DR. CHIRAPHAT KLOYPAN (Orcid ID : 0000-0003-0547-1381)

DR. PRAWAT CHANTHARIT (Orcid ID : 0000-0002-5533-5698)

DR. PAJAREE MONGKHON (Orcid ID : 0000-0002-3050-1557)

Article type : Original Article

TITLE PAGE

TITLE: Convalescent Plasma for COVID-19: A Meta-analysis of Clinical Trials and Real-World Evidence

A SHORT RUNNING TITLE: Convalescent plasma for COVID-19 patients

AUTHOR NAMES AND AFFILIATIONS:

Chiraphat Kloypan, PhD[1,2,3], Matthanaporn Saesong[1], Juthamat Sangsuemoon[1], Prawat Chantharit, BSc (Pharm) MD[4], and Pajaree Mongkhon, PharmD, PhD[5,6*]

[1]Division of Clinical Immunology and Transfusion Science, Department of Medical Technology, School of Allied Health Sciences, University of Phayao, Phayao, 56000 Thailand; chiraphat.kl@up.ac.th (C.K.); matthanaporn01.ss@gmail.com (M.S.); juthamat.mm01@gmail.com (J.S)

[2]Unit of Excellence in Integrative Molecular Biomedicine, School of Allied Health Sciences, University of Phayao, Phayao, Phayao, 56000 Thailand

[3]Institute of Transfusion Medicine, Charité Universitätsmedizin Berlin 10700 Berlin Germany

[4]Division of Infectious Diseases, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, 10400 Thailand; prawat.chn@mahidol.ac.th (P.C)

[5]Division of Pharmacy Practice, Department of Pharmaceutical Care; Unit of Excellence on Research in Health Outcomes and Patient Safety in Elderly, School of Pharmaceutical Sciences, University of Phayao, Phayao, 56000 Thailand; pajaree.mo@up.ac.th (P.M.)

[6]Pharmacoepidemiology and Statistics Research Center, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, 50200 Thailand

*Correspondence: pajaree.mo@up.ac.th

CORRESPONDENCE TO:

Pajaree Mongkhon, PharmD, PhD
Department of School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand 56000
Email: pajaree.mo@up.ac.th Tel: +66 (0)5446 6666; fax: +66 (0)5446 6661

ACKNOWLEDGMENTS:
This research project was partially supported by the Thailand Science Research and Innovation Fund and the University of Phayao (Grant No. FF64-UoE). The funding source had no role in the study design, collection, analysis, and interpretation of data.

DISCLOSURES:
The authors declare no conflict of interest.

MANUSCRIPT METRICS:
Word count: 3,984 (not including abstract, acknowledgements, funding, references, tables, and figure legends)
Word count for abstract: 249
Number of tables and/or figures: Table 3; Figure 4

ABSTRACT

Background: There is still a lack of consensus on the efficacy of convalescent plasma (CP) treatment in COVID-19 patients. We performed a systematic review and meta-analysis to investigate the efficacy of CP vs standard treatment/non-CP on clinical outcomes in COVID-19 patients.

Methods: Cochrane Library, PubMed, Embase, and ClinicalTrial.gov were searched from December 2019 to 16th July 2021, for data from clinical trials and observational studies. The primary outcome was all-cause mortality. Risk estimates were pooled using a random-effect model. Risk of bias was assessed by Cochrane Risk of Bias tool for clinical trials and Newcastle-Ottawa Scale for observational studies.

Results: In total, 18 peer-review clinical trials, 3 preprints, and 26 observational studies met the inclusion criteria. In the meta-analysis of 18 peer-reviewed trials, CP use had a 31% reduced risk of all-cause mortality compared to standard treatment use (pooled risk ratio [RR]=0.69, 95% confidence interval [CI]: 0.56-0.86, p=0.001, I^2=50.1%). Based on severity and region, CP treatment significantly reduced risk of all-cause mortality in patients with severe and critical disease and studies conducted in Asia, pooled RR=0.61, 95% CI: 0.47-0.81, p=0.001, I^2=0.0%, pooled RR=0.67, 95% CI: 0.49-0.92, p=0.013, I^2=0.0%, and pooled RR=0.62, 95% CI: 0.48- 0.80, p<0.001, I^2=20.3%, respectively. The meta-analysis of observational studies showed the similar results to the clinical trials.

Conclusions: CP use was associated with reduced risk of all-cause mortality in severe or critical COVID-19 patients. However, the findings were limited with a moderate degree of heterogeneity. Further studies with well-designed and larger sample size are needed.

Keywords: COVID-19; convalescent plasma; meta-analysis; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); donors; emerging diseases

INTRODUCTION

The coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become an enormous health problem worldwide since December 2019.[1] As of 4th August 2021, there have been 199,466,211confirmed cases of COVID-19, including 4,244,541. deaths, which were reported by the World Health Organization (WHO).[2] The current management is mostly limited to general supportive care and symptomatic treatment using antivirals remdesivir and favipiravir, antimalarials chloroquine and hydroxychloroquine, and the antibiotic azithromycin. However, no specific drug or treatment has yet proven to be effective. So, clinical trials are ongoing in search for the suitable therapy. Immunotherapy with convalescent plasma (CP), the plasma collected from patients who have recovered from an infection, is one such therapeutic option.

CP has been advocated to treat outbreaks of novel infectious diseases those affecting the respiratory system including severe acute respiratory syndrome-1 (SARS-1), Middle East respiratory syndrome (MERS), and Ebola virus disease.[3-5] The antibodies primarily target the trimeric spike (S) surface glycoproteins, which are used by the virus to enter the host cells. This resulting in the reduction of the ability of the SARS-CoV-ACE2 to enter the host cells. Additionally, the antibody is long last after the onset of infection.[6] CP is currently being explored as one of the treatment opportunities for patients suffering from COVID-19, which may contain antibodies to SARS-CoV-2 and may help suppress the virus as well as amending the inflammatory response. Therefore, in March 2020, the US Food and Drug Administration (US-FDA) approved the use of CP therapy as an emergency investigational new drug to treat patients with serious or immediately life-threatening COVID-19 infections. Additionally, in February 2021, the FDA limited the use of high titer COVID-19 CP only for the treatment of hospitalized patients with COVID-19 who have impaired humoral immunity and cannot produce an adequate antibody response.[7] The results of the use of plasma are variable, reporting efficacy if its use is in the early stage of illness, which was associated with an improvement in the first days after treatment and lower requirements for ventilatory support. On the other hand, transfusion of COVID-19 CP in hospitalized patients late in the course of illness has not been associated with clinical benefit.[8] However, evidence for therapeutic COVID-19 CP efficacy still requires definitive support from large randomized clinical trials (RCT) and observational studies.

As the situation is evolving and newer studies are being reported across the globe, there is still a lack of consensus on the efficacy of CP usage in COVID-19 patients. We, therefore, carried out the systematic review and meta-analysis to evaluate the currently available data and provide evidence on the efficacy of CP for COVID-19 patients treatment to provide an outline of the potential benefits of CP therapy in COVID-19 patients.

MATERIAL AND METHODS

This study was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[9] A predefined study protocol was established but not registered. The study did not require any ethics committee approval as the research was done without patient involvement. Reporting of the study conforms to broad EQUATOR guidelines.[10]

Data sources and search strategy

We searched the Cochrane Library, PubMed, Embase, and ClinicalTrial.gov from December 2019 to 16th July 2021. The search terms included: COVID-19, SARS-CoV-2, and convalescent plasma. The full search strategies for each database are available in Supplementary TableS1-S4. The reference lists of the included studies, prior systematic reviews, and introduction and discussion sections of retrieved studies were also reviewed to identify additional relevant studies.

Study selection and eligibility criteria

We included clinical trials and observational studies that investigated the efficacy of CP comparing to placebo/usual care/standard treatment in patients with COVID-19 regardless of severity, level of antibody titer, and health care settings. We included studies with a specific aim to treat COVID-19 because the passive antibodies administration may be an effective therapy for those patients who have yet to develop their own antibody response rather than the prevention. Studies with no comparator arm, case reports/case series, conference abstracts, and systematic reviews were excluded. For overlapping participants, the studies with the longest follow-up and the most detailed information were chosen. The primary outcome of interest was all-cause mortality at any time point. The secondary outcomes were all-cause mortality at 28 days, length of hospital stay, clinical improvement at 28 days, and discharge rate at 28 days. The summary of the PICOS criteria used to identify the relevant studies are as follows; population (P) — patients with suspected or confirmed SARS-CoV2 infection; intervention (I) — the use of CP to treat SARS-CoV2 infection; comparator (C) — standard treatment or placebo or non-CP use; outcome (O) — all-cause mortality, all-cause mortality at 28 days, length of hospital stay, clinical improvement at 28 days, and discharge rate at 28 days; study design (S) — clinical trials or observational studies.

Two investigators (M.S. and J.S.) were independently screened titles and abstracts of all studies identified by the search to determine eligibility. Full texts were independently assessed in EndNote by two investigators (M.S. and J.S.) if they met the criteria for inclusion. Disagreement between investigators were resolved by consensus, if consensus could not be obtained, by consulting a third reviewer (C.K. or P.M.) who made the final decision.

Data extraction and quality assessment

Data were collected and tabulated by two reviewers (M.S and J.S) using Microsoft Excel. The included data were checked for accuracy by C.K and P.M. A standardized data sheet was used to collect

information on study characteristics. Data extraction variables included study design, country of study, setting, COVID-19 severity, antibody titer, sample size, study sample characteristics, CP dose/volume, and type of control. Mild, moderate, severe, and critical disease were defined using World Health Organization criteria.[11] Disagreement was resolved by consensus. The risk of bias was evaluated by two investigators (M.S and J.S). Clinical trials were appraised by the Cochrane risk-of-bias tool.[12] This tool includes seven domains for methodological evaluation: i) sequence generation, ii) allocation concealment, iii) blinding of participants, personnel and outcome assessors, iv) incomplete outcome data, v) selective outcome reporting, and vi) other sources of bias. The RCT was classified as low risk of bias (low risk of bias for all domains), high risk (high risk of bias for one or more domains), or unclear risk (unclear risk of bias for one or more key domains). For observational studies, we used the Newcastle–Ottawa Scale (NOS).[13] Criteria included: adequacy selection of cohort, comparability of the study group and the outcome assessment. Studies with a total score of 8 or more were defined as high quality. Disagreement between investigators was resolved by consensus or, if consensus could not be obtained, by consulting a third reviewer (C.K. or P.M.), who made the final decision.

Statistical analysis

We analyzed clinical trials and observational studies separately. In terms of clinical trials, meta-analysis was performed separately for studies published in peer-reviewed journals (primary analysis) and preprints (secondary analysis). For dichotomous outcomes such as all-cause mortality, we performed a meta-analysis using risk ratios (RRs) with 95% confidence intervals (CIs) as the common effect estimates. We recorded the number of events and total number of participants in both CP group and standard treatment group. For continuous outcomes using the same scale such as the length of hospital stay, we conducted analyses using the mean difference with 95% CIs. We recorded mean and standard deviation (SD) in both CP group and standard treatment group. For studies which reported only sample size, median, range and/or interquartile range (IQR), we estimated the sample mean and SD by using Wan X, et al.'s method.[14] We performed meta-analyses under the DerSimonian-Laird random-effects model to pool RR with 95% CIs assuming that the true effect size varied between studies. Homogeneity was assessed using the Cochran Q test, with $p<0.10$.[15] The degree of heterogeneity was estimated by I^2. I^2 value <25% indicated low, 25–75% moderate, and >75% high heterogeneity.[15] In order to explore possible sources of heterogeneity, subgroup analyses were carried out for primary outcomes for the following variables: (i) COVID-19 severity, (ii) geographical region, (iii) blinding (opened-label vs blinded), and (iv) randomization. For observational studies, we sub-grouped based on severity, geographic region, and study design (prospective studies versus retrospective studies). Sensitivity analysis was performed by using the 'leave-one-out' approach. In addition, we included all clinical trials [peer-reviewed (n=18) and preprints (n=3)] and re-analyzed the effect of CP on all-cause mortality in order to address the robustness of the findings. Given the fact that observational studies were prone to bias and confounding by indication,

patients with severe COVID-19 were more likely to receive CP treatment compared to those with mild or moderate disease. Accordingly, we re-analyzed the primary outcome by including only adjusted effect estimates from individual observational studies. A funnel plot was used to investigate any evidence of publication bias and was statistically assessed by the Begg's and Egger's tests only when there were at least 10 studies included in the meta-analysis. Statistical tests were two-sided and used a significance threshold of $p<0.05$. All analyses were conducted using STATA, v14.1 (StataCorp, Stata Statistical Software. College Station, TX: StataCorp LP; 2015).

RESULTS

Search results and study characteristics

A total of 4,728 records were identified from databases, websites, and citation searching. There were 47 studies[16-59] fulfilled the inclusion criteria and were used for the systematic review and meta-analysis (Figure. 1). Of 47 included studies, 21 were clinical trials[16-33, 60-62] and 26 were observational studies.[31-44] Among clinical trials, there were 18 studies published in peer-reviewed journals[16-33] while the other three were preprints.[60-62] Among clinical trials, there were 14 studies used the randomization process.[17-20, 23, 25, 26, 28, 30, 31, 33, 60-62] Four studies were double-blind randomized controlled trials (RCTs)[26, 30, 31, 33] whereas the other 17 were open-label clinical trials.[16-25, 27-29, 32, 60-62] Three studies were undertaken in India, two in Iran and Argentina, and one each in China, Colombia, Kuwait, Saudi Arabia, Netherlands, Spain, Iraq, the UK, the USA, Bahrain, Chile, Italy, Austria, and the USA & Brazil. Among 21 included clinical trials, there were 7,210 patients receiving CP and 7,878 patients receiving placebo/standard treatment with different levels of severity ranging from mild to critical COVID-19 disease (Table 1). The quality of each clinical study was assessed. Based on Cochrane's risk of bias, 14 out of 21 studies had adequate generation of the allocation sequence. The majority of included clinical trials (n=16) had high risk of performance bias. All studies provided complete outcome data and were clear from reporting bias (Supplementary Table S5). For observational studies, there were ten studies conducted in the USA,[35, 42, 45, 50, 52, 54-57, 59] three in China,[36, 37, 43] three in Poland,[40, 48, 58] three in India,[41, 47, 51] two in Turkey,[34, 39] and one each in United Arab Emirates,[38] Austria,[44] Brazil,[46] Qatar,[49] and Argentina.[53] Almost of observational studies included patients with severe or critical COVID-19 disease (Table 2). Overall risk of bias assessment deemed to be good for cohort and case-control studies. Sixteen studies[34, 35, 38, 42-46, 49, 50, 52, 54, 55, 57-59] had summary scores ranging from 8 to 9 which represented as high quality (Supplementary Table S6-S7).

Convalescent plasma and mortality

Across 18 peer-reviewed clinical trials, 7,118 patients received CP and 7,780 patients received standard treatment. Patients treated with CP had a lower mortality rate than those treated with the standard

treatment [22.3% (1,590/7,118) vs 25.8% (2,004/7,780)]. In the meta-analysis, CP use had a 31% reduced risk of all-cause mortality compared to standard treatment use (pooled RR=0.69, 95% CI: 0.56-0.86, p=0.001, I^2=50.1%) (Figure 2). When subgroup analysis based on severity and geographical region, the results showed that CP treatment significantly reduced risk of all-cause mortality in patients with severe and critical COVID-19 disease and studies conducted in Asia with low degree of heterogeneity, pooled RR for severe patients =0.61, 95% CI: 0.47-0.81, p=0.001, I^2=0.0%, pooled RR for critical patients=0.67, 95% CI: 0.49-0.92, p=0.013, I^2=0.0%, and pooled RR for Asia region=0.62, 95% CI: 0.48- 0.80, p<0.001, I^2=20.3%. When restricted to randomized double-blind studies, the meta-analysis showed a trend in reduction all-cause mortality among patients receiving CP treatment when compared with standard treatment (pooled RR=0.70, 95% CI: 0.48-1.02, p=0.066, I^2=0.0%) (Table 3). Among three preprints clinical trials,[60-62] the pooled of RR for all-cause mortality with CP treatment was 0.78 (95% CI: 0.22-2.74, p=0.702, I^2=38.7%). For observational studies, 5,255 COVID-19 patients received CP treatment while 21,371 received non-CP treatment. All-cause mortality was 25.7% and 16.0% in the CP and non-CP groups, respectively. The meta-analysis showed the similar results to the peer-reviewed clinical trials illustrating that CP use was associated with a significantly reduce risk of all-cause mortality compared with non-CP use (pooled RR=0.82, 95% CI: 0.72-0.93, p=0.002, I^2=65.7%) (Figure 3). Further, results from subgroup-analysis showed that CP use was associated with a reduced risk of all-cause mortality in COVID-19 patients with severe and severe or critical disease, pooled RR=0.52, 95% CI: 0.34-0.78, p=0.002, I^2=5.3% and pooled RR=0.76, 95% CI: 0.63-0.92, p=0.005, I^2=55.3%, respectively. Based on geographical region, CP use was associated with a significantly reduced risk of all-cause mortality in Asian countries and South American countries, pooled RR=0.88, 95% CI: 0.78-0.98, p=0.024, I^2=24.1% and pooled RR=0.72, 95% CI: 0.57-0.91, p=0.007, I^2=43.8%, respectively (Supplementary Table S8). In addition, results from peer-reviewed clinical trials showed a trend toward reduced mortality at day 28 in CP-treated group compared with standard-treated group (pooled RR=0.88, 95% CI: 0.73-1.05, p=0.150, I^2=16.1%). However, for observational studies, there was a statistically significant difference between CP treatment and non-CP treatment regarding all-cause mortality at 28 days (pooled RR=0.74, 95% CI: 0.63-0.88, p<0.001, I^2=41.9%) (Figure 4).

In terms of gender and ethnicity, we found only one study[20] investigated the effect of CP on all-cause mortality stratified by gender and ethnicity. There was no significant difference in 28-day mortality between the CP use vs standard treatment across subgroup of sex (RR for male=1.03, 95% CI: 0.95-1.13 and RR for female=0.94, 95% CI: 0.82-1.07) or ethnicity (RR for White= 0.97, 95% CI: 0.90-1.06 and RR for Black, Asian or minority ethnic = 1.07, 95% CI: 0.88-1.31).[20]

Convalescent plasma and length of hospital stay

Ten clinical trials[16, 17, 21-23, 25, 31-33, 61] and eleven observational studies[34, 36, 38, 39, 46, 50-52, 54, 55, 58] reported the length of hospital stay of CP-treated patients and standard treatment-treated patients. The results from

meta-analysis of peer-reviewed clinical trials (n=9) demonstrated that there was no significant difference between two groups with respect to the duration of hospital stay (weighted mean difference [WMD] = -1.63, 95% CI: -4.16 – 0.90, p=0.208, I^2=89.2%). The results remained the same after adding the preprint studies (WMD = -1.88, 95% CI: -4.22 – 0.46, p=0.116, I^2=88.0%). The results from observational studies also showed non- significant difference in length of hospital stay between two groups with substantial heterogeneity (WMD = 1.44, 95% CI: -0.71 – 3.60, p=0.190, I^2=91.9%) (Supplementary Figure S1).

Convalescent plasma and clinical improvement at 28 days

Seven studies[18, 38, 46, 48, 49, 52, 59] reported clinical improvement at 28 days after receiving treatment. One[18] was randomized controlled trial and six[38, 46, 48, 49, 52, 59] were observational studies. The definition of clinical improvement varied among studies; therefore, the meta-analysis could not be performed. For the RCT, the finding indicated that for patients with severe disease or life-threatening disease, there was no significance difference between CP group vs control group with respect to clinical improvement at 28 days (Odds ratio=1.42, 95% CI: 0.65-3.09, p=0.37).[18]

Convalescent plasma and discharge rate at 28 days

Three clinical trials[18, 20, 22] and two observational studies[49, 50] examined the discharge rate at 28 days between CP treatment and standard treatment. The results from trials showed no significant difference in discharge rate from hospital within 28 days between CP group and standard treatment group.[18, 20, 22] For observational studies, no significant differences were found between CP group and non-CP group in the proportions of patients who were discharged within 28 days.[49, 50]

Sensitivity analysis

After omitting the individual peer-reviewed clinical trial and observational studies in leave one out analysis, the risk of all-cause mortality among CP-treated patients and standard-treated patients appeared to be robust (Supplementary Table S9-S10). In addition, the meta-analysis of 18 peer-reviewed clinical trials and three preprints showed similar results to the primary analysis (Supplementary Figure S2). Finally, when including only the adjusted estimates from observational studies, the results were identical to the primary analysis demonstrating that CP use was associated with a reduced risk of all-cause mortality in COVID-19 patients when compared with non-CP use (pooled RR=0.60, 95% CI: 0.39-0.93, p=0.024, I^2=80.6%) (Supplementary Figure S3).

Publication bias

Publication bias was assessed using the data of CP treatment vs standard treatment on the risk of all-cause mortality. An evidence of asymmetry was observed in the results of Egger's test (p=0.002) but not for Begg's test (p= 0.820). The visually inspected funnel plots of peer-reviewed clinical trials included are shown in Supplementary Figure S4. For observational studies, no evidence of small-study effect was found with Begg's (p= 0.537) and Egger's test (p= 0.575). The funnel plots of observational studies are shown in Supplementary Figure S5.

DISCUSSION

The current systemic review and meta-analysis aimed to summarize the existing data on the efficacy of CP in COVID-19 patients, which remains a challenge to explore treatment for SARS-CoV-2 pandemic to respond the increasing of the incidence of SARS-CoV-2 infection. According to the eligible criteria, 47 studies[16-62] were included and critically evaluated. Corresponding to the results of our systematic review and meta-analysis, the CP may be effective in reducing the mortality of CP-treated COVID-19 patients compared to non-CP-treated COVID-19 patients, especially in severe or critical patients and in Asia region. The results are supported by the previous study of RCT and matched-control data demonstrating that COVID-19 patients transfused with CP had a lower mortality rate compared to patients receiving standard treatments.[63] Additionally, the reduction in mortality associated with CP supports with similar analyses of previous data from CP trials of novel infectious diseases those affecting the respiratory system including severe acute respiratory syndrome-1 (SARS-1), Middle East respiratory syndrome (MERS), H1N1 influenza and Ebola virus disease. The results revealed that the pooled odds of mortality were reduced compared with placebo or no therapy (odds ratio, 0.25; 95% confidence interval, 0.14–0.45) in SARS and influenza.[4]

In severe or critical COVID- 19 patients, lung alveoli macrophages or epithelial cells can produce massive proinflammatory cytokines and chemokines, which recruit monocytes and neutrophils to the infection site to eradicate the virus and infected cells, resulting in uncontrolled inflammation. This conducts the additional infiltration of macrophage and subsequently the decline of lung functions. Therefore, the crucial rule of convalescent plasma is antibody-mediated SARS-CoV-2 viral deactivation/neutralization and interference with viral replication.[64]

CP, obtained from recovered COVID-19 patients who had established humoral immunity against the virus, contains a huge quantity of neutralizing antibodies capable of neutralizing SARS-CoV-2 and eradicating the pathogen from blood circulation and pulmonary tissues. Potential mechanisms of action of SARS-CoV-2 antibodies in COVID-19 is mediated by the interaction between the SARS-CoV-2 spike glycoprotein and the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell. Antibodies directed against the receptor-binding domain (RBD) of the spike protein can interfere with its interaction with the ACE2 receptor and prevent viral entry in the host cell. Antibodies directed against epitopes outside the RBD can also exert antiviral functions through other mechanisms.[48] Viral neutralization is then posited to reduce the massive inflammatory response and prevent the immune response progresses to lung damage, interfering of gas exchange, and death.

The strength of this study should be mentioned. First, we applied a comprehensive search strategy to ensure that the included studies were representative. Second, the meta-analysis covered updated evidence including clinical trials and real world practice data. Furthermore, our study filled the knowledge gaps from previous studies by investigating the effect of CP in COVID-19 patients with different severities and

different regions. Finally, our study adheres to the standard methodology of systematic review and meta-analysis required by the Cochrane and PRISMA checklist.[9] However, our study has certain limitations. First, a moderate to high degree of heterogeneity may limit the findings. Yet, we performed subgroup analyses and found that disease severity, geographical region, study design, and quality of included studies were potential factors contributing to heterogeneity. In addition, plasma antibody titer, dose of CP used, duration between onset of COVID-19 diagnosis and transfusion, and duration of follow up after transfusion varied among studies. This might also be considered as a source of heterogeneity in our study. Second, the results from observational studies are prone to bias and unmeasured confounders. On this point, we performed a sensitivity analysis by including only adjusted values and results remained robust. However, for observational studies, we suggested that the causality of CP use and the reduction of all-cause mortality cannot be established and the results should be interpreted with caution. Third, methodological quality of included clinical trials in this study was high risk of bias. Generally, high risk of bias was identified in the domain of selection bias, performance bias and detection bias while low risk of bias was detected in the domain of attrition bias and reporting bias using Cochrane' risk of bias. Even though inadequate random sequence generation and lack of blinding of outcome measurements were observed in some studies, it may not be possible for this type of intervention to blind the participants or investigators in this critical time. However, strong blinding of researchers should be made. Fourth, the included studies yield small sample size and the results might be influenced by small study effect, making it difficult to conclude whether CP treatment is effective in the treatment of COVID-19 patients. However, there are many ongoing randomized clinical trials which currently registered on clinical.gov that assess CP for the treatment of COVID-19. It is important to note that conclusions regarding CP await the results of large controlled trials such as those emerging from the UK.[20] Further, few studies reported duration of COVID-19 diagnosis until CP administration as well as the titer of neutralizing antibodies. FDA recommended the use of "high-titer" convalescent plasma, as defined by a neutralizing antibody titer of ≥250 in the Broad Institute's neutralizing antibody assay or an S/C cutoff of ≥12 in the Ortho VITROS IgG assay.[65] These factors were considered as an important factor affecting clinical outcomes. Finally, there has been a lack of efficacy information about CP treatment among immunocompromised and vulnerable populations which may due to the limitation of enrollment, for example, transplant recipients[66] and autoimmune diseases patients[57, 67, 68] who were immunosuppressed by mycophenolate and antimetabolites that impair humoral immunity. Recently, there were accumulated evidences demonstrated that CP administration to these population before pulmonary deterioration is observed, supporting the benefit to alleviate disease severity. However, the potential therapeutic period for immunocompromised patient from CP is exactly unknown due to impaired immune response, comparison with other patients. The well-designed and well-conducted randomized clinical trials are necessary to provide more specific, evidence-based guidance on the role of CP in the treatment of patients with COVID-19 who have humoral immunodeficiencies. Thus, these issues

should be solved to enlighten the knowledge gap. Therefore, we propose that future studies aiming to investigate the efficacy of CP treatment in COVID-19 patients, should include duration of symptom onset until study treatment and investigate the appropriateness of population for CP use, especially in resource limited countries which could not access the high-cost antiviral agents and SARS-CoV-2 specific monoclonal antibodies. The supplemental CP strategy is the valuable treatment option in this situation. In addition, rigorous study design and larger sample size are needed to confirm the effect of CP treatment on clinical outcomes including mortality in patients with COVID-19.

CONCLUSIONS

CP treatment was significantly associated with a decreased risk of all-cause mortality in severe or critical COVID-19 patients compared to standard treatment. No significant differences between CP treatment and standard treatment/non-CP were observed in the length of hospital stay. The results should be interpreted with caution due to the moderate degree of heterogeneity. Future studies with larger sample size and well-designed are warranted.

Author Contributions:

Conceptualization C.K., P.M.; methodology C.K., M.S., J.S., P.M.; formal analysis, P.M.; writing—original draft preparation, C.K., M.S., J.S., P.M.; writing—review and editing, C.K., P.C., P.M.; supervision, C.K., P.M. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it in its final format. All authors have read and agreed to the published version of the manuscript.

References

1. Cucinotta D, Vanelli M. Who declares covid-19 a pandemic. Acta bio-medica: *Atenei Parmensis.* 2020;91:157-160.

2. World Health Organization. Who coronavirus (covid-19) dashboard. 2021;2021.

3. Andreano E, Piccini G, Licastro D, Casalino L, Johnson NV, Paciello I, et al. Sars-cov-2 escape in vitro from a highly neutralizing covid-19 convalescent plasma. *bioRxiv*.2020; doi:10.1101/2020.12.28.424451.

4. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, 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;211:80-90.

5. van Griensven J, De Weiggheleire A, Delamou A, Smith PG, Edwards T, Vandekerckhove P, et al. The use of ebola convalescent plasma to treat ebola virus disease in resource-constrained settings: A perspective from the field. *Clin Infect Dis*.2016;62:69-74.

6. Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, et al. Convalescent plasma in covid-19: Possible mechanisms of action. *Autoimmun Rev*.2020;19:102554.

7. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: National Institutes of Health; Available from: https://www.covid19treatmentguidelines.nih.gov/.Accessed [04 August 2021].

8. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of Hospitalized Patients with COVID19: U.S. FDA; Available from: https://www.fda.gov/media/141478/download. Accessed [04 August 2021].

9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The prisma 2020 statement: An updated guideline for reporting systematic reviews. 2021;372:n71.

10. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. *Eur J Clin Invest*. 2010;40(1):35-53.

11. World Health Organization. Clinical management of covid-19—interim guidance. 2020;2021.

12. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. 2011;343:d5928.

13. Wells G SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses.

14. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC*.2014;14:135.

15. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.

16. Abolghasemi H, Eshghi P, Cheraghali AM, Imani Fooladi AA, Bolouki Moghaddam F, Imanizadeh S, 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.

17. 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.

18. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, 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;324:460-470.
19. Rasheed AM, Fatak DF, Hashim HA, Maulood MF, Kabah KK, Almusawi YA, 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;28:357-366.
20. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *The Lancet*. 2021;397(10289):2049-59.
21. Acosta-Ampudia Y, Monsalve DM, Rojas M, Rodríguez Y, Gallo JE, Salazar-Uribe JC, et al. Covid-19 convalescent plasma composition and immunological effects in severe patients. *J Autoimmun*.2021;118:102598.
22. Allahyari A, Seddigh-Shamsi M, Mahmoudi M, Amel Jamehdar S, Amini M, Mozdourian M, et al. Efficacy and safety of convalescent plasma therapy in severe covid-19 patients with acute respiratory distress syndrome. *Int Immunopharmacol*.2021;93:107239.
23. AlQahtani M, Abdulrahman A, Almadani A, Alali SY, Al Zamrooni AM, Hejab AH, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe covid-19 disease. *Sci Rep*.2021;11:9927.
24. Alsharidah S, Ayed M, Ameen RM, Alhuraish F, Rouheldeen NA, Alshammari FR, et al. Covid-19 convalescent plasma treatment of moderate and severe cases of sars-cov-2 infection: A multicenter interventional study. *Int J Infect Dis*.2021;103:439-446.
25. Balcells ME, Rojas L, Le Corre N, Martínez-Valdebenito C, Ceballos ME, Ferrés M, 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:e1003415.
26. Bennett-Guerrero E, Romeiser JL, Talbot LR, Ahmed T, Mamone LJ, Singh SM, 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.
27. Franchini M, Glingani C, Morandi M, Corghi G, Cerzosimo S, Beduzzi G, et al. Safety and Efficacy of Convalescent Plasma in Elderly COVID-19 Patients: The RESCUE Trial. Mayo Clin Proc Innov Qual Outcomes. 2021;5(2):403-12.
28. Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FPN, 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.

29. Hoepler WP, Weidner L, Traugott MT, Neuhold S, Meyer EL, Zoufaly A, et al. Adjunctive treatment with high-titre convalescent plasma in severely and critically ill COVID-19 patients-a safe but futile intervention. A comparative cohort study. Infect Dis (Lond).2021 Jun 15;1-10.

30. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early high-titer plasma therapy to prevent severe covid-19 in older adults. *N Engl J Med*.2021; 384:610-618.

31. O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. *J Clin Invest.* 2021 Jul 1;131(13):e150646.

32. AlShehry N, Zaidi SZA, AlAskar A, Al Odayani A, Alotaibi JM, AlSagheir A, et al. Safety and Efficacy of Convalescent Plasma for Severe COVID-19: Interim Report of a Multicenter Phase II Study from Saudi Arabia. *Saudi J Med Med Sci*. 2021;9(1):16-23.

33. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A randomized trial of convalescent plasma in covid-19 severe pneumonia. *N Engl J Med*.2021; 384:619-629. doi: 10.1056/NEJMoa2031304.

34. Altuntas F, Ata N, Yigenoglu TN, Basci S, Dal MS, Korkmaz S, et al. Convalescent plasma therapy in patients with COVID-19. *Transfus Apher Sci*. 2021;60(1): 102955.2020:102955.

35. Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, et al. Convalescent plasma treatment of severe covid-19: A propensity score-matched control study. *Nat Med*.2020;26:1708-1713.

36. Xia X, Li K, Wu L, Wang Z, Zhu M, Huang B, et al. Improved clinical symptoms and mortality among patients with severe or critical covid-19 after convalescent plasma transfusion. *Blood*.2020;136:755-759.

37. Zeng Q-L, Yu Z-J, Gou J-J, Li G-M, Ma S-H, Zhang G-F, 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.

38. Abuzakouk M, Saleh K, Algora M, Nusair A, Alameri J, Alshehhi F, et al. Convalescent plasma efficacy in life-threatening covid-19 patients admitted to the ICU: A retrospective cohort study. *J Clin Med*. 2021 May 14;10(10):2113.

39. Aktimur SH OC, Kayabas A,. The impact of convalescent (immune) plasma treatment on the clinical course of covid-19. *Int J Clin Exp Med*.2021;14:1226-1233.

40. Biernat MM, Kolasinska A, Kwiatkowski J, Urbaniak-Kujda D, Biernat P, Janocha-Litwin J, et al. Early administration of convalescent plasma improves survival in patients with hematological malignancies and COVID-19. *Viruses.* 2021 Mar 8;13(3):436.

41. Budhiraja S, Dewan A, Aggarwal R, Singh O, Juneja D, Pathak S, et al. Effectiveness of convalescent plasma in indian patients with covid-19. *Blood Cells Mol Dis*.2021;88:102548.

42. Cho K, Keithly SC, Kurgansky KE, Madenci AL, Gerlovin H, Wellman HM, et al. Early Convalescent Plasma Therapy and Mortality among US Veterans Hospitalized with Non-Severe COVID-19: An Observational Analysis Emulating a Target Trial. *J Infect Dis*. 2021 Jun 21;jiab330. doi: 10.1093/infdis/jiab330.

43. Dai W, Wu J, Li T, Shen J, Pang R, Luo T, et al. Clinical outcomes for COVID-19 patients with diabetes mellitus treated with convalescent plasma transfusion in Wuhan, China. *J Med Virol.* 2021;93(4):2321-31.

44. Hatzl S, Posch F, Sareban N, Stradner M, Rosskopf K, Reisinger AC, et al. Convalescent plasma therapy and mortality in COVID-19 patients admitted to the ICU: a prospective observational study. *Ann Intensive Care*. 2021 May 12;11(1):73.

45. Klapholz M, Pentakota SR, Zertuche JP, McKenna M, Roque W, Forsberg M, et al. Matched Cohort Study of Convalescent COVID-19 Plasma Treatment in Severely or Life Threateningly Ill COVID-19 Patients. *Open Forum Infect Dis*. 2021 Feb; 8(2): ofab001.

46. Kurtz P, Righy C, Gadelha M, Bozza FA, Bozza PT, Gonçalves B, et al. Effect of convalescent plasma in critically ill patients with covid-19: An observational study. *Front Med (Lausanne)*.2021;8:630982.

47. Mahapatra S, Rattan R, Mohanty CBK. Convalescent Plasma Therapy in the management of COVID-19 patients-The newer dimensions. *Transfus Clin Biol.* 2021 May 19;28(3):246-253.

48. Moniuszko-Malinowska A, Czupryna P, Zarebska-Michaluk D, Tomasiewicz K, Pancewicz S, Rorat M, et al. Convalescent plasma transfusion for the treatment of COVID-19-experience from Poland: A multicenter study. *J Clin Med*. 2021;10(1):1-12.

49. Omrani AS, Zaqout A, Baiou A, Daghfal J, Elkum N, Alattar RA, et al. Convalescent plasma for the treatment of patients with severe coronavirus disease 2019: A preliminary report. *J Med Virol*. 2021;93(3):1678-86.

50. Rogers R, Shehadeh F, Mylona EK, Rich J, Neill M, Touzard-Romo F, et al. Convalescent Plasma for Patients With Severe Coronavirus Disease 2019 (COVID-19): A Matched Cohort Study. *Clin Infect Dis*. 2021 Jul 1;73(1):e208-e214.

51. Sajmi S, Goutham K, Arumugam V, Gopalakrishnan N, Lamech TM, Aiswarya D, et al. Efficacy and safety of convalescent plasma therapy in SARS-CoV2 patients on hemodialysis. *Hemodial Int*. 2021; 1-8.

52. Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, 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*.2021;191:90-107.

53. Salazar MR, Gonzalez SE, Regairaz L, Ferrando NS, Gonzalez Martinez VV, Carrera Ramos PM, et al. Risk factors for COVID-19 mortality: The effect of convalescent plasma administration. *PLoS One*. 2021 Apr 29;16(4):e0250386.

54. Shenoy AG, Hettinger AZ, Fernandez SJ, Blumenthal J, Baez V. Early mortality benefit with covid-19 convalescent plasma: A matched control study. *Br J Haematol*.2021;192:706-713.

55. Sostin OV, Rajapakse P, Cruser B, Wakefield D, Cruser D, Petrini J. A matched cohort study of convalescent plasma therapy for COVID-19. *J Clin Apher*. 2021 Feb 22;10.1002/jca.21888.

56. Tang J, Grubbs G, Lee Y, Golding H, Khurana S. Impact of convalescent plasma therapy on SARS CoV-2 antibody profile in COVID-19 patients. *Clin Infect Dis*. 2021;16.

57. Thompson MA, Henderson JP, Shah PK, Rubinstein SM, Joyner MJ, Choueiri TK, et al. Association of Convalescent Plasma Therapy with Survival in Patients with Hematologic Cancers and COVID-19. *JAMA Oncol*. 2021 Jun 17. doi: 10.1001/jamaoncol.2021.1799.

58. Tworek A, Jaroń K, Uszyńska-Kałuża B, Rydzewski A, Gil R, Deptała A, et al. Convalescent plasma treatment is associated with lower mortality and better outcomes in high-risk covid-19 patients – propensity-score matched case-control study. *Int J Infect Dis*.2021;105:209-215.

59. Yoon H, Bartash R, Gendlina I, Rivera J, Nakouzi A, Bortz RH, et al. Treatment of severe COVID-19 with convalescent plasma in Bronx, NYC. *JCI Insight.* 2021 Feb 22;6(4):e142270.

60. Avendaño-Solà C, Ramos-Martínez A, Muñez-Rubio E, Ruiz-Antorán B, de Molina RM, Torres F, et al. Convalescent plasma for covid-19: A multicenter, randomized clinical trial. *medRxiv*.2020.08.26.20182444; doi: https://doi.org/10.1101/2020.08.26.20182444.

61. Bajpai M, Kumar S, Maheshwari A, Chhabra K, kale P, Gupta 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*.2020.10.25.20219337; doi: https://doi.org/10.1101/2020.10.25.20219337

62. Ray Y, Paul SR, Bandopadhyay P, D'Rozario R, Sarif J, Lahiri A, et al. Clinical and immunological benefits of convalescent plasma therapy in severe covid-19: Insights from a single center open label randomised control trial. *medRxiv*.2020.11.25.20237883; doi: https://doi.org/10.1101/2020.11.25.20237883.

63. Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, et al. The effect of convalescent plasma therapy on mortality among patients with covid-19: Systematic review and meta-analysis. *Mayo Clin Proc*.2021;96:1262-1275.

64. Gómez-Rial J, Rivero-Calle I, Salas A, Martinón-Torres F. Role of Monocytes/Macrophages in Covid-19 Pathogenesis: Implications for Therapy. *Infect Drug Resist*.2020;13:2485-2493. doi: 10.2147/IDR.S258639. PMID: 32801787; PMCID: PMC7383015.

65. U.S. Food and Drug Administration. Clinical memorandum: COVID-19 Convalescent Plasma: U.S. FDA; Available from: https://www.fda.gov/media/141480/download. Accessed [04 August 2021].

66. Kluger MA, Czogalla J, Schmidt-Lauber C, Peine S, Schmiedel S, Bangert K, et al. Convalescent plasma treatment for early post-kidney transplant acquired COVID-19. *Transpl Infect Dis* . 2021 Jul 12. doi: 10.1111/tid.13685.

67. Mira E, Yarce OA, Ortega C, Fernández S, Pascual NM, Gómez C, et al. Rapid recovery of a SARS-CoV-2-infected X-linked agammaglobulinemia patient after infusion of COVID-19 convalescent plasma. *J Allergy Clin Immunol Pract*. 2020;8(8):2793-5.

68. Gupta A, Kute VB, Patel HV, Engineer DP, Banerjee S, Modi PR, et al. Feasibility of Convalescent Plasma Therapy in Kidney Transplant Recipients With Severe COVID-19: A Single-Center Prospective Cohort Study. *Exp Clin Transplant*. 2021 Apr;19(4):304-309.

Table 1. Baseline characteristics of included clinical trials (n=21 studies)

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size	Mean age (SD)	Antibody titer	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
			Open label (Y/N)	Randomi-zation (Y/N)										
Peer-reviewed publications (n=18 studies)														
Abolghasemi H, et al. (2020)	Iran	Hospitals in Iran	Y	N	IRCT20200325046860N1	Severe	189	CP gr=54.41 (13.71), control gr =56.83 (14.98)	NR	NR	One unit of CP (500 ml) within four hrs. and another unit if not improved after 24 hrs.	Standard care	CP gr=41.7 %, control gr=50%	NR
Agarwal A, et al. (2020)	India	39 tertiary care hospitals	Y	Y	CTRI/2020/04/024775	Moderate	464	Median (IQR) CP gr = 52 (42-60), control gr = 52 (41-60)	Median (IQR)=1:40 (1:30-1:80)	NR	Two doses of 200 ml. CP, transfused 24 hrs. apart	Standard treatment	CP gr=25%, control gr=23%	NR
Li L, et al. (2020)	China	7 medical centers in Wuhan	Y	Y	ChiCTR2000029757	Severe and life-	103	Median (IQR) CP gr= 70 (62-80), control gr	At least 1:640	NR	CP dose: 4 to 13 ml/kg, transfused 10 ml	Standard treatment	CP gr=48.1 %,	NR

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size	Mean age (SD)	Antibody titer	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
			Open label (Y/N)	Randomi-zation (Y/N)										
						threatening		=69 (63-76)			for the first 15 mins, then increased 100 ml/hr		control gr=35.3 %	
Rasheed AM, et al. (2020)	Iraq	Three hospitals	Y	Y	NR	Critical	49	CP gr=55.66 (17.83), control gr= 47.82 (15.36)	NR	NR	CP 400 ml.	Standard treatment	CP gr only =42.9%	NR
Abani O, et al. (2021)	UK	177 National Health Service (NHS) hospital organizations	Y	Y	ISRCTN 50189673, NCT04381936	Mixed	11558	CP gr=63.5 (14.7), control gr=63.4 (14.6)	neutralizing antibody titer ≥1:100	NR	CP 2 units (275 ml. [200-350 ml], the first as soon as possible and the second the following day at least 12 hr. apart	Standard treatment	CP gr=37%, control gr=34%	CP gr (white 78%, black/Asian /minority 14%, unknown 8%), control gr (white 77%,

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size	Mean age (SD)	Antibody titer	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
			Open label (Y/N)	Randomi-zation (Y/N)										
														black/Asian /minority 15%, unknown 8%)
Acosta-Ampudia Y, et al. (2021)	Colombia	Clínica del Occidente, Clínica CES, Hospital Universitario Mayor Me'deri	Y	N	NCT04332380 and NCT04332835	Severe	18	CP gr=47.89 (9.69), control gr=53.67 (6.71)	Titer IgG ≥1:3200, Titer IgA≥1:800	NR	One dose of CP 250 ml, transfused two doses within 48 h.	Standard treatment	CP gr=33.3 %, control gr=55.6 %	NR
Allahyari A, et al. (2021)	Iran	Imam Reza hospital	Y	N	IRCT20200409047007N1	Critical	64	CP gr=58.74 (14.67), control gr=55.53	NR	NR	One cycle of CP 600 ml. transfused slowly	Standard treatment	CP gr=43.75 %, control	NR

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size	Mean age (SD)	Antibody titer	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
			Open label (Y/N)	Randomization (Y/N)										
								(14.10)					gr=43.75 %	
AlQahtani M, et al. (2021)	Bahrain	Two medical centers	Y	Y	NCT04356534	Severe	40	CP gr=52.6 (14.9), Control gr=50.7 (12.5)	NR	NR	CP 400 ml, given as 200 ml over 2 hrs over 2 successive days	Standard treatment	CP gr=15%, control gr=25%	NR
Alsharidah S et al. (2021)	Kuwait	Four major tertiary hospitals in Kuwait	Y	N	NR	Moderate/Severe	368	Median (IQR) CP gr=54 (48-60), control gr=54 (45-62)	NR	NR	107 patients received 2 units of CP (each unit of containing 200 ml), 12 hrs. apart. and 28 received 1 unit of CP (200-400 ml)	Standard treatment	CP gr=22.2 %, control gr=15%	NR
Balcells	Chile	A single	Y	Y	NCT04375	Moder	58	Mean	anti-SARS-	≤ 7 days	400 ml. of CP,	deferred	CP	NR

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size	Mean age (SD)	Antibody titer	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
			Open label (Y/N)	Randomi-zation (Y/N)										
ME, et al. (2021)		Chilean medical center			098	ate/severe		(range)CP gr =64.3 (33-92), control gr=67.1 (27-91)	CoV-2 (S1) IgG titers ≥ 1:400		infused as two 200 ml. units, each separated by 24 hrs.	plasma group (received CP only if a pre-specified worsening respiratory function criterion was met)	gr=46.4 %, deferred gr=53.3 %	
Gharbharan A, et al. (2021)	Netherlands	14 secondary and academic	Y	Y	NCT04342182	Moderate/severe	86	Median (IQR) CP gr=63 (55-77), control gr=61 (56-70)	neutralizing antibody titers of at least 1:80	≤ 96 hrs	CP 300 ml	Standard treatment	CP gr=33%, control gr=23%	NR

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size	Mean age (SD)	Antibody titer	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
			Open label (Y/N)	Randomization (Y/N)										
		hospitals												
Libster R, et al. (2021)	Argentina	Clinical sites and geriatric units	N	Y	NCT04479163	Mild	160	CP gr=76.4 (8.7), control gr=77.9 (8.4)	IgG titer greater than 1:1000	≤ 72 hrs	CP 250 ml, given over period of 1.5 to 2 hrs.	Placebo	CP gr=68%, control gr=58%	NR
O'Donnell MR, et al. (2021)	USA and Brazil	Five hospitals in USA and Brazil	N	Y	NCT04359810	Severe	223	Median (IQR) CP gr = 60 (48-71), control gr = 63 (49-72)	titer of ≥1:400	≤ 48 hrs	A single unit of CP (200-250 ml) was transfused over 2 hrs.	Normal control plasma	CP gr=36%, control gr=30%	NR
AlShehry N, et al. (2021)	Saudi Arabia	22 hospitals	Y	N	NCT04347681	Critical	164	CP gr=50.25 (14.90), control gr=52.59 (12.79)	NR	Anytime	CP infused 300 ml (200-400ml/dose)	Standard treatment	CP gr=17.5 %, control gr=16.1 %	NR
Simonovi	Argentin	12 clinical	N	Y	NCT04383	Severe	333	Median (IQR)	Median titer	NR	CP 500ml (IQR;	Placebo	CP	NR

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size	Mean age (SD)	Antibody titer	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
			Open label (Y/N)	Randomi-zation (Y/N)										
ch VA, et al. (2021)	a	sites and coordinated by Hospital Italiano de Buenos Aires			535			CP gr=62.5 (53-72.5), control gr=62 (49-71)	1:3200 (IQR 1:800 to 1:3200)		415- 600 ml)	and standard treatment	gr=29.4 %, control gr=39%	
Bennett-Guerrero E, et al. (2021)	USA	Hospital in New York.	N	Y	NCT04344535	Unspecified	74	CP gr=67 (15.8), control gr=64 (17.4)	NR	NR	A single dose of 2 units of CP (240 ml/unit) over 1-4 hrs.	Standard Plasma	CP gr=39%, control gr=46.7	NR
Franchini M, et al. (2021)	Italy	the city hospital of Mantua	Y	N	NCT04569188	Moderate/severe	755	Median (IQR)=87 (82-90)	Titer of 1:160 or greater	NR	1-3 units (300 ml/unit)	Non-convalescent plasma	50%	NR
Hoepler WP, et al.	Austria	Hospital setting,	Y	N	The patients had been	Critical	194	Median (range)CP	>1:100	Median=8 days	200 ml given over 30 mins	Non-CP	CP gr=16.4	NR

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size	Mean age (SD)	Antibody titer	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
			Open label (Y/N)	Randomization (Y/N)										
(2021)		single center			enrolled in the ACOVACT			gr=61 (25-86), non-CP gr=63 (20-87)					%, non-CP gr=28.9 %	
Preprints (n=3 studies)														
Avendaño-Solà C, et al. (2020)	Spain	14 hospitals	Y	Y	NCT04345523	Severe	81	Median age = 59	neutralizing antibodies titers >1:80	≤12 days	Single unit of CP (250-300 ml)	Standard treatment	45.7%	NR
Bajpai M, et al. (2020)	India	The Institute of Liver and Biliary Sciences (ILBS) and in collaborati	Y	Y	NCT04346446	Severe	29	CP gr=48.1 (9.1), control gr=48.3 (10.8)	median neutralizing antibody titer ≥80, median S1 RBD IgG antibody titer ≥640	NR	CP 500 ml in two divided doses on consecutive days	Standard treatment	CP gr=21.4 %, control gr=26.7	NR

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size	Mean age (SD)	Antibody titer	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
			Open label (Y/N)	Randomization (Y/N)										
		on with the Departmentof Internal Medicine, Lok Nayak Hospital												
Ray Y, et al. (2020)	India	A single center in Eastern India	Y	Y	CTRI/2020/05/025209	Critical	80	Overall = 64.43 (11.33)	NR	NR	two consecutive doses of ABO-matched 200 ml CP on two consecutive days	Standard treatment	28.75%	NR

Abbreviations: SD= standard deviation; IQR=interquartile range; CP=convalescent plasma; NR=not reported.

Table 2. Baseline characteristics of included observational studies (n=26)

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
Altuntas F, et al. (2020)	Turkey	The Republic of Turkey, Ministry of Health database	Retrospective cohort	Severe/critical	1776	Median (IQR) CP gr=60 (19-96), non-CP gr= 61 (21-91)	CP gr=30.6%, non-CP gr=28.6%	NR	NR	200-600 ml	Non-CP	All-cause mortality, duration of hospital stay	Matching
Liu STH, et al. (2020)	USA	The Mount Sinai Hospital in New York	Retrospective cohort	Severe	195	CP gr=55 (13), not defined control group	CP gr=36%	NR	Median (range) CP gr= 4 (0-7)	250 ml.	Non-CP	All-cause mortality	Propensity score matching and covariate adjustme

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
		City											nt
Xia X, et al. (2020)	China	Wuhan Huoshenshan Hospital	Retrospective cohort	Severe/critical	1568	Median (IQR) CP gr=65 (57-73), non-CP gr=63 (53-71)	CP gr=44.2%, non-CP=49.7%	NR	Medien (IQR) of symptoms onset to CP therapy)=45(39-54)	200-1200 ml	Non-CP	All-cause mortality, duration of hospital stay	None
Zeng Q, et al. (2020)	China	The First Affiliated Hospital of Zhengzhou Universit	Retrospective cohort	Critical	21	Median (IQR) CP gr =61.5 (31.5-77.8), non-CP gr= 73 (60-79)	CP gr=16.7%, non-CP=26.7%	NR	Median of 21.5 days	Median volume infused was 300ml.	Non-CP	All-cause mortality	None

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
		y and The Sixth People's Hospital of Zhengzhou City.											
Abuzakouk M, et a. (2021)	United Arab Emirates	Cleveland Clinic Abu Dhabi	Retrospective cohort Study	Critical	110	Median (IQR) CP gr=50 (43-60), non-CP gr=46 (39-57)	CP gr=9.4%, non-CP=10.3%	≥1:160	NR	NR	Non-CP	All cause mortality, duration of hospital stay	Covariate adjustment
Aktimur SH, et	Turkey	The hematolo	Retrospective	Critical	41	CP gr=64.90 (19.12) non-	CP gr=38.1%	NR	NR	200 ml, infused	Non-CP	All-cause	Propensity score

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
al. (2021)		gy department, Ministry of Health University, Samsun Training and Research Hospital, Samsun.	cohort			CP gr=66.60 (17.49)				over 1 to 2 hours		mortality, duration of hospital stay	matching
Biernat MM, et al. (2021)	Poland	Wroclaw Medical University	Prospective cohort	Mild/Moderate/ Severe	45	Median (Range) CP gr=57 (31-72), non-CP	CP gr=39%, non-CP gr (historical)	Greater than 1:1000	48–72 h after the diagnosis of infection	At least one plasma dose of	Non-CP	All-cause mortality	None

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
						gr=62.5 (20-80)	=36%			200–250 mL			
Budhiraja S, et al. (2021)	India	Tertiary care teaching hospitals in Delhi	Case-control study	Moderate to critical	694	CP gr=60.1 (12.1), non-CP gr=58.9 (13.8)	CP gr=19.8%, non-CP gr=27.7%	Neutralizing antibody titers of >1:640	NR	200 ml.	Non-CP	All-cause mortality, all-cause mortality at 28-day	None
Cho K, et al. (2021)	USA	Veterans Affairs medical center	Prospective cohort study	Mild to moderate (non-severe)	11269	CP gr=65.0 (11.3), non-CP gr=64.1 (12.0)	CP gr=8%, control gr=7%	NR	Within 2 days of eligibility.	NR	Non-CP	All-cause mortality	Covariate adjustment in sensitivity analysis
Dai W,	China	Wuhan	Retrospe	Mild/severe/crit	367	Median	CP	Antibod	NR	100-200	Non-	All-	Propensi

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
et a. (2021)		Huoshenshan Hospital of China	ctive cohort	ical		(range) CP gr=68 (21-93), non-CP gr=64 (33-90)	gr=41.03%, control gr= 45.43%	y titer ≥1:160		ml per unit	CP	cause mortality	ty score matching
Hatzl S, et al. (2021)	Austria	Department of Internal Medicine, Medical University of Graz	Prospective cohort	Critical	120	Median (IQR) CP gr=61 (53-72), non-CP gr=69 (55-76)	CP gr= 25%, control gr= 33%	NR	Median 4 (1-10) days	600 ml (400 ml day1, 200 ml day2)	Non-CP	All-cause mortality	Propensity score weighting
Klapholz M, et al. (2021)	USA	Hospital setting	Retrospective cohort	Severe or critical	94	CP gr=58.0 (13.0), non-CP gr=57.7 (13.7)	CP gr=38.3%, control gr=38.3%	NR	NR	Approximately 200 mL of ABO-compatibl	Non-CP	All-cause mortality	Individual-level matched controls (1:1)

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
										e plasma			
Kurtz P, et al. (2021)	Brazil	the Instituto Estadual do Cérebro Paulo Niemeyer (IECPN)	Prospective cohort	Critical	113	Median (IQR) CP gr=58(45-64), non-CP gr=63 (49-71)	CP gr= 37%, control gr= 40%	titers ≥ 1:1,080	3 days after ICU admission or respiratory failure.	200 to 250 ml	Non-CP	All-cause mortality, all-cause mortality at 28-day, duration of hospital stay, clinical improvement within 28	Propensity-score weighting

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
												days	
Mahapatra S, et al. (2021)	India	SCB Medical College & Hospital, Cuttack, Odisha, India	Multi-centric case controlled observational prospective	Moderate/severe	2432	NR	CP gr= 16.48	Neutralizing titer more than 1:160	NR	200-250 ml	Non-CP	All-cause mortality	None
Moniuszko-Malinowska A, et al. (2021)	Poland	The SARSTer database, in medical centers	Retrospective cohort	Mixed	1006 [patients who received CP during the first	CP gr=59.9 (18.2), remdesivir gr=58.6 (14.4) and other drug gr=52.5	CP gr=36.4% and non-CP gr (remdesivir and other drugs) =	NR	Mean (SD)=6.6 (9.7) days	1-2 dose of CP (one dose=200-267 ml.)	Non-CP	All-cause mortality, clinical improvement within 28	None

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
		Poland			seven days (55), remdesivir (236), and other drugs (715)]	(21.5)	45%					days	
Omrani AS, et al. (2021)	Qatar	Hamad Medical Corporation (HMC)	Retrospective cohort	Severe/critical	80	Median (IQR) CP gr=47.5(39-60.5), non-CP gr=55.5(46.5-60.5)	CP gr= 15%, non-CP gr= 12.5%	NR	Within 7 days of admission to ICU	400 ml.	Non-CP	All-cause mortality, all-cause mortality at 28-	Variable adjustment

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
												day, clinical improvement at 28-day, discharge rate at 28-day	
Rogers R, et al. (2020)	USA	Three hospitals in the Livespan health system, Rhode Island Hospital	Retrospective cohort	Severe	241	Median (IQR) CP gr=61(47-70), non-CP gr=61 (50-75)	CP gr= 42.2%, non-CP gr= 46.3%	NR	Median of 7 days after symptoms	1-2 units	Non-CP	All-cause mortality, all-cause mortality at 28-day, duration	Matching, covariate adjustment

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
		and The Miriam Hospital										of hospital stay, discharge rate at 28-day	
Sajmi S, et al. (2021)	India	The Institute of Nephrology, Madras Medical College	Prospective cohort	Moderate and severe	68	CP gr=52 (13.6), non-CP gr=56.4 (12.3)	CP gr=19.2%, non-CP gr=25.8%	NR	NR	200 ml. transfused over 4 hrs.	Non-CP	All-cause mortality, duration of hospital stay	None
Salazar E, et al. (2021)	USA	Eight Houston Methodis	Retrospective cohort	Severe/critical	903	Overall age within 60 days; median	Overall age within 60 days;	anti-RBD IgG titer	NR	300 ml.	Non-CP	All-cause mortality	Propensity score matching

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
		t hospitals				(IQR) alive=54(44.0-62.0), deceased=65 (59.0-76.0)	alive=44.6%, deceased=35.9%	of ≥1:1350				, duration of hospital stay, clinical improvement at 28-day	
Salazar MR, et al. (2021)	Argentina	Hospitals in Buenos Aires Province	Retrospective cohort	Severe/critical	3,529	CP gr=56 (13), non-CP gr=64 (17)	CP gr=30.9%, non-CP gr=41.9%	≥1:400	NR	NR	Non-CP	All-cause mortality 28-days	None
Shenoy AG, et al.	USA	Hospitals in a single	Retrospective cohort	Severe/critical	526	CP gr=55.93 (14.01), non-CP gr=56.10	CP gr=36.5%, non-CP	NA	NR	200-500 ml, transfused	Non-CP	All-cause mortality	Matching

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
(2021)		academic health system				(14.0)	gr=36.5%			one to two units		, all-cause mortality at 28-day, duration of hospital stay	
Sostin OV, et al. (2021)	USA	Five Nuvance Health Hospitals.	Retrospective cohort	Severe/critical	96	Median (IQR) CP gr=59.8(55.5-68.3), non-CP gr=59.7(48.0-78.7)	CP gr=49%, non-CP gr=49%	NR	NR	200-250 ml, infused over one to two hours	Non-CP	All-cause mortality, duration of hospital stay	Matching and adjusted for the important variables

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
Tang J, et al. (2021)	USA	Washington Adventist Medical HealthCare, Maryland	Case-control	Critical	16	58.9 (10.2)	0%	NR	Median (IQR)=16 (9.5-22.25)	NR	Non-CP	All-cause mortality	None
Thompson MA, et al. (2021)	USA	The COVID-19 and Cancer Consortium registry	Retrospective cohort	Mixed (mild, moderate, severe)	966 (143 CP gr and 823 non-CP gr)	65 (15)	CP gr=42.7%, non-CP gr=44.5%	NR	NR	NR	Non-CP	All-cause mortality	Propensity score matching
Tworek A, et al.	Poland	The Central	Prospective cohort	Severe	204 (Propen	CP gr= 63.04 (15.48), non-	CP gr=44.1%,	NR	Median (range) CP gr=	1-3 units (200 ml	Non-CP	All-cause	Propensity score

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
(2021)		Clinical Hospital of the Ministry of Internal Affairs in Warsaw			sity score-matched)	CP gr=62.74 (20.55)	non-CP gr=39.2%		20.0 (0.0-63.0), non-CP gr=13.0 (0.0-59.0)	each)		mortality, duration of hospital stay	matching and adjusted model
Yoon HA, et al. (2021)	USA	Mayo Clinic	Retrospective cohort	Severe/critical	146	Median (IQR) CP gr=67(55 - 75), non-CP gr=66 (56-77)	CP gr=43.8%, non-CP gr=35.6%	Titer≥1:2430	72 hours of admission	1 unit (200 ml.)	Non-CP	All-cause mortality, all-cause mortality at 28-day,	Propensity score matching

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)	% Female	Antibody titer	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
												clinical improvement at 28-day	

Abbreviations: SD=standard deviation; IQR=interquartile range; CP=convalescent plasma; NR=not reported; ICU=intensive care unit

Table 3. Subgroup analysis of peer-reviewed clinical trials on risk of all-cause mortality between the convalescent plasma treatment vs the standard treatment

Outcomes	No .of studies	Pooled RR (95% CI)	P-value	Heterogeneity test		
				X^2	P-value	I^2-index
Severity						
-Mild	1	0.50 (0.09-2.65)	0.416	NA	NA	NA
-Moderate	2	0.65 (0.24-1.80)	0.409	6.86	0.009	85.4%

- Moderate to severe	3	0.69 (0.26-1.85)	0.458	4.53	0.104	55.9%
-Severe	7	0.61 (0.47-0.81)	0.001	4.17	0.653	0.0%
-Critical	5	0.67 (0.49-0.92)	0.013	2.95	0.567	0.0%
-Mixed	2	0.99 (.093-1.05)	0.705	0.05	0.104	55.9%
Geographical region						
-Asia	8	0.62 (0.48-0.80)	<0.001	11.29	0.257	20.3%
-South America	4	1.06 (0.61-1.83)	0.830	2.55	0.467	0.0%
-Europe	4	0.78 (0.54-1.13)	0.188	5.90	0.116	49.2%
- North America	1	0.89 (0.34-2.31)	0.811	NA	NA	NA
-North America and South America	1	0.51 (0.29-0.92)	0.025	NA	NA	NA
Randomized vs non-randomized						
-Randomized	11	0.87 (0.71-1.07)	0.187	13.58	0.257	19.0%
-Non-randomized	7	0.57 (0.46-0.72)	<0.001	5.46	0.604	0.0%
Randomized double-blind vs open label						
-Randomized double-blinded	4	0.70 (0.48-1.02)	0.066	2.40	0.494	0.0%
- Open label	14	0.69 (0.54-0.87)	0.002	33.33	0.004	55.0%

Abbreviations: RR=risk ratio; CI=confidence interval; NA=not applicable

Figure Titles and Legends

Figure 1. PRISMA Flow Diagram

Figure 2. Forest plots showing risk of all-cause mortality in COVID-19 patients comparing using convalescent plasma treatment and standard treatment among peer-reviewed clinical trials **Abbreviations:** RR=risk ratio; CI=confidence interval

Figure 3. Forest plots showing risk of all-cause mortality in COVID-19 patients comparing using convalescent plasma treatment and non-convalescent plasma treatment among observational studies **Abbreviations:** RR=risk ratio; CI=confidence interval; CP=convalescent plasma

Figure 4. Forest plots showing risk of all-cause mortality at 28 days in COVID-19 patients comparing using convalescent plasma treatment and standard treatment/non-convalescent plasma (A) results from peer-reviewed clinical trials, (B) results from observational studies **Abbreviations:** RR=risk ratio; CI=confidence interval

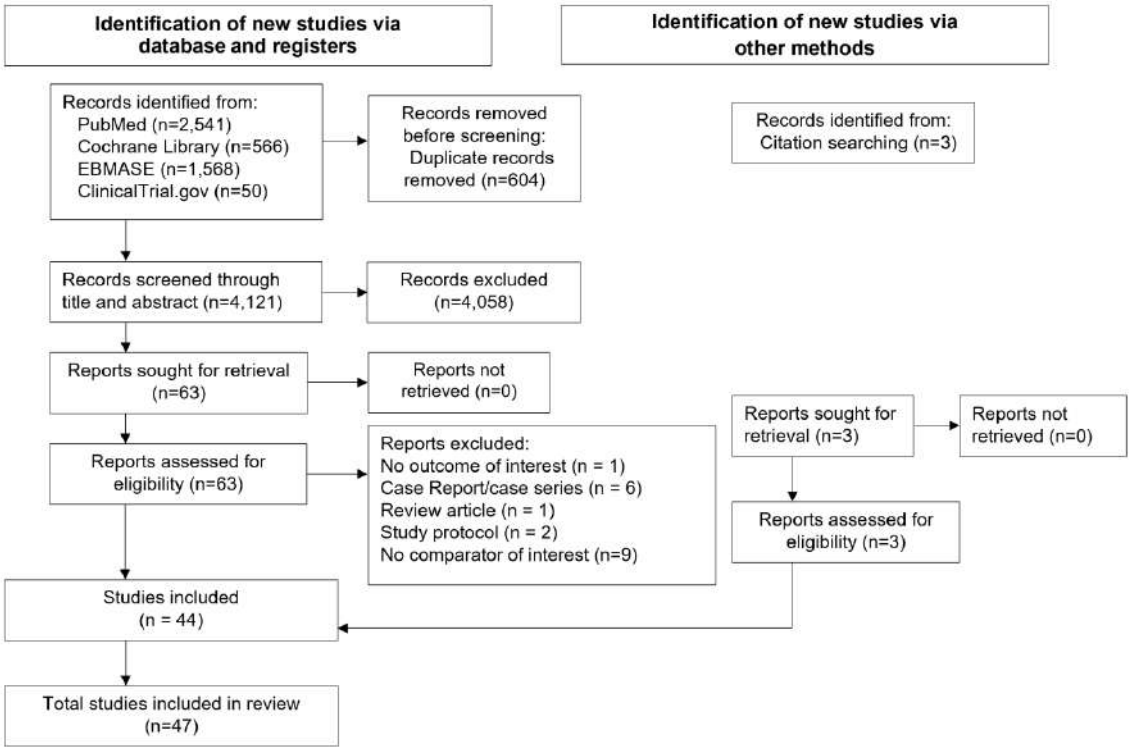

Figure 1. PRISMA Flow Diagram

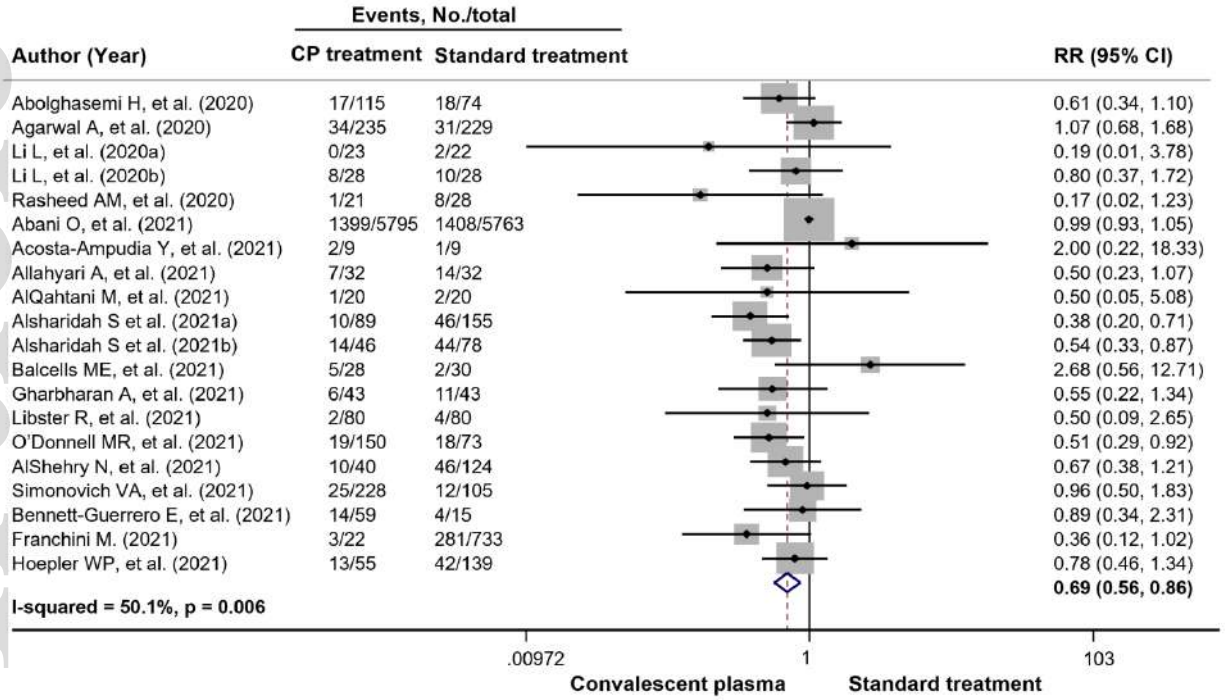

Figure 2. Forest plots showing risk of all-cause mortality in COVID-19 patients comparing using convalescent plasma treatment and standard treatment among peer-reviewed clinical trials

Abbreviations: RR=risk ratio; CI=confidence interval

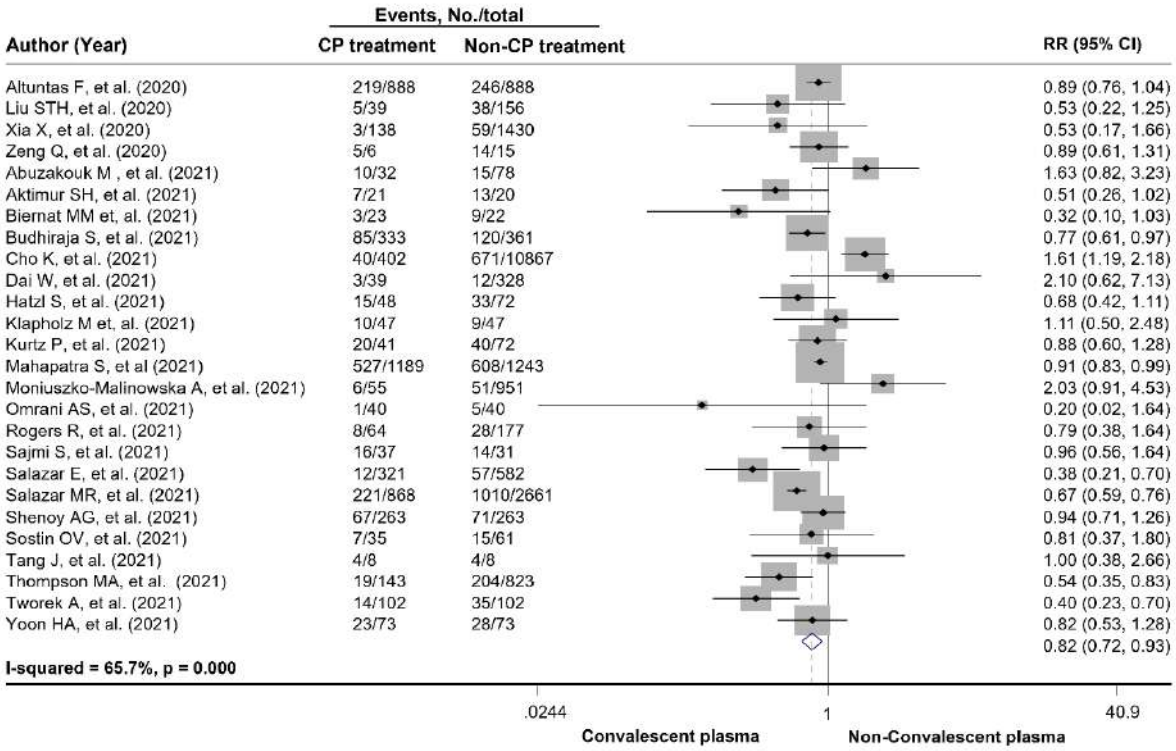

Figure 3. Forest plots showing risk of all-cause mortality in COVID-19 patients comparing using convalescent plasma treatment and non-convalescent plasma treatment among observational studies

Abbreviations: RR=risk ratio; CI=confidence interval; CP=convalescent plasma

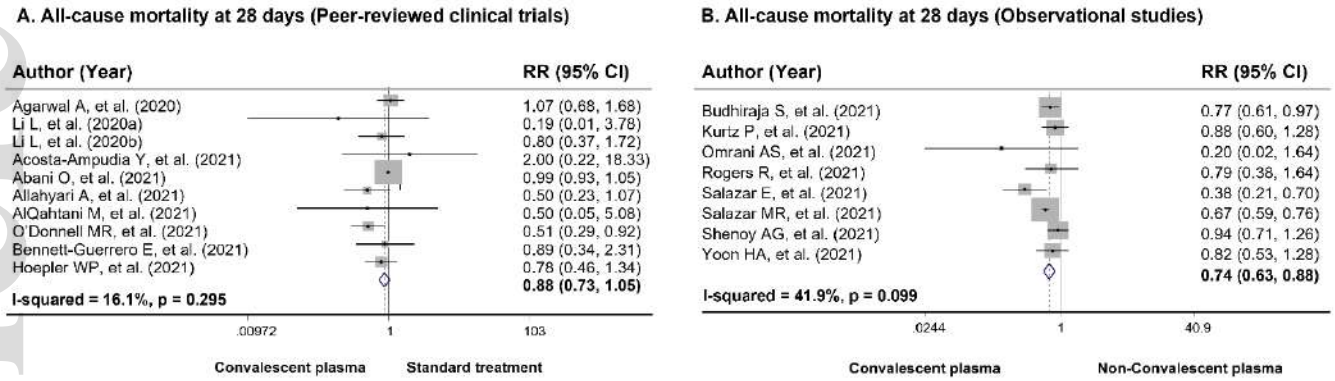

Figure 4. Forest plots showing risk of all-cause mortality at 28 days in COVID-19 patients comparing using convalescent plasma treatment and standard treatment/non-convalescent plasma (A) results from peer-reviewed clinical trials, (B) results from observational studies

Abbreviations: RR=risk ratio; CI=confidence interval