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The efficacy and safety of convalescent plasma for COVID-19 patients: a meta-analysis based on double-blinded parallel-arm randomized placebo-controlled trials

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Abstract

Background Convalescent plasma (CP) showed promising benefits in previous coronavirus pandemics regarding efficacy and safety. However, the efficacy of CP from COVID-19 patients remains controversial and uncertain based on current randomized controlled trials (RCTs). There is an urgent need to establish the efficacy and safety of CP for COVID-19 patients as soon as possible.

Objective To verify the efficacy and safety of CP using high-quality, double-blinded, parallel-arm, placebo-controlled randomized clinical trials, and to provide evidence-based support for the clinical application of CP against COVID-19.

Methods Electronic databases such as Embase, PubMed, and Web of Science were searched from inception to October 18, 2024. This meta-analysis synthesized dichotomous outcomes, including 28-day mortality, hospitalization rates, invasive mechanical ventilation, adverse events (AEs), and serious AEs, using an intention-to-treat (ITT) analysis. Statistical analysis was performed using Review Manager (RevMan) 5.4.1, the Mantel-Haenszel (M-H) statistical method, and a random effects (RE) analysis model. Risk ratios (RRs) and their 95% confidence intervals (CIs) were used as effect measures. Two reviewers independently searched, screened, and included eligible clinical trials, extracted relevant data, and assessed risks of bias (ROB) using the Cochrane ROB tool 1.0 and RevMan 5.4.1. The RRs and 95% CIs in this meta-analysis were computed as dichotomous outcomes. Statistical heterogeneity, subgroup analysis, and sensitivity analysis were conducted to explore heterogeneities and their causes. The quality of evidence was evaluated, and recommendations for clinical practice were based on the GRADE approach. The prospective meta-analysis protocol was registered on PROSPERO.

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Results A total of 996 references were identified through database and manual searches. Nine eligible double-blinded, parallel-arm, placebo-controlled randomized clinical trials, involving 1898 subjects in the intervention group and 1696 in the control group, were included in the meta-analysis. Seven, four, three, three, and three trials were judged as low ROB for mortality, hospitalization rates, invasive mechanical ventilation, AEs, and serious AEs, respectively. The remaining trials were deemed high-risk for their respective outcomes. The meta-analysis on hospitalization rates was abandoned due to high heterogeneity (I^2=92%) among the included trials. The RRs, 95% CIs, and P-values were as follows: 0.78 [0.62, 0.97], $P=0.03$ for mortality; 0.84 [0.50, 1.42], $P=0.51$ for invasive mechanical ventilation; 1.01 [0.78, 1.32], $P=0.92$ for AEs; and 0.96 [0.73, 1.28], $P=0.80$ for serious AEs, all with low or medium levels of heterogeneity. These results suggest that CP infusion in COVID-19 patients reduced mortality by 22% and exhibited excellent safety without reducing the incidence of invasive mechanical ventilation. Sensitivity analysis on mortality, using the combined effect measure (RR 0.83 [0.66, 1.06], I^2=0%, $Z=1.46$, $P=0.14$) after excluding the study by O'Donnell, showed no significant difference between the intervention and control groups, implying that the excluded study might have a stronger effect in reducing mortality. Subgroup analysis based on age indicated that CP therapy in COVID-19 patients aged ≤ 60 years reduced mortality by 36%. Sensitivity and subgroup analyses for other outcomes demonstrated robust pooled results. The PROSPERO registration code is CRD42022324324.

Conclusions Administration of CP to COVID-19 patients, especially those aged ≤ 60 years, may reduce mortality with excellent safety without more AEs, and serious AEs, but does not reduce the incidence of invasive mechanical ventilation.

Keywords COVID-19, Convalescent plasma (CP), Adverse events, Meta-analysis

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is one of seven known human-infecting coronaviruses. It was first identified in Hubei province, China, in December 2019 and caused a broad spectrum of clinical presentations, ranging from asymptomatic infection to critical illness, life-threatening conditions, and death. COVID-19, induced by multiple variants, has now spread globally, triggering a human crisis and threatening public health and socioeconomic stability [1]. The typical clinical features of COVID-19 fall into three main categories: symptoms like fever, dry cough, dyspnea, fatigue, myalgia, anosmia, and ageusia; imaging findings such as ground-glass opacity in the posterior and peripheral areas of the bilateral lungs on computed tomography; and laboratory parameters, including lymphopenia, elevated inflammatory biomarkers, and increased D-dimer levels [2, 3].

Convalescent plasma (CP) therapy uses blood from individuals who have recovered from an illness to help others recover. Although the mechanisms by which CP acts against COVID-19 are not yet fully understood, potential therapeutic mechanisms may involve one or more of the following: neutralizing antibodies in CP, which target the SARS-CoV-2 spike protein, potentially inhibiting the virus's attachment to angiotensin-converting enzyme 2 receptors on host cells [4] and blocking viral entry; immunomodulatory mechanisms such as interference with complement activation, antibody-dependent cytotoxicity, and phagocytosis, which may mitigate the inflammatory cascade triggered by the virus [5]; and the IgG anti-A isoagglutinin found in individuals with type O blood, which may prevent SARS-CoV-2 from binding to its receptor and entering target cells [6].

CP infusion showed promising clinical outcomes in previous coronavirus pandemics [7–10], early observational studies [11, 12], randomized controlled trials (RCTs) [13–15], and meta-analyses [16, 17]. However, recent RCTs [3, 18] have not demonstrated favorable clinical efficacy. To date, there is no definitive specific therapy for COVID-19, and promising therapeutic attempts, including CP, are still being explored [3]. While CP from individuals infected by SARS-CoV [10] and the influenza virus [9] has shown conclusive efficacy for decades, the efficacy of CP from COVID-19 patients remains controversial and uncertain, with differing results regarding mortality—some studies report favorable efficacy [11–15], while others do not [3, 18].

Based on whether the intravenous infusion of CP with high titers of neutralizing antibodies would benefit improvement in clinical outcomes in COVID- 19 patients; the primary aim of this meta-analysis is to evaluate the efficacy and safety of CP for COVID-19 patients based on randomized, double-blinded, placebo-controlled, parallel-arm clinical trials and provide evidence-based support for clinical practice.

Methods

This investigator-initiated systematic review and meta-analysis were conducted with a prospective protocol registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/#myprospero) and followed the methods recommended in AMSTAR 2 [19], the PRISMA statement [20], and Cochrane Collaboration guidelines [21].

Inclusion criteria

Eligible papers must meet all the following requirements: (1) published original randomized, double-blinded, placebo-controlled, parallel-arm clinical trials on the efficacy or safety of CP therapy; (2) all participants must be aged 18 years or older, laboratory-confirmed as COVID-19, with or without underlying diseases; (3) CP plus local standard care in the intervention group, and placebo (normal saline (NS) or non-convalescent plasma) plus local standard care, or local standard care alone, in the control group; (4) studies must include at least one of the following outcomes of interest: 28-day mortality, hospitalization, invasive mechanical ventilation, AEs, or serious AEs.

Exclusion criteria

Papers with any of the following will be excluded: non-RCT studies, crossover RCTs, hyperimmune RCTs, trial protocols, single-arm trials, observational trials, case reports or cohort trials, reviews or meta-analyses, position papers, letters, editorials, comments, recommendations, errata, corrections, conference abstracts, animal trials, or papers without full-text availability.

Retrieval, screening, and data extraction

We comprehensively searched medical databases such as PubMed, Embase, and Web of Science using the following search strategy: ((convalescent plasma) AND (((Covid-19) OR (Covid 19)) OR (SARS-CoV-2))) AND ((((trial) OR (trials)) AND ((control) OR (controlled))) AND ((randomized) OR (randomised))). This ensured the retrieval of accurate and complete studies up to October 18, 2024, following the PRISMA flowchart. We included all published original double-blinded, parallel-arm, placebo-controlled randomized clinical trials on the efficacy and safety of CP infusion for COVID-19 patients, limited to English. Two authors (LP and LX) independently performed the retrieval, screening based on inclusion and exclusion criteria, and data extraction. Any disagreements were resolved through mutual negotiation.

Risk of bias assessment

The Cochrane ROB 1.0 tool [22], which assesses seven domains of bias (selection bias due to random sequence generation and allocation concealment, performance bias, detection bias, attrition bias, reporting bias, and other bias), was used to evaluate the risk of bias (ROB) in the included articles. Two authors (LP and TY) independently assessed the ROB using the ROB 1.0 tool and generated a summary using RevMan 5.4.1 software. Any discrepancies were resolved through discussion when necessary.

Sensitivity and subgroup analysis

Sensitivity analysis was performed to confirm the robustness of the conclusions and to investigate the reasons for heterogeneity by successively excluding individual studies. If significant heterogeneity was found (I^2>75%), potential sources of heterogeneity were explored using subgroup or sensitivity analysis based on specific factors.

Statistical analysis

Statistical analysis was performed using RevMan Version 5.4.1, the Mantel-Haenszel (M-H) statistical method, and a random effects (RE) analysis model to synthesize eligible data and calculate the overall effect measure (RR and 95% CI) for each outcome. Heterogeneity was assessed quantitatively using the I^2 statistic (significant at $P<0.10$). Levels of heterogeneity were classified as high (75–100%), medium (50–75%), or low (0–50%). The RE analysis model was applied when I^2 was <75%; otherwise, a narrative review was considered. Cumulative effects for outcomes were presented in forest plots, showing RR and 95% CIs for each included study. Publication bias was assessed visually using funnel plots when sufficient eligible studies were included.

Quality of evidence and recommendation

A recommendation on CP infusion in COVID-19 patients was made following the GRADE guidelines [23], after the quality of evidence was rated as high, moderate, low, or very low according to the relevant criteria [24].

Role of the funding source

There was no financial support for the design, data retrieval, extraction, data synthesis, interpretation of the results, or writing of this meta-analysis. Each author had full access to the data associated with the meta-analysis and made the final decision to publish it.

Results

The systematic review and meta-analysis on the efficacy and safety of CP infusion in COVID-19 patients were registered on PROSPERO under the code CRD42022324324.

A total of 996 articles (266 in PubMed, 515 in Embase and 215 in Web of Science) were obtained through a retrieval search in the relevant medical electronic databases using the search strategy described above. After removing 327 articles for duplication in authors, titles, abstracts, or journals via EndNote or manually, and then 669 articles remained. 616 articles were excluded for not meeting the inclusion criteria or for meeting the exclusion criteria based on title and abstract inspection. Finally, 9 articles were included in the meta-analysis after eliminating 44 articles with specific reasons, i.e. 29 open-label RCTs, 4 articles without primary outcomes, 3 single-blinded RCTs, 3 prophylactic RCTs, 2

trials terminated prematurely, 1 single-arm trial, 2 secondary analysis articles distinguished by reading the full text. In total, 9 studies, with 3594 participants randomized to either the intervention group ($n = 1898$) receiving CP infusion plus local standard care or the control group ($n = 1696$) receiving either NS or non-convalescent plasma plus local standard care or local standard care alone, were included in the quantitative synthesis (meta-analysis). All procedures followed the search and selection flow diagram shown in Fig. 1.

ROB assessment for all included studies

The ROB assessments were performed using RevMan 5.4.1 software and the ROB 1.0 tool for the included clinical trials. RevMan 5.4.1 was used to create ROB summaries for each domain-level evaluation in the included studies. Of the 9 eligible studies, 7 were judged as having low ROB for mortality [2, 15, 18, 25, 26, 28, 29], 3 for invasive mechanical ventilation [2, 26, 29], 4 for hospitalization rates [2, 15, 26, 29], 3 for AEs [15, 25, 26], and 3 for serious AEs [18, 26, 28]. Any study with at least one high-risk domain or ≥ 3 unclear risk domains was identified as high ROB. The overall ROB results for all outcomes are shown in Supplemental Fig. 1 (a-e).

Although the qualitative funnel plot test for publication bias has low power when fewer than 10 studies are included in a meta-analysis or when there are confounding factors among the included trials, the publication bias test for mortality in this meta-analysis, using a visual qualitative funnel plot, shows some asymmetry at the bottom, indicating the possibility that some RCTs with small sample sizes or negative outcomes were not published, as shown in Fig. 2. The publication bias test using a funnel plot for hospitalization, invasive mechanical ventilation, AEs, and serious AEs was discarded due to the small number of available studies.

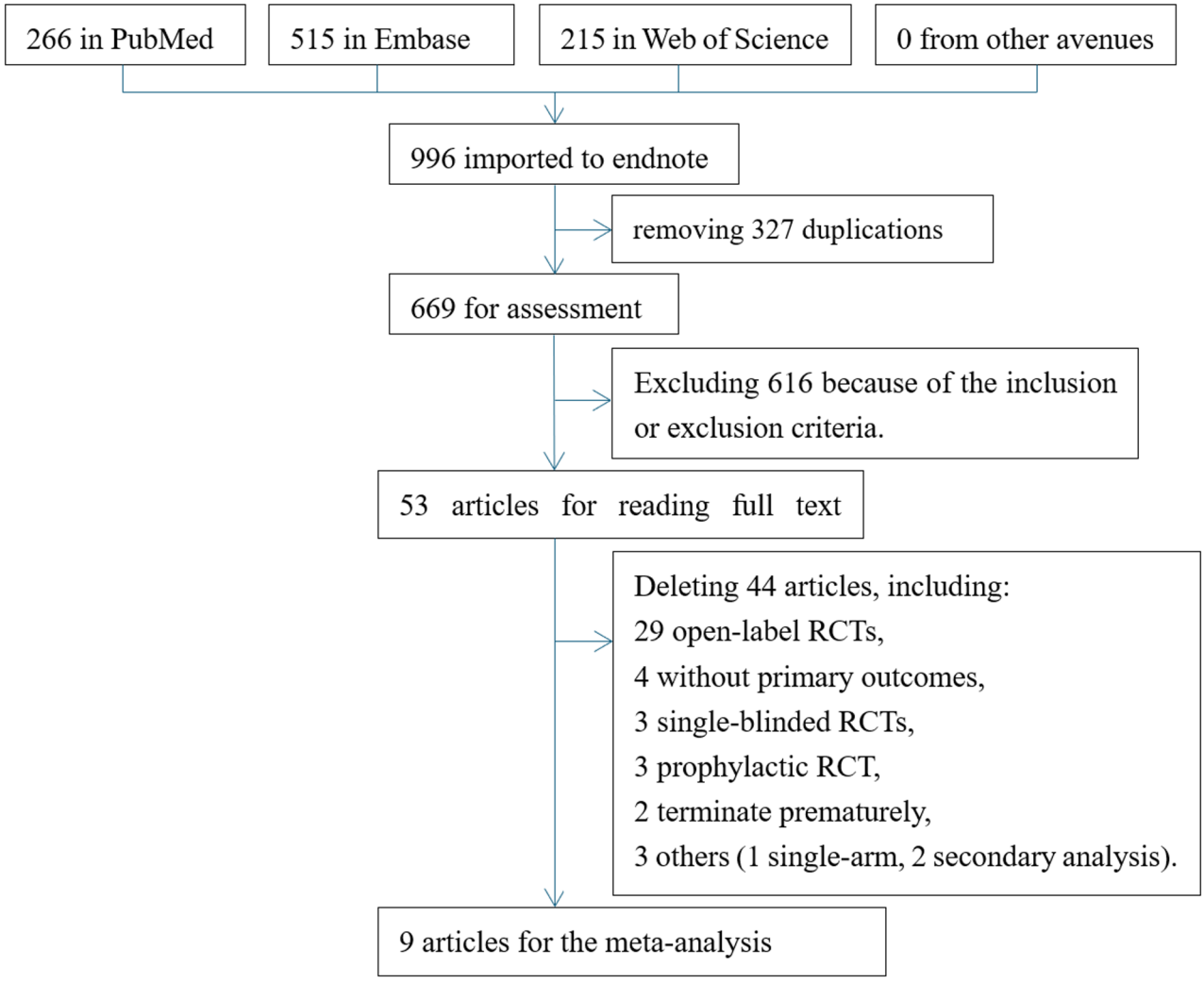

Fig. 1 Study flow diagram of search and selection

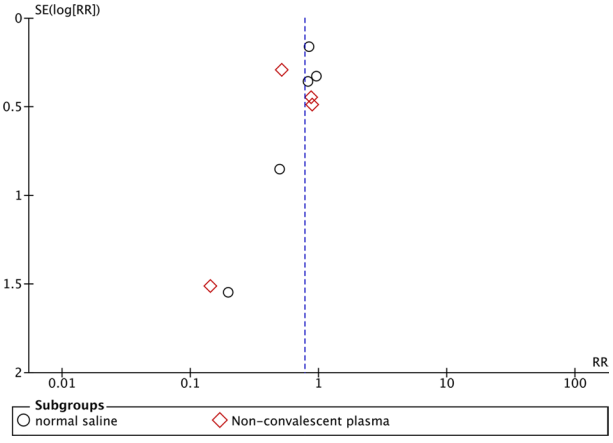

Fig. 2 Funnel plot on 28-day mortality

General characteristics and key information of the included studies

The general characteristics and key information of the 9 eligible studies included in this meta-analysis are presented in Table 1. A total of 9, 5, 4, and 5 studies were included in the quantitative synthesis on the following outcomes: mortality [2, 14, 15, 18, 25–29] (137 deaths from 1898 participants in the intervention group vs. 139 deaths from 1696 participants in the control group), invasive mechanical ventilation [2, 14, 26, 27, 29] (36 cases from 1016 participants in the intervention group vs. 25 from 898 in the control group), AEs [15, 25–27] (254 cases from 1358 participants in the intervention group vs. 175 from 1245 in the control group), and serious AEs [14, 18, 26–28] (127 cases from 552 participants in the intervention group vs. 67 from 340 in the control group). The random effects (RE) analysis model was applied due to the medium or low levels of heterogeneity among the included trials. The hospitalization rate outcome, including 4 studies [2, 15, 26, 29] (169 hospitalized cases from 1106 participants in the intervention group vs. 130 from 989 in the control group), was analyzed narratively due to the high level of heterogeneity among the included studies.

Primary and secondary outcomes

The meta-analysis on hospitalization rates was rejected due to significant heterogeneity (I^2 = 92%, $P < 0.00001$) among the included trials. Heterogeneity tests on 28-day mortality, invasive mechanical ventilation, AEs, and serious AEs, shown in Supplemental Fig. 2 (a-e), revealed homogeneity. The 28-day mortality outcome presented in Supplemental Fig. 2a shows a significant statistical difference between the two groups (RR 0.78 [95% CI 0.62–0.97], I^2 0%, $P = 0.03$), indicating that CP infusion reduced 28-day mortality by approximately 22% in COVID-19 patients. However, the incidences of invasive mechanical ventilation, AEs, and serious AEs did not show statistical

Table 1 General characteristics and key information of included clinical trials

Author and year	T-assess	Severity	Age(int;con)		Nitt(int; con)	Nmitt(int; con)	M/F(int; con)	T-int-symptoms; T-con-symptoms	Pr-PLB ; Pr-CP (ml)	Death toll(int; con)	N in-venti(int; con)	N int; con-hosp	NAE (int; con)	NSAE (int; con)
Alemany2022	Day 28	mild and moderate	Median (IQR)	56 (52–62); 56 (53–63)	188; 188	188; 188	105/83; 98/90	≤7 d	NS 250ml or 5 ml/kg; 250–300ml or 5 ml/kg	0; 2	2; 4	22; 21	NA; NA	NA; NA
Baldeón 2022	Day 28	NA	mean (SD)	56.3 (12.7); 55.0 (13.3)	63; 95	63; 95	42/21; 65/30	NA	Non-convalescent plasma 5 ml/kg; 5 ml/kg	7; 12	NA; NA	NA; NA	NA; NA	0; 0
Bennett-Guerrero 2021	Day 28	moderate to severe	mean (SD):	67 (15.8); 64 (17.4)	59; 15	58; 14	36/23; 8/7	Median (IQR): 9 (6–18)	Standard plasma 480ml; 480ml	14; 4	NA; NA	NA; NA	NA; NA	16; 4
Libster2021	Day 28	mild	mean (SD)	76.4(8.7); 77.9(8.4)	80; 80	76; 78	26/54; 34/46	≤3d	NS 250ml; 250ml	2; 4	2; 4	7; 12	NA; NA	NA; NA
Ortigoza2022	Day 28	noninvasive oxygen supplementation	Median (IQR)	62 (51-72); 64 (54-74)	468; 473	462; 462	284/184; 272/201	Median (IQR): 7(4-9)	NS 250ml; 250ml	59; 71	NA; NA	NA; NA	44; 39	NA; NA
O'Donnell 2021	Day 28	severe and critical	Median (IQR)	60 (48–71); 63 (49–72)	15073	147; 72	96/54; 51/22	Median: 9 d	control plasma 200-250ml; CP 200-250ml	19; 18	12; 4	NA; NA	NA; NA	39; 26
Simonovich 2021	Day 30	severe	Median (IQR)	62.5 (53–72.5); 62 (49–71)	228; 106	228; 105	161/67; 64/41	Median (IQR): 8 (5–10)	NS500; Median (IQR) 500(415-600)	25; 12	19; 10	123; 63	153; 66	54; 19
Sullivan 2021	Day 28	Mild moderate or severe	Median (IQR)	42 (31.5-54); 44 (33-55)	610; 615	592; 589	269/323; 237/352(Mitt)	≤8d	Standard plasma ≥175; ≥175ml	0; 3	NA; NA	17; 37	34; 53	NA; NA
van den Berg 2022	Day 28	moderate to severe	Median (IQR)	54 (46–62); 57 (47–64)	52; 51	47; 50	21/31; 21/30	Median (IQR): 9 (6–11)	NS 200; 200–250ml	11; 13	1; 3	NA; NA	23; 17	18; 18

significance between the intervention and control groups, suggesting that CP infusion in COVID-19 patients is safe without more AEs, and serious AEs but does not reduce the need for invasive mechanical ventilation.

Sensitivity analysis

Sensitivity analyses were performed for all outcomes of interest, with the results presented in Table 2. The significant heterogeneities in the hospitalization rate, shown in Table 2C, may indicate more confounders or baseline imbalances among the included trials, leading to the abandonment of quantitative synthesis for this outcome. After removing the study by O'Donnell, the combined effect measure on mortality (RR 0.83 [0.66, 1.06], I^2=0%, Z = 1.46, P = 0.14) differed from the total effect measure before the study was excluded. This suggests that the removed study may have had a greater impact on reducing mortality or that additional confounders (e.g., severe or critical illness) existed. This marked impact on the overall effect may require further identical clinical trials to verify the result and explore potential confounders. Sensitivity analyses for invasive mechanical ventilation, AEs, and serious AEs, shown in Table 2B, D, and E, demonstrate that the statistical results were not affected after excluding any trial, confirming the robustness of the findings, along with the low to medium levels of heterogeneity among the included trials.

Subgroup analysis

Subgroup analyses were performed based on age (≤ 60 years or > 60 years). The subgroup analysis on mortality, shown in Supplemental Fig. 3a, indicates that CP infusion reduced mortality by 36% compared to the control group in the ≤ 60-year-old subgroup. The incidences of hospitalization and invasive mechanical ventilation remained consistent, regardless of the age group (≤ 60 years or > 60 years), as shown in Supplemental Figs. 3b and c, suggesting that CP infusion did not reduce the rates of hospitalization or invasive mechanical ventilation in either subgroup. CP infusion resulted in similar AEs compared

Table 2 Sensitivity analysis

Deleted article	RR and 95%CI	I^2(%)	Z-value	*P*-value
A: 28-day mortality and overall effect RR (0.78 [0.62, 0.97], I^2 = 0%, Z = 2.22, P = 0.03				
Alemany 2022	0.78 [0.63, 0.98]	0	2.14	0.03
Baldeón 2022	0.77 [0.61, 0.97]	0	2.22	0.03
Bennett-Guerrero 2021	0.77 [0.61, 0.97]	0	2.22	0.03
Libster 2021	0.78 [0.63, 0.98]	0	2.13	0.03
Ortigoza 2022	0.72 [0.53, 0.99]	0	2.05	0.04
O'Donnell 2021	0.83 [0.66, 1.06]	0	1.46	0.14
Simonovich 2021	0.75 [0.59, 0.96]	0	2.32	0.02
Sullivan 2021	0.78 [0.63, 0.98]	0	2.13	0.03
Van den Berg 2022	0.77 [0.61, 0.98]	0	2.16	0.03
B: Invasive mechanical ventilation and effect RR (0.84[0.50, 1.42], I^2 = 0%, Z = 0.65, P = 0.51				
Alemany 2022	0.89 [0.51, 1.54]	0	0.42	0.67
Libster 2021	0.89 [0.51, 1.55]	0	0.42	0.67
O'Donnell 2021	0.71 [0.39, 1.29]	0	1.12	0.26
Simonovich 2021	0.79[0.37, 1.69]	0	0.60	0.55
Van den Berg 2022	0.89[0.52, 1.52]	0	0.44	0.66
C: Hospitalization rate and overall effect RR (1.11 [0.33, 3.67], I^2 = 92%, Z = 0.16, P = 0.87				
Alemany 2022	1.09 [0.17, 6.84]	94	0.09	0.93
Libster 2021	1.32[0.34, 5.18]	94	0.40	0.69
Simonovich 2021	0.67 [0.35, 1.26]	52	1.24	0.22
Sullivan 2021	1.55 [0.24, 5.76]	89	0.66	0.51
D: Any AEs and overall effect RR (1.01 [0.78, 1.32], I^2 = 55%, Z = 0.10, P = 0.92				
Ortigoza 2022	0.98 [0.67, 1.42]	70	0.13	0.90
Simonovich 2021	0.98 [0.64, 1.52]	66	0.08	0.93
Sullivan 2021	1.11 [0.95, 1.29]	0	1.32	0.19
Van den Berg 2022	0.95[0.69, 1.31]	65	0.31	0.76
E: Serious AEs and overall effect RR (0.96 [0.73, 1.28], I^2 = 16%, Z = 0.25, P = 0.80				
Baldeón 2022	0.96 [0.73, 1.28]	16	0.25	0.80
Bennett-Guerrero 2021	0.97 [0.68, 1.38]	44	0.18	0.85
O'Donnell 2021	1.14 [0.82, 1.58]	0	0.78	0.43
Simonovich 2021	0.84 [0.62, 1.13]	0	1.15	0.25
Van den Berg 2022	0.97 [0.64, 1.48]	44	0.13	0.90

with placebo across both age groups. Although CP infusion caused fewer serious AEs in the ≤60-year-old subgroup than in the >60-year-old subgroup (Supplemental Figs. 3d and e), there was no statistically significant difference in the incidence of serious AEs between the intervention and control groups in either age group, demonstrating the remarkable safety of CP infusion.

Quality of evidence and strength of recommendation

From GRADE assessment, both AEs and serious AEs were at high certainty; while invasive mechanical ventilation and mortality were at middle certainty.

The quality of evidence for CP infusion in COVID-19 patients is rated as high. Based on the current data, a strong recommendation is made for CP infusion in COVID-19 patients, particularly for those aged ≤60 years, if necessary.

Discussion

To our knowledge, this meta-analysis is the most comprehensive systematic review and meta-analysis based on double-blinded, parallel-arm, placebo-controlled randomized clinical trials, aimed at assessing the efficacy and safety of CP infusion in COVID-19 patients. Since the late 2019 emergence of SARS-CoV-2, with its high infectivity, global healthcare systems have been severely impacted, and no specific drug targeting COVID-19 has yet been developed. CP, as a passive immunotherapy, has been recommended for use in multiple infectious diseases for over a century. Various studies have shown that CP infusion can significantly reduce mortality caused by infections from the SARS virus [10], MERS-CoV [8], and the influenza virus [9]. However, due to low certainty regarding the beneficial effects of CP in COVID-19 patients, this meta-analysis was conducted to confirm its efficacy and safety for future clinical use.

This meta-analysis identified and summarized data from 9 randomized, double-blinded, parallel-arm, placebo-controlled clinical trials. The results show that CP infusion can significantly reduce mortality. These findings align with previous RCTs [14] and meta-analyses [30, 31]. However, some RCTs [2, 15, 18, 25–29] did not support this conclusion, indicating that although the results remain controversial, the available evidence from this meta-analysis could serve as a basis for CP use in COVID-19 treatment. Secondary mortality caused by SARS-CoV-2 [4] infection may have been reduced by CP infusion, likely due to various mechanisms of action, including inhibiting complement activation, countering cytokine effects, down-regulating B- and T-cell functions, strengthening neutralizing antibodies against the SARS-CoV-2 spike protein, and preventing the virus's attachment to angiotensin-converting enzyme 2 receptors. The specific mechanisms, however, remain unclear and require further clinical trials and research.

Sensitivity analysis on mortality, after excluding O'Donnell's study [14], showed significant differences before and after its removal, suggesting that CP infusion might prevent death in more severe or critical COVID-19 cases. Subgroup analysis based on age (≤ 60 or >60 years) indicated that CP therapy might be more effective for patients aged ≤ 60, hinting that age might be a common confounding factor contributing to heterogeneity. This suggests that CP infusion could be a valuable option for reducing mortality, particularly for COVID-19 patients aged ≤ 60, if other effective therapies are unavailable.

Significant heterogeneity among the included trials, in terms of hospitalization rates, might be attributed to differences in severity, sample size, age, and other factors. As a result, it was not possible to synthesize the data on hospitalization rates, and it remains uncertain whether CP infusion can reduce hospitalization. More homogeneous and high-quality RCTs are needed to verify this.

CP infusion has not been shown to significantly reduce the need for invasive mechanical ventilation, which aligns with the findings of other studies [2, 27, 29]. Sensitivity and subgroup analyses confirmed the robustness of this effect, and CP infusion did not appear to benefit COVID-19 patients in terms of reducing mechanical ventilation use, possibly due to inappropriate timing or dosage of administration.

Based on the limited safety data from this meta-analysis, there were no significant differences in the incidence of general or serious AEs between the intervention and control groups, and most AEs were mild or moderate. Subgroup analysis showed that CP infusion may lead to fewer serious AEs in the ≤60-year-old group compared to the >60-year-old group, although there were no statistically significant differences. This meta-analysis confirms that CP infusion is safe and well-tolerated in COVID-19 patients, particularly those under 60 years old.

The participants in this meta-analysis were adults with or without underlying diseases, and no children or pregnant women were included. Consequently, data on the efficacy and safety of CP infusion in these populations are lacking. However, CP infusion may be considered an optional therapy for children and pregnant women based on the principle of extrapolation, if COVID-19 cannot be controlled by other means.

The risk ratios (RRs) for both AEs (RR = 1.01, 95% CI [0.78, 1.32], $P = 0.92$) and serious AEs (RR = 0.96, 95% CI [0.73, 1.28], $P = 0.80$) were not statistically significant, with their 95% confidence intervals encompassing 1.0. This indicates no increased risk associated with CP infusion compared to the placebo control. Furthermore, the low to medium heterogeneity for these outcomes strengthens the reliability of the pooled results. The

dissociation between these safety profiles and clinical efficacy outcomes, alongside the robustness of the findings in sensitivity and subgroup analyses, collectively supports the inference of a favorable safety profile for CP in treating COVID-19 patients. Based on the meta-analysis results, Convalescent Plasma (CP) is excellent safety.

Strength and limitation

Our ongoing study has several strengths and limitations. The primary strength is that this meta-analysis is based on high-quality randomized, double-blinded, placebo-controlled parallel-arm clinical trials, resulting in fewer biases and higher-quality evidence. Additionally, CP infusion can effectively and reasonably reduce mortality in COVID-19 patients, especially those aged ≤ 60 years. However, the limitations include the small number of eligible clinical trials and the lack of focus on the optimal timing, titers, dosage, and duration of CP administration, which may influence its efficacy and safety. Further high-quality clinical trials are needed to determine the optimal timing, dosage, titer, and duration of CP administration.

Conclusions

CP therapy for COVID-19 patients, particularly those aged less than 60 years, may be more effective in reducing mortality and is considered safe. CP infusion is strongly recommended to reduce mortality in COVID-19 patients, especially those aged ≤ 60 years, based on the high quality of evidence.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-12126-4.

Supplementary Material 1

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Author contributions
LP, YJ and YW designed and alternately reviewed this study and interpreted this data.LP and DR searched, screened, and extracted the related data. LP and YW evaluated ROB. LP wrote the manuscript, interactively revised manuscript with DR and YJ. LP, YW and DR have read and approved the final manuscript to be published.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable, as this meta-analysis is a secondary study.

Consent for publication
All authors had full access to all the data associated with this meta-analysis and made the final decision to publish it. Consent for the publication of identifying images or other personal or clinical details that compromise anonymity: Not applicable.

Competing interests
The authors declare no competing interests.

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