Association between convalescent plasma and the risk of mortality among patients with COVID-19: a meta-analysis

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RESEARCH ARTICLE

REVISED Association between convalescent plasma and the risk of mortality among patients with COVID-19: a meta-analysis [version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Convalescent plasma (CCP) has been used for treating

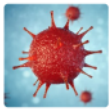
some infectious diseases; however, the efficacy of CCP in coronavirus disease 2019 (COVID-19) remains controversial. The aim of this research was to assess the efficacy of CCP as an adjunctive treatment in COVID-19 patient[6]

Methods: Embase, PubMed, Web of Science, Cochrane and MedRix were searched for potentially relevant articles. All included papers were assessed for the quality using modified jadad scale and Newcaste-ottawa scale for randomized controlled trial (RCT) and non – RCT, respectively. We used a Q test and Egger test to assess the heterogeneity and publication bias among studies, respectively. Mortality rates between patients treated with standard treatment and standard treatment with CCP were compared using a Z test.

Results: A total of 12 papers consisting of three cross-sectional studies, one prospective study, five retrospective studies, and two RCT studies were included in our analysis. Of them, a total of 1,937 patients treated with CCP and 3,405 patients without CCP were involved.. The risk of mortality was 1.92-fold higher in patients without CCP compared to patients treated with CCP (OR: 1.92; 95%CI: 1.33, 2.77; p=0.0005). In severe COVID-19 sub-group analysis, we found that patients without the CCP had a 1.32 times higher risk of mortality than those treated with the CCP (OR: 1.32; 95%CI: 1.09, 1.60; p=0.0040).

Conclusions: CCP, as adjunctive therapy, reduces the mortality rate among COVID-19 patients.

Keywords
convalescent plasma, passive immunization, COVID-19, mortality, outcomes



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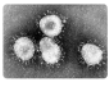

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REVISED **Amendments from Version 2**

The following changes are made between version 1 and version 2:

Abstract: the details following PRISMA checklist were added.

Method: the specific protocols were added.

Results: The baseline characteristics of studies included in our meta-analysis were added.

Table 1: the study design and quality assessment were revised.

Any further responses from the reviewers can be found at the end of the article

Introduction

The management of coronavirus disease 2019 (COVID-19) remains challenging. While the guideline for the management of COVID-19 has been established,[1-3] the mortality rate of COVID-19 remains increased over the periods.[4,5] The guideline suggests that several treatments, including antiviral, hydroxychloroquine, steroid, anticoagulation, and other supportive treatments, should be used to treat patients with COVID-19.[1-3] However, recent evidence from large scale studies failed to clarify the efficacy of those suggested treatments.[6-8] Moreover, the findings from the World Health Organization (WHO) solidarity trials also failed to clarify the benefits of hydroxychloroquine, remdesivir, interferon regimens, and lopinavir in the management of COVID-19.[8] Therefore, new approaches to COVID-19 management are required.

Convalescent plasma (CCP), an immunological therapy, is suggested to have promising efficacy for managing several infectious diseases.[9] CCP, a strategy of passive immunization, was first introduced by von Behring and Kitasato in 1890. Initially, it was used to manage diphtheria and other infectious diseases such as scarlet fever and pertussis.[10] Moreover, due to its good efficacy, this therapy was also used for the management of Ebola, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS).[11] In patients with MERS, SARS, and Ebola, the clinical improvement and reduced mortality rate were observed in patients receiving CCP than patients without CPP.[12] However, the efficacy of CCP against COVID-19 is conflicting. Furthermore, previous meta-analyses resulted in inconclusive findings due to the lack of structured methodology. Therefore, a holistic meta-analysis is needed to provide insight into the clinical efficacy of CCP for the management of COVID-19.

Methods

Study design

A systematic review and meta-analysis covering the period July 2020 - December 2020 was conducted to assess the efficacy of CCP as an adjunctive treatment in COVID-19 patients. Studies from prominent bibliographic databases were searched, and the protocols followed the checklist from Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA).[13]

Eligibility criteria

Relevant articles were assessed for inclusion and exclusion criteria before the final analysis. Our analysis included articles with the following criteria: (1) observational or randomized controlled trial studies; (2) providing sufficient data of COVID-19 diagnosis methods; and (3) well-identified methodologies represented with Newcastle-Ottawa Scale (NOS). Case reports, case series, letters to the editor, reviews, commentaries, low method quality, and those with pre-post test comparison were excluded.

Search strategy and data extraction

Relevant studies in four bibliographic databases (Embase, PubMed, Web of Science, and Cochrane) and a preprint database MedRxiv were searched as of 2 December 2020. The searches limited to English only using Medical Subjects Heading: ("COVID-19" OR "SARS-CoV-2") AND ("convalescent plasma" OR "serotherapy" OR "hyperimmune globulin therapy" OR "convalescent plasma treatment"). A reference list of the relevant articles was also retrieved for additional references. If a duplicate publication was found, the article with the larger sample size was included. Information of: (1) name of the first author; (2) year of publication; (3) country of origin; (4) sample size of cases and controls, (5) CCP administration, and (6) mortality rate were collected from each article. Search strategy and data extraction were conducted by three independent investigators (MI, AAA & YP) using a pilot form. If the disagreement was found, we performed a discussion to resolve the disagreement. Before collecting the data, the investigators performed a discussion to define the study variables and the study protocols, and the understanding among the investigators was assessed using kappa test.

Assessment of the methodology quality

All included papers were assessed for the quality using modified jadad scale for randomized controlled trial (RCT) and Newcaste-ottawa scale for non-RCT.[14] The quality of the articles could be classified as low, moderate, and high quality. Articles with low quality were excluded from our analysis. The assessment was carried out by three independent investigators (MI, AAA & YP), and when there was a discrepancy among the investigators, a discussion was performed with a senior researcher (JKF).

Outcome measure

The primary outcome measure was all causes of mortality among COVID-19 patients treated with and without CCP. The predictor variable was COVID-19 patients treated with CCP. A sub-group analysis was conducted based on the severity of COVID-19 patients treated with CCP (e.i. mild and severe).

Statistical analysis

The association between CCP and the reduction of the risk of mortality among COVID-19 patients was assessed using a Z test. Before assessing the association, the potency of bias and heterogeneity was assessed. To assess the risk of bias, an Egger test was employed to calculate tau-squared, and a p-value of less than 0.05 indicates that the potency of bias was found. A Q test was used to assess the heterogeneity among the included papers. The p-value of less than 0.10 was considered that heterogeneity across the studies was found, and the correlation was therefore determined using a random-effect model; otherwise, a fixed-effect model was employed. All analyses were carried out using Review Manager (Revman Cochrane, London, UK) version 5.3, and the cumulative calculation was presented using a forest plot.

Results

Studies selection and baseline characteristics of the studies

A total of 1,143 papers were identified, and 1,105 papers were excluded because they had irrelevant topics. A total of 38 papers were included for review in full-text, and 26 additional papers were excluded because of review, pre-post test model, commentary, and low-quality papers. In the final process, 12 papers were included in our analysis, consisting of three cross-sectional studies, one prospective study, five retrospective studies, and two RCT studies.[15-26] The article selection flowchart is depicted in Figure 1, and the study characteristics are presented in Table 1.

CCP efficacy against COVID-19

A total of 1,937 patients treated with CCP and 3,405 patients without CCP, collected from 12 papers, were included in our analysis. Data suggest that COVID-19 patients without the CCP had a 1.92-fold higher risk of mortality than patients treated with the CCP (OR: 1.92; 95%CI: 1.33, 2.77; p = 0.0005) (Figure 2A). A sub-group analysis among severe COVID-19 patients who were treated with CCP was conducted. This sub-group consisted of nine papers with 1,458 patients treated with CCP and 2,706 patients without CCP. The data revealed a 1.32-fold higher risk of mortality in COVID-19 patients without CCP compared to patients treated with CCP (OR: 1.32; 95%CI: 1.09, 1.60; p=0.0040) (Figure 2B).

Heterogeneity and potency of bias across the studies

The analysis revealed evidence of heterogeneity in total case of COVID-19. Therefore, a random-effect model was applied to assess the association. In the severe COVID-19 sub-group, we found no heterogeneity, and we used a fixed-effect model to evaluate the correlation. Our analysis using an Egger test found no publication bias in both the total and the severe COVID-19 sub-group (Funnelplot is provided in supplementary file).

Discussion

Our data suggest that CCP treatment associated with a reduction of mortality both in all cases and severe COVID-19 patients. Our current findings are consistent with the results of previous meta-analyses.[27-32] The theory underlying the mechanism of CCP in COVID-19 patients remains open to controversy. Briefly, plasma transfer is the potential aspect that bridges the CCP and the reduced risk of mortality in COVID-19 patients. Plasma consists of various immunity components, including antibodies, anti-inflammatory cytokines, clotting and or anti-clotting factors, albumin, and protein C and S.[33,34] It is believed that CCP in COVID-19 may modulate the immune response through antiviral effects and has immunomodulatory effects.[35] Antiviral effects of CCP may occur through neutralizing antibodies, and it was reported that IgG of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and IgM SARS-CoV-2 were the primary isotype antibodies identified from COVID-19 patients treated with CCP.[36] This humoral immune response may inhibit protein S of SARS-CoV-2.[37] Thereafter, they may exert the protective effects against COVID-19. The immunomodulatory effects of CCP may occur through the neutralization of cytokines and complements.[35,38] These effects may inhibit the overactive immune system, including cytokine storm, complement activation, and hypercoagulable state regulation.[39] These mechanisms may be responsible for causing clinical improvement of COVID-19 patients. Of them, it was considered that immunoglobulin transfer is the essential factor in modulating the protective effect of CCP.[40] In SARS

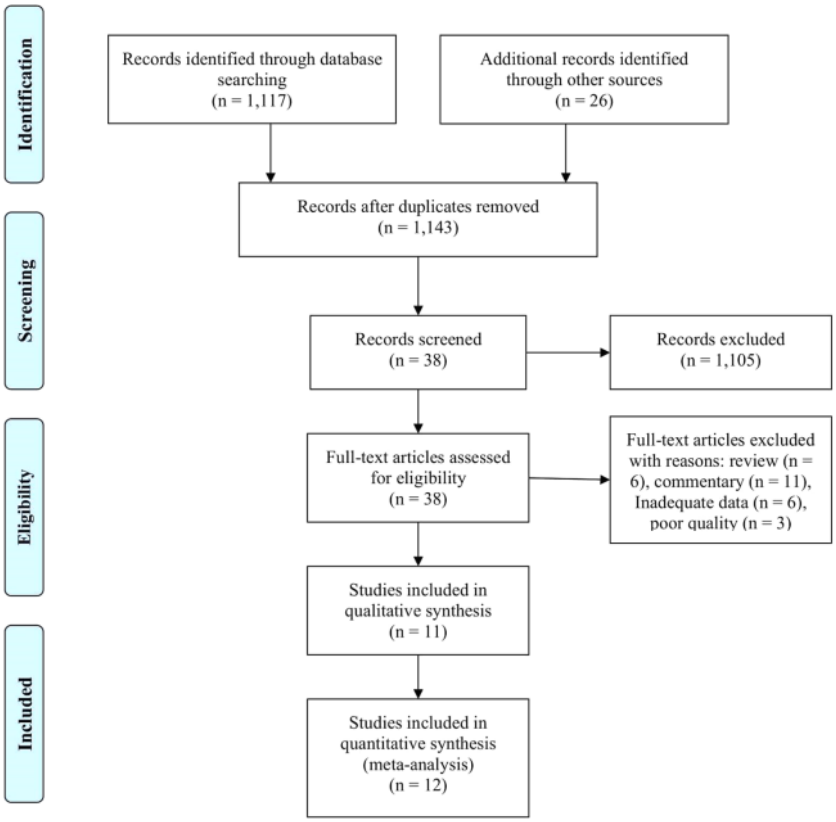

Figure 1. A flowchart of study selection in our meta-analysis.

and influenza, it was reported that immunoglobulin transfer plays a vital role in governing clinical improvement.[9,11] Moreover, in MERS, the CCP administration with the titers of antibodies 1:80 provided a significant immune response, and the titers of antibodies 1:40 did not provide a similar response.[41] Additionally, in Ebola, MERS, and SARS, the antibodies from the CCP may bind to the CD4 binding site on the viral envelope, and therefore may reduce the viral load and the risk of infection of the new cells.[42] It was also supported by previous studies that antibody titers from CCP donors also governed the clinical improvement of COVID-19 patients treated with CCP,[43,44] suggesting that antibody transfer might influence the outcomes of clinical improvement.

Six meta-analyses assessing the role of CCP in COVID-19 have been reported (Table 2).[27-32] However, they had some significant limitations: (a) they involved a smaller sample size. In our current study, we had a relatively larger sample size; (b) some studies did not perform meta-analysis calculations to synthesize the data[27,29]; (c) previous studies included several case reports and case series[28,29] in which should be excluded in the meta-analysis[13]; (d) previous meta-analyses assessed the role of CCP in similar infectious diseases (SARS and influenza), and the results were implemented to the case of COVID-19[30,31]; and (e) previous meta-analyses performed a mixed calculation where the data of the case vs. control model were combined with the data of pre-post intervention models, which might provide a high risk of bias due to the final effect that might be caused by other interventions.[29,32] In the present meta-analysis, we only calculated the model of the case (standard treatment and CCP) vs. control (standard treatment only) and therefore might provide a better correlation.

In the present study, we emphasized that CCP provided good efficacy to reduce the risk of mortality among COVID-19 patients. Our findings might contribute to better management of COVID-19 patients, particularly to prevent the risk of mortality. It is expected that a medical council should elaborate on the standard procedures of CCP, including the dosage, donor criteria, side effects management, and post-intervention management. Since early administration of CCP provided

Table 1. Baseline characteristics of articles included in our meta-analysis.

Name	Country	Study design	City	Sample size		CCP volume	Recipient	Quality assessment
				CCP	Control			
Abolghassemi et al 2020	Iran	Cross-sectional	Mixed	115	74	500 mL	Mild and severe cases	High
Altuntas et al 2020	Turkey	Retrospective	Mixed	888	888	200 - 600 mL	Severe cases	High
Chen et al 2020	China	Retrospective	Hangzhou	19	10	200-500 mL	Severe cases	Moderate
Gharbharan et al 2020	Netherlands	RCT	Mixed	43	43	300 mL	Mild and severe cases	Moderate
Hegerova et al 2020	USA	Retrospective	Washington	20	20	200 mL	Severe cases	High
Li et al 2020	China	RCT	Wuhan	52	51	100 mL	Severe cases	Moderate
Rasheed et al 2020	Iraq	Cross-sectional	Bagdad	21	28	400 mL	Severe cases	High
Salazar et al 2020 (a)	US	Cross-sectional	Mixed	321	582	NA	Mild and severe cases	High
Salazar et al 2020 (b)	US	Prospective	Mixed	85	158	NA	Severe cases	High
Xia et al 2020	China	Retrospective	Wuhan	138	1430	200-1200 mL	Severe cases	High
Zeng et al 2020	China	Retrospective	Hangzhou	6	15	300 mL	Severe cases	High

Note: CCP, convalescent plasma; NOS, Newcastle-ottawa scale.

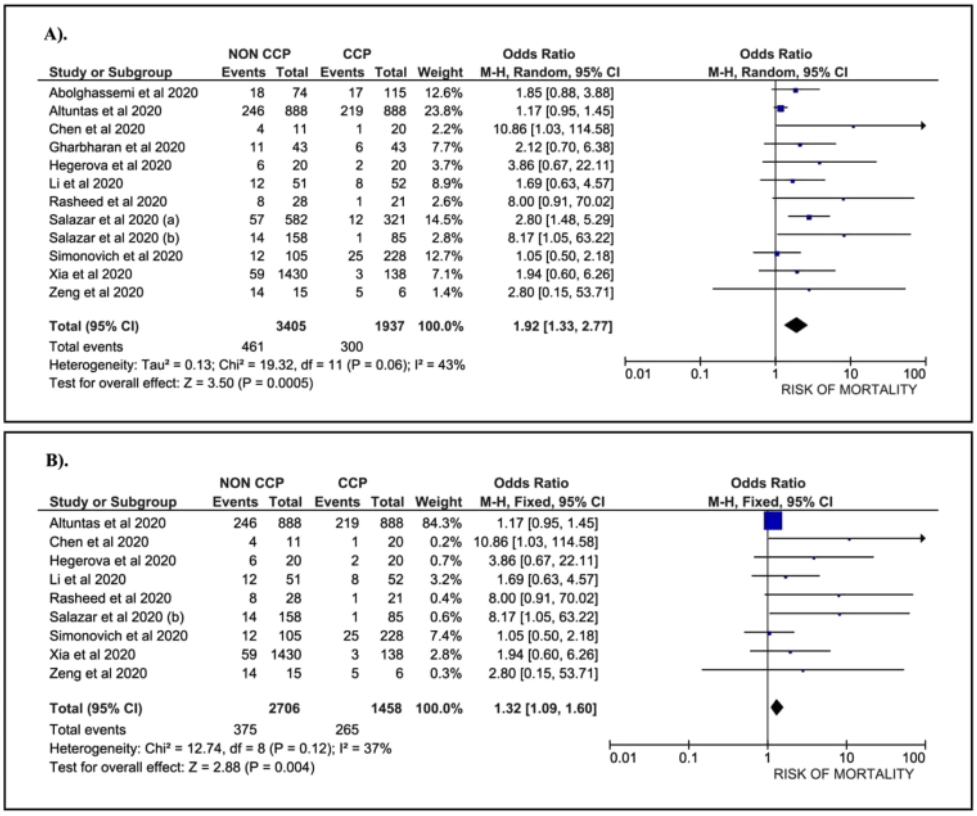

Figure 2. Forest plot of the association between convalescent plasma and the risk of mortality. A). All cases (OR: 1.92; 95%CI: 1.33, 2.77; p = 0.0005; p Egger: 0.3620; p Heterogeneity: 0.0600; I-squared: 43.00%). B). Severe COVID-19 (OR: 1.32; 95%CI: 1.09, 1.60; p = 0.0040; p Egger: 0.3790; p Heterogeneity: 0.1200; I-squared: 37.00%).

Table 2. Previous meta-analyses and some potential limitations.

Author & year	Number of studies	Sample size	Potential limitations
Bakhtawar et al 2020 [12]	10	156	- No calculation of data synthesis - Seven case report or case series articles were included - One study comparing the outcome between pre and post convalescent plasma.
Devasenapathy et al 2020	6	431	- The case is non COVID-19
Rabelo-da-Ponte et al 2020	5	75	- Three case report or case series articles were included - The comparison was pre and post convalescent plasma.
Rajendran et al 2020	5	NA	- No calculation of data synthesis
Sarkar et al 2020	7	5444	- One study comparing the outcome between pre and post convalescent plasma, other studies assessing between convalescent plasma and control (Mixed calculation). - Inappropriate calculation.
Sun et al 2020	15	1879	- The case is non COVID-19

Note: NA, Not available; CCP, convalescent plasma.

better clinical outcomes than those with later intervention,[45] the appropriate time of CCP administration should be determined, and further studies are warranted.

Several important limitations of this study should be discussed. Some confounding factors that might govern the final outcomes were not controlled, including the immunological status, the dosage of CCP, time of intervention, donor criteria, the titers of antibodies, comorbidities, and transmission area. The majority of the included papers were retrospective studies, and therefore a further meta-analysis of randomized-controlled trials with a bigger sample size might provide a better conclusion.

Conclusion

Administration of the CCP is associated with a lower risk of mortality among COVID-19 patients compared to those without CCP, and this highlights its potency to be used for the treatment of COVID-19. However, studies are warranted to formulate the dosage, time of intervention, donor criteria, and the titers of antibodies to optimize the effects.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for 'Association between convalescent plasma and the risk of mortality among patients with COVID-19: A meta-analysis', https://doi.org/10.6084/m9.figshare.13490541.v1.[46]

Extended data

The supplementary file regarding the funnel plot of our study is provided in Figshare (https://doi.org/10.6084/m9.figshare.14046254.v1).[47]

Acknowledgements

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