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CONVALESCENT plasma for COVID-19: A meta-analysis of clinical trials and real-world evidence

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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 ClinicalTrials.gov were searched from December 2019 to 16 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-reviewed 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 with standard treatment use (pooled risk ratio [RR] = 0.69, 95% confidence interval [CI]: 0.56-0.86, $P = .001$, $I^2 = 50.1\%$). 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, $P = .001$, $I^2 = 0.0\%$; pooled RR = 0.67, 95% CI: 0.49-0.92, $P = .013$, $I^2 = 0.0\%$; and pooled RR = 0.62, 95% CI: 0.48-0.80, $P < .001$, $I^2 = 20.3\%$, respectively. The meta-analysis of observational studies showed the similar results to the clinical trials.

Conclusions: Convalescent plasma 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

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

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1 | 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 4 August 2021, there have been 199,466,211 confirmed 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.

Convalescent plasma 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 results in the reduction in the ability of the SARS-CoV-ACE2 to enter the host cells. Additionally, the antibody is long-lasting 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-titre 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.

2 | MATERIALS 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]

2.1 | Data sources and search strategy

We searched the Cochrane Library, PubMed, EMBASE and ClinicalTrials.gov from December 2019 to 16 July 2021. The search terms included the following: COVID-19, SARS-CoV-2 and convalescent plasma. The full search strategies for each database are available in Tables S1-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.

2.2 | Study selection and eligibility criteria

We included clinical trials and observational studies that investigated the efficacy of CP treatment comparing to placebo/usual care/standard treatment in patients with COVID-19 regardless of severity, level of antibody titre and healthcare settings. We included studies with a specific aim to treat COVID-19 because the passive antibody 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 is 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 (MS and JS) 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 (MS and JS) if they met the criteria for inclusion. Disagreement between investigators was resolved by consensus, if consensus could not be obtained, by consulting a third reviewer (CK or PM) who made the final decision.

2.3 | 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 PM. 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 titre, sample size, study sample characteristics, CP dose/volume and type of control. Mild, moderate, severe and critical diseases 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: (a) sequence generation; (b) allocation concealment; (c) blinding of participants, personnel and outcome assessors; (d) incomplete outcome data; (e) selective outcome reporting; and (f) 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 the following: 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 (CK or PM), who made the final decision.

2.4 | Statistical analysis

We analysed 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 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 $P < .10$.[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: (a) COVID-19 severity, (b) geographical region, (c) blinding (opened-label vs. blinded) and (d) 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-analysed 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-analysed 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 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 $P < .05$. All analyses were conducted using STATA, v14.1 (StataCorp, Stata Statistical Software. College Station, TX: StataCorp LP; 2015).

3 | RESULTS

3.1 | Search results and study characteristics

A total of 4728 records were identified from databases, websites and citation searching. There were 47 studies[16-62] 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.[34-59] 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

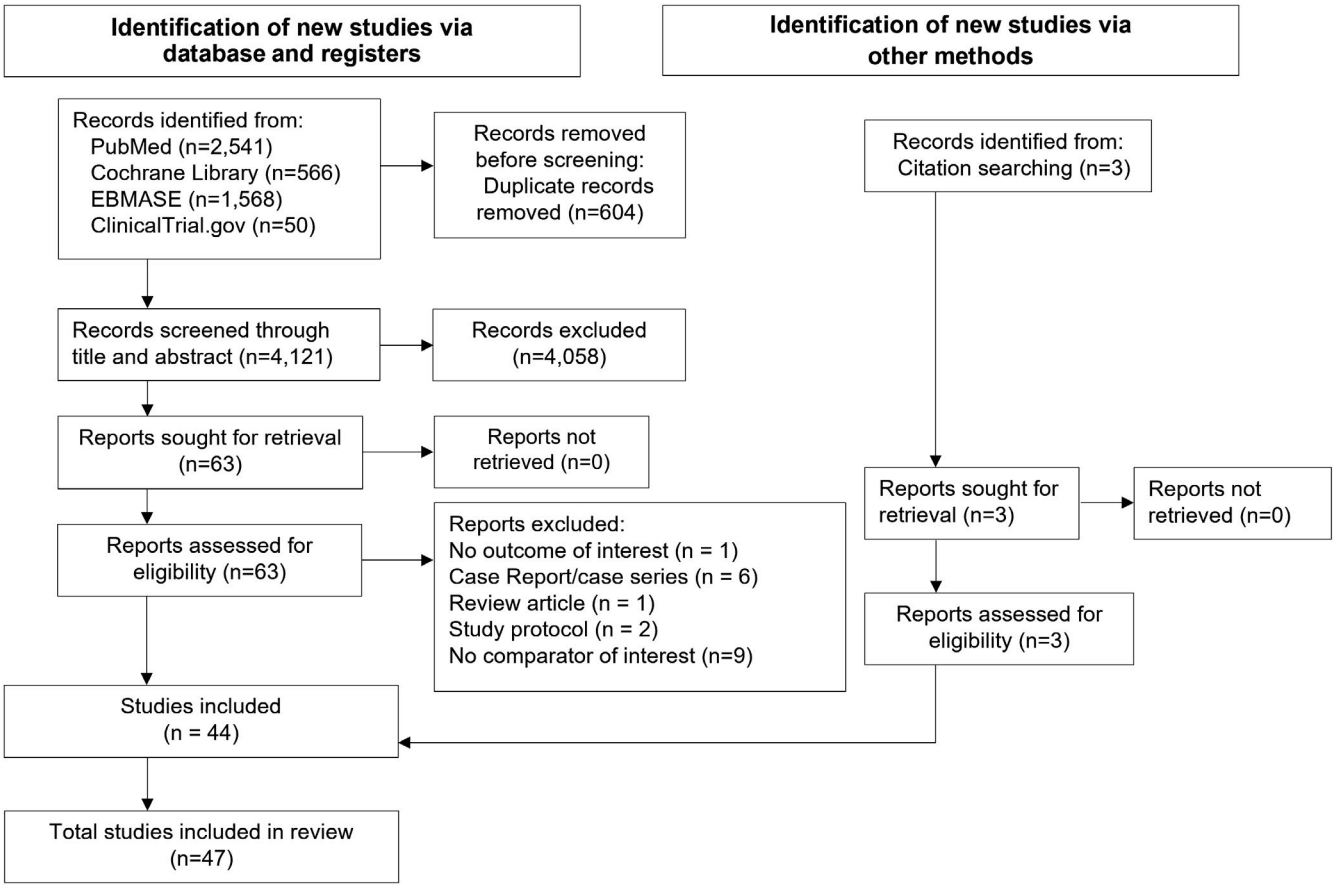

FIGURE 1 PRISMA flow diagram

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, the Netherlands, Spain, Iraq, the UK, the USA, Bahrain, Chile, Italy, Austria and the USA & Brazil. Among 21 included clinical trials, there were 7210 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 (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 (Table S6 and Table S7).

3.2 | Convalescent plasma and mortality

Across 18 peer-reviewed clinical trials, 7118 patients received CP and 7780 patients received standard treatment. Patients treated with CP had a lower mortality rate than those treated with the standard treatment [22.3% (1590/7118) vs. 25.8% (2004/7780)]. In the meta-analysis, CP use had a 31% reduced risk of all-cause mortality compared with standard treatment use (pooled RR = 0.69, 95% CI: 0.56-0.86, $P = .001$, $I^2 = 50.1\%$) (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, $P = .001$, $I^2 = 0.0\%$; pooled RR for critical patients = 0.67, 95% CI: 0.49-0.92, $P = .013$, $I^2 = 0.0\%$; and pooled RR for Asia region = 0.62, 95% CI: 0.48-0.80, $P < .001$, $I^2 = 20.3\%$. When restricted to randomized double-blind studies, the

meta-analysis showed a trend in reduction in all-cause mortality among patients receiving CP treatment when compared with standard treatment (pooled RR = 0.70, 95% CI: 0.48-1.02, $P = .066$, $I^2 = 0.0\%$) (Table 3). Among three preprint clinical trials,[60-62] the pooled RR for all-cause mortality with CP treatment was 0.78 (95% CI: 0.22-2.74, $P = .702$, $I^2 = 38.7\%$). 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 reduced risk of all-cause mortality compared with non-CP use (pooled RR = 0.82, 95% CI: 0.72-0.93, $P = .002$, $I^2 = 65.7\%$) (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, $P = .002$, $I^2 = 5.3\%$ and pooled RR = 0.76, 95% CI: 0.63-0.92, $P = .005$, $I^2 = 55.3\%$, 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, $P = .024$, $I^2 = 24.1\%$ and pooled RR = 0.72, 95% CI: 0.57-0.91, $P = .007$, $I^2 = 43.8\%$, respectively (Table S8). In addition, results from peer-reviewed clinical trials showed a trend towards reduced mortality at day 28 in CP-treated group compared with standard-treated group (pooled RR = 0.88, 95% CI: 0.73-1.05, $P = .150$, $I^2 = 16.1\%$). 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, $P < .001$, $I^2 = 41.9\%$) (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]

3.3 | 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, $P = .208$, $I^2 = 89.2\%$). The results remained the same after adding the preprint studies (WMD = −1.88, 95% CI: −4.22 to 0.46, $P = .116$, $I^2 = 88.0\%$). 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 to 3.60, $P = .190$, $I^2 = 91.9\%$) (Figure S1).

3.4 | 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 the CP group vs control group with respect to clinical improvement at 28 days (odds ratio = 1.42, 95% CI: 0.65-3.09, $P = .37$).[18]

3.5 | 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]

3.6 | 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 (Table S9 and Table S10). In addition, the meta-analysis of 18 peer-reviewed clinical trials and three preprints showed similar results to the primary analysis (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

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

Author (Year)	Country	Settings	Study design		Clinical trial identifier	Severity	Sample size
			Open-label (Y/N)	Randomization (Y/N)			
Peer-reviewed publications (n = 18 studies)							
Abolghasemi et al (2020)[16]	Iran	Hospitals in Iran	Y	N	IRCT20200325046860N1	Severe	189
Agarwal et al (2020)[17]	India	39 tertiary care hospitals	Y	Y	CTRI/2020/04/024775	Moderate	464
Li et al (2020)[18]	China	7 medical centres in Wuhan	Y	Y	ChiCTR2000029757	Severe and life-threatening	103
Rasheed et al (2020)[19]	Iraq	Three hospitals	Y	Y	NR	Critical	49
Abani et al (2021)[20]	UK	177 National Health Service (NHS) hospital organizations	Y	Y	ISRCTN 50 189 673, NCT04381936	Mixed	11 558
Acosta-Ampudia et al. (2021)[21]	Colombia	Clínica del Occidente, Clínica CES, Hospital Universitario Mayor Me'deri	Y	N	NCT04332380 and NCT04332835	Severe	18
Allahyari et al. (2021)[22]	Iran	Imam Reza hospital	Y	N	IRCT20200409047007N1	Critical	64
AlQahtani et al (2021)[23]	Bahrain	Two medical centres	Y	Y	NCT04356534	Severe	40
Alsharidah et al. (2021)[24]	Kuwait	Four major tertiary hospitals in Kuwait	Y	N	NR	Moderate/ Severe	368
Balcells et al (2021)[25]	Chile	A single Chilean medical centre	Y	Y	NCT04375098	Moderate/ severe	58
Gharbharan et al (2021)[28]	the Netherlands	14 secondary and academic hospitals	Y	Y	NCT04342182	Moderate/ severe	86
Libster et al (2021)[30]	Argentina	Clinical sites and geriatric units	N	Y	NCT04479163	Mild	160

Mean age (SD)	Antibody titre	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
CP gr = 54.41 (13.71), control gr = 56.83 (14.98)	NR	NR	One unit of CP (500 mL) within four hours and another unit if not improved after 24 hours	Standard care	CP gr = 41.7%, control gr = 50%	NR
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 hours apart	Standard treatment	CP gr = 25%, control gr = 23%	NR
Median (IQR) CP gr = 70 (62-80), control gr = 69 (63-76)	At least 1:640	NR	CP dose: 4 to 13 mL/kg, transfused 10 mL for the first 15 mins, then increased 100 mL/hr	Standard treatment	CP gr = 48.1%, control gr = 35.3%	NR
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
CP gr = 63.5 (14.7), control gr = 63.4 (14.6)	Neutralizing antibody titre ≥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%, Black/Asian/minority 15%, unknown 8%)
CP gr = 47.89 (9.69), control gr = 53.67 (6.71)	Titre IgG ≥1:3200, Titre 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
CP gr = 58.74 (14.67), control gr = 55.53 (14.10)	NR	NR	One cycle of CP 600 mL. transfused slowly	Standard treatment	CP gr = 43.75%, control gr = 43.75%	NR
CP gr = 52.6 (14.9), control gr = 50.7 (12.5)	NR	NR	CP 400 mL, given as 200 mL over 2 hours over 2 successive days	Standard treatment	CP gr = 15%, control gr = 25%	NR
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 hours apart. and 28 received 1 unit of CP (200-400 mL)	Standard treatment	CP gr = 22.2%, control gr = 15%	NR
Mean (range)CP gr = 64.3 (33-92), control gr = 67.1 (27-91)	Anti-SARS-CoV-2 (S1) IgG titres ≥1:400	≤ 7 days	400 mL. of CP, infused as two 200 mL. units, each separated by 24 hours	Deferred plasma group (received CP only if a pre-specified worsening respiratory function criterion was met)	CP gr = 46.4%, deferred gr = 53.3%	NR
Median (IQR) CP gr = 63 (55-77), control gr = 61 (56-70)	Neutralizing antibody titres of at least 1:80	≤ 96 hours	CP 300 mL	Standard treatment	CP gr = 33%, control gr = 23%	NR
CP gr = 76.4 (8.7), control gr = 77.9 (8.4)	IgG titre greater than 1:1000	≤ 72 hours	CP 250 mL, given over period of 1.5 to 2 hours.	Placebo	CP gr = 68%, control gr = 58%	NR

(Continues)

TABLE 1 (Continued)

Author (Year)	Country	Settings	Study design: Open-label (Y/N)	Study design: Randomization (Y/N)	Clinical trial identifier	Severity	Sample size
O'Donnell et al (2021)[31]	USA and Brazil	Five hospitals in USA and Brazil	N	Y	NCT04359810	Severe	223
AlShehry et al. (2021)[32]	Saudi Arabia	22 hospitals	Y	N	NCT04347681	Critical	164
Simonovich et al (2021)[33]	Argentina	12 clinical sites and coordinated by Hospital Italiano de Buenos Aires	N	Y	NCT04383535	Severe	333
Bennett-Guerrero E et al (2021)[26]	USA	Hospital in New York.	N	Y	NCT04344535	Unspecified	74
Franchini et al (2021)[27]	Italy	the city hospital of Mantua	Y	N	NCT04569188	Moderate/ severe	755
Hoepler et al (2021)[29]	Austria	Hospital setting, single centre	Y	N	The atient had been enrolled in the ACOVACT	Critical	194
Preprints (n = 3 studies)							
Avendaño-Solà et al (2020)[60]	Spain	14 hospitals	Y	Y	NCT04345523	Severe	81
Bajpai et al (2020)[61]	India	The Institute of Liver and Biliary Sciences (ILBS) and in collaboration with the Department of Internal Medicine, Lok Nayak Hospital	Y	Y	NCT04346446	Severe	29
Ray et al (2020)[62]	India	A single centre in Eastern India	Y	Y	CTRI/2020/05/025209	Critical	80

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

of all-cause mortality in COVID-19 patients when compared with non-CP use (pooled RR = 0.60, 95% CI: 0.39-0.93, $P = .024$, $I^2 = 80.6\%$; Figure S3).

3.7 | 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 ($P = .002$) but not for Begg's test ($P = .820$). The visually inspected funnel plots of peer-reviewed clinical trials included are shown in Figure S4. For observational studies, no evidence of small-study effect was found with Begg's ($P = .537$) and Egger's tests ($P = .575$). The funnel plots of observational studies are shown in Figure S5.

4 | 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 with 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 with patients receiving

Mean age (SD)	Antibody titre	Duration of COVID-19 diagnosis until study treatment	CP dose	Type of control	% female	Ethnicity
Median (IQR) CP gr = 60 (48-71), control gr = 63 (49-72)	Titre of ≥1:400	≤ 48 hours	A single unit of CP (200-250 mL) was transfused over 2 hours.	Normal control plasma	CP gr = 36%, control gr = 30%	NR
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
Median (IQR) CP gr = 62.5 (53-72.5), control gr = 62 (49-71)	Median titre 1:3200 (IQR 1:800 to 1:3200)	NR	CP 500mL (IQR; 415- 600 mL)	Placebo and standard treatment	CP gr = 29.4%, control gr = 39%	NR
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 hours.	Standard plasma	CP gr = 39%, control gr = 46.7	NR
Median (IQR) = 87 (82-90)	Titre of 1:160 or greater	NR	1-3 units (300 mL/unit)	Non- convalescent plasma	50%	NR
Median (range)CP gr = 61 (25-86), non-CP gr = 63 (20-87)	>1:100	Median = 8 days	200 mL given over 30 mins	Non-CP	CP gr = 16.4%, non-CP gr = 28.9%	NR
Median age = 59	Neutralizing antibodies titres >1:80	≤12 days	Single unit of CP (250-300 mL)	Standard treatment	45.7%	NR
CP gr = 48.1 (9.1), control gr = 48.3 (10.8)	Median neutralizing antibody titre ≥80, median S1 RBD IgG antibody titre ≥640	NR	CP 500 mL in two divided doses on consecutive days	Standard treatment	CP gr = 21.4%, control gr = 26.7	NR
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

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]

Convalescent plasma, 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 are 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

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

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)
Altuntas et al (2020)[34]	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)
Liu et al (2020)[35]	USA	The Mount Sinai Hospital in New York City	Retrospective cohort	Severe	195	CP gr = 55 (13), not defined control group
Xia et al (2020)[36]	China	Wuhan Huoshenshan Hospital	Retrospective cohort	Severe/ critical	1568	Median (IQR) CP gr = 65 (57-73), non-CP gr = 63 (53-71)
Zeng et al (2020)[37]	China	The First Affiliated Hospital of Zhengzhou University and The Sixth People's Hospital of Zhengzhou City.	Retrospective cohort	Critical	21	Median (IQR) CP gr = 61.5 (31.5-77.8), non-CP gr = 73 (60-79)
Abuzakouk et a. (2021)[38]	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)
Aktimur et al (2021)[39]	Turkey	The haematology department, Ministry of Health University, Samsun Training and Research Hospital, Samsun.	Retrospective cohort	Critical	41	CP gr = 64.90 (19.12) non-CP gr = 66.60 (17.49)
Biernat et al (2021)[40]	Poland	Wroclaw Medical University	Prospective cohort	Mild/ Moderate/ Severe	45	Median (Range) CP gr = 57 (31-72), non-CP gr = 62.5 (20-80)
Budhiraja et al (2021)[41]	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)
Cho et al (2021)[42]	USA	Veterans Affairs medical centre	Prospective cohort study	Mild to moderate (non-severe)	11 269	CP gr = 65.0 (11.3), non-CP gr = 64.1 (12.0)
Dai et al. (2021)[43]	China	Wuhan Huoshenshan Hospital of China	Retrospective cohort	Mild/ severe/ critical	367	Median (range) CP gr = 68 (21-93), non-CP gr = 64 (33-90)
Hatzl et al (2021)[44]	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)
Klapholz et al (2021)[45]	USA	Hospital setting	Retrospective cohort	Severe or critical	94	CP gr = 58.0 (13.0), non-CP gr = 57.7 (13.7)
Kurtz et al (2021)[46]	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)
Mahapatra et al (2021)[47]	India	SCB Medical College & Hospital, Cuttack, Odisha, India	Multi-centric case-controlled observational prospective	Moderate/ severe	2432	NR

% Female	Antibody titre	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
CP gr = 30.6%, non-CP gr = 28.6%	NR	NR	200-600 mL	Non-CP	All-cause mortality, duration of hospital stay	Matching
CP gr = 36%	NR	Median (range) CP gr = 4 (0-7)	250 mL.	Non-CP	All-cause mortality	Propensity score matching and covariate adjustment
CP gr = 44.2%, non-CP = 49.7%	NR	Median (IQR) of symptoms onset to CP therapy) = 45(39-54)	200-1200 mL	Non-CP	All-cause mortality, duration of hospital stay	None
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
CP gr = 9.4%, non-CP = 10.3%	≥1:160	NR	NR	Non-CP	All-cause mortality, duration of hospital stay	Covariate adjustment
CP gr = 38.1%	NR	NR	200 mL, infused over 1 to 2 hours	Non-CP	All-cause mortality, duration of hospital stay	Propensity score matching
CP gr = 39%, non-CP gr (historical) = 36%	Greater than 1:1000	48-72 h after the diagnosis of infection	At least one plasma dose of 200-250 mL	Non-CP	All-cause mortality	None
CP gr = 19.8%, non-CP gr = 27.7%	Neutralizing antibody titres of >1:640	NR	200 mL.	Non-CP	All-cause mortality, all-cause mortality at 28 days	None
CP gr = 8%, control gr = 7%	NR	Within 2 days of eligibility.	NR	Non-CP	All-cause mortality	Covariate adjustment in sensitivity analysis
CP gr = 41.03%, control gr = 45.43%	Antibody titre ≥1:160	NR	100-200 mL per unit	Non-CP	All-cause mortality	Propensity score matching
CP gr = 25%, control gr = 33%	NR	Median 4 (1-10) days	600 mL (400 mL day 1, 200 mL day 2)	Non-CP	All-cause mortality	Propensity score weighting
CP gr = 38.3%, control gr = 38.3%	NR	NR	Approximately 200 mL of ABO-compatible plasma	Non-CP	All-cause mortality	Individual-level matched controls (1:1)
CP gr = 37%, control gr = 40%	titres ≥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 days, duration of hospital stay, clinical improvement within 28 days	Propensity score weighting
CP gr = 16.48	Neutralizing titre more than 1:160	NR	200-250 mL	Non-CP	All-cause mortality	None

(Continues)

TABLE 2 (Continued)

Author (Year)	Country	Settings	Study design	Severity	Sample size	Mean age (SD)
Moniuszko-Malinowska et al. (2021)[48]	Poland	The SARSTer database, in medical centres Poland	Retrospective cohort	Mixed	1006 [patients who received CP during the first seven days (55), remdesivir (236), and other drugs (715)]	CP gr = 59.9 (18.2), remdesivir gr = 58.6 (14.4) and other drug gr = 52.5 (21.5)
Omrani et al (2021)[49]	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)
Rogers et al (2020)[50]	USA	Three hospitals in the Lifespan health system, Rhode Island Hospital and The Miriam Hospital	Retrospective cohort	Severe	241	Median (IQR) CP gr = 61(47-70), non-CP gr = 61 (50-75)
Sajmi et al (2021)[51]	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)
Salazar et al (2021)[52]	USA	Eight Houston Methodist hospitals	Retrospective cohort	Severe/ critical	903	Overall age within 60 days; median (IQR) alive = 54(44.0-62.0), deceased = 65(59.0-76.0)
Salazar et al (2021)[53]	Argentina	Hospitals in Buenos Aires Province	Retrospective cohort	Severe/ critical	3,529	CP gr = 56 (13), non-CP gr = 64 (17)
Shenoy et al (2021)[54]	USA	Hospitals in a single academic health system	Retrospective cohort	Severe/ critical	526	CP gr = 55.93 (14.01), non-CP gr = 56.10 (14.0)
Sostin et al. (2021)[55]	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)
Tang et al (2021)[56]	USA	Washington Adventist Medical HealthCare, Maryland	Case-control	Critical	16	58.9 (10.2)
Thompson et al (2021)[57]	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)
Tworek et al (2021)[58]	Poland	The Central Clinical Hospital of the Ministry of Internal Affairs in Warsaw	Prospective cohort	Severe	204 (Propensity score-matched)	CP gr = 63.04 (15.48), non-CP gr = 62.74 (20.55)
Yoon et al (2021)[59]	USA	Mayo Clinic	Retrospective cohort	Severe/ critical	146	Median (IQR) CP gr = 67(55 −75), non-CP gr = 66 (56-77)

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

% Female	Antibody titre	Duration of COVID-19 diagnosis/symptoms until study treatment	CP dose	Type of control	Outcomes for analysis	Method to account for confounders
CP gr = 36.4% and non-CP gr (remdesivir and other drugs) = 45%	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 days	None
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 days, clinical improvement at 28 days, discharge rate at 28 days	Variable adjustment
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 days, duration of hospital stay, discharge rate at 28 days	Matching, covariate adjustment
CP gr = 19.2%, non-CP gr = 25.8%	NR	NR	200 mL. transfused over 4 hours	Non-CP	All-cause mortality, duration of hospital stay	None
Overall age within 60 days; alive = 44.6%, deceased = 35.9%	Anti-RBD IgG titre of ≥1:1350	NR	300 mL.	Non-CP	All-cause mortality, duration of hospital stay, clinical improvement at 28 days	Propensity score matching
CP gr = 30.9%, non-CP gr = 41.9%	≥1:400	NR	NR	Non-CP	All-cause mortality 28 days	None
CP gr = 36.5%, non-CP gr = 36.5%	NA	NR	200-500 mL, transfused one to two units	Non-CP	All-cause mortality, all-cause mortality at 28 days, duration of hospital stay	Matching
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
0%	NR	Median (IQR) = 16 (9.5-22.25)	NR	Non-CP	All-cause mortality	None
CP gr = 42.7%, non-CP gr = 44.5%	NR	NR	NR	Non-CP	All-cause mortality	Propensity score matching
CP gr = 44.1%, non-CP gr = 39.2%	NR	Median (range) CP gr = 20.0 (0.0-63.0), non-CP gr = 13.0 (0.0-59.0)	1-3 units (200 mL each)	Non-CP	All-cause mortality, duration of hospital stay	Propensity score matching and adjusted model
CP gr = 43.8%, non-CP gr = 35.6%	Titre≥1:2430	72 hours of admission	1 unit (200 mL.)	Non-CP	All-cause mortality, all-cause mortality at 28 days, clinical improvement at 28 days	Propensity score matching

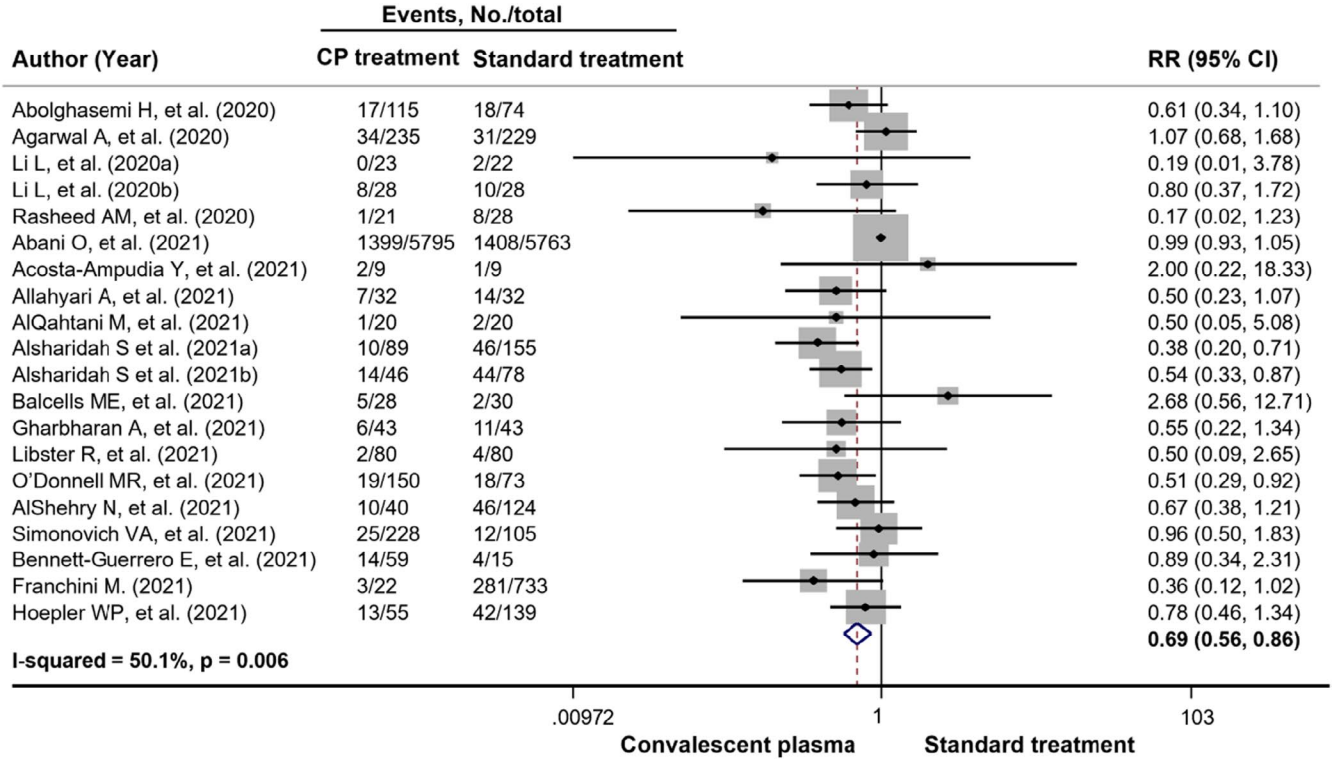

FIGURE 2 Forest plots showing risk of all-cause mortality in COVID-19 patients comparing using convalescent plasma treatment and standard treatment among peer-reviewed clinical trials. CI, confidence interval; RR, risk ratio

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		
				χ^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 (0.93-1.05)	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: CI, confidence interval; NA, not applicable; RR, risk ratio.

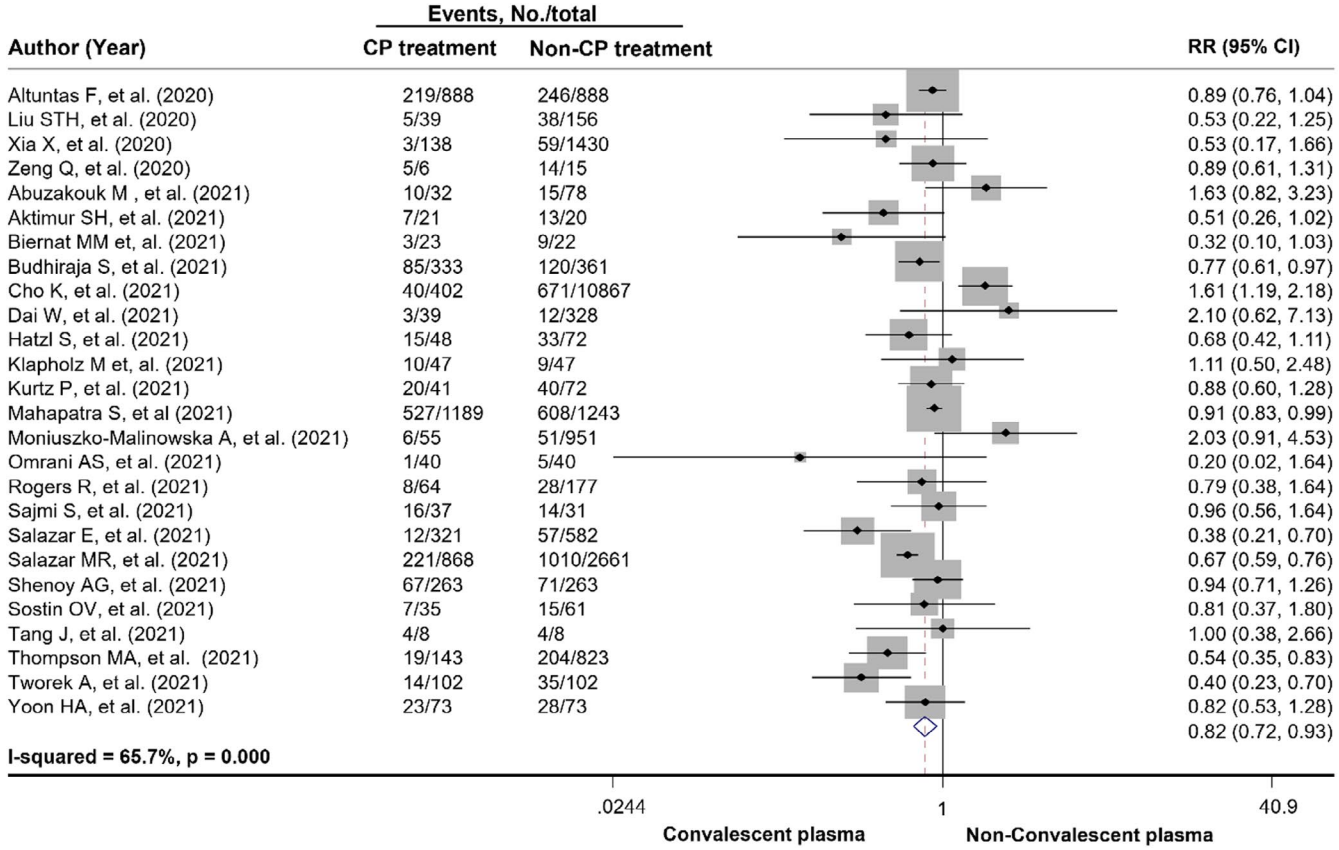

FIGURE 3 Forest plots showing risk of all-cause mortality in COVID-19 patients comparing using convalescent plasma treatment and non-convalescent plasma treatment among observational studies. CI, confidence interval; CP, convalescent plasma; RR, risk ratio

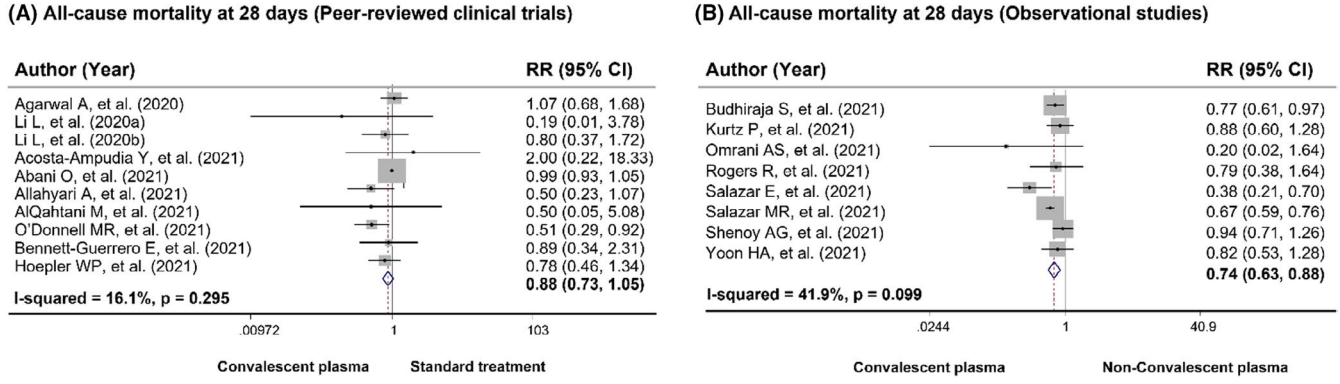

FIGURE 4 Forest plots showing risk of all-cause mortality at 28 days in COVID-19 patients comparing using convalescent plasma treatment and standard treatment/non-convalescent plasma (A) results from peer-reviewed clinical trials, (B) results from observational studies. CI, confidence interval; RR, risk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

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 titre, 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 in 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 titre of neutralizing antibodies. FDA recommended the use of 'high-titre' convalescent plasma, as defined by a neutralizing antibody titre of ≥250 in the Broad Institute's neutralizing antibody assay or an S/C cut-off 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 enrolment, for example, transplant recipients[66] and autoimmune disease 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.

5 | CONCLUSIONS

CP treatment was significantly associated with a decreased risk of all-cause mortality in severe or critical COVID-19 patients compared with 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.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

CK and PM conceptualized the study; CK, MS, JS and PM contributed to methodology; PM involved in formal analysis; CK, MS, JS and PM wrote—original draft preparation; CK, PC and PM wrote—review and editing; CK and PM supervised the study. 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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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