RESEARCH ARTICLE

REVISED Association between convalescent plasma and the risk of mortality among patients with COVID-19: a meta-analysis [version 3; peer review: 2 approved]

Shinta Oktya Wardhani[1], Jonny Karunia Fajar[2], Laksmi Wulandari[3], Gatot Soegiarto[4], Yeni Purnamasari[5], Anisa Asmiragani[5], Helnida Anggun Maliga[5], Muhammad Ilmawan[5], Gloriana Seran[6], Dheka Sapti Iskandar[7], Conchita Emiliana Ndapa[8], Viviana Hamat[8], Rafika Ajeng Wahyuni[5], Linda Oktaviana Suci Cyntia[5], Feronika Maryanti Maarang[9], Yosef Andrian Beo[9], Olivera Agnes Adar[8], Iraky Mardya Rakhmadhan[5], Emilia Tiara Shantikaratri[5], Ayu Sekarani Damana Putri[5], Rizqa Wahdini[5], Endang Pati Broto[10], Agnes Wanda Suwanto[11], Fredo Tamara[2], Aditya Indra Mahendra[2], Eden Suryoiman Winoto[2], Pratista Adi Krisna[2], Harapan Harapan[12]

[1]Division of Hematology and Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
[2]Brawijaya Internal Medicine Research Center, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
[3]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, 60286, Indonesia
[4]Division of Allergy & Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, 60286, Indonesia
[5]Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
[6]Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, Indonesia
[7]Department of Biomedical Sciences, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
[8]Department of Midwifery, Faculty of Medicine, University Brawijaya, Malang, 65145, Indonesia
[9]Department of Nursing, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
[10]Department of Neurosurgery, Faculty of Medicine, Universitas Airlangga, Surabaya, 60286, Indonesia
[11]Department of Radiology, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
[12]Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia

v3 **First published:** 03 Feb 2021, **10**:64
https://doi.org/10.12688/f1000research.36396.1
Second version: 08 Mar 2021, **10**:64
https://doi.org/10.12688/f1000research.36396.2
Latest published: 02 Jun 2021, **10**:64
https://doi.org/10.12688/f1000research.36396.3

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

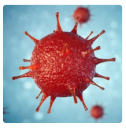
Open Peer Review

Reviewer Status ✓ ✓

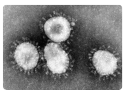
	Invited Reviewers	
	1	**2**
version 3		✓ report

research was to assess the efficacy of CCP as an adjunctive treatment in COVID-19 patients.
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 Newcastle-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 three 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 included. 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 CCP had a 1.32 times higher risk of mortality than those treated with CCP (OR: 1.32; 95%CI: 1.09, 1.60; p=0.0040).
Conclusions: CCP, as adjunctive therapy, could reduce the mortality rate among COVID-19 patients.

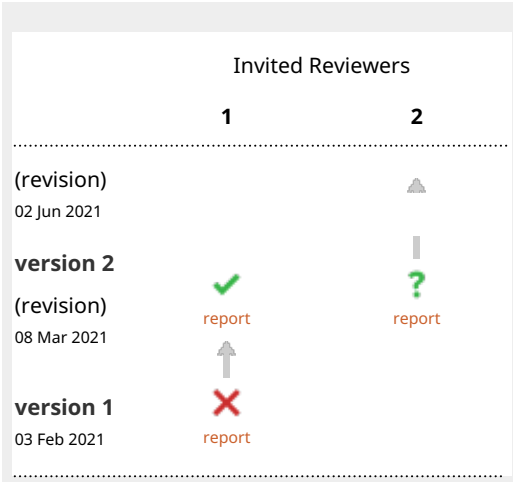
Keywords
convalescent plasma, passive immunization, COVID-19, mortality, outcomes



This article is included in the Disease Outbreaks gateway.



This article is included in the Coronavirus collection.



1. **Morteza Arab-Zozani**, Birjand University of Medical Sciences, Birjand, Iran
2. **Guilherme Welter Wendt**, Western Paraná State University (UNIOESTE), Francisco Beltrão, Brazil

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding authors: Shinta Oktya Wardhani (shinta_oktya.fk@ub.ac.id), Jonny Karunia Fajar (gembyok@gmail.com), Laksmi Wulandari (laksmi.wulandari@fk.unair.ac.id)

Author roles: Wardhani SO: Conceptualization, Investigation, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Fajar JK**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Wulandari L**: Conceptualization, Investigation, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Soegiarto G**: Conceptualization, Formal Analysis, Investigation, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Purnamasari Y**: Methodology, Software; **Asmiragani A**: Investigation, Methodology, Software; **Maliga HA**: Investigation, Methodology, Software; **Ilmawan M**: Investigation, Methodology, Software; **Seran G**: Data Curation, Investigation, Project Administration, Resources, Visualization; **Iskandar DS**: Data Curation, Project Administration, Resources, Visualization; **Ndapa CE**: Data Curation, Project Administration, Resources, Visualization; **Hamat V**: Data Curation, Investigation, Resources, Visualization; **Wahyuni RA**: Investigation, Project Administration, Resources, Visualization; **Cyntia LOS**: Data Curation, Investigation, Project Administration, Resources, Visualization; **Maarang FM**: Data Curation, Investigation, Project Administration, Resources; **Beo YA**: Data Curation, Project Administration, Resources, Visualization; **Adar OA**: Data Curation, Project Administration, Resources, Visualization; **Rakhmadhan IM**: Data Curation, Project Administration, Resources, Visualization; **Shantikaratri ET**: Data Curation, Project Administration, Resources, Visualization; **Putri ASD**: Data Curation, Project Administration, Resources, Visualization; **Wahdini R**: Data Curation, Investigation, Project Administration, Resources; **Broto EP**: Conceptualization, Project Administration, Resources; **Suwanto AW**: Conceptualization, Resources, Visualization; **Tamara F**: Data Curation, Project Administration, Resources, Visualization; **Mahendra AI**: Data Curation, Project Administration, Resources; **Winoto ES**: Data Curation, Methodology, Resources, Visualization; **Krisna PA**: Data Curation, Project Administration, Visualization; **Harapan H**: Supervision, Validation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

How to cite this article: Wardhani SO, Fajar JK, Wulandari L *et al.* **Association between convalescent plasma and the risk of mortality among patients with COVID-19: a meta-analysis [version 3; peer review: 2 approved]** F1000Research 2021, **10**:64 https://doi.org/10.12688/f1000research.36396.3

First published: 03 Feb 2021, **10**:64 https://doi.org/10.12688/f1000research.36396.1

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] some reports still reported high mortality rate among COVID-19 patients.[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, 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 treat 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 compared to patients without CPP.[12] However, the efficacy of CCP against COVID-19 is conflicting. Furthermore, the 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 guideline 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 MedRix 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. Disagreements were resolved in group discussions through a consensus approach. 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 was 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 (i.e. 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 three 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 between CCP and the risk of mortality among COVID-19 patients. 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 and IgM anti-severe acute respiratory syndrome coronavirus 2 (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

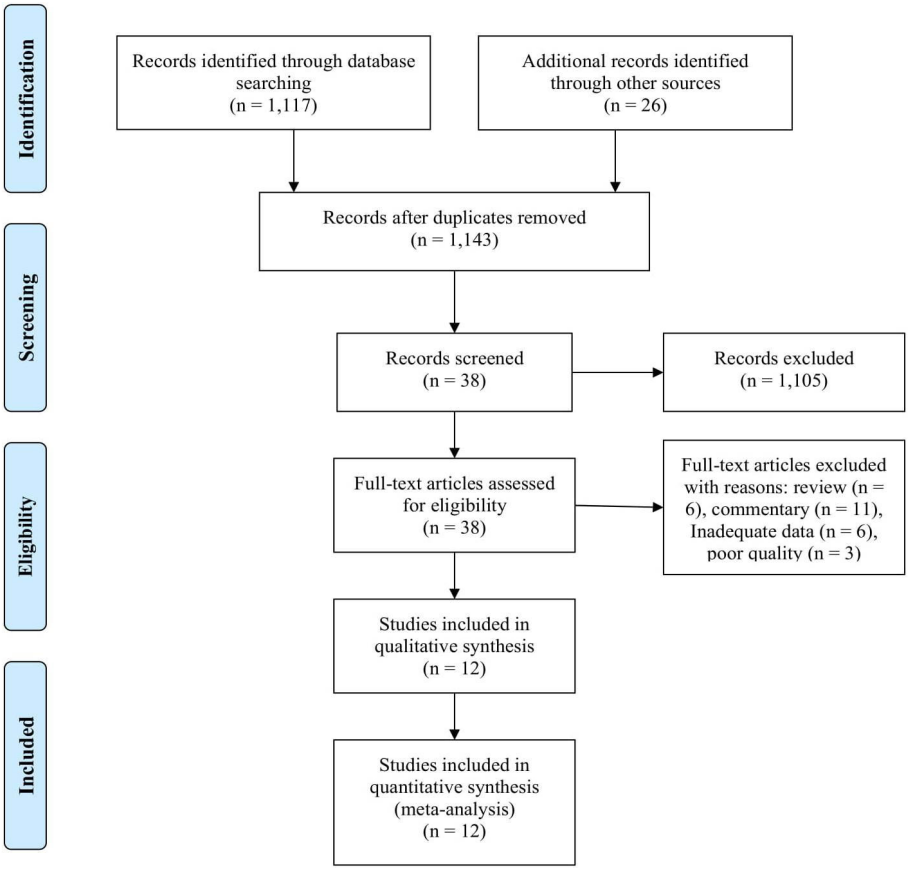


Figure 1. A flowchart of study selection in our meta-analysis.

modulating the protective effect of CCP.[40] In SARS 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 systematic-reviews assessing the role of CCP in COVID-19 have been reported (Table 2).[27-32] However, they had some significant limitations: (a) the systematic reviews involved had a small sample size while 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) some 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.

F1000Research 2021, 10:64 Last updated: 04 JUN 2021

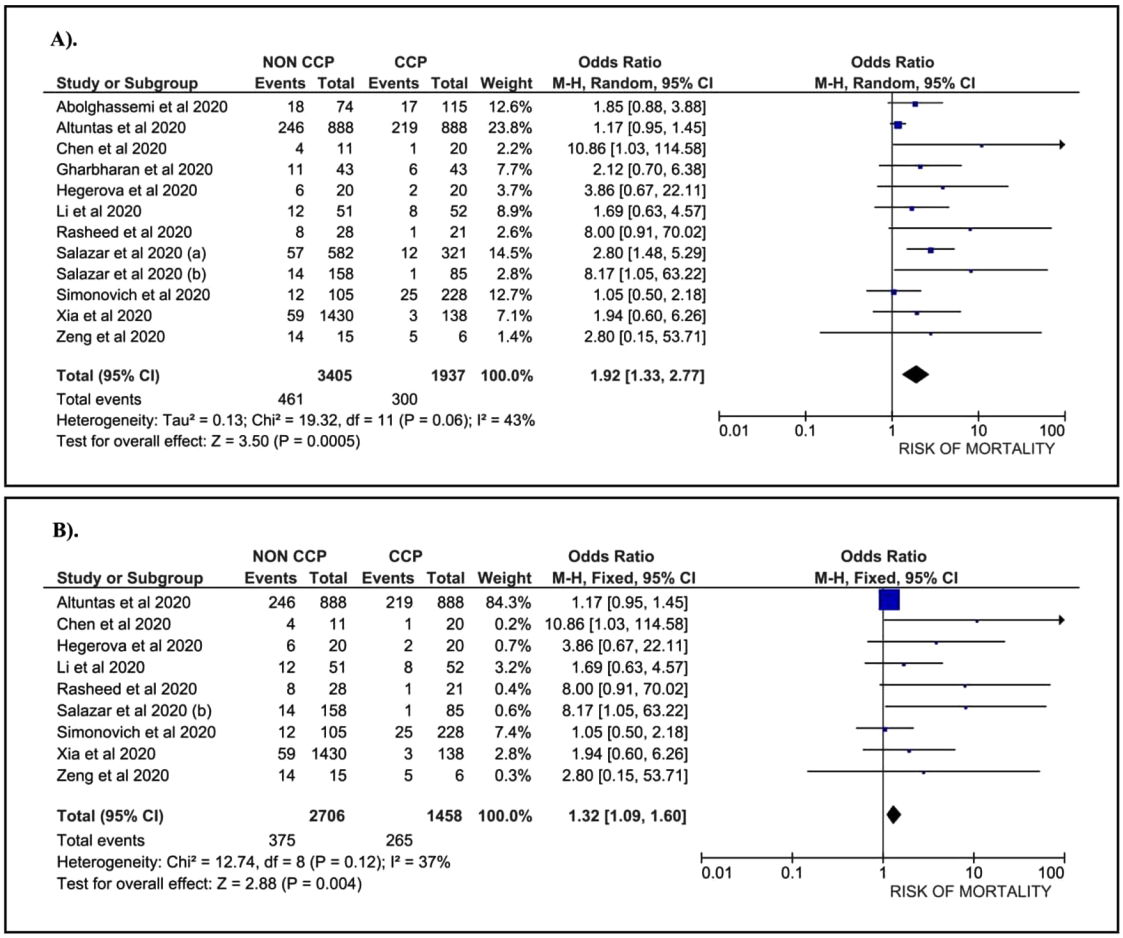


Figure 2. Forest plot of the association between convalescent plasma and the risk of mortality. A). All cases (OR: 1.92; 95%CI: 1.33, 2.77; p = 0.0005; p Egger: 0.3620; p Heterogeneity: 0.0600; I-squared: 43.00%). B). Severe COVID-19 (OR: 1.32; 95%CI: 1.09, 1.60; p = 0.0040; p Egger: 0.3790; p Heterogeneity: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

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

Author & year	Number of studies	Sample size	Potential limitations
Bakhtawar et al 2020	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

We thank to Lembaga Pengelola Dana Pendidikan (LPDP) Republik Indonesia for supporting this project.

References

1. Lamontagne F, Agoritsas T, Macdonald H, *et al.*: **A living WHO guideline on drugs for covid-19.** *BMJ* 2020; **370**: m3379.
PubMed Abstract | Publisher Full Text

2. Falavigna M, Colpani V, Stein C, *et al.*: **Guidelines for the pharmacological treatment of COVID-19. The task-force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology.** *Rev Bras Ter Intensiva* 2020; **32**: 166–96.
PubMed Abstract | Publisher Full Text | Free Full Text

3. Jin YH, Cai L, Cheng ZS, *et al.*: **A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version).** *Mil Med Res* 2020; **7**: 4.
PubMed Abstract | Publisher Full Text | Free Full Text

4. Baud D, Qi X, Nielsen-Saines K, *et al.*: **Real estimates of mortality following COVID-19 infection.** *Lancet Infect Dis* 2020; **20**: 773.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Karimullah MDH, Niazta NA, Ardining H: **Venous Thromboembolism Prevention in COVID-19: A Review of Latest Evidences.** *Heart Science J* 2020; **1**: 10–14.
Publisher Full Text

6. Singh AK, Singh A, Singh R, *et al.*: **Hydroxychloroquine in patients with COVID-19: A Systematic Review and meta-analysis.** *Diabetes Metab Syndr* 2020; **14**: 589–96.
PubMed Abstract | Publisher Full Text | Free Full Text

7. Wang Y, Zhang D, Du G, *et al.*: **Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial.** *Lancet* 2020; **395**: 1569–78.
PubMed Abstract | Publisher Full Text | Free Full Text

8. Consortium WHOSTPan H, Peto R, *et al.*: **Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results.** *N Engl J Med* 2020.
PubMed Abstract | Publisher Full Text | Free Full Text

9. Yeh KM, Chiueh TS, Siu LK, *et al.*: **Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital.** *J Antimicrob Chemother* 2005; **56**: 919–22.
PubMed Abstract | Publisher Full Text | Free Full Text

10. Kaufmann SH: **Remembering Emil von Behring: from Tetanus Treatment to Antibody Cooperation with Phagocytes.** *mBio* 2017; **8**.
PubMed Abstract | Publisher Full Text | Free Full Text

11. Liya G, Yuguang W, Jian L, *et al.*: **Studies on viral pneumonia related to novel coronavirus SARS-CoV-2, SARS-CoV, and MERS-CoV: a literature review.** *APMIS* 2020; **128**: 423–32.
PubMed Abstract | Publisher Full Text

12. Marano G, Vaglio S, Pupella S, *et al.*: **Convalescent plasma: new evidence for an old therapeutic tool?** *Blood Transfus* 2016; **14**: 152–7.
PubMed Abstract | Publisher Full Text | Free Full Text

13. Liberati A, Altman DG, Tetzlaff J, *et al.*: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.** *PLoS Med* 2009; **6**: e1000100.
PubMed Abstract | Publisher Full Text | Free Full Text

14. Stang A: **Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses.** *Eur J Epidemiol* 2010; **25**: 603–5.
PubMed Abstract | Publisher Full Text

15. 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**:

102875.
PubMed Abstract | Publisher Full Text | Free Full Text

16. Altuntas F, Ata N, Yigenoglu TN, *et al.*: **Convalescent plasma therapy in patients with COVID-19.** *Transfus Apher Sci* 2020; 102955.
PubMed Abstract | Publisher Full Text | Free Full Text

17. Chen B, Xia R: **Early experience with convalescent plasma as immunotherapy for COVID-19 in China: Knowns and unknowns.** *Vox Sang* 2020; **115**: 507–14.
PubMed Abstract | Publisher Full Text | Free Full Text

18. Gharbharan A, Jordans CC, GeurtsvanKessel C, *et al.*: **Convalescent Plasma for COVID-19. A randomized clinical trial.** *MEDRxiv* 2020.
Publisher Full Text

19. Hegerova L, Gooley TA, Sweerus KA, *et al.*: **Use of convalescent plasma in hospitalized patients with COVID-19: case series.** *Blood* 2020; **136**: 759–62.
PubMed Abstract | Publisher Full Text | Free Full Text

20. 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: A Randomized Clinical Trial.** *JAMA* 2020; **324**: 460–70.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Rasheed AM, Fatak DF, Hashim HA, *et al.*: **The therapeutic potential of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq.** *Infez Med* 2020; **28**: 357–66.
PubMed Abstract

22. Salazar E, Christensen PA, Graviss EA, *et al.*: **Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG.** *Am J Pathol* 2020.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Salazar E, Christensen PA, Graviss EA, *et al.*: **Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality.** *Am J Pathol* 2020; **190**: 2290–303.
PubMed Abstract | Publisher Full Text | Free Full Text

24. 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**: 755–9.
PubMed Abstract | Publisher Full Text | Free Full Text

25. Zeng QL, Yu ZJ, Gou JJ, *et al.*: **Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in Patients With Coronavirus Disease 2019.** *J Infect Dis* 2020; **222**: 38–43.
PubMed Abstract | Free Full Text | Free Full Text

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* 2020.
PubMed Abstract | Publisher Full Text | Free Full Text

27. Rajendran K, Krishnasamy N, Rangarajan J, *et al.*: **Convalescent plasma transfusion for the treatment of COVID-19: Systematic review.** *J Med Virol* 2020; **92**: 1475–83.
PubMed Abstract | Publisher Full Text | Free Full Text

28. Rabelo-da-Ponte FD, Silvello D, Scherer JN, *et al.*: **Convalescent Plasma Therapy in Patients With Severe or Life-Threatening COVID-19: A Metadata Analysis.** *J Infect Dis* 2020; **222**: 1575–8.
PubMed Abstract | Publisher Full Text | Free Full Text

29. Bakhtawar N, Usman M, Khan MMU: **Convalescent Plasma Therapy and Its Effects On COVID-19 Patient Outcomes: A Systematic Review of Current Literature.** *Cureus* 2020; **12**: e9535.
PubMed Abstract | Publisher Full Text | Free Full Text

30. 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.** *CMAJ* 2020; **192**: E745–E55.
PubMed Abstract | Publisher Full Text

31. Sun M, Xu Y, He H, *et al.*: **A potentially effective treatment for COVID-19: A systematic review and meta-analysis of convalescent plasma therapy in treating severe infectious disease.** *Int J Infect Dis* 2020; **98**: 334–46.
PubMed Abstract | Publisher Full Text | Free Full Text

32. Sarkar S, Soni KD, Khanna P: **Convalescent plasma is a clutch at straws in COVID-19 management! A systematic review and meta-analysis.** *J Med Virol* 2020.
PubMed Abstract | Publisher Full Text | Free Full Text

33. Rojas M, Rodriguez Y, Monsalve DM, *et al.*: **Convalescent plasma in Covid-19: Possible mechanisms of action.** *Autoimmun Rev* 2020; **19**: 102554.
PubMed Abstract | Publisher Full Text | Free Full Text

34. Mudatsir M, Fajar JK, Wulandari L, *et al.*: **Predictors of COVID-19 severity: a systematic review and meta-analysis.** *F1000Res* 2020; **9**: 1107.
PubMed Abstract | Publisher Full Text | Free Full Text

35. Alijotas-Reig J, Esteve-Valverde E, Belizna C, *et al.*: **Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: A comprehensive review.** *Autoimmun Rev* 2020; **19**: 102569.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Dulipsingh L, Ibrahim D, Schaefer EJ, *et al.*: **SARS-CoV-2 serology and virology trends in donors and recipients of convalescent plasma.** *Transfus Apher Sci* 2020; 102922.
PubMed Abstract | Publisher Full Text | Free Full Text

37. Xi Y: **Convalescent plasma therapy for COVID-19: a tried-and-true old strategy?** *Signal Transduct Target Ther* 2020; **5**: 203.
PubMed Abstract | Publisher Full Text | Free Full Text

38. Focosi D, Anderson AO, Tang JW, *et al.*: **Convalescent Plasma Therapy for COVID-19: State of the Art.** *Clin Microbiol Rev* 2020; **33**.
PubMed Abstract | Publisher Full Text | Free Full Text

39. Jaiswal V, Nasa P, Raouf M, *et al.*: **Therapeutic plasma exchange followed by convalescent plasma transfusion in critical COVID-19-An exploratory study.** *Int J Infect Dis* 2020; **102**: 332–4.
PubMed Abstract | Publisher Full Text | Free Full Text

40. Langhi DMJ, Santis GC, Bordin JO: **COVID-19 convalescent plasma transfusion.** *Hematol Transfus Cell Ther* 2020; **42**: 113–5.
PubMed Abstract | Publisher Full Text | Free Full Text

41. Ko JH, Seok H, Cho SY, *et al.*: **Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience.** *Antivir Ther* 2018; **23**: 617–22.
PubMed Abstract | Publisher Full Text

42. Schoofs T, Klein F, Braunschweig M, *et al.*: **HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1.** *Science* 2016; **352**: 997–1001.
PubMed Abstract | Publisher Full Text | Free Full Text

43. Wu F, Liu M, Wang A, *et al.*: **Evaluating the Association of Clinical Characteristics With Neutralizing Antibody Levels in Patients Who Have Recovered From Mild COVID-19 in Shanghai, China.** *JAMA Intern Med* 2020; **180**: 1356–62.
PubMed Abstract | Publisher Full Text

44. Bradfute SB, Hurwitz I, Yingling AV, *et al.*: **Severe Acute Respiratory Syndrome Coronavirus 2 Neutralizing Antibody Titers in Convalescent Plasma and Recipients in New Mexico: An Open Treatment Study in Patients With Coronavirus Disease 2019.** *J Infect Dis* 2020; **222**: 1620–8.
PubMed Abstract | Publisher Full Text | Free Full Text

45. Cheng Y, Wong R, Soo YO, *et al.*: **Use of convalescent plasma therapy in SARS patients in Hong Kong.** *Eur J Clin Microbiol Infect Dis* 2005; **24**: 44–6.
PubMed Abstract | Publisher Full Text | Free Full Text

46. Fajar J: **PRISMA CHECLIST for Association between convalescent plasma and the risk of mortality among patients with COVID-19: A meta-analysis.** *figshare* 2020.
Publisher Full Text

47. Fajar J: **Supplementary file 2. The association between convalescent plasma and the risk of mortality.** *figshare. Dataset* 2021.
Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 3

Reviewer Report 04 June 2021

https://doi.org/10.5256/f1000research.55951.r86549

✔ **Guilherme Welter Wendt**
Health Sciences Center, Western Paraná State University (UNIOESTE), Francisco Beltrão, Brazil

After reading the revised version of the paper, I can see that authors addressed the previous suggestions and their manuscript seems suitable for appproval.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Quantitative research methods; systematic reviews; meta-analyses

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 29 March 2021

https://doi.org/10.5256/f1000research.54795.r81757

? **Guilherme Welter Wendt**
Health Sciences Center, Western Paraná State University (UNIOESTE), Francisco Beltrão, Brazil

The study sought to assess the efficacy of CCP as an adjunctive treatment in COVID-19 patients. The authors are encouraged to:

1. Correctly report the names of the instruments used (Newcastle-Ottawa, and not Newcaste-

ottawa; Jadad scale, and not jadad) in the whole text, including the abstract.

2. There are two dots in the end of the second sentence of the results section in the abstract.

3. In the introduction, the following sentence could be expanded: “the mortality rate of COVID-19 remains increased over the periods”. Please, focus on the literature you cited and be specific as possible. For instance, some reports show the opposite, that is, that treatment has improved so the mortality rate has decreased. The authors’ very own findings point to lower OR for death among those treated with CCP.

4. Albeit it is true that the solidarity trial showed little efficacy of the drugs mentioned in the introduction, a robust finding was found in severe patients that were treated with dexamethasone.

5. Would you please give more information on clinical improvement of the diseases treated with CCP cited in the second paragraph (introduction, ref. n. 12)?

6. The following sentence needs a few supporting references: “However, the efficacy of CCP against COVID-19 is conflicting”.

7. I would suggest the authors to remove the word “holistic” when presenting their goal.

8. When presenting the eligibility criteria, I was wondering why pre-post comparisons were excluded. Would be worth it to justify this choice.

9. I would change this sentence “If the disagreement was found, we performed a discussion to resolve the disagreement” into “Disagreements were resolved in group discussions”. Also, did you ask for an external judge to assist in the discussion of disagreements? Or a consensus approach was used? This is unclear.

10. There is a typo in the section describing the outcome variable (e.i. mild and severe). Please, correct to “i.e.”; Also, the outcome variables could be more clear. Do you mean “the number or COVID-19 patients treated with CCP”?

11. In the section “Heterogeneity and potency of bias across the studies”, please be clear/complete in the following sentence “a random-effect model was applied to assess the Association…”. Association between what?

12. This sentence needs more information: “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”. Would you please justify why your approach provides better ‘correlation’?

13. Please, double check the comprehensiveness of Table 2. The table is supposed to present previous meta-analyses and some of the studies included there were judged to not calculate data synthesis. However, I see that some studies are only systematic reviews, such as Rajendran and collaborators.

14. Supplementary file 2 has some typos (https://figshare.com/articles/dataset/SUPPLEMENTARY_FILE_2_THE_ASSOCIATION_BETWEEN_CONVALES), including “Funnel plot of tha association”. Would you please correct it?

15. The supplementary Prisma checklist contains information not covered in the study. For instance, the authors said that the systematic review registration number has been given in the abstract, albeit I was not able to find it. This checklist also asks the authors to be explicit about the language of papers under “eligibility”. This should be made clear in the text and in the supplementary checklist. Item 19 of the same checklist asks that authors “present data on risk of bias of each study”. I could not locate this in the text. Please, revise this item.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Quantitative research methods; systematic reviews; meta-analyses

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 06 Apr 2021

Jonny Fajar, Universitas Brawijaya, Malang, Indonesia

Response to reviewer comments:
The study sought to assess the efficacy of CCP as an adjunctive treatment in COVID-19 patients. The authors are encouraged to:

Correctly report the names of the instruments used (Newcastle-Ottawa, and not Newcaste-ottawa; Jadad scale, and not jadad) in the whole text, including the abstract.

Response: The phrase has been revised.

There are two dots in the end of the second sentence of the results section in the abstract.
Response: We have revised the sentence.

In the introduction, the following sentence could be expanded: "the mortality rate of COVID-19 remains increased over the periods". Please, focus on the literature you cited and be specific as possible. For instance, some reports show the opposite, that is, that treatment has improved so the mortality rate has decreased. The authors' very own findings point to lower OR for death among those treated with CCP.
Response: The sentence has been revised.

Albeit it is true that the solidarity trial showed little efficacy of the drugs mentioned in the introduction, a robust finding was found in severe patients that were treated with dexamethasone.
Response: We only reported the findings of the trial. The trial did not include dexametasone.

Would you please give more information on clinical improvement of the diseases treated with CCP cited in the second paragraph (introduction, ref. n. 12)?
Response: The clinical improvement indicated the improvement of disease manifestation.

The following sentence needs a few supporting references: "However, the efficacy of CCP against COVID-19 is conflicting".
Response: In this sentence, we tried to explained that, among all included studies in our analysis, some studies found the efficacy of CCP for treating COVID-19, while other studies failed to clarify the efficacy. The references were provided in the results section.

I would suggest the authors to remove the word "holistic" when presenting their goal.
Response: the word "holistic" has been removed.

When presenting the eligibility criteria, I was wondering why pre-post comparisons were excluded. Would be worth it to justify this choice.
Response: The reason why pre-post comparisons were excluded from our study is we considered that the outcomes of therapy might have high risk of bias due to the final outcomes were affected by CCP or other medications.

I would change this sentence "If the disagreement was found, we performed a discussion to resolve the disagreement" into "Disagreements were resolved in group discussions". Also, did you ask for an external judge to assist in the discussion of disagreements? Or a consensus approach was used? This is unclear.
Response: The sentence has been revised.

There is a typo in the section describing the outcome variable (e.i. mild and severe). Please, correct to "i.e."; Also, the outcome variables could be more clear. Do you mean "the number or COVID-19 patients treated with CCP"?
Response: The sentence has been revised.

In the section “Heterogeneity and potency of bias across the studies”, please be clear/complete in the following sentence “a random-effect model was applied to assess the Association...”. Association between what?
Response: The sentence has been revised.

This sentence needs more information: “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”. Would you please justify why your approach provides better ‘correlation’?
Response: We considered that the design of standard treatment and CCP vs. standard treatment only, and the patients were followed up after the periods might have better efficacy than the design of pre-post comparisons. In the design of pre-post comparisons, the outcomes of therapy might have high risk of bias due to the final outcomes were affected by CCP or other medications.

Please, double check the comprehensiveness of Table 2. The table is supposed to present previous meta-analyses and some of the studies included there were judged to not calculate data synthesis. However, I see that some studies are only systematic reviews, such as Rajendran and collaborators.
Response: The sentence has been revised.

Supplementary file 2 has some typos (https://figshare.com/articles/dataset/SUPPLEMENTARY_FILE_2_THE_ASSOCIATION_BETWEEN_CONVALESCE including “Funnel plot of tha association”. Would you please correct it?
Response: The supplementary file 2 has been revised.

The supplementary Prisma checklist contains information not covered in the study. For instance, the authors said that the systematic review registration number has been given in the abstract, albeit I was not able to find it. This checklist also asks the authors to be explicit about the language of papers under “eligibility”. This should be made clear in the text and in the supplementary checklist. Item 19 of the same checklist asks that authors “present data on risk of bias of each study”. I could not locate this in the text. Please, revise this item.
Response: The study registration is on process. The risk of bias was assessed using Egger test. The quality of each study was assessed using Newcastle-ottawa scale and Modified Jadad scale.

Competing Interests: We have no competing interest

Reviewer Report 09 March 2021

https://doi.org/10.5256/f1000research.54795.r81042

Morteza Arab-Zozani
Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran

Thank you for clearly addressing my previous comments. In my opinion, the manuscript is acceptable in this way.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health-related issues and systematic review and meta-analysis methodology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 15 February 2021

https://doi.org/10.5256/f1000research.39458.r78924

Morteza Arab-Zozani
Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand,

Iran

This meta-analysis aimed to investigate the association between convalescent plasma and the risk of mortality among patients with COVID-19. This is a great area of research but, in my opinion, the manuscript needs some major revisions as follows:

- Please indicate the name of the searched databases in the abstract section.
- Please indicate the quality appraisal checklist in the abstract section.
- Please indicate the method for investigating the heterogeneity and publication bias in the abstract section.
- Please indicate the type of the included studies in the abstract, results, and table 1.
- What is your reason for selecting this period for your search?
- Search strategy is not complete.
- Please restructure the method section following the PRISMA item as you claim.
- There are some problems regarding figure 1. Was there no duplicate record? It does not make much sense.
- It needs to mention the type of the included studies and then we can speak about the quality appraisal checklist. it seems that NOS is not sufficient. NOS is for nonrandomized studies.
- Please indicate inter-rater reliability between three raters.
- Result section, please add a subheading for "study characteristics" based on PRISMA and first write a brief and then refer to table 1. Also, add the type of the control in column control.
- Figure 1 has some problems. Your study is a meta-analysis. How were 11 studies included in qualitative synthesis? Which qualitative synthesis?
- There is a 6 % difference between I2 for A and B, what is your rationale for selecting the fixed or random-effect model? Please provide a reference for your claim. Please add the details in the method section.
- Please add the funnel plot as a supplement.
- Please remove table 2 from the discussion and also discuss the added value of your study regarding the existing meta-analysis. What is the novelty of your work?
- The conclusion is very optimistic. How did you come to that conclusion based solely on mortality?

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health-related issues and systematic review and meta-analysis methodology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.