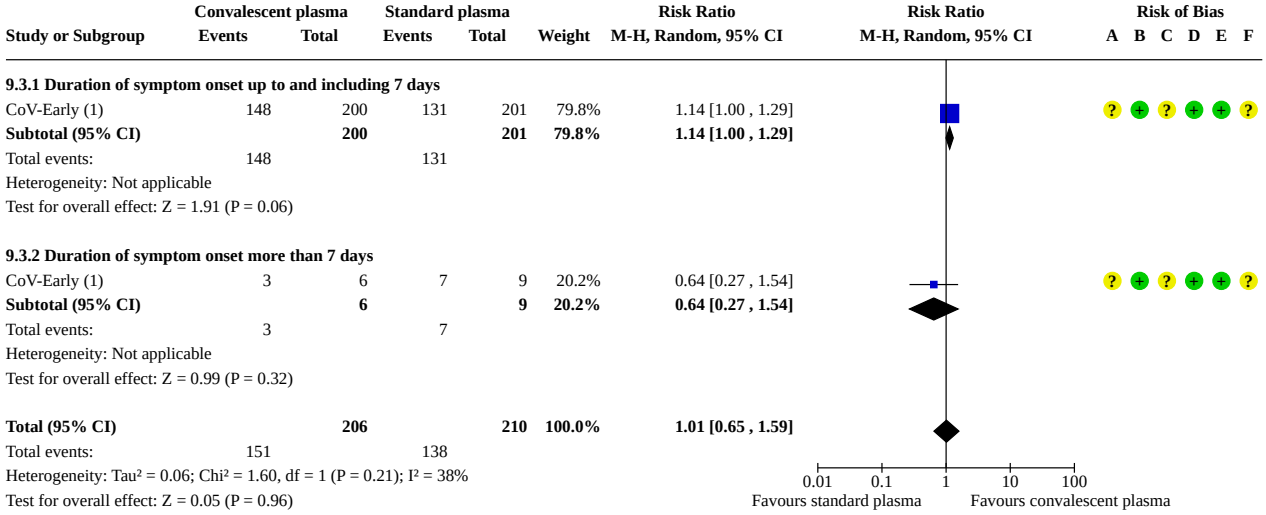
Footnotes

(1) Study is not published yet, data obtained from study investigator

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.3. Comparison 9: Subgroup analysis: length of time since symptom onset for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 3: All initial symptoms resolved (asymptomatic) at up to day 28



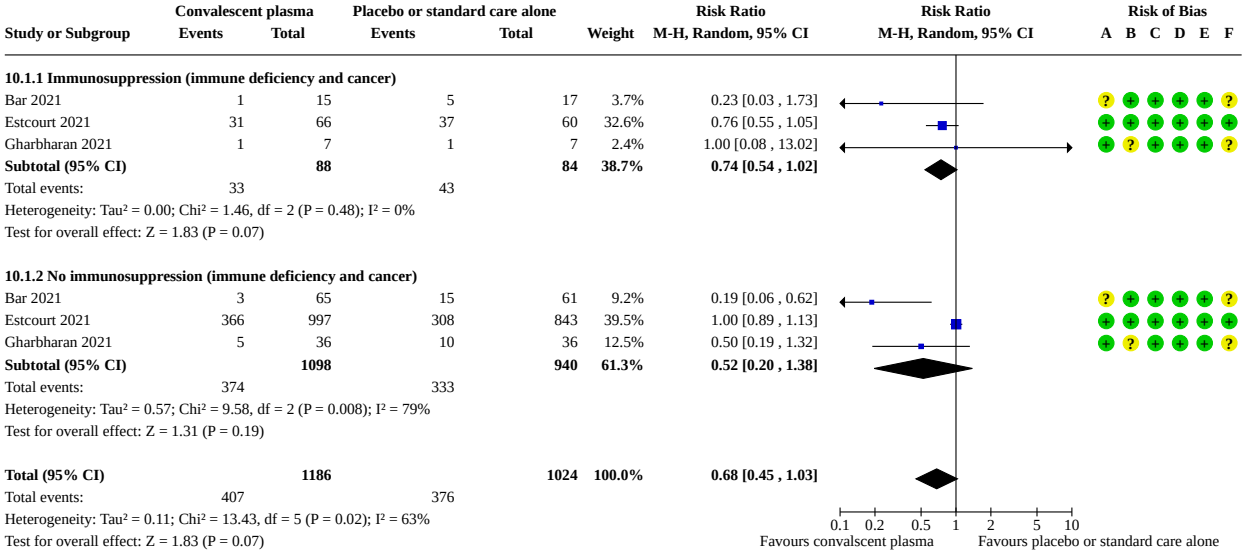
Footnotes
(1) Study is not published yet, data obtained from study investigator

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 10. Subgroup analysis: pre-existing condition immunosuppression for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 All-cause mortality at up to day 28 (random-effects model)	3	2210	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.45, 1.03]
10.1.1 Immunosuppression (immune deficiency and cancer)	3	172	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.54, 1.02]
10.1.2 No immunosuppression (immune deficiency and cancer)	3	2038	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.20, 1.38]
10.2 Clinical improvement: participants discharged from hospital	1	86	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.83, 1.41]
10.2.1 Immunosuppression (immune deficiency and cancer)	1	14	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.65, 1.53]
10.2.2 No immunosuppression (immune deficiency and cancer)	1	72	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.81, 1.59]

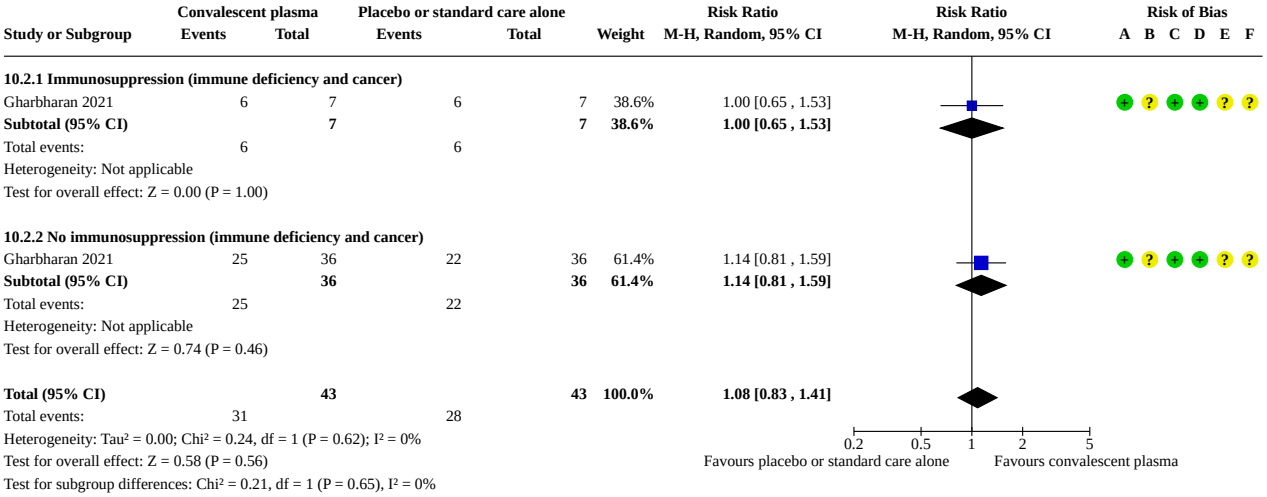
Analysis 10.1. Comparison 10: Subgroup analysis: pre-existing condition immunosuppression for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28 (random-effects model)



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 10.2. Comparison 10: Subgroup analysis: pre-existing condition immunosuppression for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: Clinical improvement: participants discharged from hospital



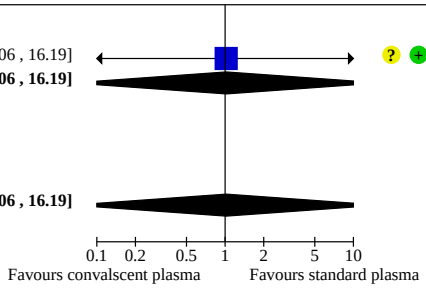
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 11. Subgroup analysis: pre-existing condition immunosuppression for the comparison of convalescent plasma vs. standard plasma for outpatients with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 All-cause mortality at up to day 28	1	416	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.06, 16.19]
11.1.1 No immunosuppression (immune deficiency and cancer)	1	416	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.06, 16.19]
11.2 Admission to hospital or death within 28 days	1	414	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.26, 1.08]
11.2.1 No immunosuppression (immune deficiency and cancer)	1	414	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.26, 1.08]
11.3 All initial symptoms resolved (asymptomatic) at up to day 28	1	416	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.27]
11.3.1 No immunosuppression (immune deficiency and cancer)	1	416	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.27]

Analysis 11.1. Comparison 11: Subgroup analysis: pre-existing condition immunosuppression for the comparison of convalescent plasma vs. standard plasma for outpatients with mild disease, Outcome 1: All-cause mortality at up to day 28

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
11.1.1 No immunosuppression (immune deficiency and cancer)						
CoV-Early (1)	1	206	1	210	100.0%	1.02 [0.06 , 16.19]
Subtotal (95% CI)		**206**		**210**	**100.0%**	**1.02 [0.06 , 16.19]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**206**		**210**	**100.0%**	**1.02 [0.06 , 16.19]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Not applicable						



Footnotes
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Risk of bias legend
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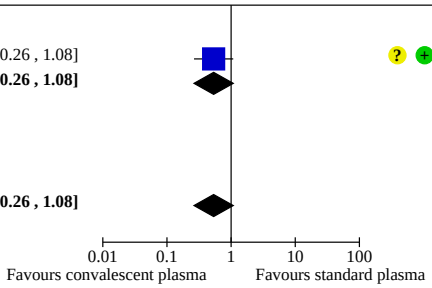
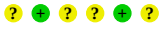
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 11.2. Comparison 11: Subgroup analysis: pre-existing condition immunosuppression for the comparison of convalescent plasma vs. standard plasma for outpatients with mild disease, Outcome 2: Admission to hospital or death within 28 days

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
11.2.1 No immunosuppression (immune deficiency and cancer)						
CoV-Early (1)	11	205	21	209	100.0%	0.53 [0.26 , 1.08]
Subtotal (95% CI)		**205**		**209**	**100.0%**	**0.53 [0.26 , 1.08]**
Total events:	11		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**205**		**209**	**100.0%**	**0.53 [0.26 , 1.08]**
Total events:	11		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.75 (P = 0.08)						
Test for subgroup differences: Not applicable						





Footnotes
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Risk of bias legend
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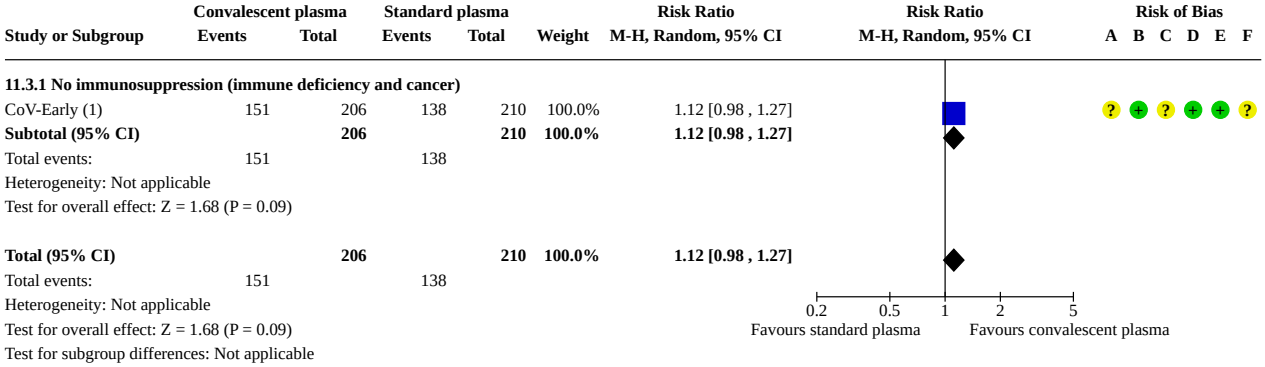
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 11.3. Comparison 11: Subgroup analysis: pre-existing condition immunosuppression for the comparison of convalescent plasma vs. standard plasma for outpatients with mild disease, Outcome 3: All initial symptoms resolved (asymptomatic) at up to day 28



Footnotes
(1) Study is not published yet, data obtained from study investigator

Risk of bias legend
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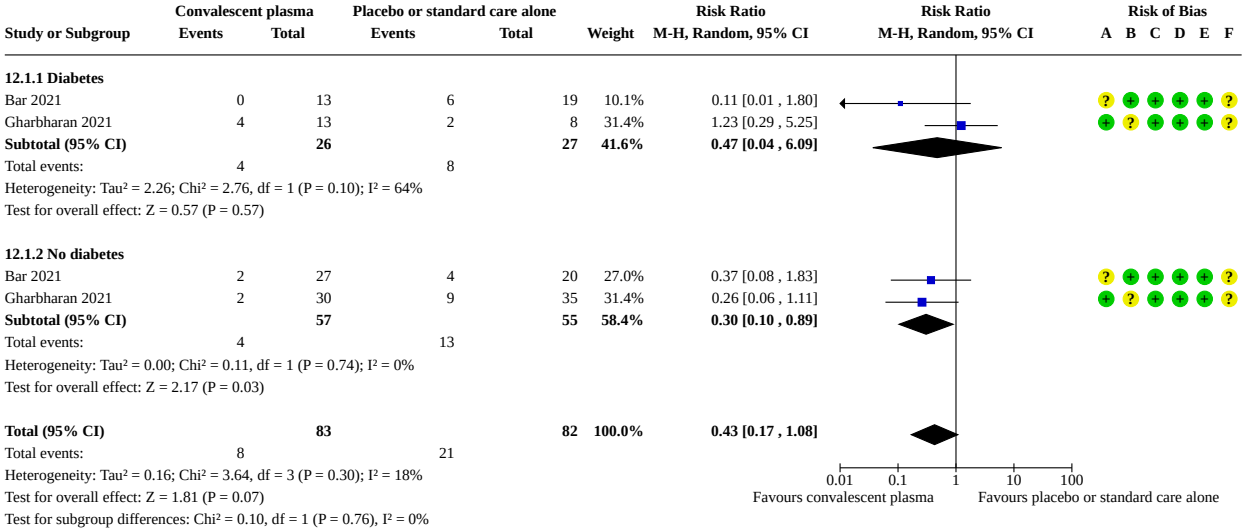
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 12. Subgroup analysis: pre-existing condition diabetes for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 All-cause mortality at up to day 28	2	165	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.08]
12.1.1 Diabetes	2	53	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.04, 6.09]
12.1.2 No diabetes	2	112	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.10, 0.89]
12.2 Clinical worsening: need for invasive mechanical ventilation or death	1	921	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.93, 1.43]
12.2.1 Diabetes	1	318	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.89, 1.85]
12.2.2 No diabetes	1	603	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.84, 1.42]
12.3 Clinical improvement: participants discharged from hospital	1	86	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.85, 1.50]
12.3.1 Diabetes	1	21	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.50, 1.96]
12.3.2 No diabetes	1	65	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.86, 1.59]

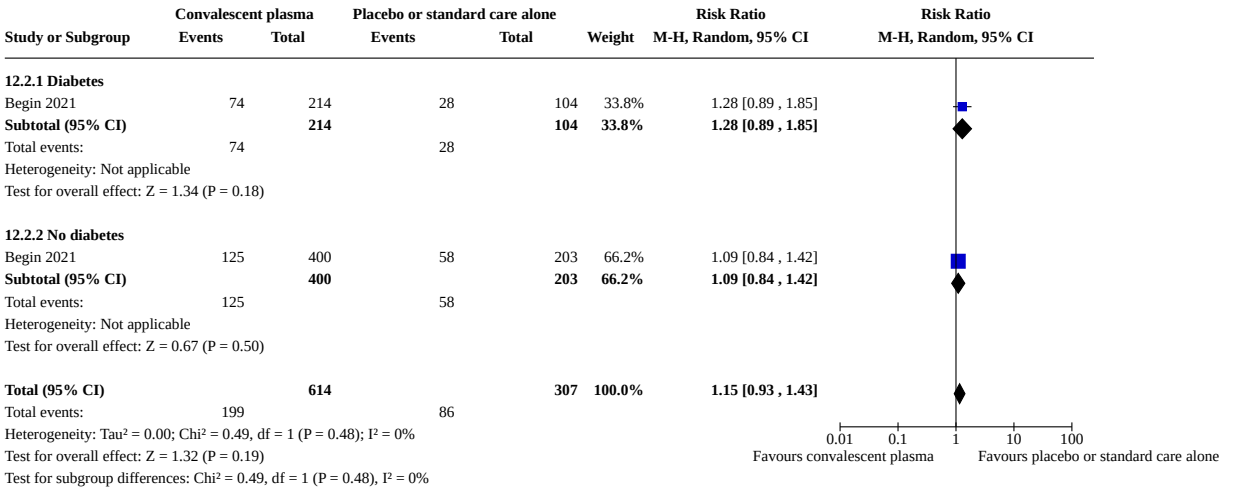
Analysis 12.1. Comparison 12: Subgroup analysis: pre-existing condition diabetes for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



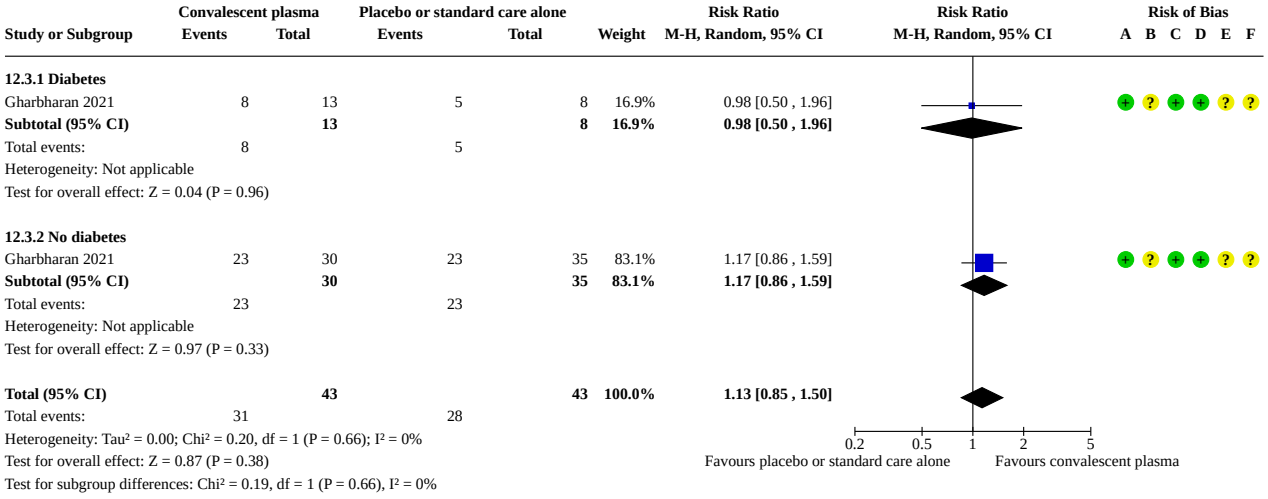
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 12.2. Comparison 12: Subgroup analysis: pre-existing condition diabetes for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: Clinical worsening: need for invasive mechanical ventilation or death



Analysis 12.3. Comparison 12: Subgroup analysis: pre-existing condition diabetes for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: Clinical improvement: participants discharged from hospital



Risk of bias legend
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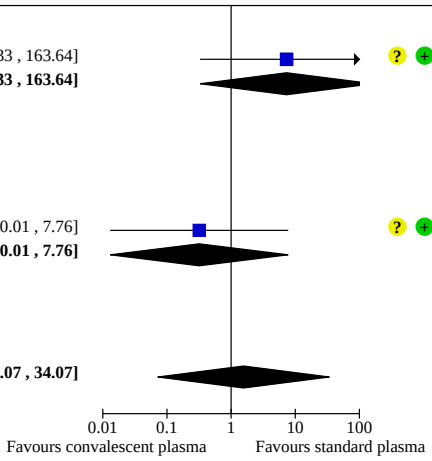
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

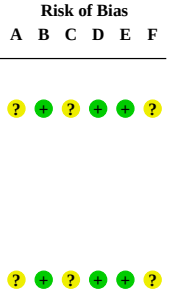
Comparison 13. Subgroup analysis: pre-existing condition diabetes for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 All-cause mortality at up to day 28	1	414	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.07, 34.07]
13.1.1 Diabetes	1	29	Risk Ratio (M-H, Random, 95% CI)	7.33 [0.33, 163.64]
13.1.2 No diabetes	1	385	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.76]
13.2 Admission to hospital or death within 28 days	2	1593	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.32, 0.76]
13.2.1 Diabetes	2	128	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.09, 4.77]
13.2.2 No diabetes	2	1465	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.31, 0.80]
13.3 All initial symptoms resolved (asymptomatic) at up to day 28	1	414	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.88, 1.37]
13.3.1 Diabetes	1	29	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.35, 1.60]
13.3.2 No diabetes	1	385	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.99, 1.29]

Analysis 13.1. Comparison 13: Subgroup analysis: pre-existing condition diabetes for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 1: All-cause mortality at up to day 28

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
13.1.1 Diabetes						
CoV-Early (1)	1	8	0	21	50.7%	7.33 [0.33 , 163.64]
Subtotal (95% CI)		**8**		**21**	**50.7%**	**7.33 [0.33 , 163.64]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
13.1.2 No diabetes						
CoV-Early (1)	0	197	1	188	49.3%	0.32 [0.01 , 7.76]
Subtotal (95% CI)		**197**		**188**	**49.3%**	**0.32 [0.01 , 7.76]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**205**		**209**	**100.0%**	**1.56 [0.07 , 34.07]**
Total events:	1		1			
Heterogeneity: Tau² = 2.36; Chi² = 1.91, df = 1 (P = 0.17); I² = 48%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Chi² = 1.91, df = 1 (P = 0.17), I² = 47.5%						





Footnotes

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Risk of bias legend

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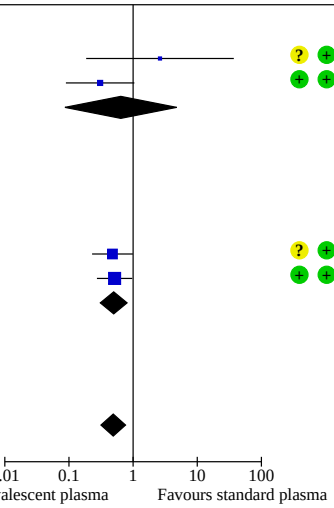
(F) Overall bias

Analysis 13.2. Comparison 13: Subgroup analysis: pre-existing condition diabetes for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 2: Admission to hospital or death within 28 days

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
13.2.1 Diabetes						
CoV-Early (1)	1	8	1	21	2.8%	2.63 [0.19 , 37.14]
Sullivan 2022	3	49	10	50	12.9%	0.31 [0.09 , 1.05]
Subtotal (95% CI)		**57**		**71**	**15.6%**	**0.64 [0.09 , 4.77]**
Total events:	4		11			
Heterogeneity: Tau² = 1.21; Chi² = 2.09, df = 1 (P = 0.15); I² = 52%						
Test for overall effect: Z = 0.43 (P = 0.67)						
13.2.2 No diabetes						
CoV-Early (1)	10	196	20	187	36.2%	0.48 [0.23 , 0.99]
Sullivan 2022	14	543	27	539	48.2%	0.51 [0.27 , 0.97]
Subtotal (95% CI)		**739**		**726**	**84.4%**	**0.50 [0.31 , 0.80]**
Total events:	24		47			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.85 (P = 0.004)						
Total (95% CI)		**796**		**797**	**100.0%**	**0.49 [0.32 , 0.76]**
Total events:	28		58			
Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 3 (P = 0.54); I² = 0%						
Test for overall effect: Z = 3.17 (P = 0.001)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%						



Footnotes

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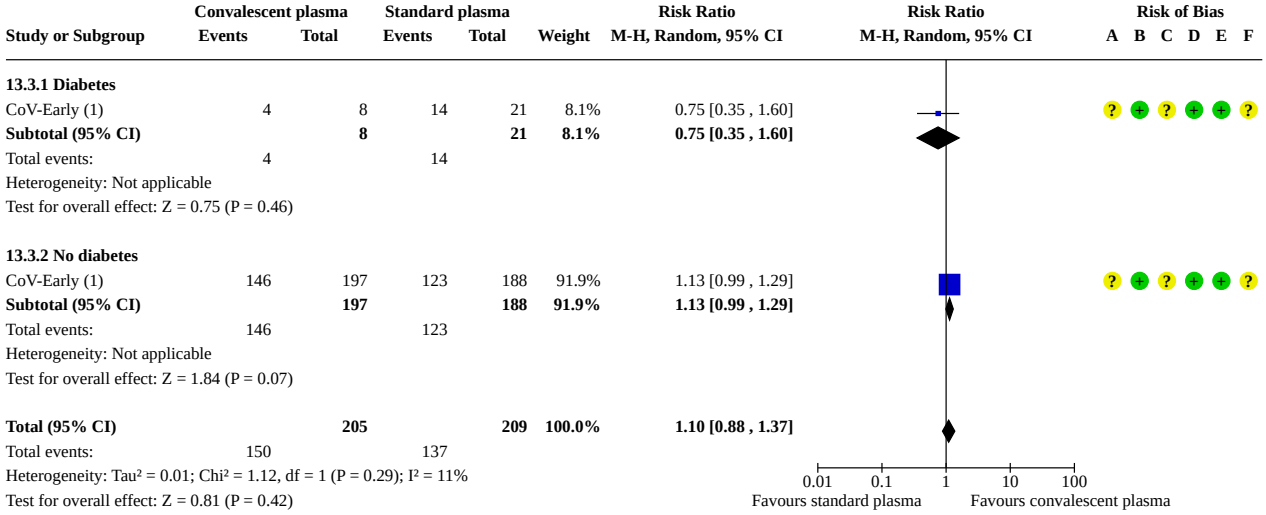
(F) Overall bias

Analysis 13.3. Comparison 13: Subgroup analysis: pre-existing condition diabetes for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 3: All initial symptoms resolved (asymptomatic) at up to day 28



Footnotes

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Risk of bias legend

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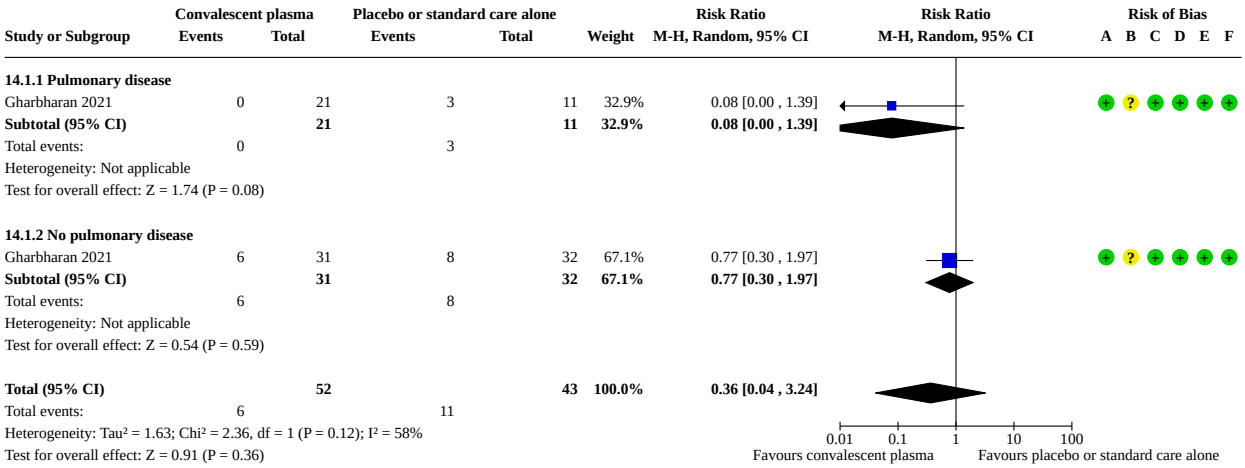
(F) Overall bias

Comparison 14. Subgroup analysis: pre-existing condition respiratory disease for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 All-cause mortality at up to day 28	1	95	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.04, 3.24]
14.1.1 Pulmonary disease	1	32	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.39]
14.1.2 No pulmonary disease	1	63	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.30, 1.97]
14.2 Clinical worsening: need for invasive mechanical ventilation or death	1	921	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.94, 1.43]
14.2.1 Respiratory disease	1	224	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.81, 1.88]
14.2.2 No respiratory disease	1	697	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.88, 1.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.3 Clinical improvement: participants discharged from hospital	1	86	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.83, 1.49]
14.3.1 Pulmonary disease	1	23	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.78, 2.19]
14.3.2 No pulmonary disease	1	63	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.73, 1.46]

Analysis 14.1. Comparison 14: Subgroup analysis: pre-existing condition respiratory disease for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



Risk of bias legend
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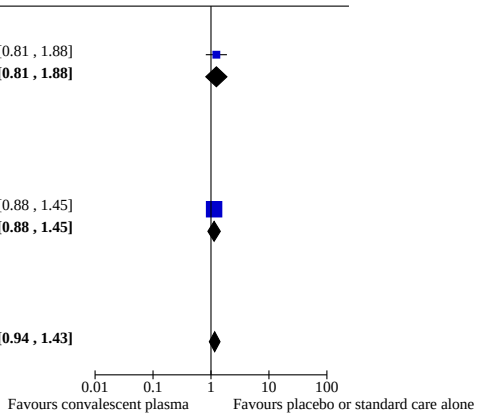
(F) Overall bias

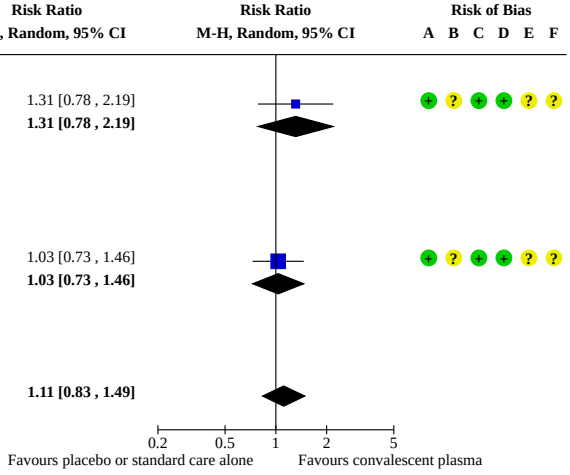
Analysis 14.2. Comparison 14: Subgroup analysis: pre-existing condition respiratory disease for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: Clinical worsening: need for invasive mechanical ventilation or death

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.2.1 Respiratory disease						
Begin 2021	50	145	22	79	25.6%	1.24 [0.81 , 1.88]
Subtotal (95% CI)		**145**		**79**	**25.6%**	**1.24 [0.81 , 1.88]**
Total events:	50		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
14.2.2 No respiratory disease						
Begin 2021	149	469	64	228	74.4%	1.13 [0.88 , 1.45]
Subtotal (95% CI)		**469**		**228**	**74.4%**	**1.13 [0.88 , 1.45]**
Total events:	149		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.32)						
Total (95% CI)		**614**		**307**	**100.0%**	**1.16 [0.94 , 1.43]**
Total events:	199		86			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.35 (P = 0.18)						
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%						



Analysis 14.3. Comparison 14: Subgroup analysis: pre-existing condition respiratory disease for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: Clinical improvement: participants discharged from hospital

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
14.3.1 Pulmonary disease							
Gharbharan 2021	10	12	7	11	31.6%	1.31 [0.78 , 2.19]	+ ? + + ? ?
Subtotal (95% CI)		**12**		**11**	**31.6%**	**1.31 [0.78 , 2.19]**	
Total events:	10		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.03 (P = 0.30)							
14.3.2 No pulmonary disease							
Gharbharan 2021	21	31	21	32	68.4%	1.03 [0.73 , 1.46]	+ ? + + ? ?
Subtotal (95% CI)		**31**		**32**	**68.4%**	**1.03 [0.73 , 1.46]**	
Total events:	21		21				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.18 (P = 0.86)							
Total (95% CI)		**43**		**43**	**100.0%**	**1.11 [0.83 , 1.49]**	
Total events:	31		28				
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%							
Test for overall effect: Z = 0.73 (P = 0.47)							
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.45), I² = 0%							



Risk of bias legend
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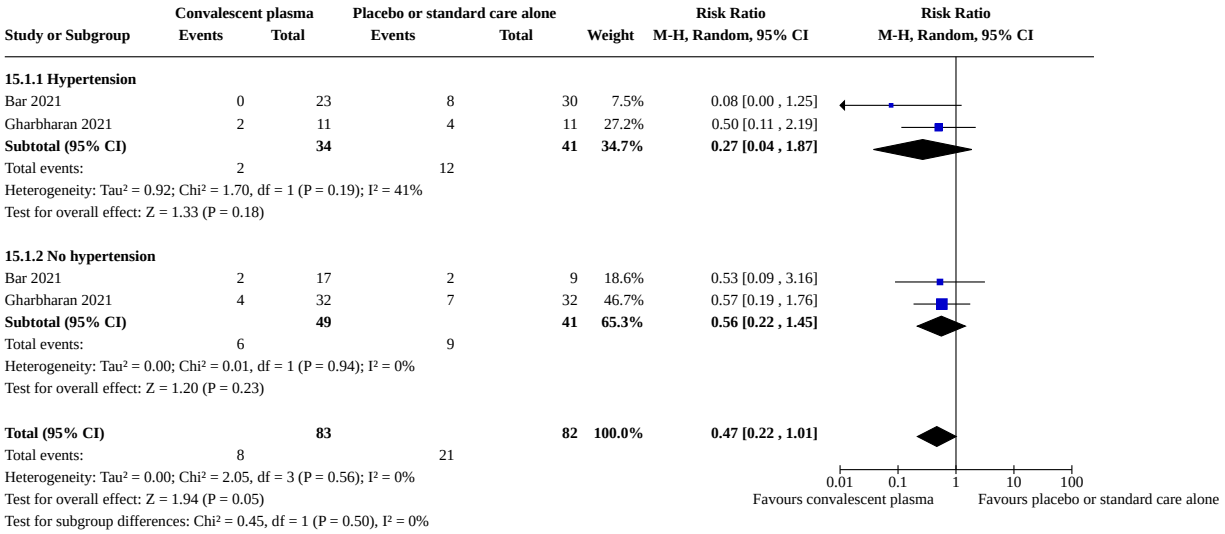
(F) Overall bias

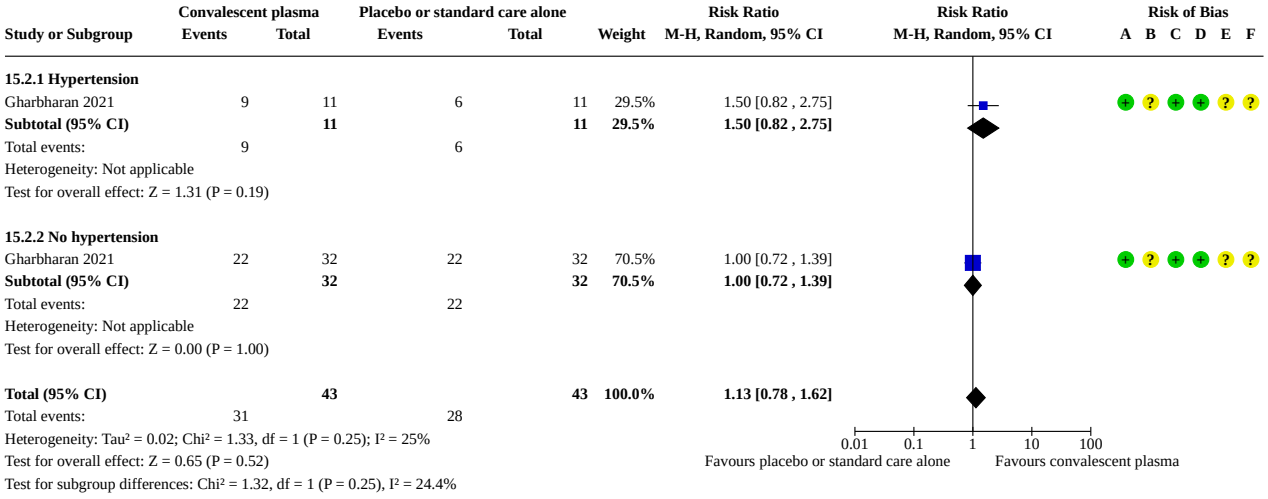
Comparison 15. Subgroup analysis: pre-existing condition hypertension for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 All-cause mortality at up to day 28	2	165	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.22, 1.01]
15.1.1 Hypertension	2	75	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.04, 1.87]
15.1.2 No hypertension	2	90	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.22, 1.45]
15.2 Clinical improvement: participants discharged from hospital	1	86	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.78, 1.62]
15.2.1 Hypertension	1	22	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.82, 2.75]
15.2.2 No hypertension	1	64	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.72, 1.39]

Analysis 15.1. Comparison 15: Subgroup analysis: pre-existing condition hypertension for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



Analysis 15.2. Comparison 15: Subgroup analysis: pre-existing condition hypertension for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: Clinical improvement: participants discharged from hospital



Risk of bias legend
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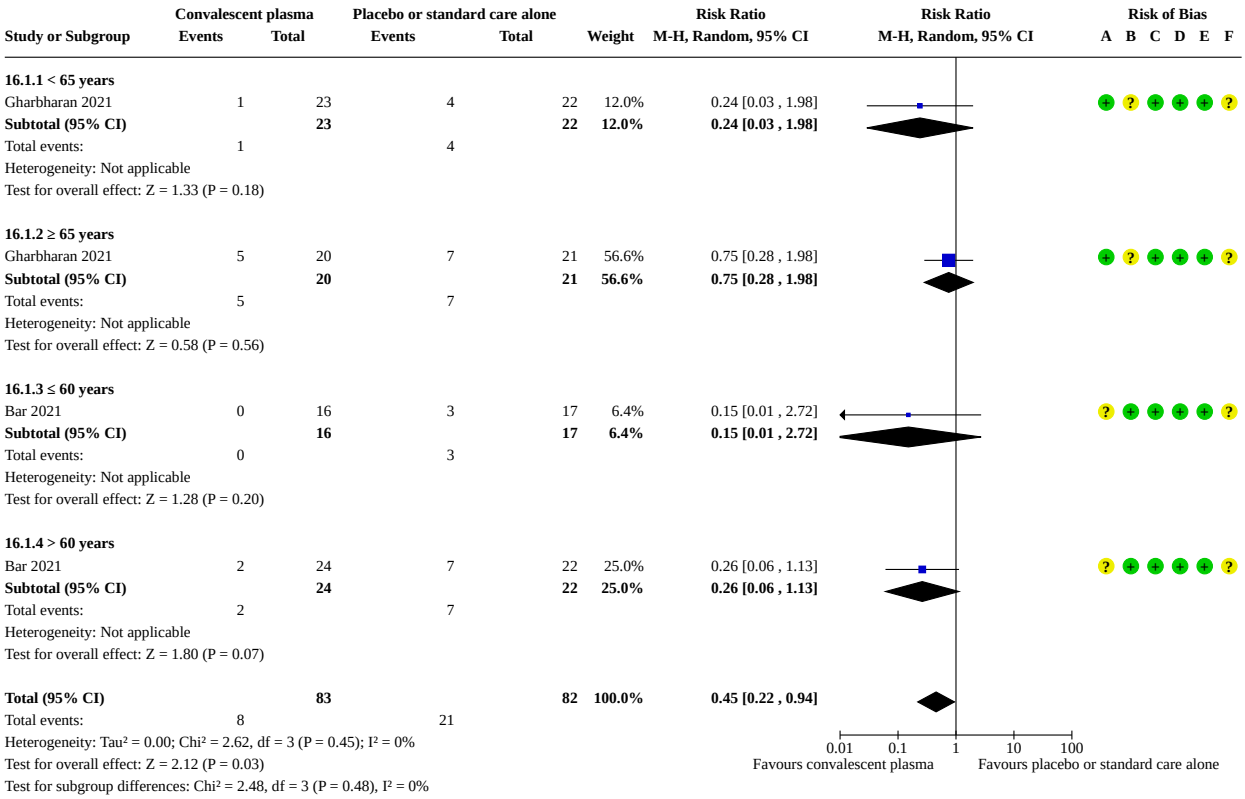
(F) Overall bias

Comparison 16. Subgroup analysis: age of participants for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 All-cause mortality at up to day 28	2	165	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.22, 0.94]
16.1.1 < 65 years	1	45	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.03, 1.98]
16.1.2 ≥ 65 years	1	41	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.28, 1.98]
16.1.3 ≤ 60 years	1	33	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.72]
16.1.4 > 60 years	1	46	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.06, 1.13]
16.2 Clinical worsening: need for invasive mechanical ventilation, or death	2	12042	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.13]
16.2.1 < 60 years	1	272	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.64, 2.37]
16.2.2 ≥ 60 years	1	649	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.92, 1.42]
16.2.3 < 70 years	1	6972	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.11]
16.2.4 ≥ 70 years	1	4149	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.82, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.3 Clinical improvement: participants discharged from hospital	2	11644	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.98, 1.02]
16.3.1 < 65 years	1	45	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.74, 1.38]
16.3.2 ≥ 65 years	1	41	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.74, 2.09]
16.3.3 < 70 years	1	7453	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.02]
16.3.4 > 70 years	1	4105	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]

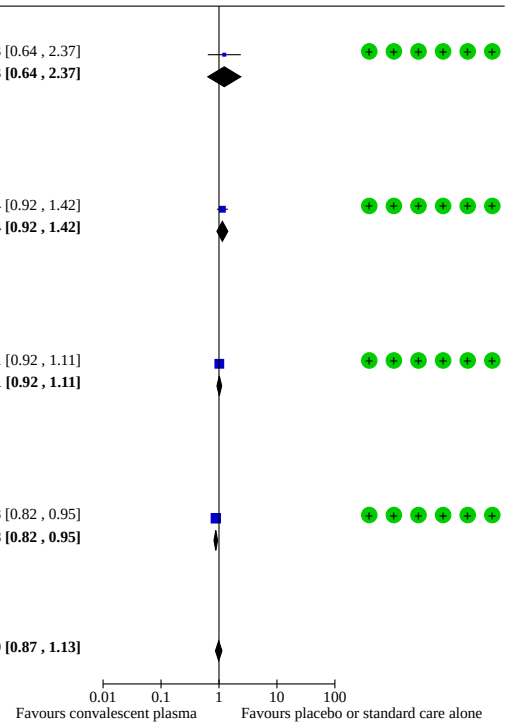
Analysis 16.1. Comparison 16: Subgroup analysis: age of participants for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

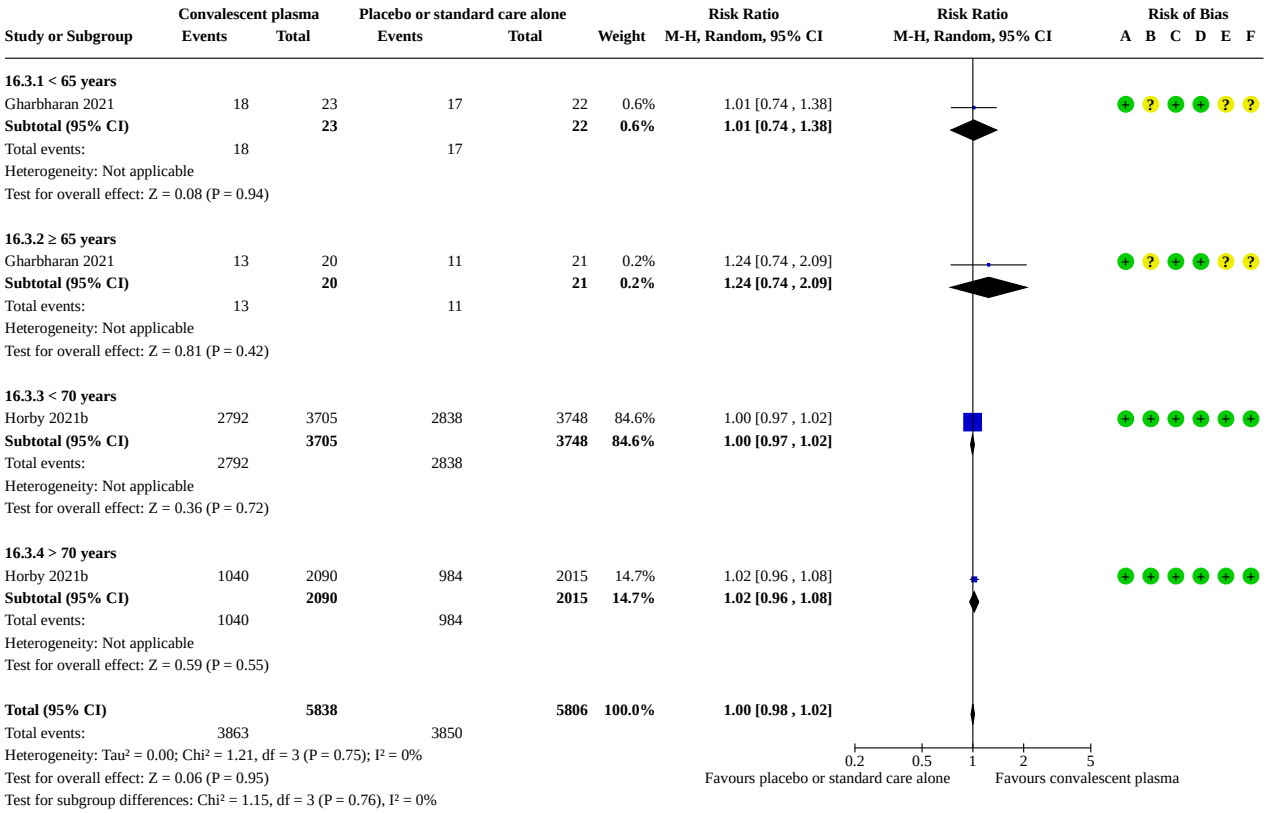
Analysis 16.2. Comparison 16: Subgroup analysis: age of participants for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: Clinical worsening: need for invasive mechanical ventilation, or death

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
16.2.1 < 60 years						
Begin 2021	27	181	11	91	3.6%	1.23 [0.64 , 2.37]
Subtotal (95% CI)		**181**		**91**	**3.6%**	**1.23 [0.64 , 2.37]**
Total events:	27		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
16.2.2 ≥ 60 years						
Begin 2021	172	433	75	216	19.9%	1.14 [0.92 , 1.42]
Subtotal (95% CI)		**433**		**216**	**19.9%**	**1.14 [0.92 , 1.42]**
Total events:	172		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
16.2.3 < 70 years						
Horby 2021b	704	3471	701	3501	36.7%	1.01 [0.92 , 1.11]
Subtotal (95% CI)		**3471**		**3501**	**36.7%**	**1.01 [0.92 , 1.11]**
Total events:	704		701			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
16.2.4 ≥ 70 years						
Horby 2021b	864	2202	867	1947	39.8%	0.88 [0.82 , 0.95]
Subtotal (95% CI)		**2202**		**1947**	**39.8%**	**0.88 [0.82 , 0.95]**
Total events:	864		867			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.45 (P = 0.0006)						
Total (95% CI)		**6287**		**5755**	**100.0%**	**0.99 [0.87 , 1.13]**
Total events:	1767		1654			
Heterogeneity: Tau² = 0.01; Chi² = 9.53, df = 3 (P = 0.02); I² = 69%						
Test for overall effect: Z = 0.17 (P = 0.86)						
Test for subgroup differences: Chi² = 9.39, df = 3 (P = 0.02), I² = 68.0%						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 16.3. Comparison 16: Subgroup analysis: age of participants for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: Clinical improvement: participants discharged from hospital



Risk of bias legend
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(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

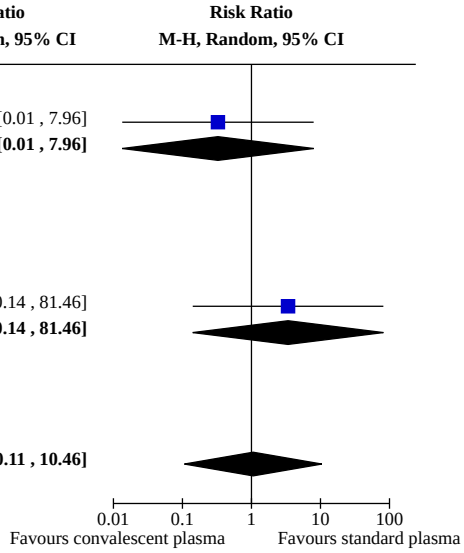
Comparison 17. Subgroup analysis: age of participants for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 All-cause mortality at up to day 28	1	416	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.11, 10.46]
17.1.1 < 65 years	1	303	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.96]
17.1.2 ≥ 65 years	1	113	Risk Ratio (M-H, Random, 95% CI)	3.39 [0.14, 81.46]
17.2 Admission to hospital or death within 28 days	2	1595	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.32, 0.84]
17.2.1 < 65 years	2	1403	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.21, 0.67]
17.2.2 ≥ 65 years	2	192	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.40, 1.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.3 All initial symptoms resolved (asymptomatic) at up to day 28	1	416	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.98, 1.26]
17.3.1 < 65 years	1	303	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.99, 1.35]
17.3.2 ≥ 65 years	1	113	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.83, 1.28]

Analysis 17.1. Comparison 17: Subgroup analysis: age of participants for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 1: All-cause mortality at up to day 28

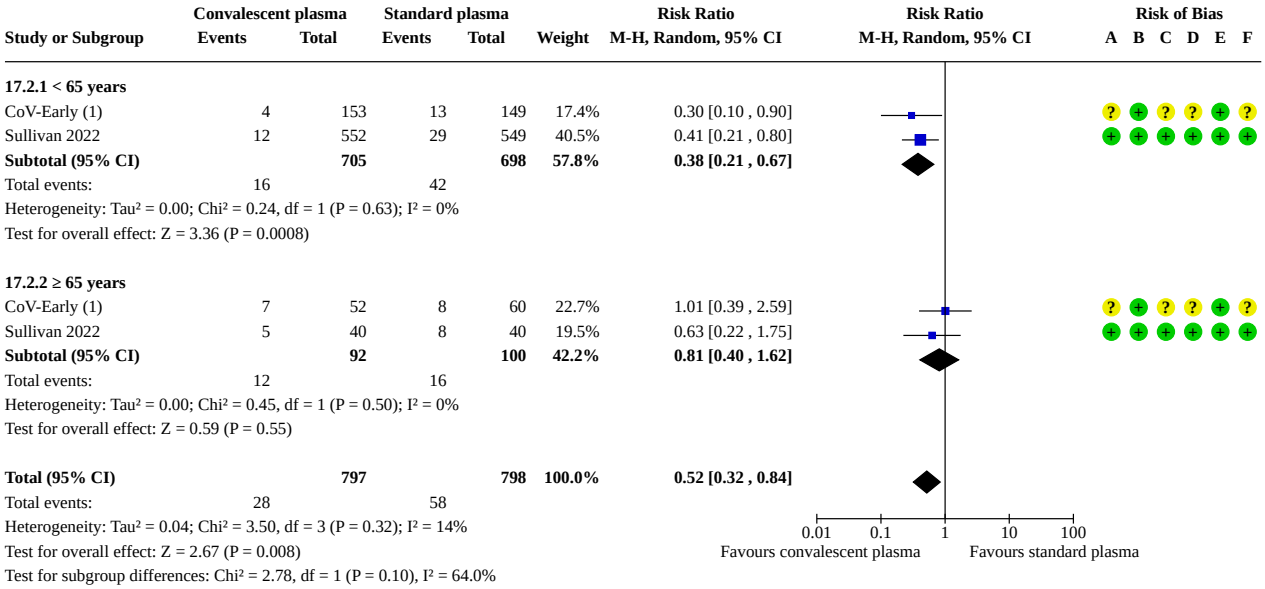
Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
17.1.1 < 65 years						
CoV-Early (1)	0	153	1	150	49.8%	0.33 [0.01 , 7.96]
Subtotal (95% CI)		**153**		**150**	**49.8%**	**0.33 [0.01 , 7.96]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
17.1.2 ≥ 65 years						
CoV-Early (1)	1	53	0	60	50.2%	3.39 [0.14 , 81.46]
Subtotal (95% CI)		**53**		**60**	**50.2%**	**3.39 [0.14 , 81.46]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.75 (P = 0.45)						
Total (95% CI)		**206**		**210**	**100.0%**	**1.06 [0.11 , 10.46]**
Total events:	1		1			
Heterogeneity: Tau² = 0.09; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 3.4%						



Footnotes

(1) Study is not published yet, data obtained from study investigator

Analysis 17.2. Comparison 17: Subgroup analysis: age of participants for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 2: Admission to hospital or death within 28 days



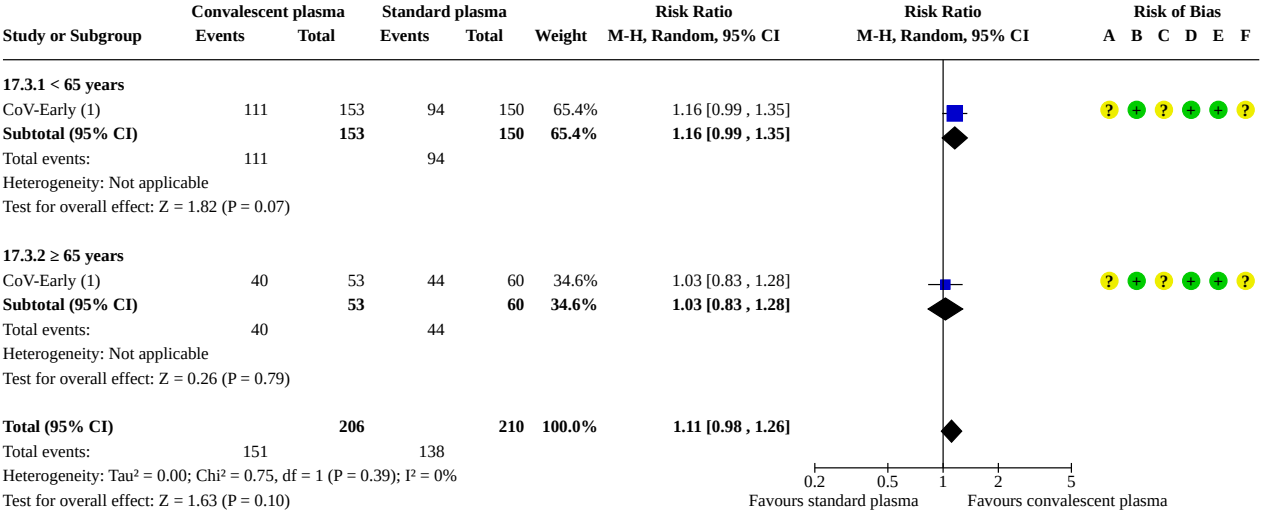
Footnotes

(1) Study is not published yet, data obtained from study investigator

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 17.3. Comparison 17: Subgroup analysis: age of participants for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 3: All initial symptoms resolved (asymptomatic) at up to day 28



Footnotes

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Risk of bias legend

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(C) Bias due to missing outcome data
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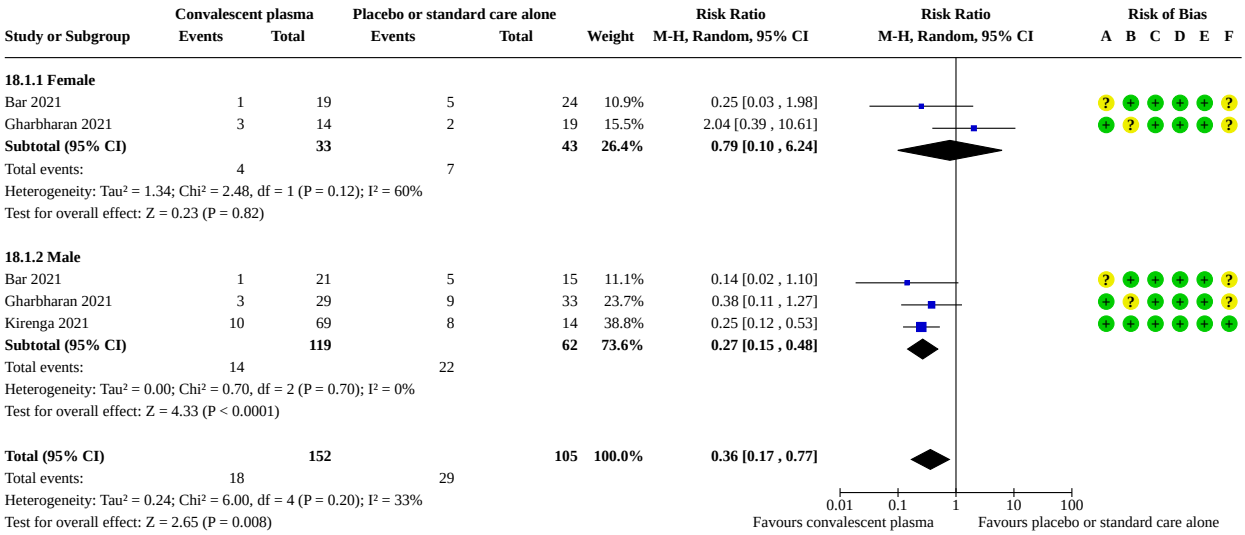
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 18. Subgroup analysis: sex of participants for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 All-cause mortality at up to day 28	3	257	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.17, 0.77]
18.1.1 Female	2	76	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.10, 6.24]
18.1.2 Male	3	181	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.15, 0.48]
18.2 Clinical worsening: need for invasive mechanical ventilation or death	3	11332	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.88, 1.36]
18.2.1 Female	3	4481	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.08]
18.2.2 Male	3	6851	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.01, 1.54]
18.3 Clinical improvement: participants discharged from hospital	2	11644	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.3.1 Female	2	4152	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.96, 1.05]
18.3.2 Male	2	7492	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.96, 1.02]

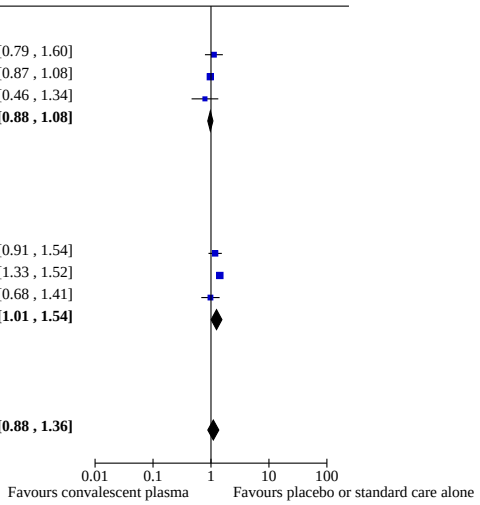
Analysis 18.1. Comparison 18: Subgroup analysis: sex of participants for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

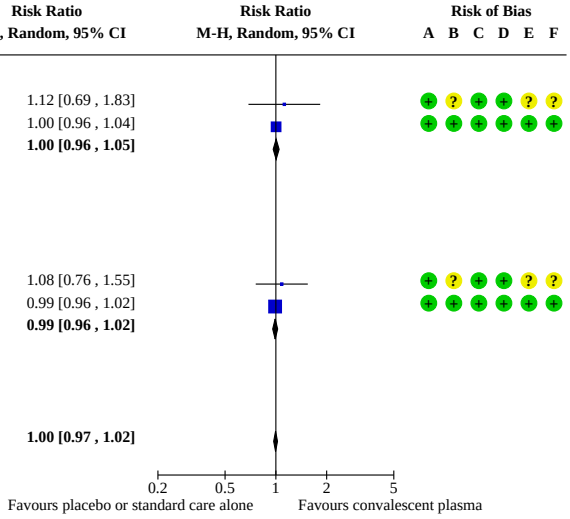
Analysis 18.2. Comparison 18: Subgroup analysis: sex of participants for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: Clinical worsening: need for invasive mechanical ventilation or death

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
18.2.1 Female						
Begin 2021	73	252	32	124	14.3%	1.12 [0.79 , 1.60]
Horby 2021b	499	2052	472	1885	21.9%	0.97 [0.87 , 1.08]
Menichetti 2021	18	82	24	86	9.8%	0.79 [0.46 , 1.34]
Subtotal (95% CI)		**2386**		**2095**	**46.0%**	**0.98 [0.88 , 1.08]**
Total events:	590		528			
Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
18.2.2 Male						
Begin 2021	126	362	54	183	17.3%	1.18 [0.91 , 1.54]
Horby 2021b	1069	2441	1096	3563	22.6%	1.42 [1.33 , 1.52]
Menichetti 2021	41	149	43	153	14.1%	0.98 [0.68 , 1.41]
Subtotal (95% CI)		**2952**		**3899**	**54.0%**	**1.25 [1.01 , 1.54]**
Total events:	1236		1193			
Heterogeneity: Tau² = 0.02; Chi² = 5.55, df = 2 (P = 0.06); I² = 64%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Total (95% CI)		**5338**		**5994**	**100.0%**	**1.10 [0.88 , 1.36]**
Total events:	1826		1721			
Heterogeneity: Tau² = 0.05; Chi² = 40.59, df = 5 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 0.83 (P = 0.41)						
Test for subgroup differences: Chi² = 4.10, df = 1 (P = 0.04), I² = 75.6%						



Analysis 18.3. Comparison 18: Subgroup analysis: sex of participants for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: Clinical improvement: participants discharged from hospital

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
18.3.1 Female						
Gharbharan 2021	11	14	7	10	0.3%	1.12 [0.69 , 1.83]
Horby 2021b	1500	2152	1373	1976	41.0%	1.00 [0.96 , 1.04]
Subtotal (95% CI)		**2166**		**1986**	**41.3%**	**1.00 [0.96 , 1.05]**
Total events:	1511		1380			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
18.3.2 Male						
Gharbharan 2021	20	29	21	33	0.5%	1.08 [0.76 , 1.55]
Horby 2021b	2332	3643	2449	3787	58.2%	0.99 [0.96 , 1.02]
Subtotal (95% CI)		**3672**		**3820**	**58.7%**	**0.99 [0.96 , 1.02]**
Total events:	2352		2470			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**5838**		**5806**	**100.0%**	**1.00 [0.97 , 1.02]**
Total events:	3863		3850			
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 3 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.77)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						



Risk of bias legend

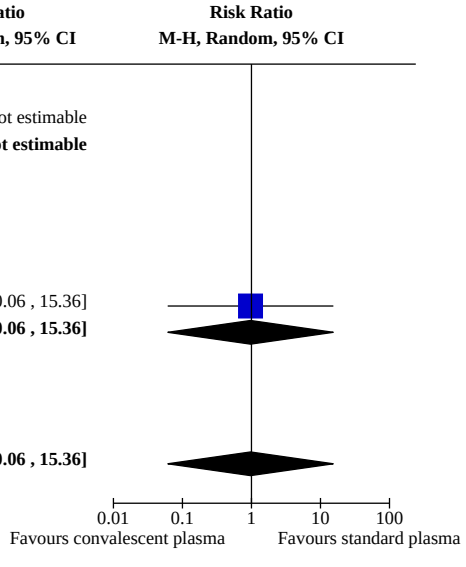
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 19. Subgroup analysis: sex of participants for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 All-cause mortality at up to day 28	1	416	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 15.36]
19.1.1 Female	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
19.1.2 Male	1	321	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 15.36]
19.2 Admission to hospital or death within 28 days	2	1595	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.32, 0.77]
19.2.1 Female	2	770	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.21, 0.82]
19.2.2 Male	2	825	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.31, 1.02]
19.3 All initial symptoms resolved (asymptomatic) at up to day 28	1	416	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.98, 1.26]
19.3.1 Female	1	95	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.78, 1.44]
19.3.2 Male	1	321	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.98, 1.29]

Analysis 19.1. Comparison 19: Subgroup analysis: sex of participants for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 1: All-cause mortality at up to day 28

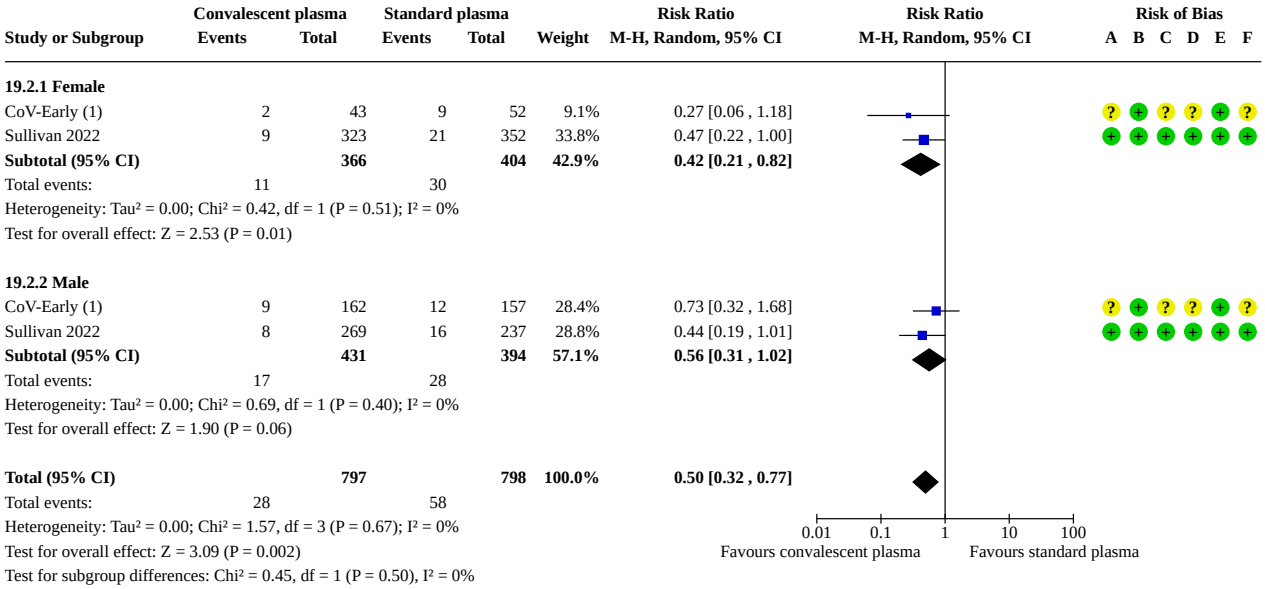
Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
19.1.1 Female						
CoV-Early (1)	0	43	0	52		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
19.1.2 Male						
CoV-Early (1)	1	163	1	158	100.0%	0.97 [0.06 , 15.36]
Subtotal (95% CI)		**163**		**158**	**100.0%**	**0.97 [0.06 , 15.36]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
Total (95% CI)		**206**		**210**	**100.0%**	**0.97 [0.06 , 15.36]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Study is not published yet, data obtained from study investigator

Analysis 19.2. Comparison 19: Subgroup analysis: sex of participants for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 2: Admission to hospital or death within 28 days



Footnotes

(1) Study is not published yet, data obtained from study investigator

Risk of bias legend

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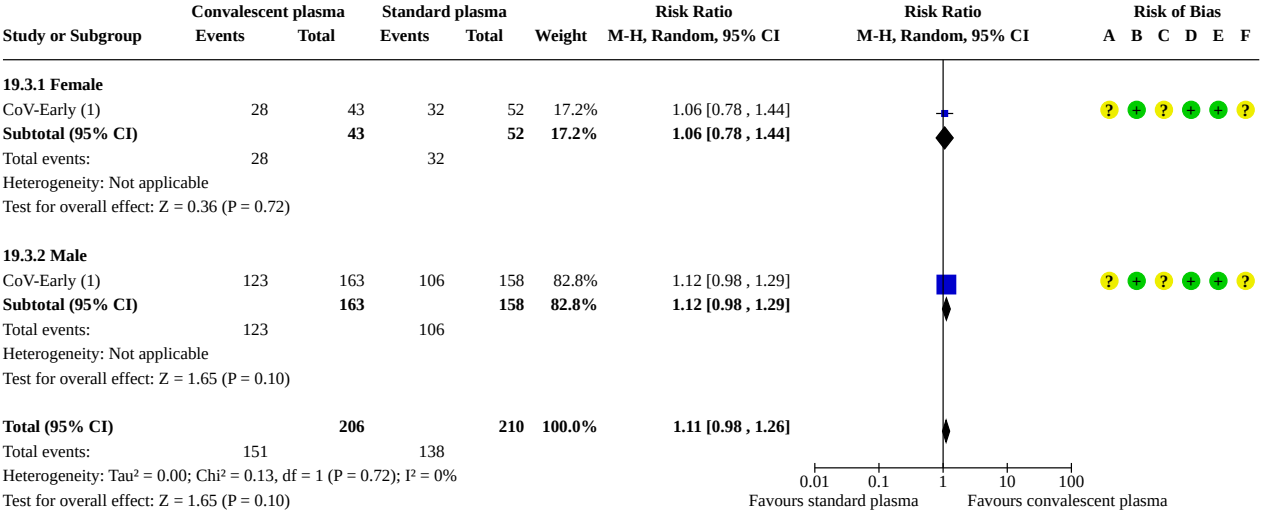
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 19.3. Comparison 19: Subgroup analysis: sex of participants for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 3: All initial symptoms resolved (asymptomatic) at up to day 28



Footnotes

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Risk of bias legend

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(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
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(F) Overall bias

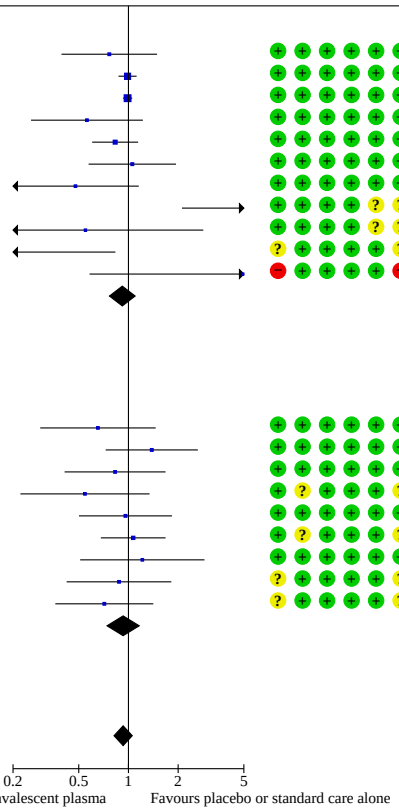
Comparison 20. Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 All-cause mortality at up to day 28	20	18100	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
20.1.1 High-income countries	11	16530	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.10]
20.1.2 Low- to middle-income countries	9	1570	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.16]
20.2 Clinical worsening: need for invasive mechanical ventilation, or death at up to day 28	5	13556	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.09]
20.2.1 High-income countries	3	12759	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.93, 1.16]
20.2.2 Low- to middle-income countries	2	797	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.74, 1.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.3 Clinical improvement: participants discharged from hospital	6	12721	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.02]
20.3.1 High-income countries	2	12041	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.02]
20.3.2 Low- to middle-income countries	4	680	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.13]
20.4 Grades 3 and 4 adverse events	5	1471	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.77, 1.80]
20.4.1 High-income countries	2	527	Risk Ratio (M-H, Random, 95% CI)	3.06 [1.00, 9.36]
20.4.2 Low- to middle-income countries	3	944	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.83, 1.40]
20.5 Serious adverse events	5	3980	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.81, 1.24]
20.5.1 High-income countries	4	3647	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.19]
20.5.2 Low- to middle-income countries	1	333	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.82, 2.09]

Analysis 20.1. Comparison 20: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
20.1.1 High-income countries							
Menichetti 2021	14	231	19	240	3.2%	0.77 [0.39 , 1.49]	+ + + + + +
Estcourt 2021	352	1074	300	904	22.0%	0.99 [0.87 , 1.12]	+ + + + + +
Horby 2021b	1399	5795	1408	5763	26.1%	0.99 [0.93 , 1.05]	+ + + + + +
Koerper 2021	8	53	14	52	2.4%	0.56 [0.26 , 1.22]	+ + + + + +
Ortigoza 2022	59	462	71	462	10.1%	0.83 [0.60 , 1.14]	+ + + + + +
Devos 2021	29	320	14	163	3.8%	1.06 [0.57 , 1.94]	+ + + + + +
Avendano-Sola 2021	7	179	14	171	1.9%	0.48 [0.20 , 1.15]	+ + + + + +
AlQahtani 2021	16	20	2	20	0.9%	8.00 [2.11 , 30.34]	+ + + + ? ?
Holm 2021	2	17	3	14	0.6%	0.55 [0.11 , 2.84]	+ + + + ? ?
Bar 2021	2	40	10	39	0.7%	0.20 [0.05 , 0.83]	? + + + + ?
Korley 2021	5	257	1	254	0.3%	4.94 [0.58 , 42.00]	− + + + + −
Subtotal (95% CI)		**8448**		**8082**	**72.1%**	**0.92 [0.77 , 1.10]**	
Total events:	1893		1856				
Heterogeneity: Tau² = 0.03; Chi² = 23.14, df = 10 (P = 0.01); I² = 57%							
Test for overall effect: Z = 0.94 (P = 0.35)							
20.1.2 Low- to middle-income countries							
Li 2020	8	51	12	50	2.3%	0.65 [0.29 , 1.46]	+ + + + + +
Sekine 2021	18	80	13	80	3.4%	1.38 [0.73 , 2.63]	+ + + + + +
Van den Berg 2022	11	52	13	51	2.9%	0.83 [0.41 , 1.68]	+ + + + + +
Gharbharan 2021	6	43	11	43	1.9%	0.55 [0.22 , 1.34]	+ ? + + + ?
Simonovich 2020	25	228	12	105	3.4%	0.96 [0.50 , 1.83]	+ + + + + +
Agarwal 2020	34	235	31	229	6.2%	1.07 [0.68 , 1.68]	+ ? + + + ?
Kirenga 2021	10	69	8	67	2.0%	1.21 [0.51 , 2.89]	+ + + + + +
De Santis 2022	8	36	18	71	2.7%	0.88 [0.42 , 1.82]	? + + + + ?
Ray 2022	10	40	14	40	3.1%	0.71 [0.36 , 1.41]	? + + + + ?
Subtotal (95% CI)		**834**		**736**	**27.9%**	**0.93 [0.74 , 1.16]**	
Total events:	130		132				
Heterogeneity: Tau² = 0.00; Chi² = 5.00, df = 8 (P = 0.76); I² = 0%							
Test for overall effect: Z = 0.65 (P = 0.52)							
Total (95% CI)		**9282**		**8818**	**100.0%**	**0.93 [0.82 , 1.05]**	
Total events:	2023		1988				
Heterogeneity: Tau² = 0.02; Chi² = 28.33, df = 19 (P = 0.08); I² = 33%							
Test for overall effect: Z = 1.14 (P = 0.25)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%							

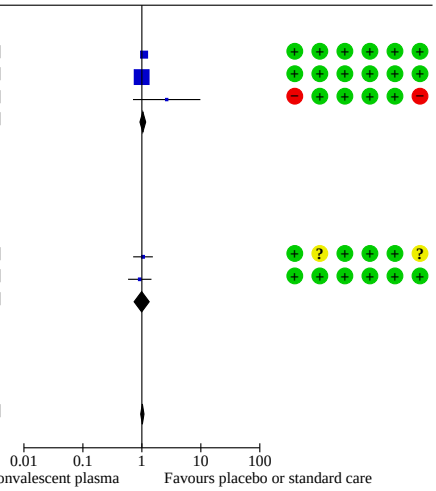


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 20.2. Comparison 20: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: Clinical worsening: need for invasive mechanical ventilation, or death at up to day 28

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
20.2.1 High-income countries						
Estcourt 2021	347	701	275	606	25.9%	1.09 [0.97 , 1.22]
Horby 2021b	1568	5493	1568	5448	69.3%	0.99 [0.93 , 1.05]
Korley 2021	8	257	3	254	0.2%	2.64 [0.71 , 9.82]
Subtotal (95% CI)		**6451**		**6308**	**95.4%**	**1.04 [0.93 , 1.16]**
Total events:	1923		1846			
Heterogeneity: Tau² = 0.00; Chi² = 4.13, df = 2 (P = 0.13); I² = 52%						
Test for overall effect: Z = 0.65 (P = 0.51)						
20.2.2 Low- to middle-income countries						
Agarwal 2020	44	235	41	229	2.7%	1.05 [0.71 , 1.54]
Simonovich 2020	44	228	22	105	1.9%	0.92 [0.58 , 1.45]
Subtotal (95% CI)		**463**		**334**	**4.6%**	**0.99 [0.74 , 1.33]**
Total events:	88		63			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		**6914**		**6642**	**100.0%**	**1.02 [0.96 , 1.09]**
Total events:	2011		1909			
Heterogeneity: Tau² = 0.00; Chi² = 4.32, df = 4 (P = 0.36); I² = 7%						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
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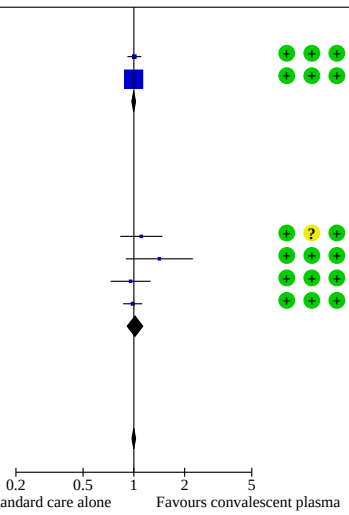
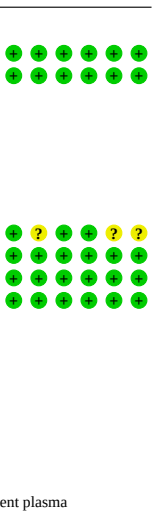
(F) Overall bias

Analysis 20.3. Comparison 20: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: Clinical improvement: participants discharged from hospital

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
20.3.1 High-income countries						
Devos 2021	257	320	130	163	6.7%	1.01 [0.92 , 1.11]
Horby 2021b	3832	5795	3822	5763	88.0%	1.00 [0.97 , 1.02]
Subtotal (95% CI)		**6115**		**5926**	**94.7%**	**1.00 [0.97 , 1.02]**
Total events:	4089		3952			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.86)						
20.3.2 Low- to middle-income countries						
Gharbharan 2021	31	43	28	43	0.7%	1.11 [0.83 , 1.48]
Li 2020	26	51	18	50	0.3%	1.42 [0.90 , 2.24]
Sekine 2021	44	80	46	80	0.8%	0.96 [0.73 , 1.26]
Simonovich 2020	171	228	80	105	3.5%	0.98 [0.86 , 1.12]
Subtotal (95% CI)		**402**		**278**	**5.3%**	**1.02 [0.91 , 1.13]**
Total events:	272		172			
Heterogeneity: Tau² = 0.00; Chi² = 2.89, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**6517**		**6204**	**100.0%**	**1.00 [0.97 , 1.02]**
Total events:	4361		4124			
Heterogeneity: Tau² = 0.00; Chi² = 2.93, df = 5 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						



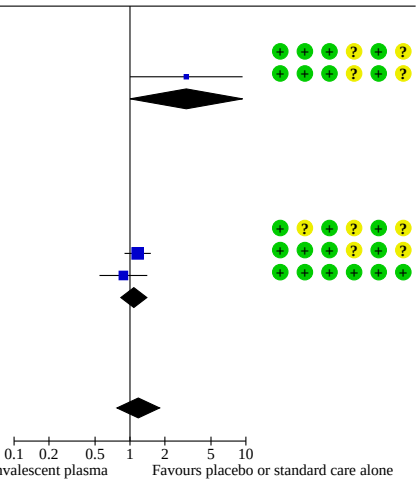


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 20.4. Comparison 20: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 4: Grades 3 and 4 adverse events

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
20.4.1 High-income countries						
AlQahtani 2021	0	20	0	20		Not estimable
Menichetti 2021	12	241	4	246	11.8%	3.06 [1.00 , 9.36]
Subtotal (95% CI)		**261**		**266**	**11.8%**	**3.06 [1.00 , 9.36]**
Total events:	12		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
20.4.2 Low- to middle-income countries						
Agarwal 2020	0	227	0	224		Not estimable
Sekine 2021	50	79	44	81	52.4%	1.17 [0.90 , 1.51]
Simonovich 2020	40	228	21	105	35.9%	0.88 [0.55 , 1.41]
Subtotal (95% CI)		**534**		**410**	**88.2%**	**1.08 [0.83 , 1.40]**
Total events:	90		65			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.16$, df = 1 (P = 0.28); $I^2 = 14\%$						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**795**		**676**	**100.0%**	**1.18 [0.77 , 1.80]**
Total events:	102		69			
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 4.22$, df = 2 (P = 0.12); $I^2 = 53\%$						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: $Chi^2 = 3.17$, df = 1 (P = 0.07), $I^2 = 68.5\%$						



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
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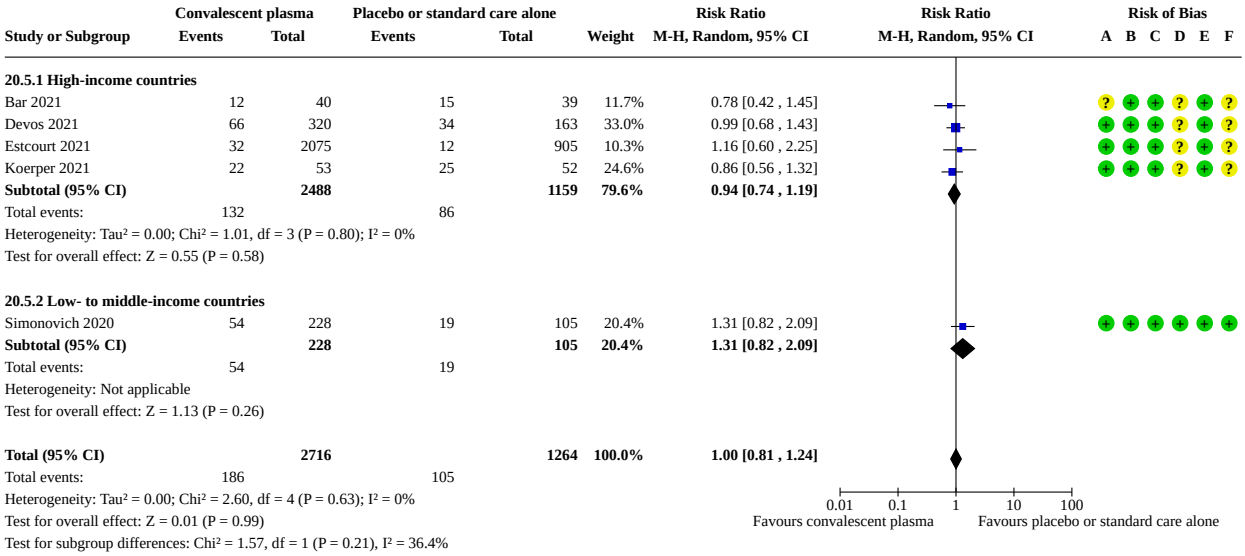
(F) Overall bias

Analysis 20.5. Comparison 20: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 5: Serious adverse events



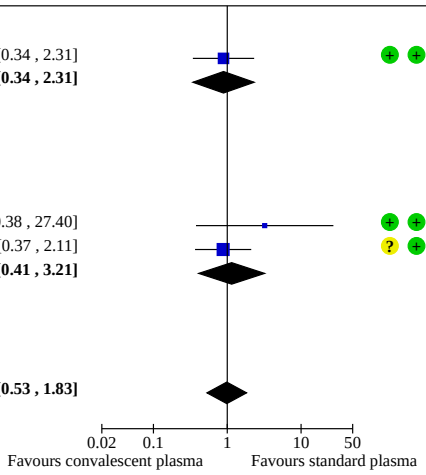
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 21. Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus standard plasma for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 All-cause mortality at up to day 28	3	261	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.53, 1.83]
21.1.1 High-income countries	1	74	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.34, 2.31]
21.1.2 Low- to middle-income countries	2	187	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.41, 3.21]
21.2 Clinical worsening: need for invasive mechanical ventilation or death at up to day 28	1	34	Risk Ratio (M-H, Random, 95% CI)	5.59 [0.29, 108.38]
21.2.1 High-income countries	1	34	Risk Ratio (M-H, Random, 95% CI)	5.59 [0.29, 108.38]
21.3 Serious adverse events	2	108	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.48, 2.71]
21.3.1 High-income countries	2	108	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.48, 2.71]

Analysis 21.1. Comparison 21: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28

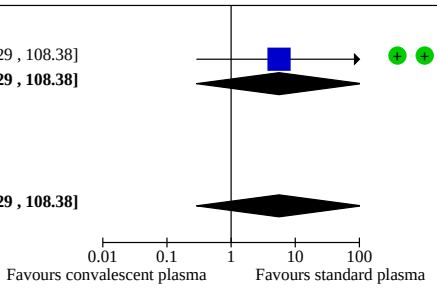
Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
21.1.1 High-income countries							
Bennett-Guerrero 2021	14	59	4	15	41.9%	0.89 [0.34 , 2.31]	+ + + + + +
Subtotal (95% CI)		**59**		**15**	**41.9%**	**0.89 [0.34 , 2.31]**	
Total events:	14		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.24 (P = 0.81)							
21.1.2 Low- to middle-income countries							
Bajpai 2020	3	14	1	15	8.3%	3.21 [0.38 , 27.40]	+ + + + + +
Baldeon 2022	7	63	12	95	49.8%	0.88 [0.37 , 2.11]	? + + + + ?
Subtotal (95% CI)		**77**		**110**	**58.1%**	**1.15 [0.41 , 3.21]**	
Total events:	10		13				
Heterogeneity: Tau² = 0.15; Chi² = 1.21, df = 1 (P = 0.27); I² = 17%							
Test for overall effect: Z = 0.26 (P = 0.79)							
Total (95% CI)		**136**		**125**	**100.0%**	**0.98 [0.53 , 1.83]**	
Total events:	24		17				
Heterogeneity: Tau² = 0.00; Chi² = 1.29, df = 2 (P = 0.53); I² = 0%							
Test for overall effect: Z = 0.05 (P = 0.96)							
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

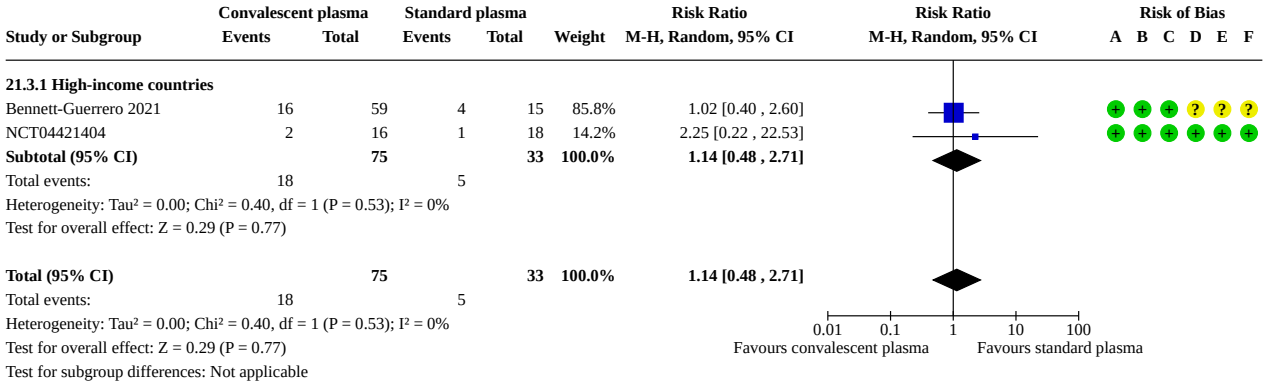
Analysis 21.2. Comparison 21: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 2: Clinical worsening: need for invasive mechanical ventilation or death at up to day 28

Study or Subgroup	Convalescent plasma Events	Total	Standard plasma Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
21.2.1 High-income countries							
NCT04421404	2	16	0	18	100.0%	5.59 [0.29 , 108.38]	+ + + + + +
Subtotal (95% CI)		**16**		**18**	**100.0%**	**5.59 [0.29 , 108.38]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.14 (P = 0.26)							
Total (95% CI)		**16**		**18**	**100.0%**	**5.59 [0.29 , 108.38]**	
Total events:	2		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.14 (P = 0.26)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 21.3. Comparison 21: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 3: Serious adverse events



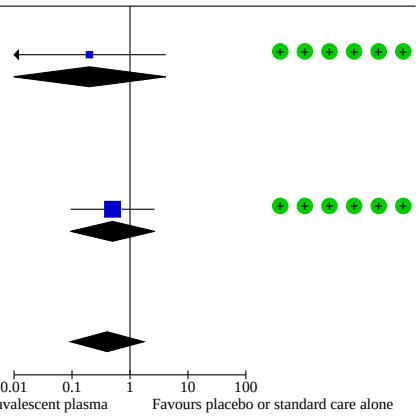
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 22. Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for outpatients with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 All-cause mortality at up tp day 28	2	536	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.09, 1.74]
22.1.1 High-income countries	1	376	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.14]
22.1.2 Low- to middle-income countries	1	160	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.09, 2.65]
22.2 Grades 3 and 4 adverse events	1	376	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.75, 2.19]
22.2.1 High-income countries	1	376	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.75, 2.19]
22.3 Serious adverse events	1	376	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.66, 1.94]
22.3.1 High-income countries	1	376	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.66, 1.94]

Analysis 22.1. Comparison 22: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 1: All-cause mortality at up tp day 28

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
22.1.1 High-income countries						
Alemany 2022	0	188	2	188	23.3%	0.20 [0.01 , 4.14]
Subtotal (95% CI)		**188**		**188**	**23.3%**	**0.20 [0.01 , 4.14]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
22.1.2 Low- to middle-income countries						
Libster 2020	2	80	4	80	76.7%	0.50 [0.09 , 2.65]
Subtotal (95% CI)		**80**		**80**	**76.7%**	**0.50 [0.09 , 2.65]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
Total (95% CI)		**268**		**268**	**100.0%**	**0.40 [0.09 , 1.74]**
Total events:	2		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%						



Risk of bias legend
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(B) Bias due to deviations from intended interventions
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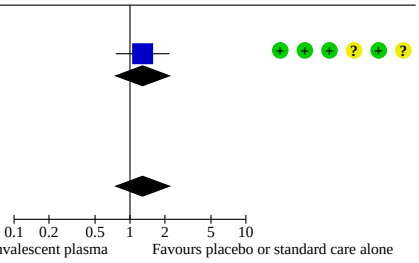
(F) Overall bias

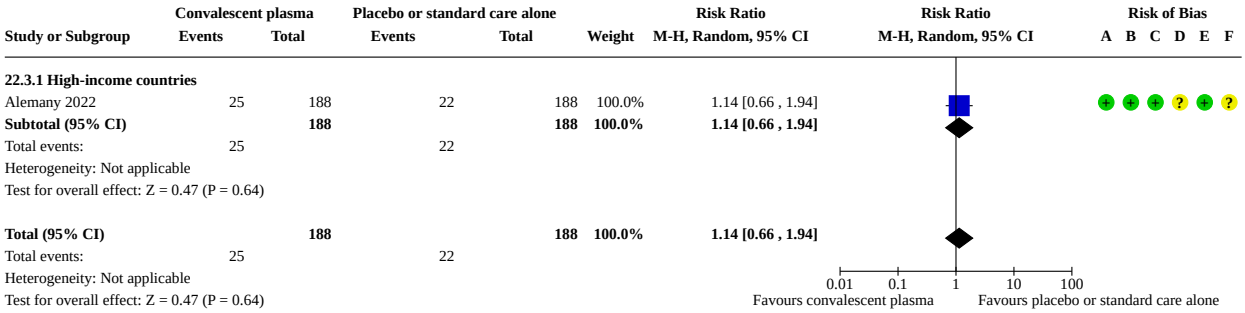
Analysis 22.2. Comparison 22: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 2: Grades 3 and 4 adverse events

Study or Subgroup	Convalescent plasma Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
22.2.1 High-income countries						
Alemany 2022	27	188	21	188	100.0%	1.29 [0.75 , 2.19]
Subtotal (95% CI)		**188**		**188**	**100.0%**	**1.29 [0.75 , 2.19]**
Total events:	27		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Total (95% CI)		**188**		**188**	**100.0%**	**1.29 [0.75 , 2.19]**
Total events:	27		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 22.3. Comparison 22: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus placebo or standard care alone for outpatients with mild disease, Outcome 3: Serious adverse events

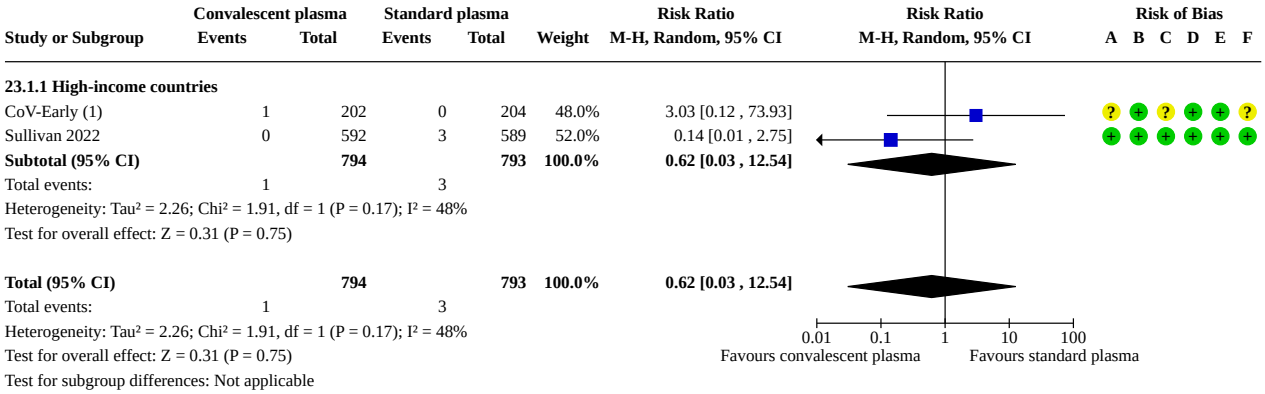


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 23. Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 All-cause mortality at up to day 28	2	1587	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.03, 12.54]
23.1.1 High-income countries	2	1587	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.03, 12.54]

Analysis 23.1. Comparison 23: Subgroup analysis: income levels of countries for the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, Outcome 1: All-cause mortality at up to day 28



Footnotes

(1) Study is not published yet, data obtained from pooled analyses of published study

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Summary of PICO development from protocol stage to current review version

	Publication date	Participants	Interventions	Comparators	Outcomes	Study designs

Protocol
 	
Piechotta 2020a
	17 April 2020	**Inclusion**
		• Individuals with a confirmed diagnosis of COVID-19
		• No age, gender or ethnicity restrictions
		
		Exclusion
		• Populations with other coronavirus diseases
			Inclusion
			• Convalescent plasma
			• Hyperimmune immunoglobulin
				Inclusion
				• Standard care
				• Placebo
				• Control treatment (e.g. drug treatments)
					All criteria based on COMET Initiative for COVID-19 patients (COMET 2020)
					
					Primary outcomes
					• All-cause mortality at hospital discharge
					• Time to death
					
					Secondary outcomes
					• Improvement of clinical symptoms, assessed through need for respiratory support:
					  ○ oxygen by mask or nasal prongs
					  ○ oxygen by NIV or high-flow
					  ○ Intubation and MV
					  ○ MV
					  ○ ECMO
					• 30-day and 90-day mortality
					• Admission to the ICU
					• Length of stay on the ICU
					• Time to discharge from hospital
					• Number of participants with grades 3 and grade 4 AEs
						Planned inclusion priority, determined by availability of sufficient evidence
						1. RCTs
						2. Prospective controlled NRSIs, including quasi-RCTs, CBA studies, and ITS studies
						3. Prospective observa-

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

		• Populations with mixed virus diseases, unless the trial authors provide subgroup data for people with COVID-19			• Number of participants with SAEs	tional studies with a control group 4. Prospective non-comparative study designs (e.g. case series)
Version 1 **Valk 2020**	14 May 2020	See above	**Inclusion** • Convalescent plasma • Hyperimmune immunoglobulin **Exclusion** • Studies on standard immunoglobulin	See above	All criteria based onCOMET Initiative for COVID-19 patients (COMET 2020) **Primary outcomes** • All-cause mortality at hospital discharge • Time to death **Secondary outcomes** • Improvement of clinical symptoms, assessed through need for respiratory support: ○ oxygen by mask or nasal prongs ○ oxygen by NIV or high-flow ○ intubation and MV ○ MV plus high-flow oxygen ○ ECMO ○ 30-day and 90-day mortality • Admission to the intensive care unit • Length of stay on the intensive care unit • Time to discharge from hospital • Number of participants with grade 3 and grade 4 adverse events • Number of participants with serious adverse events	**Inclusion** • Prospective non-comparative study designs (e.g. case series) **No evidence available for** • RCTs • NRSIs • Prospective observational studies with a control group
Changes[b]		None	Added exclusion criteria • For studies on standard immunoglobulin	None	Revised secondary outcome "Improvement of clinical symptoms, assessed through need for respiratory support": • added to the fourth bullet point (MV) "plus high-flow oxygen"	None

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

Version 2
 	
Piechotta 2020b
	10 July 2020	See above	See above	**Inclusion**
				• Standard care
				• Placebo
				• Control treatment (e.g. drug treatments, standard immunoglobulin)
					All criteria based on COMET Initiative for COVID-19 patients
					
					(COMET 2020)
					
					Primary outcomes
					• All-cause mortality at hospital discharge
					• Time to death
					
					Secondary outcomes
					• Improvement of clinical symptoms, assessed through need for respiratory support:
					  ○ Oxygen by mask or nasal prongs
					  ○ Oxygen by NIV or high flow
					  ○ Intubation and MV
					  ○ MV plus high-flow oxygen
					  ○ ECMO
					• 30-day and 90-day mortality
					• Admission to the intensive care unit
					• Length of stay on the intensive care unit
					• Time to discharge from hospital
					• Quality of life
					• Number of participants with grade 3 and grade 4 adverse events
					• Number of participants with serious adverse events
						Inclusion
						• RCTs
						• Prospective controlled NRSIs
						
						Further inclusion
						• Prospective and retrospective controlled NRSIs
						• Safety data of prospective and retrospective non-comparative study designs
						
						According to originally planned inclusion priorities

Changes[b]		None	None	Added eligible control treatment • Standard immunoglobulin	Added a secondary outcome: • Quality of life	Added inclusion criteria for safety data • Retrospective controlled NRSIs
Version 3 **Chai 2020**	12 October 2020	See above	See above	See above	All criteria based on COMET Initiative for COVID-19 patients (COMET 2020) **Primary outcomes** • All-cause mortality at hospital discharge • Time to death **Secondary outcomes** • Improvement of clinical symptoms, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO	**Inclusion** • RCTs • Prospective controlled NRSIs **Further inclusion** • Prospective and retro-

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

				Ordinal Scale for Clinical Improvement (WHO 2020f)) • 30-day and 90-day mortality • Admission to the intensive care unit • Length of stay on the intensive care unit • Time to discharge from hospital • Virological response • Quality of life • Number of participants with grade 3 and grade 4 adverse events • Number of participants with serious adverse events	spective controlled NRSIs • Safety data of prospective and retrospective non-comparative study designs According to originally planned inclusion priorities **Exclusion** • Unregistered non-comparative studies (e.g. case series) • Efficacy data of non-comparative studies
Changes[b]	None	None	None	Revised and renamed secondary outcome "Improvement of clinical symptoms" • Cut-offs are no longer self-set, but now based on standardised scales Added secondary outcome: • Virological response	Added exclusion criteria: • Unregistered non-comparative studies (e.g. case series) • Efficacy data of non-comparative studies

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

Piechotta 2021	**Inclusion**
	• Individuals with a confirmed diagnosis of COVID-19
	• No age, gender or ethnicity restrictions
	• Participants with any disease severity
	• Separate analyses for populations with ambulatory mild disease and for hospitalised participants with moderate to severe disease[c]
	
	Exclusion
	• Populations with other coronavirus diseases
	• Populations with mixed virus diseases, unless the trial authors provide
		See above	**Inclusion**
			• Standard care
			• Placebo (saline solution)
			• Control treatment (e.g. drug treatments, standard immunoglobulin)
			• Standard plasma
				All criteria based on COMET Initiative for COVID-19 patients (COMET 2020), and outcomes prioritised by consumer representatives, referees of previous versions of this review, and the German guideline panel for inpatient therapy of people with COVID-19.
				
				Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease Effectiveness of convalescent plasma
				
				Prioritised outcomes
				• All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge
				• Clinical status at up to day 28, day 60, and up to longest follow-up); including
				  ○ Improvement of clinical status
				  ■ Liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4 on the Clinical Progression Scale (WHO 2020e) (for the subgroup of participants requiring any supplemental oxygen or ventilator support at baseline, i.e. WHO ≥ 5);
				  ■ Weaning or liberation from invasive MV in surviving patients i.e. WHO ≤ 6 (for the subgroup of participants requiring invasive mechanical ventilation at baseline, i.e WHO ≥ 7);
				  ○ Worsening of clinical status
				  ■ Need for invasive MV i.e. WHO 7-9 (for the subgroup of participants not requiring invasive MV at baseline, i.e. WHO ≤ 6)
				  ■ Need for non-invasive MV or high flow i.e. WHO = 6 (for the subgroup of participants not requiring non-invasive or non-invasive MV, or high flow oxygen at baseline, i.e WHO ≤ 5);
				  ■ Need for oxygen by mask or nasal prongs i.e. WHO = 5 (for the subgroup of participants not requiring any supplemental oxygen or ventilator support at baseline, i.e WHO ≤ 4)
				• Quality of life, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available
				
				Additional outcomes
					Inclusion
					• RCTs
					• Prospectively registered single-arm studies with inclusion of ≥ 500 participants, even if upcoming RCTs report safety data for both groups

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

	sub-group data for people with COV-ID-19	• Duration of hospitalisation, or time to discharge from hospital
		• Admission to the intensive care unit (ICU)
		• Length of stay on the ICU, or time to discharge from ICU
		• Viral clearance at baseline, up to 3, 7, and 15 days
		• Need for dialysis
		
		Safety of convalescent plasma
		
		• Adverse events (any grade, grade 1-2, grade 3-4)
		• Serious adverse events
		
		Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease
		
		Effectiveness of convalescent plasma
		
		Prioritised outcomes
		
		• All-cause mortality at day 28, day 60, time-to-event, and at longest follow-up.
		• Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 4 (WHO 2020e), up to longest follow-up
		  ○ Need for invasive MV, non-invasive MV or high flow i.e. WHO ≥ 6, severe disease;
		  ■ Need for invasive MV i.e. WHO 7-9;
		  ■ Need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
		  ○ Need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease;
		  ■ Need for oxygen by mask or nasal prongs i.e. WHO = 5;
		  ■ Need for hospitalisation without oxygen therapy i.e. WHO = 4.
		• Quality of life at up to 7 days, up to 30 days, and longest follow-up available
		
		Additional outcomes
		
		• Admission to hospital
		• Time to symptom onset
		• Length of hospital stay, for subgroup of participants hospitalised during course of disease
		• Admission to the ICU
		• Viral clearance at baseline, up to 3, 7, and 15 days
		
		Safety of convalescent plasma

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

				• Adverse events (any grade, grade 1-2, grade 3-4) • Serious adverse events	
Changes[b]	Introduced separate populations[c] • Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease • Individuals with with confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease	None	Added eligible control treatment • Standard plasma Added specifications on placebo treatment • Saline solution	Changed primary and secondary outcomes to prioritised (included in 'Summary of findings' table) and additional outcomes (not included in 'Summary of findings' table). Revised and specified outcomes per population. Individuals with moderate to severe disease • Outcome measures for all-cause mortality were summarised below one outcome • Sub-outcomes for clinical improvement, and clinical worsening were introduced • 'Need for dialysis' was added as additional outcome • 'Time to discharge from hospital' was renamed to 'duration of hospitalisation, or time to discharge from hospital' to clarify that we are interested in both, continuous and time-to-event data. • 'Virological response' was renamed to 'viral clearance' to clarify that we are interested in test-negativity and not in changes of viral load. Added outcomes for individuals with asymptomatic or mild disease	Added inclusion criteria • For prospectively registered single-arm studies with inclusion of ≥ 500 participants, even if upcoming RCTs report safety data for both groups Added exclusion criteria • Controlled studies not being truly randomised • Studies comparing early versus deferred plasma • Studies on plasma donors • Pharmacokinetics studies • Studies terminated early be-

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

						cause the sponsor was changed

Version 5	(Current version)	See above	**Inclusion**
			• Convalescent plasma
			Exclusion
			• Hyperimmune immunoglobulin
				See above	**Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease**Effectiveness of convalescent plasma
					Primary outcomes
					• All-cause mortality at day 28, day 60, time to event, and during hospital stay;
					• Clinical status, at day 28, day 60, and up to the longest follow-up, including the following:
					  ○ worsening of clinical status: participants with clinical deterioration (new need for IMV) or death;
					  ○ Improvement of clinical status: participants discharged from hospital. Participants should be discharged without clinical deterioration
					• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100, a standardised scale for assessing quality of life) at up to 7 days, up to 28 days, and longest follow-up available;
					• AEs (any grade, grades 1-2, grades 3-4), defined as the number of participants with any event and including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions, headache, thromboembolic events);
					• SAEs, defined as the number of participants with any event.
					Secondary outcomes
					• Improvement of clinical status, at day 28 and up to the longest follow-up, including:
					  ○ weaning or liberation from IMV in surviving participants;
					  ○ ventilator-free days (defined as days alive and free from MV);
					  ○ liberation from supplemental oxygen in surviving participants;
					• Need for dialysis at up to 28 days;
					• Admission to the ICU on day 28;
					• Duration of hospitalisation;
					• Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 14 days.
						Inclusion
						• RCTs

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

				Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease
				
				Effectiveness of convalescent plasma
				
				Primary outcomes
				• All-cause mortality at day 28, day 60, time to event, and at the longest follow-up;
				• Admission to hospital or death within 28 days;
				• Symptom resolution:
				  ○ all initial symptoms resolved (asymptomatic) at day 14, day 28, and up to the longest follow-up;
				  ○ time to symptom resolution.
				• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 28 days, and longest follow-up available;
				• AEs (any grade, grades 1-2, grades 3-4)
				• SAEs, defined as the number of participants with any event.
				
				Secondary outcomes
				• Worsening of clinical status, at day 28 and up to the longest follow-up, including (moderate to severe COVID-19 symptoms):
				  ○ need for hospitalisation with the need for oxygen by mask or nasal prongs, or death;
				  ○ Need for IMVor death
				• Viral clearance, assessed with RT-PCR for SARS-CoV-2 at baseline, up to 3, 7, and 14 days.	

Changes[b]	None	Removed inclusion criteria: • Hyperimmune immunoglobulin	None	We renamed 'Prioritised outcomes' to 'Primary outcomes' and 'Additional outcomes' to 'Secondary outcomes'. We revised and redefined outcomes for individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease: • For the primary outcomes, we renamed the outcome 'all-cause mortality at hospital discharge' to 'all-cause mortality during hospital stay' • We redefined the outcome of worsening of clinical status to 'new need for IMV or death' (including the competing event of death) and the outcome of improvement of clinical status to 'participants discharged alive'.	Added exclusion criteria • Prospectively registered single-arm studies with inclusion of ≥ 500 participants

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

	• We added the outcome: 'improvement of clinical status' with 3 sub-outcomes (weaning or liberation from IMV in surviving participants; ventilator-free days; and liberation from supplemental oxygen in surviving participants). • We removed the secondary outcome 'Length of stay on the ICU or time to discharge from ICU'.
	We revised and redefined outcomes for individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease.

	• We added the outcome
	  ○ 'admission to hospital or death' (including the competing event of death)
	  ○ 'symptom resolution' with 2 sub-outcomes (all initial symptoms resolved and time to symptom resolution)
	  ○ 'need for hospitalisation with the need for oxygen by mask or nasal prongs, or death'
	  ○ 'need for IMV or death' (including the competing event of death)
	• We removed the outcome
	  ○ 'development of moderate to severe clinical COVID-19 symptoms' including all the sub-outcomes
	  ○ 'admission to hospital'
	  ○ 'time to symptom onset'
	  ○ 'length of hospital stay'
	  ○ 'admission to the ICU'

AE: adverse event; **CBA:** controlled before-and-after; **COMET:** Core Outcome Measures in Effectiveness Trials; **ECMO:** extracorporeal membrane oxygenation; **ICU:** intensive care unit;**IMV:** invasive mechanical ventilation; **ITS:** interrupted time series; **MV:** mechanical ventilation; **NIV:** non-invasive ventilation; **NRSI:** non-randomised studies of interventions; **RCT:** randomised controlled trial; **RT-PCR:** reverse-transcription polymerase chain reaction; **SAE:** serious adverse event; **TACO:** transfusion-associated circulatory overload;**TAD:** transfusion-associated dyspnoea; **TRALI:** transfusion-related acute lung injury; **WHO:** World Health Organization; **WHO-QOL-100:** World Health Organization quality-of-life scale

[a]Including changes in study designs and methodology.
[b]Changes in PICO compared to the previously published version.
[c]According to the latest WHO clinical progression score (WHO 2020e).

Table 2. World Health Organization clinical progression scale [a]

Patient state	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2

Table 2. World Health Organization clinical progression scale [a] *(Continued)*

	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy[b]	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe disease	Hospitalised; oxygen by non-invasive mechanical ventilation or high flow	6
	Intubation and mechanical ventilation; $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Invasive mechanical ventilation; $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Invasive mechanical ventilation; $pO_2/FiO_2 < 150$ and vasopressors, dialysis or ECMO	9
Dead	Dead	10

ECMO: extracorporeal membrane oxygenation; **FiO_2:**fraction of inspired oxygen; **pO_2**: partial pressure of oxygen; **SpO_2:** oxygen saturation

[a]World Health Organization (WHO) clinical progression scale (WHO 2020e).
[b]If hospitalised for isolation only, record status as for ambulatory patient.

Table 3. Summary of ongoing convalescent plasma studies: design and planned completion date

Study ID	Title	Link	Design	Planned number of participants	Planned completion date	Results available	Other study ID
ChiC-TR2000030010	A randomized, double-blind, parallel-controlled, trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)	www.chictr.org.cn/showproj.aspx?proj=49777	RCT	100	31 May 2020	no	
ChiC-TR2000030179	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)	www.chictr.org.cn/showproj.aspx?proj=50059	RCT	100	24 April 2020	no	
ChiC-TR2000030627	Study on the application of convalescent plasma therapy in severe COVID-19	www.chictr.org.cn/showproj.aspx?proj=50727	RCT	30	30 May 2020	no	
ChiC-TR2000030702	Convalescent plasma for the treatment of common COVID-19: a prospective randomized controlled trial	www.chictr.org.cn/showproj.aspx?proj=50537	RCT	30	15 August 2020	no	
ChiC-TR2000030929	A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel	www.chictr.org.cn/showproj.aspx?proj=50696	RCT	30	16 June 2020	no	
CTRI/2020/04/024915	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 associated complications	www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43332	RCT	100	9 May 2021	no	
CTRI/2020/05/025346	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma in severe COVID-19 patients	www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43005	RCT	90	1 June 2022	no	
CTRI/2020/06/026123	Plasma therapy in corona patients (severe COVID-19)	www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=44667	RCT	472	25 December 2020	no	

Table 3. Summary of ongoing convalescent plasma studies: design and planned completion date *(Continued)*

EUC-TR2020-001632-10	A randomized open label phase-II clinical trial with or without infusion of plasma from subjects after convalescence of SARS-CoV-2 infection in high-risk patients with confirmed severe SARS-CoV-2 disease	www.clinicaltrialsregister.eu/ctr-search/trial/2020-001632-10/DE	RCT	174	NR	no	NCT04433910
EUC-TR2020-001936-86	A prospective, randomized, open label phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19	www.clinicaltrialsregister.eu/ctr-search/trial/2020-001936-86/DE	RCT	340	NR	no	
EUC-TR2020-002122-82	Prospective open-label randomized controlled phase 2b clinical study in parallel groups for the assessment of efficacy and safety of immune therapy with COVID-19 convalescent plasma plus standard treatment vs. standard treatment alone of subjects with severe COVID-19	www.clinicaltrialsregister.eu/ctr-search/trial/2020-002122-82/DE	RCT	58	NR	no	
EUC-TR2020-005410-18	Multicentre, randomized, double-blind, placebo-controlled, non-commercial clinical trial to evaluate the efficacy and safety of specific anti-SARS-CoV-2 immunoglobulin in the treatment of COVID-19	www.clinicaltrialsregister.eu/ctr-search/trial/2020-005410-18/PL	RCT	480	NR	no	
ISRCTN49832318	SURCOVID trial: A randomized controlled trial using convalescent plasma early during moderate COVID-19 disease course in Suriname	https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN49832318	RCT	210	01/04/2022	no	
jRCTs031200374	An open-label, randomized, controlled trial to evaluate the efficacy of convalescent plasma therapy for COVID-19	https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/en/ictrp-JPRN-jRCTs031200374	RCT	200	NR		

Table 3. Summary of ongoing convalescent plasma studies: design and planned completion date *(Continued)*

NCT04333251	Evaluating convalescent plasma to decrease coronavirus associated complications. A phase I study comparing the efficacy and safety of high-titer anti-SARS-CoV-2 plasma vs best supportive care in hospitalized patients with interstitial pneumonia due to COVID-19.	clinicaltrials.gov/show/NCT04333251	RCT	115	31 December 2022	no	
NCT04345289	Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia (CCAP)	clinicaltrials.gov/show/NCT04345289	RCT	1500	15 June 2021	no	EUC-TR2020-001367-88
NCT04372979	Efficacy of convalescent plasma therapy in the early care of COVID-19 patients	clinicaltrials.gov/show/NCT04372979	RCT	80	May 2021	no	
NCT04374487	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 associated complications	clinicaltrials.gov/show/NCT04374487	RCT	100	9 May 2021	no	
NCT04376788	Exchange transfusion versus plasma from convalescent patients with methylene blue in patients with COVID-19	clinicaltrials.gov/show/NCT04376788	RCT	15	1 June 2020	no	
NCT04380935	Effectiveness and safety of convalescent plasma therapy on COVID-19 patients with acute respiratory distress syndrome	clinicaltrials.gov/show/NCT04380935	RCT	60	31 August 2020	no	
NCT04385043	Hyperimmune plasma in patients with COVID-19 severe infection	clinicaltrials.gov/show/NCT04385043	RCT	400	15 May 2021	no	
NCT04385186	Inactivated convalescent plasma as a therapeutic alternative in patients CoViD-19	clinicaltrials.gov/show/NCT04385186	RCT	60	30 November 2020	no	
NCT04388410	Safety and efficacy of convalescent plasma transfusion for patients with SARS-CoV-2 infection	clinicaltrials.gov/show/NCT04388410	RCT	410	31 December 2020	no	
NCT04390503	Convalescent plasma for COVID-19 close contacts	clinicaltrials.gov/ct2/show/NCT04390503	RCT	150	1 April 2021	no	

Table 3. Summary of ongoing convalescent plasma studies: design and planned completion date *(Continued)*

NCT04391101	Convalescent plasma for the treatment of severe SARS-CoV-2 (COVID-19)	clinicaltrials.gov/show/NCT04391101	RCT	231	31 December 2021	no	
NCT04403477	Convalescent plasma therapy in severe COVID-19 infection	clinicaltrials.gov/show/NCT04403477	RCT	20	30 October 2020	no	
NCT04415086	Treatment of patients with COVID-19 with convalescent plasma	clinicaltrials.gov/show/NCT04415086	RCT	120	22 May 2022	no	
NCT04418518	A trial of convalescent plasma for hospitalized adults with acute COVID-19 respiratory illness	clinicaltrials.gov/show/NCT04418518	RCT	1200	31 December 2021	no	
NCT04425837	Effectiveness and safety of convalescent plasma in patients with high-risk COVID-19	clinicaltrials.gov/show/NCT04425837	RCT	236	28 February 2021	no	
NCT04438057	Evaluating the efficacy of convalescent plasma in symptomatic outpatients infected with COVID-19	clinicaltrials.gov/ct2/show/NCT04438057	RCT	150	6 July 2021	no	
NCT04442191	Convalescent plasma as a possible treatment for COVID-19	clinicaltrials.gov/show/NCT04442191	RCT	50	31 May 2021	no	
NCT04452812	Statistical and epidemiological study based on the use of convalescent plasma for the management of patients with COVID-19	clinicaltrials.gov/ct2/show/NCT04452812	RCT	15	1 April 2021	no	
NCT04456413	Convalescent plasma as treatment for subjects with early COVID-19 infection	clinicaltrials.gov/show/NCT04456413	RCT	306	31 July 2021	no	
NCT04483960	Australasian COVID-19 trial (ASCOT)	clinicaltrials.gov/ct2/show/NCT04483960	RCT	2400	12 July 2022	no	ACTRN12620000445976
NCT04521036	Convalescent plasma for COVID-19 patients (CPCP)	clinicaltrials.gov/show/NCT04521036	RCT	44	30 October 2021	no	

Table 3. Summary of ongoing convalescent plasma studies: design and planned completion date *(Continued)*

NCT04528368	Convalescent plasma for treating patients with COVID-19 pneumonia without iIndication of ventilatory support	clinicaltrials.gov/ct2/show/NCT04528368	RCT	60	31 December 2020	no
NCT04558476	Efficacy of convalescent plasma in patients with COVID-19 treated with mechanical ventilation	clinicaltrials.gov/ct2/show/NCT04558476	RCT	500	30 September 2022	no
NCT04567173	Convalescent plasma as adjunctive therapy for hospitalized patients with COVID-19	clinicaltrials.gov/show/NCT04567173	RCT	136	30 June 2021	no
NCT04634422	Plasma exchange (PLEX) and convalescent plasma (CCP) in COVID-19 patients with multiorgan failure (COVID-PLEX)	clinicaltrials.gov/ct2/show/NCT04634422	RCT	220	30 June 2021	no
NCT04712344	Assessment of efficacy and safety of therapy with COVID-19 convalescent plasma in subjects with severe COVID-19 (IPCO) (IPCO)	clinicaltrials.gov/ct2/show/NCT04712344	RCT	58	30 September 21	no
NCT04730401	Convalescent plasma in the treatment of COVID-19 (CP_COVID-19)	clinicaltrials.gov/ct2/show/NCT04730401	RCT	390	31 December 2021	no
NCT04803370	Efficacy of Reinforcing Standard Therapy in COVID-19 Patients With Repeated Transfusion of Convalescent Plasma	https://clinicaltrials.gov/ct2/show/NCT04803370	RCT	100	1 September 2021	no
NCT05077930	Convalescent Plasma Therapy for Hospitalized Patients With COVID-19	https://clinicaltrials.gov/ct2/show/NCT05077930	RCT	200	January 2022	no
NL8633	A randomized, double blinded clinical trial of convalescent plasma compared to standard plasma for treatment of hospitalized non-ICU patients with COVID-19 infections	www.trialregister.nl/trial/8633	RCT	430	1 May 2021	no
PACTR202006760881890	Lagos COVID-19 convalescent plasma trial (LACCPT)	pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=12168	RCT	100	30 November 2020	no

Table 3. Summary of ongoing convalescent plasma studies: design and planned completion date *(Continued)*

PACTR202007653921168	A clinical trial comparing use of convalescent plasma therapy plus standard treatment to standard treatment alone in patients with severe COVID-19 infection	pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=11047	RCT	206	31 December 2021	no
PER-013-20	Convalescent plasma as treatment for COVID-19	www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPB-NuevoEN.asp?numec=013-20	RCT	192	30 June 2021	no
PER-060-20	Randomized phase 2 clinical trial to evaluate safety and efficacy of the use of plasma from convalescent plasma with the Coronavirus disease (COVID-19) for the experimental treatment of patients hospitalized in the Centro Médico Naval "Cirujano Mayor Santiago Távara"	www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPB-NuevoEN.asp?numec=060-20	RCT	100	7 March 2021	no
RBR-7jqpnw	Effect of COVID-19 convalescent plasma produced by HEMOPE: a randomized study, with a comparative group in several centers	www.ensaiosclinicos.gov.br/rg/RBR-7jqpnw/	RCT	110	30 July 2021	no

RCT: randomised controlled trial

Table 4. Sensitivity analyses for the comparison of convalescent plasma versus placebo or standard care alone for the population of individuals with moderate to severe disease

Outcome	Main analysis	Risk of bias (excluding studies[a] at high risk of bias)	Publication status (excluding preprints[b])	Study termination (excluding studies terminated early[c])
All-cause mortality at up to day 28	RR 0.98 (95% CI 0.92 to 1.03); including 19,021 participants from 21 studies	RR 0.98 (95% CI 0.93 to 1.03); including 18,510 participants from 20 studies[a]	RR 0.98 (95% CI 0.92 to 1.03); including 19,021 participants from 21 studies	RR 0.98 (95% CI 0.93 to 1.03); including 17,460 participants from 16 studies[c]
Clinical worsening: need for invasive mechanical ventilation (for the subgroup of participants not requiring invasive mechanical ventilation at baseline, i.e. WHO ≤ 6)	RR 1.03 (95% CI 0.97 to 1.11); including 14,477 participants from 6 studies	RR 1.02 (95% CI 0.97 to 1.07); including 13,966 participants from 5 studies[a]	RR 1.03 (95% CI 0.97 to 1.11); including 14,477 participants from 6 studies	RR 1.02 (95% CI 0.96 to 1.09); including 13,556 participants from 5 studies[c]
Clinical improvement: participants discharged from hospital	RR 1.00 (95% CI 0.97 to 1.02); including 12,721 participants from 6 studies	RR 1.00 (95% CI 0.97 to 1.02); including 12,721 participants from 6 studies	RR 1.00 (95% CI 0.97 to 1.02); including 12.,21 participants from 6 studies	RR 1.00 (95% CI 0.97 to 1.02); including 12,534 participants from 4 studies[c]
Quality of life	MD 1.00 (−2.14 to 4.14); including 483 participants from 1 study	MD 1.00 (−2.14 to 4.14); including 483 participants from 1 study	MD 1.00 (−2.14 to 4.14); including 483 participants from 1 study	MD 1.00 (−2.14 to 4.14); including 483 participants from 1 study
Grades 3 and 4 adverse events	RR 1.17 (95% CI 0.96 to 1.42); including 2392 participants from 6 studies	RR 1.17 (95% CI 0.96 to 1.42); including 2392 participants from 6 studies	RR 1.17 (95% CI 0.96 to 1.42); including 2392 participants from 6 studies	RR 1.18 (95% CI 0.77 to 1.80); including 1471 participants from 5 studies[c]
Serious adverse events	RR 1.14 (95% CI 0.91 to 1.44) including 3901 participants from 6 studies	RR 1.14 (95% CI 0.91 to 1.44) including 3901 participants from 6 studies	RR 1.14 (95% CI 0.91 to 1.44) including 3901 participants from 6 studies	RR 1.10 (95% CI 0.81 to 1.50); including 2980 participants from 5 studies[c]

CI: confidence interval; **MD:** mean difference; **NR:** not reported; **RR:** risk ratio; **WHO:** World Health Organization

[a]Excluded studies with high risk of bias (Korley 2021).
[b]Excluded preprints: no study.
[c]Excluded studies with premature termination (Avendano-Sola 2021; Begin 2021; Gharbharan 2021; Li 2020; Van den Berg 2022).

Table 5. Adverse events of any grade

Study	Number of participants	Any grade AEs	
		Convalescent plasma group	Control group
Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease			

Table 5. Adverse events of any grade *(Continued)*

Agarwal 2020	227 in CP group and 224 in control group	• 0 individuals with grades 3-4 AEs, included in Analysis 1.14
		• 15 individuals with transfusion-related events, within 6 h of CP transfusion
		  ○ 1 with pain at the infusion site
		  ○ 1 with chills
		  ○ 1 with nausea
		  ○ 1 with bradycardia
		  ○ 1 with dizziness
		  ○ 3 with fever and tachycardia
		  ○ 2 with dyspnoea
		  ○ 2 with blockage of an intravenous catheter
		  ○ 3 with mortality possibly related to CP transfusion
			• 0 individuals with grades 3-4 AEs, included in Analysis 1.14

AlQahtani 2021	20 in CP group and 20 in control group	• 0 individuals with grades 3-4 AEs, included in Analysis 1.14 • 3 transient adverse reactions, but not considered to be related to therapy	• 0 individuals with grades 3-4 AEs, included in Analysis 1.14

Avendano-Sola 2021	179 in CP group and 172 in control group	• 4 individuals with grade 3-4 AEs, included in Analysis 1.14
		• 10 individuals with transfusion-related events:
		  ○ 2 fever
		  ○ 1 nausea/vomiting
		  ○ 5 dyspnoea
		  ○ 2 allergic reaction (immediate)
		  ○ 0 TRALI
			• 0 individuals with grades 3-4 AEs, included in Analysis 1.14

Bar 2021	40 in CP and 39 in control group	• 3 treatment-related AEs ○ nausea, pruritis, and an acute allergic reaction; all grade 2	NR

Begin 2021	614 in CP group, 307 in control group	• 35 individuals with infusion-related complications:
		  ○ 13 TAD
		  ○ 9 minor allergic reaction
		  ○ 5 TACO
		  ○ 4 febrile non-haemolytic reaction
		  ○ 2 other (hypertensive reaction
		  ○ 1 hypotensive reaction
		  ○ 1 possible TRALI
			NR

De Santis 2022	36 in CP and 71 in control group	• 0 serious adverse reactions (≥ grade 3) attributable to CP transfusion were observed during study follow-up	NR

Devos 2021	320 in CP group, 163 in control group	• 19 individuals with infusion-related side effects:
		  ○ 0 TRALI
		  ○ 2 serious allergic transfusion reactions
		  ○ 3 TACO
		  ○ 5 non-haemolytic febrile reaction
		  ○ 9 other related side effects
			NR

Estcourt 2021	1078 in CP group, 909 in control group	• 1 transfusion reaction	• 0 transfusion reactions
Gharbharan 2021	43 in CP group and 43 in control group	• 0 individuals with serious transfusion-related AEs	NR

Table 5. Adverse events of any grade *(Continued)*

Hamdy Salman 2020	15 in CP group and 15 in control group	• 0 individuals with transfusion-related complications	NR
Holm 2021	17 in CP and 14 in control group	• 1 patient developed high fever within two hours after the first plasma administration	• 0 AEs reported
Horby 2021b	5795 in CP group and 5763 in control group	• 13 individuals with transfusion-related serious adverse reactions reported to SHOT: ○ 9 with pulmonary reactions (including 3 deaths possibly related to transfusion) ○ 4 with serious febrile, allergic or hypotensive reactions	NR
Kirenga 2021	69 in CP, 67 in control group	• 15 AEs, of these, 3 AEs were judged definitely related and 3 judged to be possibly related to plasma transfusion, while the rest were thought to be unrelated to plasma transfusion.	• 14 AEs
Koerper 2021	53 in CP, 52 in control group	• Only number of SAEs reported	NR
Korley 2021	257 in CP group and 254 in control group	• 3 participants had serious infusion reactions	NR
Li 2020	52 in CP group and 51 in control group	• 2 individuals with transfusion-related AEs ○ 1 with possible severe TAD (shortness of breath, cyanosis, and severe dyspnoea) within 6 h of transfusion ○ 1 with non-severe allergic transfusion reaction and probable non-severe febrile non-haemolytic transfusion reaction (chills and rashes) within 2 h of transfusion	NR
Menichetti 2021	232 in CP and 241 in control group	• 2 events with worsening of respiratory failure without fever • 2 events with worsening of respiratory failure with fever and a skin rash	NR
Ortigoza 2022	463 in CP and 463 in control group	• 8 transfusion reactions ○ 1 of these TRALI or TACO	• 2 transfusion reactions
Pouladzadeh 2021	30 in CP and 30 in control group	• 0 participants with any serious side effects	NR
Ray 2022	40 in CP group 40 in control group	• 0 individuals with transfusion-related AEs	NR
Sekine 2021	80 in CP and 80 in control group	• 2 individuals with transfusion-related AEs: ○ 2 allergic reactions	• 4 allergic reactions
Simonovich 2020	228 in CP group and 105 in control group	• 11 individuals with transfusion-related events: ○ 0 TRALI ○ 0 TACO ○ 5 non-haemolytic febrile reaction ○ 4 allergic reaction ○ 1 unexplained event ○ 1 technical resolution event	• 2 individuals with transfusion-related events: ○ allergic reactions
Van den Berg 2022	52 in CP group and 51 in control group	• 1 grade 1 allergic reaction	• 1 grade 1 allergic reaction

Table 5. Adverse events of any grade *(Continued)*

Convalescent plasma versus standard plasma for individuals with moderate to severe disease			
Bajpai 2020	14 in CP group and 15 in control group	• 1 individual with transfusion-related events: signs of mild urticaria during plasma transfusion	• 1 individual with transfusion-related events: signs of mild urticaria during plasma transfusion
Baldeon 2022	63 in CP group and 95 in control group	• 0 SAEs associated with plasma treatments	NR
Bennett-Guerrero 2021	59 in CP, 15 in control group	• 1 participant experienced a serious transfusion reaction after a small volume was administered and thus did not complete the 2-unit administration	NR
NCT04421404	16 in CP group, 18 in control group	• 0 infusion-related reactions	• 1 infusion-related reaction (hypotension)
O'Donnell 2021	147 in CP group and 72 in control group	• 4 individual with probably or definitely transfusion-related events, included worsening anaemia, urticaria, skin rash, and transfusion-associated circulatory overload	• 3 individuals with probably or definitely transfusion-related events
Convalescent plasma versus human immunoglobulin for individuals with moderate to severe disease			
Beltran Gonzalez 2021	130 in CP, 60 in control group	• The CP group did not develop adverse effects attributable to its administration	• 2 participants in the IVIg group developed AEs associated with its administration ◦ 1 anaphylactic reaction ◦ 1 hypertensive crisis
Convalescent plasma versus placebo or standard care alone for individuals with asymptomatic or mild disease			
Libster 2020	80 in CP group and 80 in control group	• 0 individuals with solicited AEs (the definition was unclear and we were unsure whether only drug-related adverse events were assessed, and we did not receive additional information from the study authors)	• 0 individuals with solicited AEs (the definition was unclear and we were unsure whether only drug-related adverse events were assessed, and we did not receive additional information from the study authors)
Alemany 2022	188 in CP, 188 in control group	• 24 treatment-related AEs: ◦ mild allergic reactions, fever, and local reactions	• 8 treatment-related AEs

Table 5. Adverse events of any grade *(Continued)*

			◦ 2 local reactions ◦ 3 vasovagal syndrome ◦ 2 fever or chills ◦ 1 gastrointestinal symptoms
Convalescent plasma versus standard plasma for individuals with asymptomatic or mild disease			
Sullivan 2022	592 in CP and 589 in control group	• 2 severe transfusion reactions ◦ 1 pneumonia ◦ 1 unspecified	• 2 participants with Infusion-related reaction and 0 severe reactions

AE: adverse event; **CP:** convalescent plasma; **IVIg:** intravenous immunoglobulin; **NR:** not reported; **SAE:** serious adverse event; **SHOT:** serious hazards of transfusion; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TRALI:** transfusion-related acute lung injury

Table 6. Serious adverse events

Study	Number of participants	Serious adverse events	
		CP group	Control group
Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease			
Agarwal 2020	227 in CP group and 224 in control group	NR	NR
AlQahtani 2021	20 in CP group and 20 in control group	NR	NR
Avendano-Sola 2021	38 in CP group and 43 in control group	NR	NR
Bar 2021	40 in CP group and 39 in control group	• 12 individuals with SAEs, included in analysis	• 15 individuals with SAEs, included in analysis
Begin 2021	614 in CP group, 307 in control group	• 205 individuals with SAEs, included in analysis	• 81 individuals with SAEs, included in analysis
CoV-Early	202 in CP group, 204 in control group	NR	NR
De Santis 2022	36 in CP group, 71 in control group	NR	NR
Devos 2021	320 in CP group, 163 in control group	• 66 individuals with SAEs, included in analysis	• 34 individuals with SAEs, included in analysis

Table 6. Serious adverse events *(Continued)*

Estcourt 2021	1078 in CP group, 909 in control group	• 32 individuals with SAEs, included in analysis	• 12 individuals with SAEs, included in analysis
Gharbharan 2021	43 in group and 43 in control group	NR	NR
Hamdy Salman 2020	15 in group and 15 in control group	NR	NR
Holm 2021	17 in CP group and 14 in control group	NR	NR
Horby 2021b	5795 in group and 5763 in control group	NR	NR
Kirenga 2021	69 in CP group, 67 in control group	NR	NR
Koerper 2021	53 in CP, 52 in control group	• 22 individuals with SAEs, included in analysis	• 25 individuals with SAEs, included in analysis
Korley 2021	257 in CP group and 254 in control group	NR	NR
Menichetti 2021	232 in CP group and 241 in control group	NR	NR
Ortigoza 2022	463 in CP group and 463 in control group	NR	NR
Pouladzadeh 2021	30 in CP group and 30 in control group	NR	NR
Ray 2022	40 in CP group and 40 in control group	NR	NR
Sekine 2021	80 in CP group and 80 in control group	NR	NR
Simonovich 2020	228 in CP group and 105 in control group	• 54 individuals with SAEs, included in analysis	• 19 individuals with SAEs, included in analysis
Van den Berg 2022	52 in CP group and 51 in control group	NR	NR
Convalescent plasma versus standard plasma for individuals with moderate to severe disease			
Bajpai 2020	14 in CP group and 15 in control group	NR	NR
Baldeon 2022	63 in CP group and 95 in control group	NR	NR
Bennett-Guerrero 2021	59 in CP group, 15 in control group	• 16 individuals with SAEs, included in analysis	• 4 individuals with SAEs, included in analysis
NCT04421404	16 in CP group, 18 in control group	• 2 individuals with SAEs, included in analysis	• 1 individual with SAEs, included in analysis
O'Donnell 2021	147 in CP group an 72 in control group	• 39 individuals with SAEs, included in analysis	• 26 individuals with SAEs, included in analysis
Convalescent plasma versus human immunoglobulin for individuals with moderate to severe disease			

Table 6. Serious adverse events *(Continued)*

Beltran Gonzalez 2021	130 in CP group and 60 in control group	NR	NR
Convalescent plasma versus placebo or standard care alone for individuals with mild disease			
Alemany 2022	188 in CP group and 188 in control group	• 25 individuals with SAEs, included in analysis	• 22 individuals with SAEs, included in analysis
Libster 2020	80 in CP group and 80 in control group	NR	NR
Convalescent plasma versus standard plasma for individuals with mild disease			
Sullivan 2022	592 in CP group and 589 in control group	NR	NR

CP: convalescent plasma; **NR:** not reported; **TACO:** transfusion-associated circulatory overload; **TRALI:** transfusion-related acute lung injury; **SAEs:** serious adverse events

Table 7. Sensitivity analyses for the comparison of convalescent plasma versus standard plasma for the population of individuals with moderate to severe disease

Outcome	Main analysis	Risk of bias (excluding studies[a] at high risk of bias)	Publication status (excluding preprints[b])	Study termination (excluding studies terminated early[c])
All-cause mortality at up to day 28	RR 0.73 (95% CI 0.45 to 1.19); including 484 participants from 4 studies	RR 0.73 (95% CI 0.45 to 1.19); including 484 participants from 4 studies	RR 0.65 (95% CI 0.43 to 1.01); including 455 participants from 3 studies[b]	RR 0.95 (95% CI 0.17 to 5.29); including 252 participants from 2 studies[c]
Clinical worsening: need for invasive mechanical ventilation (for the subgroup of participants not requiring invasive mechanical ventilation at baseline, i.e. WHO ≤ 6)	RR 5.59 (95% CI 0.29 to 108.38) including 34 participants from 1 study	RR 5.59 (95% CI 0.29 to 108.38) including 34 participants from 1 study	No study included[b]	RR 5.59 (95% CI 0.29 to 108.38) including 34 participants from 1 study
Clinical improvement: participants discharged from hospital	NR	NR	NR	NR
Quality of life	NR	NR	NR	NR
Grades 3 or 4 adverse events	NR	NR	NR	NR
Serious adverse events	RR 0.80 (95% CI 0.55 to 1.15); including 327 participants from 3 studies	RR 0.80 (95% CI 0.55 to 1.15); including 327 participants from 3 studies	RR 0.77 (95% CI 0.53 to 1.13); including 293 participants from 2 studies[b]	RR 0.76 (95% CI 0.51 to 1.14); including 253 participants from 2 studies[c]

CI: confidence interval;**NR:** not reported; **RR:** risk ratio; **WHO:** World Health Organization

[a]Excluded studies with high risk of bias: no study.
[b]Excluded preprints (no peer reviewed results published; Bajpai 2020; NCT04421404)
[c]Excluded studies with premature termination (Baldeon 2022; Bennett-Guerrero 2021)

APPENDICES

Appendix 1. Search strategies

MEDLINE

Searches

1. Coronavirus Infections/ or Coronavirus/ or SARS-CoV-2/ or COVID-19/

2. ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2" or anti-flu* or anti-influenza* or antiflu* or antinfluenza*).tw,kf.

3. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kf.

4. "severe acute respiratory syndrome coronavirus 2".tw,kf,nm.

5. or/1-4

6. Plasma/ or Immunoglobulins/ or Immunoglobulins, Intravenous/ or Immune Sera/

7. ((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus neutrali* or virus inactivated or antibod* or high-titre* or high-titer*) adj6 (plasma or blood or serum or sera)).tw,kf.

8. (high-dos* adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kf.

9. ((plasma adj1 therap*) or gamma-globulin or gammaglobulin or "y-Globulin" or hyper-lg or "C19-IG").tw,kf.

10. (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).tw,kf.

11. ((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus inactivated or antibody-positive) adj5 (donor* or donat*)).tw,kf.

12. (hyperimmune* or hyper-immune* or serotherap* or sero-therap*).tw,kf.

13. exp Immunization, Passive/

14. (passiv* adj3 (antibod* transfer* or immunization* or immunotherap* or immuno-therap* or vaccin*)).tw,kf.

15. (passiv* adj3 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kf.

16. ((immunoglobulin* or immune globulin*) adj2 (therap* or treatment* or prevent* or protect* or prophylax*)).tw,kf.

17. (passive immunit* or hIVIG or CSL760 or INM005 or XAV-19 or SAB-185 or equine or IgY-110 or IgY110 or GIGA-2050 or GIGA2050 or GC5131 or 5131A).tw,kf.

18. (((anti-coronavirus or anticoronavirus) adj1 immunoglobulin*) or ITAC or "Hyperimmune anti-COVID-19 IVIG" or C-IVIG or CIVIG or equine polyclonal antibod* or EpAbs or BSVEQAb or EqAb-COV-19 or flebogamma or "F(ab)2").tw,kf.

19. ((bovine adj2 (colostrum* or milk*)) or bioblock*).tw,kf.

20. or/6-19

21. 5 and 20

22. "Covid-19 Serotherapy".px.

23. or/21-22

24. randomized controlled trial.pt.

25. controlled clinical trial.pt.

26. randomi?ed.ab.

27. placebo.ab.

28. drug therapy.fs.

29. randomly.ab.

30. trial.ab.

31. groups.ab.

32. or/24-31

33. exp animals/ not humans/

34. 32 not 33

35. clinical trial, phase iii/

36. ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.

37. (35 or 36) not 33

38. 34 or 37

39. 23 and 38

40. limit 39 to yr="2020 -Current"

41. remove duplicates from 40

Embase

Searches

1. coronavirinae/ or coronaviridae/ or coronaviridae infection/ or coronavirus disease 2019/ or Coronavirus infection/

2. sars-related coronavirus/ or "Severe acute respiratory syndrome coronavirus 2"/

3. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kw.

4. ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2").tw,kw.

5. "Severe acute respiratory syndrome coronavirus 2".mp.

6. or/1-5

7. Plasma Transfusion/ or exp Immunoglobulin/

8. ((convalesc* or recovered or cured or survivor* or survived or rehabilitat* or virus-positive or virus-neutrali* or virus inactived or antibody-rich or high-tire* or high-titer*) adj6 (plasma or blood or serum or sera)).mp.

9. ((plasma adj1 therap*) or gamma-globulin or gammaglobulin or "y-Globulin" or hyper-lg or "C19-IG").tw,kw.

10. (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).tw,kw.

11. (high-dos* adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kw.

12. ((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus inactivated or antibody-positive) adj5 (donor* or donat*)).tw,kw.

13. (serotherap* or sero-therap* or hyperimmune* or hyper-immune*).tw,kw.

14. passive immunization/

15. (passiv* adj3 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kw.

16. (passive immunit* or hIVIG or CSL760 or INM005 or XAV-19 or SAB-185 or equine or IgY-110 or IgY110 or GIGA-2050 or GIGA2050 or GC5131 or 5131A).tw,kw.

17. (passiv* adj3 (antibod* transfer* or immunization* or immunotherap* or immuno-therap* or vaccin*)).tw,kw.

18. ((immunoglobulin* or immune globulin*) adj2 (therap* or treatment* or prevent* or protect* or prophylax*)).tw,kw.

19. (((anti-coronavirus or anticoronavirus) adj1 immunoglobulin*) or ITAC or "Hyperimmune anti-COVID-19 IVIG" or C-IVIG or CIVIG or equine polyclonal antibod* or EpAbs or BSVEQAb or EqAb-COV-19 or flebogamma or "F(ab)2").tw,kw.

20. ((bovine adj2 (colostrum* or milk*)) or bioblock*).tw,kw.

21. or/7-20

22. Randomized controlled trial/

23. Controlled clinical trial/

24. random*.ti,ab.

25. randomization/

26. intermethod comparison/

27. placebo.ti,ab.

28. (compare or compared or comparison).ti.

29. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

30. (open adj label).ti,ab.

31. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

32. double blind procedure/

33. parallel group*1.ti,ab.

34. (crossover or cross over).ti,ab.

35. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.

36. (assigned or allocated).ti,ab.

37. (controlled adj7 (study or design or trial)).ti,ab.

38. (volunteer or volunteers).ti,ab.

39. human experiment/

40. trial.ti.

41. or/22-40

42. (random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

43. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

44. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

45. (Systematic review not (trial or study)).ti.

46. (nonrandom$ not random$).ti,ab.

47. Random field$.ti,ab.

48. (random cluster adj3 sampl$).ti,ab.

49. (review.ab. and review.pt.) not trial.ti.

50. we searched.ab. and (review.ti. or review.pt.)

51. update review.ab.

52. (databases adj4 searched).ab.

53. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/

54. Animal experiment/ not (human experiment/ or human/)

55. or/42-54

56. 41 not 55

57. phase 3 clinical trial/

58. ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.

59. (animal experiment/ or Animal experiment/) not (human experiment/ or human/)

60. (57 or 58) not 59

61. 57 or 58

62. 61 not 59

63. 6 and 21 and (56 or 60)

64. limit 63 to yr="2020 -Current"

65. limit 64 to medline

66. 64 not 65

67. remove duplicates from 66

Cochrane COVID-19 Study Register

plasma or convalesc* or serum or sera or donor* or donation* or serotherapy or "sero-therapy" or "flu-IVIG" or "passive immunity" or hyperimmune* or "hyper-immune" or IVIG or immunoglobulin* or "immune-globulin" or "immune-globuline" or globulin* or "gamma-globulin" or "γ-Globulin" or "hyper-Ig" or immunization or immunisation or immunotherap* or "immuno-therapy" or CSL760 or INM005* or equine* or "XAV-19" or "SAB-185" or hIVIG* or INOSARS* or "GIGA-2050" or GIGA2050 or "IGY-110" or IGY1109 or "GC5131" or "5131A" or ITAC* or "C-IVIG" or CIVIG or flebogamma* or EpAbs* or BSVEQAb* or "EqAb-COV-19" or "F(ab)2" or "bovine colostrum" or "bovine milk" or "SARS-CoV-2-IG" or "hyper-Ig" or bioblock*

Study characteristics:

1) Intervention assignment: randomised, unclear

2) Study design: parallel/crossover, unclear"

PubMed

#1 "2019 ncov"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "corona virus"[Title/Abstract] OR "corona viruses"[Title/Abstract] OR "Coronavirus"[Title/Abstract] OR "coronaviruses"[Title/Abstract] OR "COVID"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "ncov 2019"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "COVID-19"[MeSH Terms] OR "Coronavirus"[MeSH Terms:noexp] OR "SARS-CoV-2"[MeSH Terms] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]

#2 ("convalesc*"[Title/Abstract] OR "recovered"[Title/Abstract] OR "cured"[Title/Abstract] OR "rehabilitat*"[Title/Abstract] OR "survivor*"[Title/Abstract] OR "survived"[Title/Abstract] OR "virus-positive"[Title/Abstract] OR "virus neutrali*"[Title/Abstract] OR "virus inactivated"[Title/Abstract] OR "antibod*"[Title/Abstract] OR "high titre*"[Title/Abstract] OR "high titer*"[Title/Abstract]) AND ("plasma"[Title/Abstract] OR "blood"[Title/Abstract] OR "donor*"[Title/Abstract] OR "donat*"[Title/Abstract])

#3 ("plasma"[Title] AND ("immun*"[Title/Abstract] OR "transfus*"[Title/Abstract] OR "infus*"[Title/Abstract] OR "exchange*"[Title/Abstract]))

#4 "high dos*"[Title/Abstract] AND ("plasma"[Title/Abstract] OR "immunoglobulin*"[Title/Abstract] OR "ivig*"[Title/Abstract] OR "immune globulin*"[Title/Abstract] OR "globulin*"[Title/Abstract] OR "IgG"[Title/Abstract])

#5 "immunization, passive"[MeSH Terms] OR "passive immunit*"[Title/Abstract] OR "hyperimmune"[Title/Abstract] OR "hyperimmunity"[Title/Abstract] OR "serotherap*"[Title/Abstract] OR "sero therap*"[Title/Abstract] OR "therapeutic plasma"[Title/Abstract] OR "plasma therapy"[Title/Abstract] OR "immune plasma"[Title/Abstract] OR "plasma exchange"[Title/Abstract] OR "serum"[Title] OR "sera"[Title]

#6 "passiv*"[Title/Abstract] AND (("antibod*"[Title/Abstract] AND "transfer*"[Title/Abstract]) OR "immunisation*"[Title/Abstract] OR "vaccin*"[Title/Abstract] OR "immunization*"[Title/Abstract] OR "immunotherap*"[Title/Abstract] OR "immuno therap*"[Title/Abstract])

#7 ("immunoglobulin*"[Title] OR "immune globulin*"[Title]) AND ("therap*"[Title/Abstract] OR "treat*"[Title/Abstract] OR "prevent*"[Title/Abstract] OR "protect*"[Title/Abstract] OR "prophylax*"[Title/Abstract])

#8 "bovine colostrum"[Title/Abstract] OR "bovine milk"[Title/Abstract] OR "F(ab)2"[Title/Abstract] OR "equine*"[Title/Abstract] OR "Hyperimmune anti-COVID-19 IVIG"[Title/Abstract] OR "c ivig*"[Title/Abstract] OR "XAV-19"[Title/Abstract] OR "5131A"[Title/Abstract] OR "equine polyclonal antibod*"[Title/Abstract] OR "EpAbs"[Title/Abstract] OR "flebogamma*"[Title/Abstract] OR "BSVEQAb"[Title/Abstract] OR "EqAb-COV-19"[Title/Abstract] OR "γ-Globulin"[Title/Abstract] OR "hyper-Ig"[Title/Abstract] OR Title/Abstract] OR INM005*[Title/Abstract] OR "SAB-185"[Title/Abstract] OR hIVIG*[Title/Abstract] OR INOSARS*[Title/Abstract] OR "GIGA-2050"[Title/Abstract] OR GIGA2050[Title/Abstract] OR "IGY-110"[Title/Abstract] OR "GC5131"[Title/Abstract] OR "5131A"[Title/Abstract] OR ITAC*[Title/Abstract] OR "C-IVIG"[Title/Abstract] OR CIVIG[Title/Abstract] OR XVR011* [Title/Abstract] OR bioblock*[Title/Abstract] OR "gammaglobulin*"[Title/Abstract] OR "gamma-globulin"[Title/Abstract] OR "hyper-Ig"[Title/Abstract]

#9 (("anti-coronavirus"[Title/Abstract] OR "anticoronavirus"[Title/Abstract]) AND "immunoglobulin*"[Title/Abstract]))

#10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 #1 AND #10

#12 ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh]))

#13 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#14 #11 AND #12 AND #13

Filters: from 2020/1/1 - 3000/12/12

World Health Organization COVID-19 Global literature on coronavirus disease

Advanced search: search fileds: title, abstract subject (ohne Embase, Medline ICTRP, PubMed)

I:

random* or placebo or trial or groups or "phase 3" or "phase3" or p3 or "pIII"

and

convalesc*~6plasma or convalesc*~6blood or convalesc*~6serum or convalesc*~6sera or cured~6plasma or cc-ured~6blood or cured~6serum or cured~6sera or survivor*~6plasma or survivor*~6blood or survivor*~6serum or survivor*~6sera or survived*~6plasma or survived*~6blood or survived*~6serum or survived*~6sera or rehabilitat*~6plasma or rehabilitat*~6blood or rehabilitat*~6serum or rehabilitat*~6sera or virus-positive~6plasma or virus-positive~6blood or virus-positive~6serum or virus-positive~6sera or virus-neutrali*~6plasma or virus-neutrali*~6blood or virus-neutrali*~6serum or virus-neutrali*~6sera or virus inactived~6plasma or virus inactived~6blood or virus inactived~6serum or virus inactived~6sera or antibody-rich~6plasma or antibody-rich~6blood or antibody-rich~6serum or antibody-rich~6sera or high-tire*~6plasma or high-tire*~6blood or high-tire*~6serum or high-tire*~6sera or high-titer*~6plasma or high-titer*~6blood or high-titer*~6serum or high-titer*~6sera or plasma~1therap*

II:

random* or placebo or trial or groups or "phase 3" or "phase3" or p3 or "pIII"

and

gamma-globulin or "y-Globulin" or hyper-Ig or plasma~5immun* or plasma~5antibod* or plasma~5exchange* or plasma~5donor* or plasma~5 donat* or plasma~5transfus* or plasma~5infus* or high-dos*~3plasma or high-dos*~3immunoglobulin* or high-dos*~3IVIG* or high-dos*~3immune globulin* or high-dos*~3globulin* or high-dos*~3IgG or convalesc*~5donor* or recovered~5donor* or cured~5donor* or rehabilitat*~5donor* or survivor*~5donor* or survived~5donor* or virus-positive~5donor* or virus inactivated~5donor* or antibody-positive~5donor* or convalesc*~5donat or recovered~5donat or cured~5donat or rehabilitat*~5donat or survivor*~5donat or survived~5donat or virus-positive~5donat or virus inactivated~5donat or antibody-positive~5donat or serotherap* or sero-therap* or hyperimmune*

III:

random* or placebo or trial or groups or "phase 3" or "phase3" or p3 or "pIII"

and

hyper-immune* or passiv*~3therap* or passiv*~3treatment* or passiv*~3neutralising or passiv*~3neutralizing or passiv*~3prevent* or passiv*~3protect* or passiv*~3prophylax* or immunoglobulin*~2therap* or immunoglobulin*~2treat* or immunoglobulin*~2prevent* or immunoglobulin*~2protect* or immunoglobulin*~2prophylax* or immune globulin*~2therap* or immune globulin*~2treat* or immune globulin*~2prevent* or immune globulin*~2protect* or immune globulin*~2 or passive immunit*

IV:

random* or placebo or trial or groups or "phase 3" or "phase3" or p3 or "pIII"

and

hIVIG or CSL760 or INM005 or "XAV-19" or "SAB-185" or equine or "IgY-110" or IgY110 or "GIGA-2050" or GIGA2050 or GC5131 or 5131A or ITAC or "Hyperimmune anti-COVID-19 IVIG" or C-IVIG or CIVIG or EpAbs or BSVEQAb or "EqAb-COV-19" or flebogamma or bovine~2colostrum* or bovine~2milk*

V:

random* or placebo or trial or groups or "phase 3" or "phase3" or p3 or "pIII"

and

passiv*~3antibod* or passiv*~3transfer* or passiv*~3immunization* or passiv*~3immunotherap* or passiv*~3immuno-therap* or passiv*~3vaccin* or anti-coronavirus~1immunoglobulin* or anticoronavirus~1immunoglobulin*

Epistemonikos, L*OVE List Coronavirus disease (COVID-19)

Covid-19 by PICO

Prevention or treatment: passive immunization: antibody therapies: convalescent plasma

Filtered by primary studies and results by RCT

Prevention or treatment: passive immunization: antibody therapies: immunoglobulin therapy

Filtered by primary studies and results by RCT

Prevention or treatment: passive immunization: Heterologous antibodies

Filtered by primary studies and results by RCT

Appendix 2. Transformations and recalculations of outcomes

Table A8.1: moderate to severe disease

Convalescent plasma versus placebo, standard care alone, standard plasma, or human immunoglobulin in moderate to severe disease			
Outcome	**Study**	**Source of data**	**Transformation or recalculation**

(Continued)

Mortality at longest follow-up	Beltran Gonzalez 2021	Beltran Gonzalez 2021	Recalculation of HR and 95% CI according to methods by Tierney 2007 based on number of events and P value
	De Santis 2022	De Santis 2022	
	Kirenga 2021	Kirenga 2021	
	Koerper 2021	Koerper 2021	
	Menichetti 2021	Menichetti 2021	
	O'Donnell 2021	O'Donnell 2021	

Table A8.2: mild disease

Convalescent plasma versus placebo, standard care alone, standard plasma, or human immunoglobulin in outpatients with mild disease			
Outcome	**Study**	**Source of data**	**Transformation or recalculation**
Mortality up to day 28	CoV-Early	Unpublished data provided by the primary study authors	Recalculation based on provided data; any death within 28 days

Appendix 3. Planned methodology for study designs that are no longer included in this systematic review

Criteria for considering studies for this review

Types of studies

In case of insufficient evidence available from randomised controlled trials (RCTs), we planned to include prospective controlled non-randomised studies of interventions (NRSIs), including quasi-RCTs (e.g. assignment to treatment by alternation or by date of birth), controlled before-and-after (CBA) studies, and interrupted time series (ITS) studies. We planned to use the methods proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* for the inclusion of controlled NRSIs in systematic reviews (Reeves 2022).

We further planned to include retrospective controlled NRSIs, in case of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs and prospective controlled NRSIs and to adapt the methods for the inclusion of controlled NRSIs in systematic reviews as specified by the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2022).

In case the evidence that we found from RCTs was at high risk of bias and at critical risk of bias for the controlled NRSIs for safety outcomes, we planned to also included safety data from prospectively and retrospectively registered non-controlled NRSIs, for example, case series, and followed the methodology as specified in the protocol (Piechotta 2020a).

Data collection and analysis

Assessment of risk of bias in included studies

Controlled non-randomised studies of interventions

As reported above, we planned to include controlled non-randomised studies of intervention (NRSI) trials if there was insufficient evidence from RCTs.

Two review authors (VP, NS) would have independently assessed eligible studies for methodological quality and risk of bias (using the Risk Of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool; Sterne 2016). The quality assessment strongly depends upon information on the design, conduct and analysis of the trial. The two review authors would have resolved any disagreements regarding quality assessments by discussion, and in case of discrepancies among their judgements, or inability to reach consensus, we had to consult a third review author until consensus could be reached. We asked the Cochrane Editorial and Methods Department (Theresa Moore) to review our judgements for reasonability for previous versions of this review. The categories for risk of bias judgements for controlled NRSIs using ROBINS-I are 'low risk', 'moderate risk', 'serious risk' and 'critical risk' of bias.

We planned to assess the following domains of bias.

- Bias due to confounding
- Bias in selection of participants into the study
- Bias in classification of interventions
- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

For every criterion we planned to make a judgement using one of five response options.

- Yes
- Probably yes
- Probably no
- No
- No information

Measures of treatment effect

Controlled non-randomised studies of interventions

For dichotomous outcomes, if available, we planned to extract and report the risk ratio (RR) with a 95% confidence interval from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR post-intervention/RR pre-intervention).

For continuous variables, if available, we planned to extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models or hierarchical models), or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups/the post-intervention level in the control group; EPOC 2017).

Data synthesis

We planned to not synthesise efficacy data from controlled NRSIs if they were at critical risk of bias. If a meta-analysis had been feasible for controlled NRSIs we planned to analyse the different types of studies separately. We planned to only analyse outcomes with adjusted effect estimates if these were adjusted for the same factors using the inverse-variance method as recommended in Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2022).

Summary of findings and assessment of the certainty of the evidence

As we had planned to use the ROBINS-I tool to assess risk of bias for controlled NRSIs, we planned to follow GRADE guidance 18 to rate the certainty in the evidence for controlled NRSIs; starting from high-certainty evidence with the opportunity to downgrade by three points for critical risk of bias (Schünemann 2019).

WHAT'S NEW

Date	Event	Description
10 May 2023	New citation required but conclusions have not changed	Amendments outlined below; overall conclusions not changed
10 May 2023	Amended	For the comparison of convalescent plasma versus standard plasma for outpatients with mild disease, we corrected small errors in the analyses 13.2 and 17.2 for the outcome "admission to hospital or death within 28 days" (Sullivan 2022). The correction of analysis 17.2 changed the conclusion for the subgroup analysis age of participants, as the test for subgroup differences was not significant anymore. This conclusion was adjusted in the SOF table 5 and in the results and discussion part, where necessary.

Date	Event	Description
		In the conclusion of the abstract, the statement regarding the certainty in the evidence for primary outcomes in individuals with mild disease was further elaborated. In the results section of the risk of bias assessment, we adjusted the judgement reasoning for the Korley 2021 study accordingly: "We rated the overall risk of bias to be high in Korley 2021, because of baseline differences in hospitalisation between the groups".

HISTORY

Review first published: Issue 5, 2020

Date	Event	Description
31 January 2023	New search has been performed	33 RCTs included
31 January 2023	New citation required and conclusions have changed	Only RCTs were searched for this update. High-certainty evidence on further primary outcomes and more safety data available. Subgroup analyses were conducted and further studies on individuals with mild disease were included in the meta-analysis.
19 March 2021	New citation required and conclusions have changed	High certainty in the evidence for some of the prioritised outcomes
17 March 2021	New search has been performed	12 RCTs and one NRSI included
30 August 2020	New search has been performed	Two RCTs, eight controlled NRSIs and nine non-controlled NRSIs included
30 August 2020	New citation required and conclusions have changed	Additional safety data included (more than 20,000 participants)
3 June 2020	New citation required and conclusions have changed	We included results from one RCT and three controlled NRSIs and added further safety data from non-controlled NRSIs.
31 May 2020	New search has been performed	We included eight new studies.

CONTRIBUTIONS OF AUTHORS

CI: methodological expertise, study selection, data extraction and assessment, conception and writing of the manuscript

KLC: clinical expertise, study selection and advice

VP: methodological expertise, study selection and data extraction

SJV: clinical expertise, study selection and advice

CK: clinical expertise, study selection, and advice

EA: study selection, data extraction and assessment

IM: development of the search strategy

EMW: clinical expertise and advice

AL: clinical expertise and advice

DJR: clinical expertise and advice

ZM: clinical expertise and advice

CS-O: clinical expertise and advice

AJ: clinical expertise and advice

NC: data extraction and assessment

LJE: clinical expertise, and conception and writing of the manuscript

NK: methodological expertise, study selection, data extraction and assessment

NS: methodological expertise, study selection, data extraction and assessment, conception and writing of the manuscript

DECLARATIONS OF INTEREST

CI: none known, Managing Editor of Cochrane Haematology, but not involved in the editorial process for this review

KLC: HSANZ Leukaemia Foundation PhD scholarship to support studies at Monash University. This is not related to the work in this review.

VP: none known

SJV: is receiving a PhD scholarship from the not-for-profit Sanquin blood bank.

CK: none known

EA: none known

IM: none known

EMW: I have received funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

AL: none known

DJR: investigator on the REMAP-CAP and RECOVERY trial. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

ZM: I have received funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

CS-O: is a member of the BEST Collaborative Clinical Study Group and Associate Editor for *Transfusion Medicine* Journal. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

AJ: Investigator of PLACID Trial. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

NC: none known

LJE: co-lead of the COVID-19 immunoglobulin domain of the REMAP-CAP trial and investigator on the RECOVERY trial. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

NK: none known, staff of Cochrane Haematology

NS: none known; she is Co-ordinating Editor of Cochrane Haematology, but was not involved in the editorial process for this review.

SOURCES OF SUPPORT

Internal sources

- Sanquin Blood Supply, Netherlands

  Center for Clinical Transfusion Research

- University Hospital of Cologne, Germany

  Cochrane Cancer, Department I of Internal Medicine
- Monash University, Australia

  Transfusion Research Unit, Department of Epidemiology and Preventive Medicine
- NHS Blood and Transplant, UK

  NHS Blood and Transplant
- Leukaemia Foundation and HSANZ, Australia

  Haematology Society of Australia and New Zealand (HSANZ)

External sources

- European Union's Horizon 2020 research and innovation programme, Belgium

  SUPorting high quality evaluation of COVID-19 convalescent plasma thrOughouT Europe (SUPPORT-E)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this section, we do not only report the differences between the protocol and the current review version but the changes between each published version of the review. The summary of amendments are also provided in Table 1.

Types of studies

Differences between first and second published review version

(Valk 2020 to Piechotta 2020b)

As the evidence we found from the randomised controlled trial (RCT) was at unclear or high risk of bias and at serious risk of bias for the controlled non-randomised studies of interventions (NRSIs), and as none of these studies reported safety data for the control arm, we also included safety data from prospective and retrospective non-comparative study designs (e.g. case series) and followed the methodology as specified in the protocol Piechotta 2020a). Because of the missing comparator, efficacy data of non-controlled studies cannot be placed in context and therefore do not provide any useful evidence. In contrast to the protocol, we therefore decided to only include safety data of non-controlled studies.

Differences between second and third published review version

(Piechotta 2020b to Chai 2020)

We decided to include registered non-controlled NRSIs only to minimise selection bias.

Differences between third and fourth published review version

(Chai 2020 to Piechotta 2021)

Originally we had planned to include different study designs in a top-down approach: RCTs, prospective and retrospective controlled NRSIs, and prospective and retrospective registered non-controlled NRSIs. We had planned to include the next lower level in case we had low or very low certainty in the evidence of higher-quality studies.

However, because large-scale or expanded access studies could still provide valuable information on the safety of convalescent plasma or hyperimmune immunoglobulins, we decided to include prospectively registered single-arm studies, even if upcoming RCTs reported safety data for both groups. We decided to consider prospectively registered single-arm studies only for safety data, and if 500 or more participants were included.

Differences between fourth and current published review version

(Piechotta 2021 to current version)

Since we were aware that more RCTs had become available, we decided to only include data from RCTs in this update to have the best available quality of study design. We identified more safety data, so we decided to exclude prospectively registered single-arm studies with inclusion of 500 or more participants and expanded access studies.

Types of participants

Differences between third and fourth published version

(Chai 2020 to Piechotta 2021)

After discussion with several attending physicians and clinical experts, we decided to perform separate analyses for populations with asymptomatic infection or mild disease and for hospitalised participants with moderate to severe disease, according to the latest WHO clinical progression score (WHO 2020e). We discussed that patient and study characteristics were not homogeneous enough to be combined and outcomes of interest differ.

Types of intervention

Differences between first and second published review version

(Valk 2020 to Piechotta 2020b)

We added standard immunoglobulin as an eligible control treatment.

Differences between fourth and current published review version

(Piechotta 2021 to current version)

We removed hyperimmune immunoglobulin as an eligible intervention treatment.

Types of outcome measures

Differences between protocol and first published review version

(Piechotta 2020a to Valk 2020)

We revised the secondary outcome 'Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days and added the fourth bullet point: 'plus high-flow oxygen', to differentiate from the third bullet point. After revision, it read:

- oxygen by mask or nasal prongs
- oxygen by NIV (non-invasive ventilation) or high flow
- intubation and mechanical ventilation
- extracorporeal membrane oxygenation (ECMO)

Differences between first and second published review version

(Valk 2020 to Piechotta 2020b)

We added the outcome 'quality of life' after discussion with a patient representative.

Differences between second and third published review version

(Piechotta 2020b to Chai 2020)

We renamed the outcome 'time to death' as 'mortality (time to event)'. This did not change the outcome measurement we are interested in.

We revised the secondary outcome 'Improvement of clinical symptoms' according to the revised outcome measure set for COVID-19 clinical research (COMET 2020). Instead of defining cut-offs ourselves, we refer to the recommended standardised scales:

- Improvement of clinical symptoms, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days.

We added the outcome 'virological response assessed with reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days because this was suggested during the peer review of the last version of this review.

Differences between third and fourth published review version

(Chai 2020 to Piechotta 2021)

We divided efficacy outcomes for hospitalised individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease and ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, according to WHO clinical progression scale (WHO 2020e).

For individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, we added the outcomes admission to hospital, development of moderate to severe clinical COVID-19 symptoms, time to symptom onset, and any grade adverse events; and length of hospital stay for the subgroup of participants being hospitalised in the course of disease.

We revised and redefined outcomes for individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease after discussion with intensive care specialists and the German guideline panel for inpatient therapy of people with COVID-19. We summarised different outcome measures for all-cause mortality below one outcome, added sub-outcomes for clinical improvement, and added clinical worsening to better reflect the course of disease and to detect group differences. We also added the outcome need for dialysis, and extended the definition of quality of life to also include fatigue and functional independence.

We renamed the outcome 'time to discharge from hospital' to 'Duration of hospitalisation, or time to discharge from hospital' to clarify that we are interested in both, continuous and time-to-event data. We renamed the outcome 'virological response' to 'viral clearance' to clarify that we are interested in test-negativity and not in changes of viral load.

Differences between fourth and current published review version

(Piechotta 2021 to current version)

We renamed 'Prioritised outcomes' to 'Primary outcomes' and 'Additional outcomes' to 'Secondary outcomes'.

We revised and redefined outcomes for individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease. For the primary outcomes, we renamed the outcome 'all-cause mortality at hospital discharge' to 'all-cause mortality during hospital stay' and we redefined the outcome of worsening of clinical status to 'new need for invasive mechanical ventilation, or death' (including the competing event of death) and the outcome of improvement of clinical status to 'participants discharged from hospital'. For the secondary outcomes, we added the outcome 'improvement of clinical status' with three sub-outcomes (weaning or liberation from invasive mechanical ventilation in surviving participants; ventilator-free days; and liberation from supplemental oxygen in surviving participants). We removed the secondary outcome 'Length of stay on the intensive care unit (ICU) or time to discharge from ICU'.

We revised and redefined outcomes for individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease. For the primary outcomes, we added the outcome 'admission to hospital or death' (including the competing event of death), 'symptom resolution' with two sub-outcomes (all initial symptoms resolved and time to symptom resolution). We removed the outcome 'development of moderate to severe clinical COVID-19 symptoms' including all the sub-outcomes. For the secondary outcomes, we removed 'admission to hospital', 'time to symptom onset', 'length of hospital stay', and 'admission to the ICU'. We added the outcome of worsening of clinical status with two sub-outcomes 'need for hospitalisation with the need for oxygen by mask or nasal prongs, or death' and 'need for invasive mechanical ventilation, or death' (including the competing event of death).

Electronic searches

Differences between protocol and first published review version

(Piechotta 2020a to Valk 2020)

As publication bias might influence all subsequent analyses and conclusions, we searched all potentially relevant trials registries in detail to detect ongoing studies as well as completed but not yet published studies. Nowadays, it is mandatory to provide results at least in the trials registry. In case results were not published elsewhere, we had planned to extract and analyse these data. However, no outcome data had yet been added to the trials registries.

Differences between first and second published review version

(Valk 2020 to Piechotta 2020b)

We decided to exclude individual trials registries from the search strategy because they are already included in the Cochrane COVID-19 Study Register, which is updated Monday to Friday, and to also exclude the WHO COVID-19 Global Research Database. The WHO COVID-19 Global Research Database and LitCov are included in the collection of the Center for Disease Control and Prevention COVID-19 Research Article Database. The search part for COVID-19 was updated for the search strategies from IM and CD peer reviewed it.

Differences between third and fourth published review version

(Chai 2020 to Piechotta 2021)

In the list of databases, The Living Overview of Evidence (L*OVE) Covid-19 provided from Epistemonikos is included due to the variety of sources it contains (since September 2020) and the WHO COVID-19 global literature on coronavirus disease was added because it integrates the CDC database (since October 2020).

New identified search terms like the MeSH term Immunization, Passive exploded and these search strings (passiv* adj3 (antibod* transfer* or immunization* or immunotherap* or immuno-therap*)).tw,kf.; ((immunoglobulin* or immune globulin*) adj2 (therap* or treat*)).tw,kf.; (INM005 or CSL760).tw,kf.; (XAV-19 or SAB-185 or hIVIG or equine).tw,kf. were searched from November 2020. Due to the availability of

more studies, the searches were focused on non-RCTs and RCTs with adequate study filters (since December 2020). At the beginning of 2021, new MeSH or EMTREE terms were inserted in Medline and Embase, so the whole search strategies were revised and new search terms like IGY-110 or GIGA-2050 or GC5131 or 5131A or INOSARS were added. The search string (passive adj2 vaccin*).tw,kf. and new terms for hyperimmune like equine polyclonal antibodies (EpAbs), hyperimmune anti-COVID-19 IVIG (C-IVIG), anti-coronavirus immunoglobulin (ITAC), flebogamma were included in February 2021.

Differences between fourth and current published review version

(Piechotta 2021 to current version)

From April 2021 onwards the searches were restricted to RCTs with the use of RCT study filters. In May 2021, the new terms F(ab)2, BSVEQAb and EqAb-COV-19 were included and the search time was limited from 01 January 2019 to 01 January 2020. Since August 2021, we have run the searches monthly instead of weekly. In September 2021, we added the search terms bovine colostrum and bovine milk.

In March 2022, the search terms bioblock, γ-Globulin, hyper-Ig and C19-IG, gammaglobulin were added. The search lines (Flu-IVIG or ((anti-flu* or anti-influenza* or antiflu* or antinfluenza*) adj5 plasma)).mp. and (anti-flu* or anti-influenza* or antiflu* or antifluenza*) from MEDLINE and Embase were deleted. The RCT filter for Embase was replaced by the RCT-filter Embase Cochrane Highly Sensitive Search Strategy (Lefebvre 2022b) for identifying controlled trials in Embase: (2018 revision); Ovid format. The WHO search strategy was revised and refined by adjacency searching.

Data extraction and management

Differences between protocol and first published review version

(Piechotta 2020a to Valk 2020)

We had planned to extract data using a standardised data extraction form developed in Covidence. However, we could not adapt the standardised form to our needs. Therefore we generated a customised data extraction form in Microsoft Excel (Microsoft Corporation 2018).

Differences between first and second published review version

(Valk 2020 to Piechotta 2020b)

Assessment of risk of bias in included studies

Randomised controlled trials

We had planned to use RoB 2 to judge the risk of bias in the underlying study results (Sterne 2019). However, RoB 2 was not yet available in RevMan Web (RevMan Web 2022), and the Cochrane Editorial and Methods Department recommended that we use the previous risk of bias tool instead (RoB 1; Higgins 2011).

Differences between second and third published review version

(Piechotta 2020b to Chai 2020)

Measures of treatment effect

We had planned to use the Excel tool of the purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007), to estimate hazard ratios (HRs) with the reported data, if HRs were not available. We were able to read off mortality data from the Kaplan-Meier curve provided by Gharbharan 2020 [https://revman.cochrane.org/#/6600200410134635556/dashboard/htmlCompare/3.6/2.11#STD-Gharbharan-2020] per day. Because we did not have the rights to edit the Excel tool to add a greater number of time intervals, we could not use the Excel tool. We therefore used a digitising software (GetData Graph Digitizer [https://revman.cochrane.org/#/6600200410134635556/dashboard/htmlCompare/3.6/2.11#REF-GetData-Graph-Digitizer]) to estimate the HR for Gharbharan 2020 [https://revman.cochrane.org/#/6600200410134635556/dashboard/htmlCompare/3.6/2.11#STD-Gharbharan-2020].

Assessment of risk of bias in included studies

Randomised controlled trials

RoB became available in RevMan Web. We therefore decided to revert to our originally planned methodology for risk of bias assessment in RCTs and used RoB 2.0 for any assessments.

Differences between third and fourth published review version

(Chai 2020 to current Piechotta 2021)

Subgroup analysis and investigation of heterogeneity

We had added subgroup analyses for the following characteristics in this update of the review.

- Duration since symptom onset
- Level of antibody titre in donors
- Level of antibody titre in recipients at baseline
- SARS-CoV-2 variants

Considering the currently available evidence, we decided to add these subgroups, because their role in the effectiveness of convalescent plasma is currently being discussed and needs to be further investigated.

Differences between fourth and current published review version

(Piechotta 2021 to current version)

Subgroup analysis and investigation of heterogeneity

We had added subgroup analyses for the following characteristics in this update of the review.

- Equity impact: sex (divided into female and male)
- Equity impact: country income groups, according to the World Bank definitions, divided into high- and low- or middle-income countries)
- Equity impact: ethnicity

We further defined the following subgroups:

- Severity of condition for inpatients only (assessed with need for respiratory support according to WHO clinical progression scale (WHO 2020e) are divided into:
  - moderate when at least 90% of participants are WHO level 4 or above and below WHO level 6
  - severe disease when at least 90% of participants are WHO level 6, or above, and
  - moderate to severe when 90% of participants are in both the "moderate" and "severe" category
- Level of antibody titre in donors (divided into high and low titres, using the US Food and Drug Administration (FDA) definition for 'low' and 'high' titre, using the definitions in the studies)

In case of missing data, we conducted an available-case analysis.

Summary of findings and assessment of the certainty of the evidence

Differences between protocol and first published review version

(Piechotta 2020a to Valk 2020)

At protocol stage, we had planned to assess the certainty in the evidence for our primary outcomes (all-cause mortality at hospital discharge and time to death) only. However, as none of the included studies reported any deaths during their study periods, we decided to assess the certainty in the evidence also for prioritised secondary outcomes (clinical improvement, grades 3 and 4 adverse events, and serious adverse events) to increase the informative value on effectiveness and safety of convalescent plasma therapy.

Differences between first and second published review version

(Valk 2020 to Piechotta 2020b)

For the living systematic review we also prioritised patient quality of life as an important patient outcome and added this outcome to the summary of findings table. We specified in the methods how we graded the certainty of the evidence, especially for non-randomised controlled trials using ROBINS-I for risk of bias assessment, for calculation of absolute effects for time-to-event outcomes, and for writing informative statements for the findings and certainty of the evidence.

Differences between third and fourth published review version

(Chai 2020 to current Piechotta 2021)

We decided to include two summary of findings tables, one for each population.

We amended the outcomes for inclusion in the summary of findings table, in accordance with redefining the types of outcome measures. We summarised the outcome all-cause mortality and provided a hierarchy of outcome measures that we would consider for inclusion in the summary of findings table. We added clinical worsening, in addition to clinical improvement, to better reflect the course of disease, and also provide a hierarchy for sub-outcomes of all-cause mortality.

Differences between fourth and current published review version

(Piechotta 2021 to current version)

We decided to include a summary of findings table for each comparison and for each population.

We amended the outcomes for inclusion in the summary of findings table, in accordance with redefining the types of outcome measures.

INDEX TERMS

Medical Subject Headings (MeSH)

*COVID-19 [therapy]; COVID-19 Serotherapy; Immunoglobulins; SARS-CoV-2; *Virus Diseases

MeSH check words

Humans

Appendix E. Declaration of an oath (dt. Eidesstattliche Versicherung)

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertationsschrift selbstständig und ohne die Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Alle Stellen - einschließlich Tabellen, Karten und Abbildungen -, die wörtlich oder sinngemäß aus veröffentlichten und nicht veröffentlichten anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, sind in jedem Einzelfall als Entlehnung kenntlich gemacht. Ich versichere an Eides statt, dass diese Dissertationsschrift noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen - noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss der Promotion nicht ohne Genehmigung der / des Vorsitzenden des IPHS-Promotionsausschusses vornehmen werde. Die Bestimmungen dieser Ordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Frau Prof. Dr. Nicole Skoetz betreut worden.

Darüber hinaus erkläre ich hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten der Universität zu Köln gelesen und sie bei der Durchführung der Dissertation beachtet habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen.

Übersicht der Publikationen:

1. **Iannizzi C**, Dorando E, Burns J, Weibel S, Dooley C, Wakeford H, Estcourt LJ, Skoetz N, Piechotta V. Methodological challenges for living systematic reviews conducted during the COVID-19 pandemic: A concept paper. J Clin Epidemiol. 2022 Jan;141:82-89. doi:10.1016/j.jclinepi.2021.09.013.
2. **Iannizzi C**, Akl EA, Anslinger E, Weibel S, Kahale LA, Aminat AM, Piechotta V, Skoetz N. Methods and guidance on conducting, reporting, publishing, and appraising living systematic reviews: a scoping review. Syst Rev. 2023 Dec 14;12(1):238. doi: 10.1186/s13643-023-02396-x.
3. **Iannizzi C**, Chai KL, Piechotta V, Valk SJ, Kimber C, Monsef I, Wood EM, Lamikanra AA, Roberts DJ, McQuilten Z, So-Osman C, Jindal A, Cryns N, Estcourt LJ, Kreuzberger N, Skoetz N. Convalescent plasma for people with COVID-19: a living systematic review. Cochrane Database of Systematic Reviews 2023, Issue 5. Art. No.: CD013600. DOI: 10.1002/14651858.CD013600.pub6.

Ich versichere, dass ich alle Angaben wahrheitsgemäß nach bestem Wissen und Gewissen gemacht habe und verpflichte mich, jedmögliche, die obigen Angaben betreffenden Veränderungen, dem IPHS-Promotionsausschuss unverzüglich mitzuteilen.

17.04.2024
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Datum Unterschrift