Received: 21 May 2022 | Revised: 18 October 2022 | Accepted: 31 October 2022

DOI: 10.1111/tme.12942

TRANSFUSION MEDICINE WILEY

ORIGINAL ARTICLE

A systematic review of the safety and efficacy of convalescent plasma or immunoglobulin treatment for people with severe respiratory viral infections due to coronaviruses or influenza

Catherine Kimber[1,2] | Abigail A. Lamikanra[2,3] | Louise J. Geneen[1,2] | Josie Sandercock[1,2] | Carolyn Dorée[1,2] | Sarah J. Valk[2,4] | Lise J. Estcourt[1,2,5]

[1]Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK

[2]Nuffield Division of Clinical Laboratory Sciences, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[3]Pathology Directorate, National Health Service (NHS) Blood and Transplant, Oxford, UK

[4]Jon J van Rood Center for Clinical Transfusion Research, Sanquin/Leiden University Medical Center, Leiden, Netherlands

[5]Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK

Correspondence
Lise J. Estcourt, Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK.
Email: lise.estcourt@nhsbt.nhs.uk

Abstract

Objective: Evaluate the safety and effectiveness of convalescent plasma (CP) or hyperimmune immunoglobulin (hIVIG) in severe respiratory disease caused by coronaviruses or influenza, in patients of all ages requiring hospital admission.

Methods: We searched multiple electronic databases for all publications to 12th October 2020, and RCTs only to 28th June 2021. Two reviewers screened, extracted, and analysed data. We used Cochrane ROB (Risk of Bias)1 for RCTs, ROBINS-I for non-RCTs, and GRADE to assess the certainty of the evidence.

Results: Data from 30 RCTs and 2 non-RCTs showed no overall difference between groups for all-cause mortality and adverse events in four comparisons. Certainty of the evidence was downgraded for high ROB and imprecision. (1) CP versus standard care (SoC) (20 RCTS, 2 non-RCTs, very-low to moderate-high certainty); (2) CP versus biologically active control (6 RCTs, very-low certainty); (3) hIVIG versus SoC (3 RCTs, very-low certainty); (4) early CP versus deferred CP (1 RCT, very-low certainty). Subgrouping by titre improved precision in one outcome (30-day mortality) for the 'COVID high-titre' category in Comparison 1 (no difference, high certainty) and Comparison 2 (favours CP, very-low certainty). *Post hoc* analysis suggests a possible benefit of CP in patients testing negative for antibodies at baseline, compared with those testing positive.

Conclusion: A minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not yet produced antibodies to the virus would be useful to target therapies at groups who will potentially benefit the most.

KEYWORDS
convalescent, hyper-immune immunoglobulin, infection, plasma, respiratory, safety

1 | INTRODUCTION

Severe acute respiratory infections caused by strains of influenza or coronavirus often lead to hospitalisation and sometimes death. Symptomatic infection with SARS CoV-2 (COVID-19) has surpassed the annual global burden of death due to influenza or coronaviruses.[1] Although there are several effective vaccines for COVID-19 therapeutic treatments are still required. Patients particularly at risk are those with disorders that affect the immune system, for example, haematological malignancies or those receiving drugs that suppress an immune response, for example, after organ transplantation.[2,3]

Passive antibody therapies, including monoclonal antibody combinations have proven effective for COVID-19[4] However, the cost of these therapies is prohibitive[5] and new SARS-CoV variants may become resistant to anti-virals developed in response to previous variants.[6] Alternative and affordable responses to emerging strains of virus are needed.

Convalescent plasma (CP) is typically collected from donors with confirmed diagnosis of infection at least 2 weeks after recovery.[7] CP contains neutralising antibodies specific to the infectious agent but may also contain other immune modulators and clotting factors that can be fractionated out to produce hyperimmune-immunoglobulin (hIVIG).[8]

CP containing high titres of polyclonal antibody (Ab), has been used to treat patients hospitalised with respiratory syndromes caused by viral infections. Many studies have been poorly controlled but such series suggested decreased mortality in H1N1 Influenza infections in 1918–1920 and in 2009/2010, SARS-CoV-1 infections in 2003 and most recently COVID-19. Recent systematic reviews lacked data from RCTs and analysis did not consider the titre used within trials.[9] Moreover, there are concerns that CP may cause harm, potentially causing severe transfusion reactions such as transfusion-associated acute lung injury (TRALI) or antibody dependent enhancement of the viral infection.[10]

Prior to the COVID-19 pandemic, studies investigating the effectiveness of CP for viral infections varied in quality and the outcomes reported may not have reflected current international guidelines.[11,12]

2 | OBJECTIVE

To evaluate the evidence for the safety and effectiveness of using convalescent plasma (CP) or hyperimmune immunoglobulin (hIVIG) to treat severe respiratory disease caused by coronaviruses or influenza.

3 | METHODS

The protocol for this review was prospectively registered on PROSPERO (CRD42020176392), and the review was carried out in accordance with Cochrane methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

3.1 | Search strategy

We searched multiple electronic databases (MEDLINE, PubMed, The Cochrane Library, Embase, Epistemonikos), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform for ongoing studies, without language restriction, for all publication types on 12th October 2020 (see Appendix A1 in Data S1). We updated our search on 28th June 2021, increasing the number of databases (Cochrane COVID-19 Study Register, Transfusion Evidence Library, Web of Science). We limited the update search to systematic reviews and RCTs due to the significant number of randomised trials available at this point. Ongoing studies identified in our searches were checked on 30th November 2021 and included if published in full (peer-reviewed) by this date. We hand searched reference lists of systematic reviews and included RCTs.[11]

3.2 | Selection criteria

For assessments of effectiveness, we included RCTs comparing transfusion of CP products to any control arm with participants of any age who were admitted to hospital with severe respiratory illness. For assessments of safety, we included all study designs where patients received CP or hIVIG.

Two reviewers (CK, AL, LJG, SV) independently screened title and abstract, and then full-text using Covidence.

Where a publication was in a non-English language, we used electronic translation tools and sought the help of native speakers where appropriate (Appendix A2 in Data S1).

3.3 | Data extraction

Two of four reviewers (CK, AL, LJG, JS) independently extracted data using Covidence and Excel. Reviewers who were involved with any original trials (AL, LE) were not involved in the data extraction for those trials.

Extracted data included: details of study participants (demographic and disease characteristics), details of interventions (including titre, volume, timing of CP/hIVIG), and outcomes.

Outcomes extracted: all-cause mortality up to 30 and 90 days; need for mechanical ventilation (MV) and non-invasive ventilation (NIV) at up to 30 days; duration of MV or NIV; length of hospital stay; length of intensive care unit (ICU) stay; duration of viral detection from admission up to 30 days; transfusion-related serious adverse events (SAEs).

In a deviation from our protocol, we also assessed SAEs up to 30 days due to substantial variability in the way that SAEs were reported. For papers from the 1918 to 1920 influenza pandemic, reporting style was substantially different and, if reported, there was no grading of AEs. We recorded any potential AE described in these publications.

Where data were not available for a particular timepoint, we extracted data to the nearest possible timepoint. We sought clarification from trial authors where necessary.

3.4 | Risk of bias assessment

Two review authors (CK, AL, LJG, JS) independently assessed all eligible studies for risk of bias (ROB), using the Cochrane ROB tools. ROB1 for RCTs[14] and ROBINS-I for observational studies according to the Cochrane Handbook for Systematic Reviews of Interventions.[15] Reviewers who had worked on a trial (AL, LE) did not participate in ROB assessments for those studies.

Observational studies assessed as having "critical" ROB were not included in quantitative analyses.

3.5 | Data analysis

Statistical analyses were undertaken in Review Manager 5.4,[16] R[17] and the *metafor* package in R.[18] For dichotomous outcomes, we used the Mantel–Haenszel method, or Peto OR for rare events. We calculated the pooled risk ratio (RR) with a 95% confidence interval (CI), using the random effects model in RevMan5.[16] We used Tau^2 and I^2 in the assessment of heterogeneity, according to the guidelines laid out in the Cochrane handbook.[19]

We have not combined RCTs and non-RCTs and so have reported the results separately.

We planned to analyse continuous outcomes using mean difference (MD) or standardised mean difference (SMD) where different scales had been used. Continuous outcomes reported as median (IQR/range) could not be meta-analysed or pooled and have been reported narratively within tables.

Information from observational studies was collated in tables and not meta-analysed. Certainty of the evidence (based on meta-analysable data only) was assessed using GRADEPro.[20]

3.5.1 | Subgroup and sensitivity analysis

We subgrouped included trials by the type of respiratory infection.

We also subgrouped COVID-19 studies by their use of high titre or low titre/unselected plasma (see Appendix A3 in Data S1) in response to emerging research that highlighted the wide variability in CP titres used in practice.

We intended to undertake sensitivity analyses based on selection bias to examine evidence from 'low risk' studies only. However, this was not necessary for the RCTs as all included RCTs were assessed as low (or unclear) risk for mortality endpoints within this domain.

3.5.2 | *Post hoc* analysis of seropositivity

We performed a *post hoc* analysis of trials where there were sufficient data to assess the impact of SARS-CoV-2 antibody status at baseline due to emerging evidence of greater effectiveness of passive antibody therapy (monoclonal antibodies) for patients who are antibody negative at baseline.[21] Meta-regression for *post hoc* analysis of seropositivity was performed using the metafor[18] package in R.

4 | RESULTS

Our search yielded 4826 references (Figure 1 PRISMA flow diagram; for excluded studies see Appendix A4 in Data S1).

4.1 | Study Characteristics

We identified 110 completed studies (Figure 1), including 30 RCTs (four for influenza, n = 578; and 26 for COVID-19 SARS-CoV-2, *n* = 18 204).[3,7,22–49] There were no RCTs or non-randomised controlled trials identified for MERS or SARS (SARS-CoV-1) (Appendix A Supplementary Table A1 in Data S1). We included 76 non-randomised studies (Appendix B in Data S1). Of these, eleven were controlled studies, of which only two were at less than "critical" ROB[50,51] (Appendix A Supplementary Table A2 in Data S1) We included 67 uncontrolled studies: 12 assessing influenza A; two on MERS-CoV; four on SARS-CoV, and 49 on COVID-19 (SARS-CoV-2).

We also identified 143 ongoing studies (Appendix C) which were either controlled trials or single arm studies, which listed at least one safety outcome in their intended primary or secondary outcomes.

Study size in the quantitative analyses ranged from 29 to 11 555 (34 to 308 for influenza).

Of the four RCTs assessing influenza: two included children (*n* = 24/236 < 18 years)[39,45]; three RCTs[39,45,47] included pregnant women (3/270 pregnant women).

Of the 26 RCTs and 2 non-randomised studies that assessed COVID-19: one RCT included children (*n* = 26/11558 < 18 years).[3] Three RCTs[29,34,44] did not report whether they included children. Three RCTs[3,29,35] included pregnant women (*n* = 36/12575 pregnant women). Eight RCTs[22,24,30–33,36,44] did not report whether they included pregnant women.

4.2 | Comparisons

We identified four comparisons within the data that could be combined in quantitative analysis:

(1) CP versus standard care (SoC) or biologically inactive placebo (saline) (20 RCTs): 19 RCTs compared CP to SoC,[3,7,22–25,27–31,33–36,38,39] one RCT[26] compared SoC with saline placebo, and two retrospective observational studies[50,51] compared CP patients with matched controls;

(2) CP versus biologically active control (FFP or IVIG) (6 RCTs): five RCTs compared CP to non-immune FFP,[40–43,45] and one compared CP with IVIG.[44]

(3) hIVIG versus control (3 RCTs) Of these, two compared hIVIG with SoC,[46,47] one compared hIVIG with saline placebo.[48]

(4) early CP versus deferred CP (1 RCT).[49]

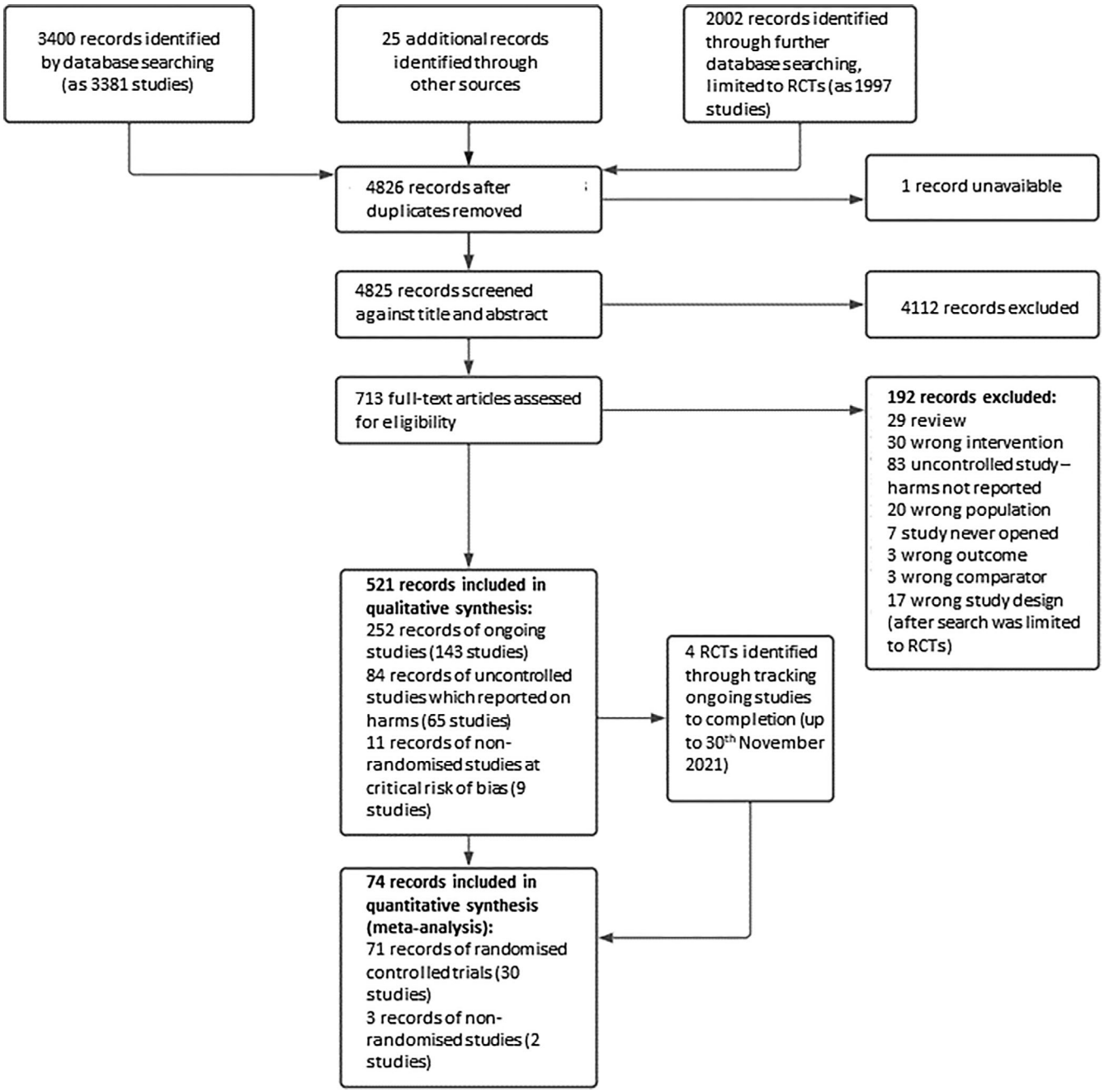


FIGURE 1 PRISMA flow diagram. Caption: The reasons for exclusion at each stage are shown with arrows to the right.

The comparators and baseline characteristics of participants in each of the thirty RCTs and two non-RCTs (retrospective observational studies)[50,51] within meta-analyses are summarised in Appendix A Table A1 in Data S1.

4.3 | Outcomes

We could only extract sufficient data to meta-analyse mortality and serious adverse events. We have presented remaining data from controlled studies in tables (Appendix A, Tables A3–A6 in Data S1). A summary of all outcomes reported is available in Appendix A5.

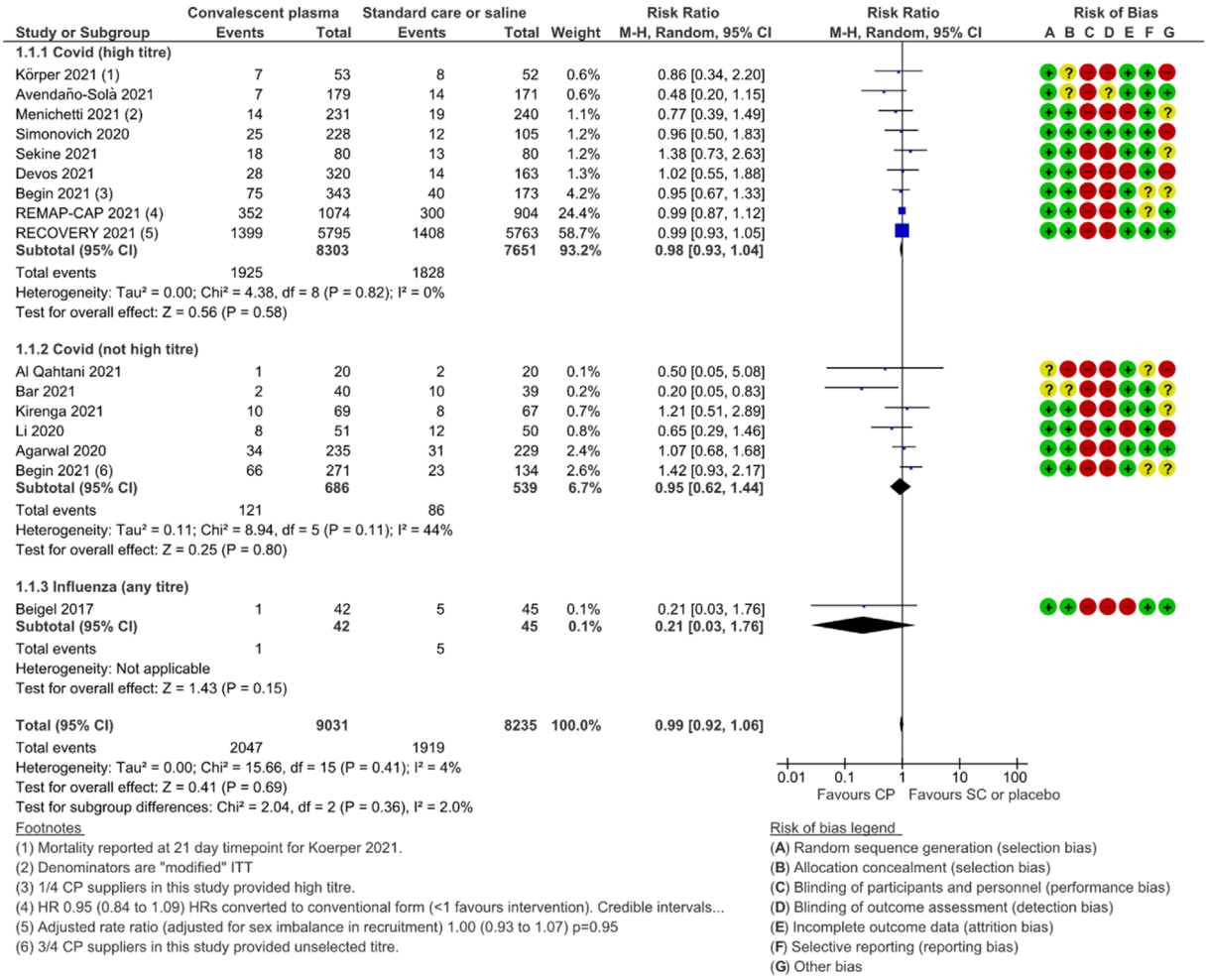
Most trials did not describe any method for dealing with competing risks when reporting their results. A competing risk is one which prevents the event of interest from occurring. Death is a competing risk for both (time to) mechanical ventilation and (time to) discharge. Devos 2021[28] approached competing risks using competing events analysis[52] to obtain cause-specific hazard ratios (HR). REMAP-CAP[30] used ordinal logistic regression by assigning each participant a category labelled with the number of ventilator-free days up to 21 days, with people who died up to day 90 being assigned −1, people who were on MV at

TABLE 1 Overview of meta-analysed results from patients hospitalised with severe respiratory infections

Comparison	30-day mortality		90-day mortality	Grade 3 or 4 transfusion related AEs	SAEs
Comparison 1: CP versus SoC or biologically inactive placebo (saline)	**All RCTs:** RR 0.99 (0.92 to 1.06) 15 RCTs[a], *n* = 17 266 (37 children, 38 pregnant women) ⨁⨁⨁◯ $I^2 = 4\%$ $Tau^2 = 0.00$	**High Titre subgroup:** RR 0.98 (0.93 to 1.04) 9 RCTs[b], *n* = 15 954 (26 children, 33 pregnant women) ⨁⨁⨁⨁ $I^2 = 0\%$ $Tau^2 = 0.00$	RR 0.92 (0.74 to 1.15) 6 RCTs[b], *n* = 3210 (8 pregnant women) ⨁⨁◯◯ $I^2 = 0\%$ $Tau^2 = 0.02$	*No transfusion in control group; results in intervention group are summarised in table A12*	RR 1.14 (0.92 to 1.41) 13 RCTs[a], *n* = 16 730 (37 children, 38 pregnant women) ⨁◯◯◯ $I^2 = 56\%$ $Tau^2 = 0.07$
Comparison 2: CP versus biologically active control (FFP or IVIG)	RR 0.85 (0.56 to 1.29) 5 RCTs[a] *n* = 700 (13 children, 1 pregnant woman) ⨁◯◯◯ $I^2 = 33\%$ $Tau^2 = 0.07$		RR 0.99 (0.75 to 1.29) 2 RCTs[b], *n* = 264 ⨁◯◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$	POR 0.43 (0.14 to 1.33) 6 RCTs[a], *n* = 716 (13 children, 1 pregnant woman) ⨁◯◯◯ $I^2 = 4\%$ $Chi^2 = 4.18$	RR 0.88 (0.65 to 1.19) 4 RCTs[b], *n* = 523 (13 children, 1 pregnant woman) ⨁⨁◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$
Comparison 3: hIVIG versus control	RR 0.77 (0.34 to 1.73) 3 RCTs[c] *n* = 392 ⨁◯◯◯ $I^2 = 50\%$ $Tau^2 = 0.26$		*No RCTs reported mortality at 90 days in this comparison*	RD 0.00 (−0.08 to 0.08) 2 RCTs[a] *n* = 84 ⨁◯◯◯ $I^2 = 0\%$ $Tau^2 = 0.00$	RR 1.10 (0.76 to 1.58) 2 RCTs[a] *n* = 342 ⨁◯◯◯ I^2 = n/a Tau^2 = n/a
Comparison 4: Early CP versus deferred CP	RR 2.68 (0.56 to 12.71) 1 RCT[b], *n* = 58 ⨁◯◯◯ I^2 = n/a Tau^2 = n/a		*No RCTs reported mortality at 90 days in this comparison*	*Transfusion-related AEs were only reported for patients receiving CP; results are summarised in table A12*	*No RCTs reported SAEs in this comparison*

Note: Key: ⨁◯◯◯ very-low certainty evidence; ⨁⨁◯◯ low certainty evidence; ⨁⨁⨁◯ moderate certainty evidence; ⨁⨁⨁⨁ high certainty evidence.
Abbreviations: POR, Peto odds ratio; RD, risk difference; RR, risk ratio.
[a]Includes 1 RCT in influenza.
[b]All COVID-19.
[c]Includes 2 RCTs in influenza.

(a) 30-day mortality



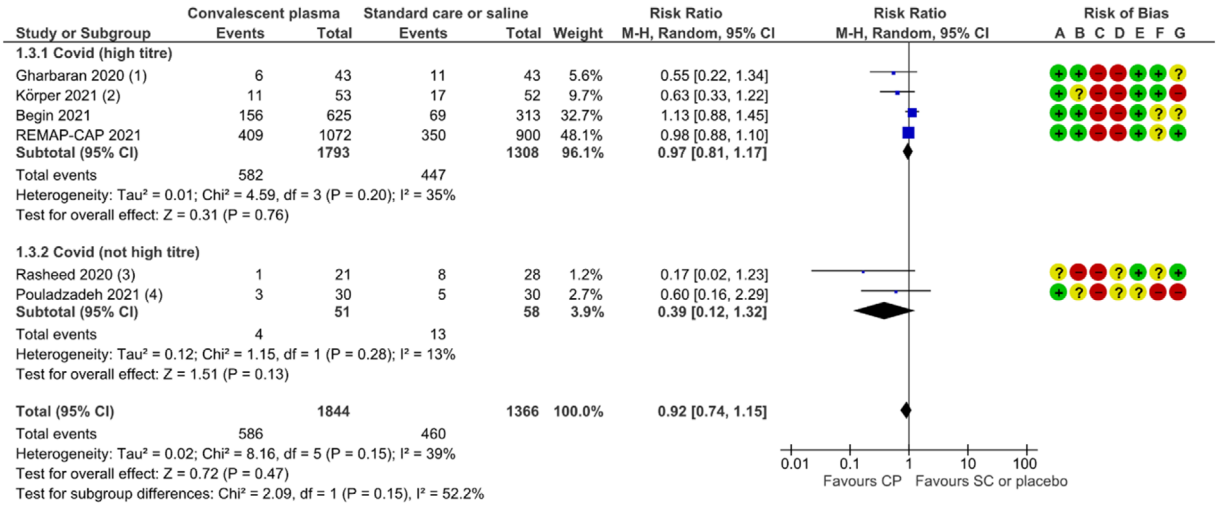
Footnotes

(1) Mortality reported at 21 day timepoint for Koerper 2021.
(2) Denominators are "modified" ITT
(3) 1/4 CP suppliers in this study provided high titre.
(4) HR 0.95 (0.84 to 1.09) HRs converted to conventional form (<1 favours intervention). Credible intervals...
(5) Adjusted rate ratio (adjusted for sex imbalance in recruitment) 1.00 (0.93 to 1.07) p=0.95
(6) 3/4 CP suppliers in this study provided unselected titre.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

(b) 90-day mortality



Footnotes

(1) Reported at 60 day timepoint.
(2) Reported at 60 day timepoint
(3) Mortality reported at 56 day timepoint.
(4) Reported at 60 day timepoint

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

FIGURE 2 Forest plot of all-cause mortality, for comparison 1 (CP compared to SoC or a biologically inactive placebo) at up to (A) 30 days, and (B) 90 days

randomisation being assigned 0, and people who remained ventilator-free beyond day 21 being assigned 22. This is a useful way to compare the two groups while accounting for the very different possible outcomes but the resulting odds ratio (OR) and medians are difficult to interpret. No other trials used these methods and so we cannot combine the results but instead report the summary within Table A4 in Data S1.

Duration of viral detection was expressed as time (median IQR) to first negative test (2 RCTs).[23,36] One study,[25] reported the number of patients who had had two consecutive negative tests by day 30. See table A5 for viral detection data and table A6 for details of changes in viral loads.

4.4 | ROB in included studies

4.4.1 | RCTs (using Cochrane ROB1)

Nineteen RCTs were open-label, comparing CP to SoC, and were therefore assessed as having a high ROB for all outcomes except mortality, as knowledge of treatment allocation may have affected clinical decision-making. A summary of ROB judgements is available in Table A7 and Figure A1 in Data S1.

4.4.2 | Non-RCTs (using ROBINS-I)

Two non-RCTs[50,51] were assessed at serious RoB for selection bias and confounding at baseline. The remaining 9 studies[53–61] were at critical ROB due to baseline confounding or selection bias and were therefore not meta-analysed.

4.5 | Certainty of the evidence (GRADE)

Certainty of the evidence was GRADEd as very-low to high; primary reasons for downgrading were ROB and imprecision (wide confidence intervals and small sample size) (Tables A8–A11 in Data S1). We assessed publication bias through the generation of a funnel plot (Figure A2 in Data S1) for 30-day mortality in comparison 1, which suggests that some small studies have not been published. However, this was not significant enough to downgrade the certainty of the evidence because the analysis is dominated by two large, high-quality, and RCTs.

4.6 | Effect of the Intervention

See Table 1 for an overview of meta-analysed results.

4.6.1 | Comparison 1: CP versus SoC or biologically inactive placebo

Twenty RCTs and two retrospective studies assessed CP compared with SoC or a biologically inactive placebo.

All-cause mortality

30-day mortality data were available from 15 RCTs (30 days, 5 RCTs; 28 days, 9 RCTs; 21 days, 1 RCT) (Figure 2a); 90-day mortality data were available from 6 RCTs (56 days, 1 RCT; 60 days, 3 RCTs; 90 days, 2 RCTs) (Figure 2b).

Overall, CP did not reduce 30-day mortality (15 RCTs, n = 17 266; moderate-to-high certainty of evidence [Table A8 and footnotes in Data S1]) and there may be no effect on 90-day mortality (6 RCTs $n = 3210$; low certainty of evidence [Table A8]).

Two non-RCTs reported in-hospital mortality, and showed results consistent with the randomised evidence (2 studies, $n = 436$; very-low certainty evidence) (Figure A3A Table A8 in Data S1).

Improvement of clinical symptoms

Duration of NIV was reported in 4 studies (2 RCTs),[3,24,50,51] and duration of MV was reported by 11 studies (9 RCTs).[3,24,25,28–30,35,38,39,50,51] Two RCTs[27,31] reported any ventilatory support, but did not differentiate between MV, NIV, and passive oxygen support. One RCT[29] reported any ventilation, but also reported separately a composite outcome of patients who progressed to MV or death. Most studies reported the data as duration of support, either median (IQR) or mean (SD) (Table A4 in Data S1).

These outcomes were very variably reported, and many did not fully account for competing events, or report methods of analysis in sufficient detail. Based on what was reported, there was no apparent difference in duration of MV, NIV or ECMO support between the two groups.

Length of stay (LOS): hospital and ICU

Length of hospital stay was reported by 16 RCTs[7,23,25–28,30,31,38,39,42–47] and 1 non-RCT,[51] and length of ICU stay was reported by 9 RCTs[23,26,28,29,33,39,43,45,47] (Table A3 in Data S1). There was no evidence of an effect in length of hospital stay or length of ICU stay (Table A3 in Data S1).

Duration of viral detection from admission up to 30 days (viraemia, nasopharyngeal swabs, bronchoalveolar lavage, stool)

The 3 RCTs which reported time to negative test do not suggest any evidence of an effect (Table A5 in Data S1).

Adverse events

AEs due to transfusion were reported in 15 RCTs[3,7,22–39] (Table S10 in Data S1).

Seven RCTs reported no Grade 3 or 4 AEs due to transfusion.[22,24,26,27,31,35,39] Both non-RCTs reported AEs due to transfusion. All but one RCT[26] had SoC comparators, and therefore no transfusion-related SAEs are reported for the control group. Group comparison was not possible; results are summarised in Table A12 of in Data S1.

There was no evidence of an effect on reported SAEs[3,23–31,35,36,39] (13 RCTs, $n = 16\,730$, very-low certainty of evidence) (Figure A3B).

Data were not available on SAEs in seven RCTs.[7,22,32–34,37,38]

See forest plots Figure A3 in Data S1 and GRADE profile Table A8 in Data S1 for further detail.

4.6.2 | Comparison 2: CP versus biologically active control (FFP or IVIG)

RCTS assessed CP compared to FFP[40–43,45] or IVIG[44]

All-cause mortality

There was insufficient evidence to say whether or not there is a difference between groups in all-cause mortality at up to 30 days (5 RCTs $n = 700$; very-low certainty evidence, Figure A4A in Data S1), or at up to 90 days (2 RCTs, $n = 264$; very-low certainty evidence Figure A4B in Data S1). See forest plots Figures A4A and A4B in Data S1 and GRADE profile Table A9 in Data S1 for further detail.

Adverse events

Six RCTs reported transfusion-related Grade 3 or 4 AEs.[40–45] Events were rare (~2%) with no clear evidence of a difference (6 RCTs, $n = 716$; very-low certainty evidence. [Figure A4C in Data S1]). Four RCTs[40–42,45] reported SAEs up to 30 days, showing no evidence of an effect, although the rate of SAEs seems very low, given the severity of disease in hospitalised individuals (4 RCTs, $n = 523$; low certainty evidence, Figure A4D in Data S1). See forest plots Figure A4 and GRADE profile Table A9 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV[40,43,45] and any ventilatory support[41] were reported as median (IQR) or mean (SD). Given the difficulties of dealing with competing events, and the small number of patients involved, it is very unclear if CP therapy had any effect on the duration of MV, NIV or ECMO support between the two groups. We have presented the data in Table A4 in Data S1 as reported by the individual studies.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.3 | Comparison 3: hyperimmune immunoglobulin versus control

Three assessed hIVIG compared with SoC or a biologically inactive placebo.

All-cause mortality

There was insufficient evidence to say whether or not there is an effect on mortality compared to control at up to 30 days (3 RCTs $n = 392$; very-low certainty evidence) (Table 1, Figure A5A, Table A10 in Data S1). There were no data for 90-day mortality.

Adverse events

Two RCTs reported transfusion-related AEs; neither reported any AEs due to transfusion in either group (2 RCTs, $n = 84$; very-low certainty evidence, Figure A5B in Data S1). Two RCTs reported SAES (2 RCTs $n = 342$; very-low certainty evidence. [Figure A5C in Data S1]). See forest plots Figure A5 and GRADE profile Table A10 in Data S1 for further detail.

Improvement of clinical symptoms

One RCT in influenza[48] reported on duration of MV and NIV. However, the data were presented using an ordinal scale that was not mappable to our outcomes or other trial results, and we were unable to extract the data.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.6.4 | Comparison 4: early CP versus deferred CP

One RCT assessed early CP compared to deferred CP.

All-cause mortality

There was insufficient evidence to say whether there is a difference in 30-day mortality between early CP and deferred CP (1 RCT $n = 58$; very-low certainty of evidence) (Figure A6 in Data S1). There were no data for 90-day mortality. See forest plots Figure A6 and GRADE profile Table A11 in Data S1 for further detail.

Adverse events

There were three Grade 3 or 4 transfusion-related AEs within 24 h, all in the early CP group: (1 RCT $n = 58$, very-low certainty evidence) (Table A12 in Data S1). SAEs were not reported. See forest plots and GRADE profile Table A11 in Data S1 for further detail.

Improvement of clinical symptoms

Duration of MV and NIV was reported as median (IQR). We have presented the data in Table A4 in Data S1 as reported by the RCT. Both groups had similar duration of ventilatory support. It is unclear if the authors accounted for competing events.

Data were not available for LOS (hospital or ICU), and duration of viral load.

4.7 | Results from uncontrolled studies (for safety only)

We identified 73 non-randomised or uncontrolled studies [49 case reports or case series] that assessed the use of CP or hIVIG in respiratory viral infection and reported AEs: 12 in influenza A, 2 in MERS-CoV, and 4 in SARS-CoV-1, and 67 in SARS-CoV-2 (COVID-19). Of the influenza studies, 10 were from the 1918 to 1920 pandemic. Fifty-one studies reported that no AEs were observed (37/49 case reports or case series). Eighteen studies reported transfusion-related AEs, and four studies reported other SAEs. These data are presented in Appendix B in Data S1.

4.8 | Post hoc subgroup analysis: seropositivity at baseline

Three RCTs,[3,30,62] including the two largest, reported 30-day mortality for subgroups defined by seropositivity at baseline. These results are shown in Figure 3.

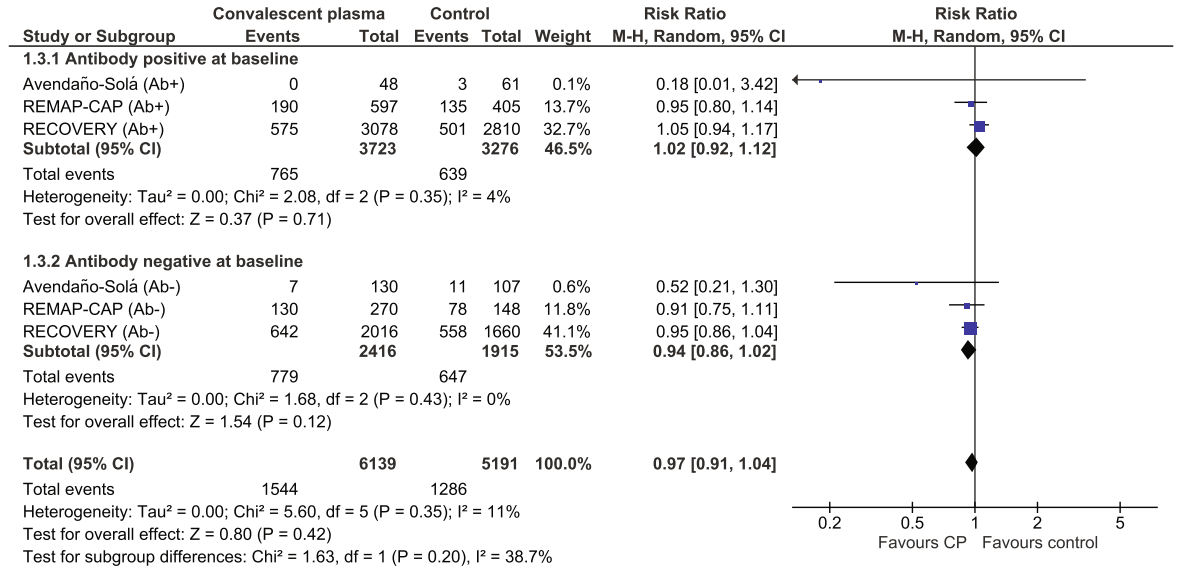


FIGURE 3 Subgrouped by seropositivity at baseline: RCTs reporting 30-day mortality for comparison 1 (CP compared to SoC or a biologically inactive placebo)

With almost all the information coming from the two large, high-quality RCTs,[3,30] the pooled estimates from these three RCTs are: RR 1.02 (0.92 to 1.12) for people who are seropositive at baseline and 0.94 (0.86 to 1.02) for those who are seronegative. The test for interaction (subgroup difference) gives a *p*-value of 0.20 with very little heterogeneity either within or between groups.

We explored this further using meta-regression on the group of trials comparing high titre CP with SoC which reported the proportion seropositive at baseline and 30-day mortality. This analysis produced near identical results with an estimated RR at 0% seropositivity of 0.93 (0.85, 1.01) and 1.02 (0.93, 1.12) at 100% seropositivity (See Appendix A6 in Data S1. Mortality results are summarised in Table A14 in Data S1).

5 | DISCUSSION

The objective of this review was to determine the safety and effectiveness of CP or hIVIG from CP to treat patients with serious respiratory disease due to influenza or coronavirus infection. In order to increase the relevance of our findings to the COVID-19 pandemic we used the core outcome set[63] for assessing treatments for patients infected with SARS-CoV-2. We aimed to use high-quality evidence from RCTs to assess safety and effectiveness. We also used all other study designs to describe serious harms reported following transfusion with CP or hIVIG.

5.1 | Main findings

We were able to meta-analyse 32 studies for our primary outcome of 30-day mortality (30 RCTs and 2 non-RCTs). We found little evidence of any difference between the groups in either benefits or harms for patients hospitalised with a severe viral respiratory infection requiring hospital admission. Most evidence was of low or very-low certainty. The only high-certainty evidence was for the COVID high-titre subgroup in the outcome all-cause mortality at up to 30 days in CP versus SoC (Table 1).

Adverse events were variably reported. No RCTs reported a high number of transfusion-related AEs (proportion 0% to 5.67%[22–24,26,27,31,35,38,39,43,44,46,47]) (very-low to low certainty evidence). There was no evidence of an increase in harms compared with standard plasma.

5.2 | Quality (certainty) of the evidence

Where meta-analysis was possible, we used GRADE to assess our certainty in the result (Table 1). Certainty in the evidence was assessed as very-low to low certainty for all outcomes apart from mortality data in the comparison CP versus standard care.

Evidence was downgraded for serious ROB (lack of blinding, baseline imbalance, randomisation processes, missing data and unclear reporting of outcomes) and imprecision (wide confidence intervals around the effect estimate, and small sample sizes for the outcome of interest). Some of the sources of potential bias (such as patient and personnel blinding) would be hard to overcome in future trials due to the issues in finding an ethical control infusion: even saline is problematic, with the risk of volume overload, and ease with which it can be differentiated from plasma.

SAEs were also downgraded for inconsistency as the heterogeneity was significant between studies, this is likely to be due to the variation in reporting of the SAEs. This may be in part due to differing regulatory environments and different classifications of CP, requiring

varying levels of AE reporting including the need to use a grading system (e.g., MedDRA[64]).

We included lower-level evidence for the assessment of safety outcomes. However, we were unable to perform quantitative analyses, and so have only presented these data as reported in Appendix B in Data S1.

There were very few endpoints reported consistently enough for meta-analysis. The difficulty in defining endpoints, especially time-to-event endpoints,[65] is discussed further in Appendix A6 in Data S1.

5.3 | Strengths and Limitations of this review

We have attempted to minimise potential bias in the review process, using Cochrane methods and PRISMA guidelines for reporting. We conducted a comprehensive search: searching data sources to ensure that all relevant studies would be captured, using multiple databases and reference lists of included studies. We included conference proceedings and included a search of clinical trial registries. We also attempted to contact authors for additional data and for clarification of their data.

There were no restrictions for the language in which the paper was originally published. We pre-specified outcomes prior to analysis and have explained the rationale for including one additional outcome (any SAEs).

We undertook duplicate screening, data extraction, and assessment of bias. Additionally, the clinical advisor (LE) was consulted for disagreements, or need for clarification.

The limitations of this review mostly arose due to gaps in the evidence base, which are discussed more fully in the next section.

5.4 | Interpretation and context

A recent analysis of individual patient data (IPD) pooled from eight RCTs[9] IPD reported an OR for mortality of 0.85 at day 28 (95% credible interval, 0.62 to 1.18; posterior probability of OR <1 of 84%). These results are broadly comparable and in agreement with our own aggregate analyses for 30-day mortality. However, it should be noted that the IPD analysis included two RCTs[66,67] published after our 30th November 2021 cut-off, but did not include the two largest RCTs of CP RECOVERY[3] and REMAP-CAP[30] which we have analysed, and which together contribute 83% of sample size contributing to our analysis of 30-day mortality for CP versus SoC.

A limitation of the current evidence base is that of the 30 RCTs and two non-randomised studies included in our meta-analysis, 26 studies (24 RCTs) excluded children and 16 RCTs excluded pregnant women, with 1 RCT[39] admitting pregnant women only on the second round of recruitment. Given that children and pregnant women are both considered to be at increased risk of serious disease and death from many severe respiratory viral infections, their exclusion from trials is concerning. Of the 144 ongoing studies we identified, most trials will exclude children and pregnant women. Many ongoing studies have an upper age cut-off (of 65, 70 or 80 years), despite older age being one of the biggest risk factors for COVID-19.

The precision of our meta-analysis was affected by the different titres of CP-neutralising antibodies between trials (Table A1 in Data S1). We tried to address this by subgrouping studies based on the CP-titre reported, and whether it was considered high enough according to FDA criteria (see Appendix A3 in Data S1). However, several studies used local assays that could not be correlated with an FDA reference method. Since we conducted our first search, several variants of SARS-CoV-2 have arisen worldwide and may require much higher antibody titres measured using ELISA assays.[68] Much higher titre CP, from vaccinated convalescent donors, may be active against future variants[69] indicating that new COVID CP trials should aim to use very high titre CP standardised using internationally recognised methods.

Similarly, between trials, there was heterogeneity of patient groups and severity of illness on admission to hospital (Table 1). The RCTs in COVID may not have used the same criteria to categorise trial participants at enrolment and trials designed to treat different patient groups based on comorbidities and immune states were absent. Several COVID-19 studies reported clinical improvement using the WHO ordinal scale. However, the scale was revised several times over the course of 2020–2021, going from an 8-point scale[70] to a 10-point scale at its latest revision[71] which have made comparisons between trials difficult.

The results of our post hoc subgroup analysis by seropositivity at baseline are very similar to the results reported by RECOVERY alone. We have not found stronger evidence of this potential interaction than that reported by RECOVERY (with a similar trend also reported by REMAP-CAP, especially for organ support-free days) but similarly, we have not found any reason to discount the possibility that there is a small but important interaction, with immunocompromised individuals potentially benefitting more. This hypothesis is consistent with the REGN-COV2 RECOVERY trial,[21] which has shown no benefit of monoclonal antibodies for seropositive patients who either have advanced disease or who are immunocompetent. The very high baseline risk of immunocompromised individuals might translate very small relative risks into substantial absolute risk differences. REMAP-CAP has recently reopened for immunocompromised people to test this hypothesis.[72]

5.5 | Implications for research and practice

There is currently no evidence for a benefit of CP in an unselected population of patients hospitalised with coronaviruses or influenza. It is likely that the titre of the CP and the immune response of the recipient may both be important factors affecting response to treatment.

Studies should use CP of a high enough titre to elicit a biological response, and report the actual titre used as well as the minimum as described in the protocol. Matching variants between donor and recipient may not be feasible, but viral variants circulating at the time of collection of plasma and during the study should be recorded.

Studies should assess and publish antibody status (seropositivity) at baseline in both intervention and control groups, and identify and

report immunocompromised patients separately, to establish whether certain groups of patients are more likely to benefit from this intervention.

There are difficulties in designing truly blinded RCTs of CP or hIVIG (see Reference 73 for review). There are ethical problems with using a placebo which is assumed to have no clinical benefit, but has known harms.[74] One RCT[26] used a saline placebo, with potential concerns about volume overload, and six RCTs used a biologically active control, (FFP in 5 RCTs,[40–43,45] and IVIG in one[44]) which raises additional concerns about transfusion reactions.

Unless reported explicitly by investigators, it was difficult to distinguish the AEs experienced following transfusion from the symptoms of severe respiratory disease.[75] This limited the number of RCTs that we could include in our meta-analysis of AEs due to transfusion. There was also substantial variability in the way that AEs were recorded and reported in these studies. It was not always possible to determine the severity of AEs, and different studies used different criteria for SAEs. In some cases, it was hard to determine if SAE reporting was per event or per patient, making it extremely difficult to compare rates of AEs between studies. Blood components in the UK are not classified as medicines and so require a different grading system for reporting AEs to countries that classify CP as a medicine, e.g. Germany. A consensus on how AEs associated with blood products are reported in RCTs would help to address this problem.

6 | CONCLUSION

This review has highlighted several issues regarding study design and reporting which should be addressed in current and future research. A minimum titre should be established and ensured for a positive biological response to the therapy. Further research on the impact of CP/hIVIG in patients who have not produced antibodies to the virus prior to hospital admission or who are immunocompromised would be useful to target therapies at groups who will potentially benefit the most.

AUTHOR CONTRIBUTIONS

Catherine Kimber: screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Abigail A. Lamikanra:** screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Louise J. Geneen:** screening and full text assessment, retrieved full text publications, data extraction, risk of bias assessment, entered data into RevMan and undertook subgroup analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Josie Sandercock:** data extraction, risk of bias assessment, and undertook all metaregression analyses, performed GRADE assessments, interpreted the results, contributed to the development of the manuscript. **Carolyn Doree:** developed and performed all search strategies and de-duplication, retrieved full text publications, contributed to the development of the manuscript. **Sarah J. Valk:** screening and full text assessment, retrieved full text publications, contributed to the development of the manuscript. **Lise J. Estcourt:** developed the initial idea of the review, developed, wrote, and registered the protocol, interpreted the results, and contributed to the development of the manuscript.

ACKNOWLEDGEMENTS

We would like to thank Lev E. Korobchenko of the Almazov National Medical Research Center, Hoi Pat Tsang and Matthew Yip for their assistance with translation. We would like to thank Prof. Maria Elvira Balcells, Dr Richard T. Davey and Prof. Lise Estcourt for providing additional unpublished data.

FUNDING INFORMATION

This work was supported by NHS Blood and Transplant intramural funding, and the Systematic Review Initiative (SRI), funded by the four UK blood services. The funders had no influence over the conduct or reporting of this review.

ORCID

Catherine Kimber https://orcid.org/0000-0002-7796-9931
Abigail A. Lamikanra https://orcid.org/0000-0002-9287-2177
Louise J. Geneen https://orcid.org/0000-0001-6759-0437
Josie Sandercock https://orcid.org/0000-0001-7337-8635
Carolyn Dorée https://orcid.org/0000-0001-6955-7497
Sarah J. Valk https://orcid.org/0000-0003-3964-2505
Lise J. Estcourt https://orcid.org/0000-0003-4309-9162

REFERENCES

1. WHO Coronavirus (COVID-19) Dashboard. World Health Organisation (WHO) Emergency Dashboard. 2022. Accessed May 19, 2022. https://covid19.who.int/
2. Sun J, Zheng Q, Madhira V, et al. Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. *JAMA Int Med*. 2022;182(2):153-162.
3. Recovery CG. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet*. 2021;397(10289):2049-2059.
4. ACTIV-3. Therapeutics for inpatients with COVID-19 (TICO). Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. *Lancet Infect Dis*. 2021;22:622-635.
5. Wellcome and IAVI. *Expanding Access to Monoclonal Antibody-Based Products: a Global Call to Action*. 2020. https://wellcome.org/reports/expanding-access-monoclonal-antibodies.
6. Susceptibility data. Table 1. Virus Variants and Spike Mutations vs Monoclonal Antibodies. Fold reduced neutralizing susceptibility to monoclonal antibodies under Emergency Use Authorization(EUA). Accessed Mar 18, 2022. https://covdb.stanford.edu/
7. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19. *JAMA*. 2020;324(5):460-470.
8. Rojas M, Rodriguez Y, Monsalve DM, et al. Convalescent plasma in Covid-19: possible mechanisms of action. *Autoimmun Rev*. 2020;19(7):102554.

9. Troxel AB, Petkova E, Goldfeld K, et al. Association of convalescent plasma treatment with clinical status in patients hospitalized with COVID-19. *JAMA Netw Open*. 2022;5(1):e2147331.
10. Roubinian N. TACO and TRALI: biology, risk factors, and prevention strategies. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):585-594.
11. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and Hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis*. 2015;211(1):80-90.
12. Devasenapathy N, Ye Z, Loeb M, et al. Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis. *Can Med Assoc J*. 2020;192(27):E745-E755.
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
14. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
15. Sterne J, Hernan M, McAleenan A, Reeves B, Higgins JPT. Chapter 25: assessing risk of bias in a non-randomized study. In: Higgins J, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (Updated February 2022)*. Cochrane; 2022. www.training.cochrane.org/handbook
16. RevMan5: Review Manager (RevMan). [computer program]. Version 5.4: The Cochrane Collaboration. 2020.
17. Team RC. *R: A Language and Environment for Statistical Computing*. *R Foundation for Statistical Computing* Vienna; 2020.
18. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Software*. 2010;36(3):338-341.
19. Deeks J, Higgins J, Altman D. Chapter 10: Analysing data and undertaking meta-analyses. In: JPT H, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (Updated February 2022)*. Cochrane; 2022. www.training.cochrane.org/handbook
20. *GRADEpro Guideline Development Tool. Available from gradepro.org [Computer Program]*. McMaster University and Evidence Prime; 2021.
21. Abani O, Abbas A, Abbas F, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2022;399(10325):665-676.
22. Gharbharan A, Jordans CCE, Geurtsvankessel C, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. *Nat Commun*. 2021;12(1):3189.
23. Körper S, Weiss M, Zickler D, et al. Results of the CAPSID randomized trial for high-dose convalescent plasma in patients with severe COVID-19. *J Clin Investig*. 2021;131(20):e152264.
24. Avendaño-Solá C, Ramos-Martínez A, Muñez-Rubio E, et al. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. *J Clin Investig*. 2021;131(20):e152740.
25. Menichetti F, Popoli P, Puopolo M, et al. Effect of high-titer convalescent plasma on progression to severe respiratory failure or death in hospitalized patients with COVID-19 pneumonia. *JAMA Netw Open*. 2021;4(11):e2136246.
26. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med*. 2021;384(7):619-629.
27. Sekine L, Arns B, Fabro BR, et al. Convalescent plasma for COVID-19 in hospitalised patients: an open-label, randomised clinical trial. *Eur Respir J*. 2021;59:2101471.
28. Devos T, Van Thillo Q, Compernolle V, et al. Early high antibody titre convalescent plasma for hospitalised COVID-19 patients: DAWn-plasma. *Eur Respir J*. 2022;59(2):2101724.
29. Bégin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med*. 2021;27(11):2012-2024.
30. Writing Committee for the RCI, Estcourt LJ, Turgeon AF, et al. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2021;326(17):1690-1702.
31. Alqahtani M, Abdulrahman A, Almadani A, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. *Sci Rep*. 2021;11(1):9927.
32. Hamdy Salman O, Ail Mohamed HS. Efficacy and safety of transfusing plasma from COVID-19 survivors to COVID-19 victims with severe illness. A double-blinded controlled preliminary study. *Egypt J Anaesth*. 2020;36(1):264-272.
33. Rasheed AM, Fatak DF, Hashim HA, et al. The therapeutic effectiveness of convalescent plasma therapy on treating COVID-19 patients residing in respiratory care units in Baghdad, Iraq. *medRxiv Preprint*. 2020.
34. Pouladzadeh M, Safdarian M, Eshghi P, et al. A randomized clinical trial evaluating the immunomodulatory effect of convalescent plasma on COVID-19-related cytokine storm. *Int Emerg Med*. 2021;16(8):2181-2191.
35. Bar KJ, Shaw PA, Choi GH, et al. A randomized controlled study of convalescent plasma for individuals hospitalized with COVID-19 pneumonia. *J Clin Investig*. 2021;131(24):e155114.
36. Kirenga B, Byakika-Kibwika P, Muttamba W, et al. Efficacy of convalescent plasma for treatment of COVID-19 in Uganda. *BMJ Open Respir Res*. 2021;8(1):e001017.
37. Ray Y, Paul SR, Bandopadhyay P, et al. A phase 2 single center open label randomised control trial for convalescent plasma therapy in patients with severe COVID-19. *Nat Commun*. 2022;13(1):1-9.
38. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID trial). *BMJ*. 2020;371:m3939.
39. Beigel JH, Tebas P, Elie-Turenne M-C, et al. Immune plasma for the treatment of severe influenza: an open-label, multicentre, phase 2 randomised study. *Lancet Respir Med*. 2017;5(6):500-511.
40. Baklaushev VP, Averyanov AV, Sotnikiva AG, et al. Safety and efficacy of convalescent plasma for COVID-19: the first results of a clinical study. *Int J Clin Pract*. 2020;11(2):38-50.
41. Bennett-Guerrero E, Romeiser JL, Talbot LR, et al. Severe acute respiratory syndrome coronavirus 2 convalescent plasma versus standard plasma in coronavirus disease 2019 infected hospitalized patients in New York: a double-blind randomized trial. *Crit Care Med*. 2021;49(7):1015-1025.
42. O'Donnell MR, Grinsztejn B, Cummings MJ, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. *J Clin Investig*. 2021;131(13):e150646.
43. Bajpai M, Kumar S, Maheshwari A, et al. Efficacy of convalescent plasma therapy compared to fresh frozen plasma in severely ill COVID-19 patients: a pilot randomized controlled trial. *medRxiv Preprint*. 2020.
44. Beltran Gonzalez JL, González Gámez M, Mendoza Enciso EA, et al. Efficacy and safety of convalescent plasma and intravenous immunoglobulin in critically ill COVID-19 patients. A controlled clinical trial. *medRxiv Preprint*. 2021.
45. Beigel JH, Aga E, Elie-Turenne MC, et al. Anti-influenza immune plasma for the treatment of patients with severe influenza a: a randomised, double-blind, phase 3 trial. *Lancet Respir Med*. 2019;7(11):941-950.

46. Ali S, Uddin SM, Shalim E, et al. Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: a phase I/II randomized control trial. *EClinicalMedicine*. 2021;36:100926.
47. Hung IFN, To KKW, Lee CK, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest*. 2013; 144(2):464-473.
48. Davey RT, Fernández-Cruz E, Markowitz N, et al. Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial. *Lancet Respir Med*. 2019;7(11):951-963.
49. Balcells ME, Rojas L, Le Corre N, et al. Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: a randomized phase II clinical trial. *PLoS Med*. 2021;18(3):e1003415.
50. Liu STH, Lin H-M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study. *Nat Med*. 2020;26:1708-1713.
51. Rogers R, Shehadeh F, Mylona EK, et al. Convalescent plasma for patients with severe coronavirus disease 2019 (COVID-19): a matched cohort study. *Clin Infect Dis*. 2021;73(1):e208-e214.
52. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
53. Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis*. 2011;52(4):447-456.
54. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect*. 2004;10(7):676-678.
55. Abolghasemi H, Eshghi P, Cheraghali AM, et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study. *Transfus Apher Sci*. 2020;59(5):102875.
56. Altuntas F, Ata N, Yigenoglu TN, et al. Convalescent plasma therapy in patients with COVID-19. *Transfus Apher Sci*. 2021;60(1):102955.
57. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A*. 2020; 117(17):9490-9496.
58. Hegerova L, Gooley TA, Sweerus KA, et al. Use of convalescent plasma in hospitalized patients with COVID-19: case series. *Blood*. 2020;136(6):759-762.
59. Omrani AS, Pathan SA, Thomas SA, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. *eClinicalMedicine*. 2020;29:100645.
60. Xia X, Li K, Wu L, et al. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. *Blood*. 2020;136(6):755-759.
61. Zeng F, Chen X, Deng G. Convalescent plasma for patients with COVID-19. *Proc Natl Acad Sci U S A*. 2020;117(23):12528.
62. Avendaño-Solà C, Ramos-Martínez A, Muñez-Rubio E, et al. Convalescent plasma for COVID-19: a multicenter, randomized clinical trial. *medRxiv Preprint*. 2020.
63. COMET I. *Core Outcome Measures in Effectiveness Trials*. Department of Biostatistics, University of Liverpool; 2010 https://www.comet-initiative.org/Studies
64. MedDRA. Medical Dictionary for Regulatory Activities. https://www.meddra.org/
65. McCaw ZR, Claggett BL, Tian L, et al. Practical recommendations on quantifying and interpreting treatment effects in the presence of terminal competing risks: a review. *JAMA Cardiol*. 2022;7(4):450-456.
66. Ortigoza MB, Yoon H, Goldfeld KS, et al. Efficacy and safety of COVID-19 convalescent plasma in hospitalized patients. *JAMA Int Med*. 2022;182(2):115-126.
67. Nicola AM. Brasília Covid-19 convalescent plasma (BCCP). 2022. Accessed March 8, 2022. https://med.nyu.edu/departments-institutes/population-health/divisions-sections-centers/biostatistics/research/continuous-monitoring-pooled-international-trials-convalescent-plasma-covid19-hospitalized-patients
68. Nguyen D, Xiao J, Simmonds P, et al. Effects of SARS-CoV-2 strain variation on virus neutralisation titres: therapeutic use of convalescent plasma. *J Infect Dis*. 2021;225:971-976.
69. Schmidt F, Muecksch F, Weisblum Y, et al. Plasma neutralization of the SARS-CoV-2 omicron variant. *N Engl J Med*. 2022;386(6):599-601.
70. WHO. *COVID-19 Therapeutic Trial Synopsis Draft February 18*. WHO; 2020.
71. Marshall JC, Murthy S, Diaz J, et al. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020; 20(8):e192-e197.
72. Estcourt L, Callum J. Convalescent plasma for Covid-19 — making sense of the inconsistencies. *N Engl J Med*. 2022;386(18):1753-1754.
73. Millum J, Grady C. The ethics of placebo-controlled trials: methodological justifications. *Contemp Clin Trial*. 2013;36(2):510-514.
74. Sciences CfIOoM. International ethical guidelines for biomedical research involving human subjects. *Bull Med Ethics*. 2002;182:17-23.
75. Benson AB, Moss M. Trauma and acute respiratory distress syndrome. *Anesthesiology*. 2009;110:PAP-217.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kimber C, Lamikanra AA, Geneen LJ, et al. A systematic review of the safety and efficacy of convalescent plasma or immunoglobulin treatment for people with severe respiratory viral infections due to coronaviruses or influenza. *Transfusion Medicine*. 2023;33(1):26-38. doi:10.1111/tme.12942