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Review

Benefits of plasma exchange on mortality in patients with COVID-19: a systematic review and meta-analysis [☆]Jinlv Qin ^{1, #}, Guizuo Wang ^{2, #}, Dong Han ^{2, *}¹ Radioimmunoassay Center, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi 710068, China.² Department of Respiratory and Critical Care Medicine, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi 710068, China

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ABSTRACT

Objective: The COVID-19 pandemic continues, and the death toll continues to surge. This systematic review and meta-analysis aimed to determine the efficacy of therapeutic plasma exchange (TPE) on mortality in patients with COVID-19.

Methods: A systematic search was made of PubMed, Embase, Cochrane Library, and clinicaltrials.gov, without language restrictions. Controlled clinical trials on treatment of COVID-19 with TPE, compared with standard of care, were reviewed. Studies were pooled according to risk ratios (RRs) and weighted mean differences, with 95% confidence intervals (CIs).

Results: A total of six trials (enrolling 343 participants) met the inclusion criteria. Therapeutic plasma exchange showed significant effect on mortality (RR 0.41, 95% CI 0.24 to 0.69; $P = 0.0008$).

Conclusion: TPE significantly reduced mortality in hospitalized patients with moderate-to-critical COVID-19. Plasma exchange therapy should be considered for patients with COVID-19.

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Introduction

The COVID-19 pandemic is the worst in more than 100 years, causing numerous infections and deaths worldwide. Despite the use of multiple drugs with different mechanisms, mortality from COVID-19 remains high, especially in critically ill patients with acute respiratory distress syndrome (ARDS), sepsis, and associated cytokine release syndrome (CRS) (Cegolon et al., 2022; Cegolon et al., 2020; Memish et al., 2021). Therapeutic plasma exchange (TPE) is a safe and effective method for treating various diseases by removing pathological substances and replenishing the deficient plasma components (Cegolon et al., 2022; Fernández-Zarzo et al., 2019). Several controlled clinical trials have evaluated the effects of TPE in severely ill patients with COVID-19, with varying results.

Therefore, this study aimed to perform a systematic review and meta-analysis of controlled trials to determine the efficacy of TPE on mortality in patients with COVID-19.

Methods

Data sources and search strategy

This systematic review and meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Moher et al., 2009). The protocol was previously registered in April 2022 in the International Prospective Register of Systematic Reviews database (Review register: CRD42022325020). PubMed, Embase, Cochrane Library, and clinicaltrials.gov were searched for studies up to April 2022.

Study selection

To be eligible for inclusion in the meta-analysis, studies had to meet the following criteria: (a) inclusion of hospitalized patients with COVID-19 aged 18 years or older; (b) polymerase chain reaction positive for SARS-CoV-2; and (c) use of a controlled design to make a comparison of standard of care (SOC) plus TPE with SOC. The search strings used for the databases were ("COVID-19"

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OR “SARS-CoV-2” OR “SARS-CoV-19” OR “novel coronavirus 2019” OR “novel coronavirus pneumonia”) AND (“plasma exchange” OR “therapeutic plasma exchange” OR “plasmapheresis” OR “TPE”). The reference lists of relevant review articles were also screened to identify studies that might have been missed in this search. No language restrictions were applied to our study selection process.

Data extraction and quality assessment

Two reviewers independently screened articles according to the inclusion criteria. The reviewers compared selected studies, and differences were resolved by consensus. Data tables were used to collect all relevant data from texts, tables, and figures of each included trial, including author, year of publication or last update posted, severity of the disease, patient number and age, body mass index, co-morbidities, Acute Physiology and Chronic Health Evaluation II score, Sequential Organ Failure Assessment score, and outcomes such as mortality, length of intensive care unit (ICU) stay, and duration of invasive mechanical ventilation (IMV). Study quality was assessed using the Detsky Quality Assessment Scale (Detsky et al., 1992; Qin et al., 2022; Shang et al., 2022). This is a 20-point scale for studies with statistically significant results and a 21-point scale for studies without statistically significant results.

Data synthesis and statistical analysis

Meta-analyses were conducted where applicable; otherwise, outcomes were presented in narrative form. Data were analyzed using the RevMan Version 5.4.1 (The Cochrane Collaboration). Next, risk ratios (RRs) for discontinuous outcomes and weighted mean differences (WMDs) for continuous outcomes, with corresponding 95% confidence intervals (CIs), were computed for individual trials. Chi-squared and Higgins I^2 tests were used to assess heterogeneity among included trials. If significant heterogeneity ($P \leq 0.10$ for Chi-squared test results or $I^2 \geq 50\%$) was obtained, we used a random-effects model, otherwise, a fixed-effects model was used. A P -value < 0.05 was considered to indicate statistical significance.

To assess the robustness of the results, meta-regression analyses (STATA 12.0) were carried out for sensitivity analysis (Shang et al., 2021) to test the influence of potential effect modifiers such as randomization, sample size, sex, co-morbidities, and Detsky quality score. Begg's rank correlation test (Shang et al., 2022) (STATA 12.0) was used to assess the presence of publication bias in included articles for each outcome.

Results

Study selection and characteristics

Of 1484 trials recognized by the initial search, 58 were retrieved for more detailed assessment, and six trials (Cegolon et al., 2022; Faqih et al., 2021; Gucyetmez et al., 2020; Kamran et al., 2021; Khamis et al., 2020; Novacescu et al., 2022) were included in this meta-analysis (Figure 1). Baseline characteristics of trials included in this meta-analysis are listed in Table 1. A total of 343 patients were included: 173 were assigned to the TPE groups and 170 to the control groups.

Mortality

Data on mortality were available from six controlled trials (343 patients). Compared with the SOC, the mortality was significantly lower in the TPE groups (RR 0.41, 95% CI 0.24 to 0.69; $P = 0.0008$ [Figure 2]), with a rate of 17.92% versus 44.71%. There was significant heterogeneity ($I^2 = 48\%$; $P = 0.09$). Begg's test ($P = 0.091$) did not show evidence of publication bias. Results did not change

significantly after excluding two trials (Gucyetmez et al., 2020; Khamis et al., 2020) with lower quality scores (RR 0.46, 95% CI 0.27 to 0.80; $P = 0.005$).

Length of ICU stay

Data on length of ICU stay were available from three trials (93 patients). The length of ICU stay was significantly shorter in the SOC groups (WMD 7.44 days, 95% CI 4.24 to 10.64 days; $P < 0.00001$ [Figure 3]). There was no significant heterogeneity ($I^2 = 0\%$; $P = 0.84$). Begg's test ($P = 0.602$) did not show evidence of publication bias.

Duration of IMV

Data on the duration of IMV were extracted from three studies (149 patients). There was no statistically significant difference in the duration of IMV between the two groups (WMD 1.14 days, 95% CI -4.36 to 6.64 days; $P = 0.68$ [Figure 4]). There was significant heterogeneity ($I^2 = 66\%$; $P = 0.05$). Begg's test ($P = 0.602$) did not show evidence of publication bias.

Sensitivity analysis

Our results were mostly confirmed when potential effect modifiers were introduced as covariates in the meta-regression analysis. In this analysis, no significant impact was found on either mortality, length of ICU stay, or duration of IMV (Table 2).

Discussion

This meta-analysis is designed specifically to evaluate the efficacy of TPE in hospitalized patients with COVID-19. Based on the present results, we observed that TPE significantly reduced mortality. The length of ICU stay was significantly shorter in the SOC groups, possibly because of the premature death of patients in the SOC groups (Novacescu et al., 2022). In one included trial (Novacescu et al., 2022), seven (36.8%) patients in the SOC group died before day 7, resulting in a significant reduction in ICU stay and IMV duration. Therefore, TPE may avoid premature death in critically ill patients, thereby prolonging ICU stay.

COVID-19 is caused by SARS-CoV-2 and has caused a global pandemic. Although most patients have mild symptoms, mortality remains high in critically ill patients, which may be largely attributable to an overactive immune response rather than the viral infection itself (Beraud et al., 2022). This excessive inflammatory response, commonly referred to as cytokine storm syndrome or CRS, can lead to lung damage, ARDS, multiple organ dysfunction syndrome (MODS), sepsis, and ultimately death (Huang et al., 2020; Ye et al., 2020; Yuki et al., 2020). Healthcare systems in most countries are overwhelmed as the global COVID-19 surge continues. Therefore, there is an urgent need for safe and effective therapeutic approaches to inhibit excessive cytokine release, halt disease progression, and reduce mortality.

Persistent mutations in SARS-CoV-2 may lead to resistance to vaccines and antiviral drugs, leading to treatment failure (Cegolon et al., 2022). Therefore, non-drug treatments such as TPE may be an option for COVID-19. For over a century, TPE has been extensively studied and used to treat a variety of serious illnesses (Fernández-Zarzoso et al., 2019), including ARDS (Cegolon et al., 2022), influenza (Patel et al., 2011), and sepsis-related MODS (Busund et al., 2002; Keith et al., 2020). TPE may interrupt the progression of CRS by removing increased cytokines and inflammatory mediators, thereby reducing fatal complications such as septic shock, pulmonary embolism, renal injury, or disseminated intravascular coagulation (Cegolon et al., 2022; Cegolon et al., 2020). TPE

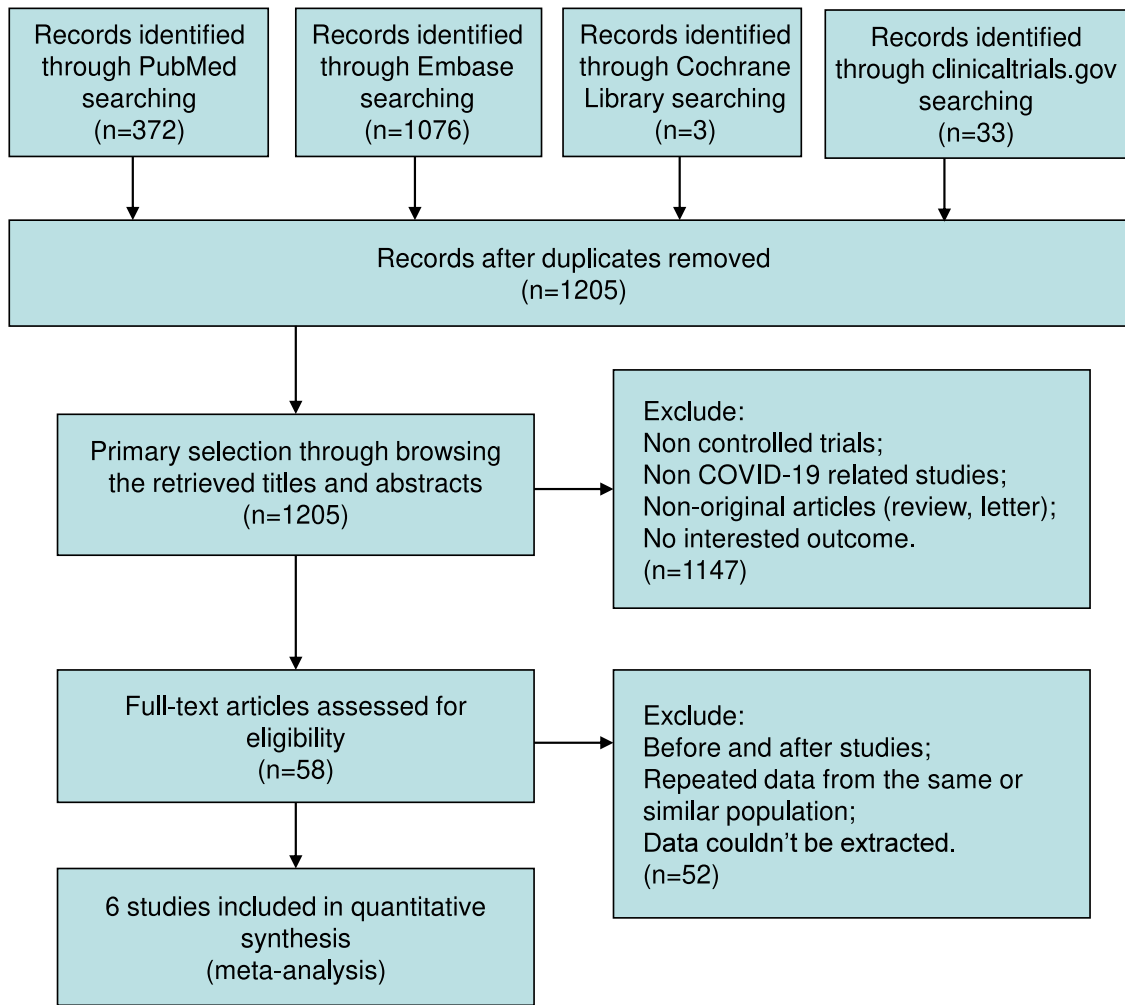


Figure 1. Flow chart for selection of studies.

^aConsider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

^bIf automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: 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. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71.

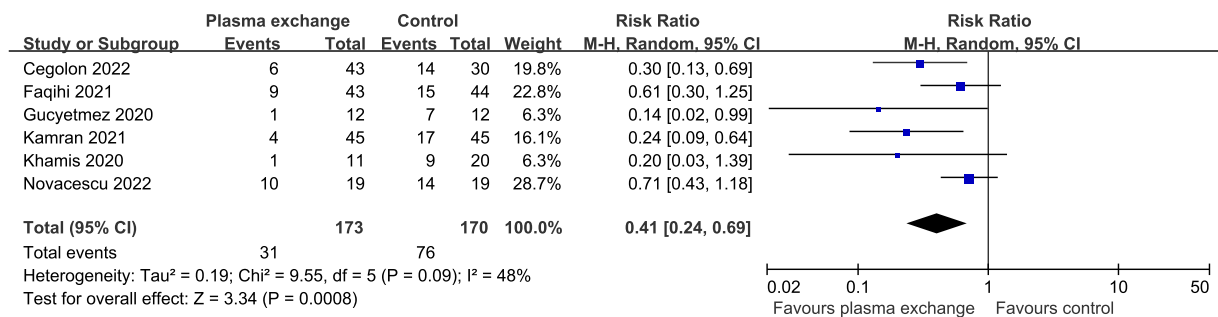


Figure 2. Forest plot assessing the efficacy of therapeutic plasma exchange on mortality.

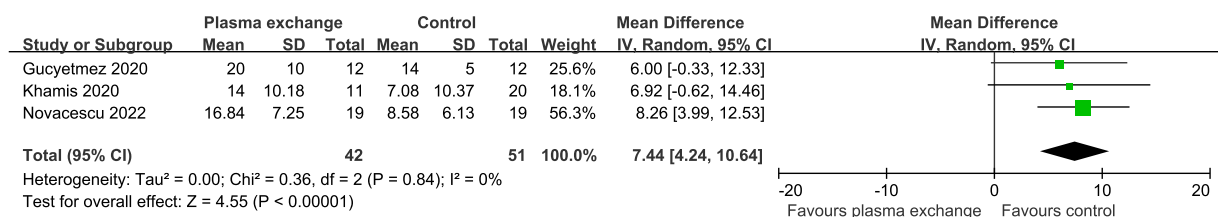


Figure 3. Forest plot assessing the efficacy of therapeutic plasma exchange on length of ICU stay. ICU = intensive care unit.

Table 1
Baseline characteristics of trials included in meta-analysis.

Study	Year	Quality Score	Randomization	WHO classification	Sort of plasma	Hospital location	Admission time	n
Cegolon	2022	14	Non-randomized	Severe	Standard	Tehran, Iran	March 4 to May 20, 2020	43
Faqihi	2021	19	Randomized	Critical	Standard	Riyadh, Saudi Arabia	July 1 to October 1, 2020	43
Gucyetmez	2020	10	Non-randomized	Severe-to-critical	NR	Istanbul, Turkey	March 10 to May 10, 2020	12
Kamran	2021	12	Non-randomized	Moderate-to-critical	Standard	Rawalpindi, Pakistan	April 1 to July 31, 2020	45
Khamis	2020	10	Non-randomized	Severe-to-critical	Standard	Muscat, Oman	April 17 to May 11, 2020	11
Novacescu	2022	12	Non-randomized	Severe-to-critical	Standard ^a	Timisoara, Romania	August 8, 2020 to January 9, 2021	19
Age, years (SD)	Male, %	BMI, kg/m² (SD)	Co-morbidities, %	Diabetes, %	Hyper-tension, %	APACHE II score (SD)	SOFA score (SD)	
NR	67	NR	42	26	37	NR	NR	
NR	40	NR	53	43	50	NR	NR	
48 (33–63) ^b	83.7	27 (22–32) ^b	51.2	46	86	23 (21–25) ^b	10 (8–13) ^b	
49 (33–63) ^b	81.8	26 (20–33) ^b	43.2	42	84	22 (21–23) ^b	9 (6–12) ^b	
61 (14)	67	28.5 (6.1)	NR	NR	NR	17 (3.3)	6 (2)	
64 (17)	67	25.0 (6.6)	NR	NR	NR	17.5 (5.6)	6 (2)	
60 (32–73) ^b	100	NR	53.3	24	20	NR	NR	
60 (37–75) ^b	100	NR	53.3	24	20	NR	NR	
50 (10)	100	NR	NR	73	55	NR	6 (3–9) ^b	
51 (17)	85	NR	NR	35	30	NR	3 (2–6) ^b	
58.7 (7.8)	68.4	29.8 (5.0)	95	NR	NR	5.7 (3.2)	NR	
62 (12)	57.9	27.2 (6.9)	89	NR	NR	7.6 (6.5)	NR	

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body mass index; NR = not reported; SD = standard deviation; SOFA = Sequential Organ Function Assessment; WHO = World Health Organization.

^a Followed by 500ml convalescent plasma transfusion

^b Values are median and interquartile range.

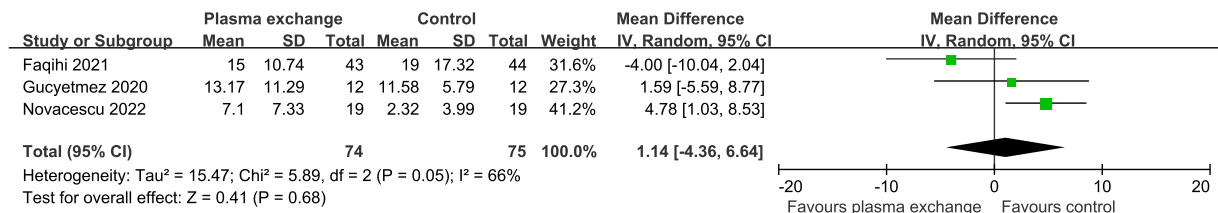


Figure 4. Forest plot assessing the efficacy of therapeutic plasma exchange on duration of invasive mechanical ventilation.

Table 2
Potential effect modifier with change in tau² and statistical significance for each outcome.

	Change in tau ²	P-value
Mortality		
Randomization	-0.81	0.461
Detsky quality score	0.91	0.415
Sample size	-0.04	0.973
Men	-0.54	0.618
Co-morbidities	1.11	0.384
Length of intensive care unit stay		
Detsky quality score	1.14	0.459
Sample size	0.93	0.524
Men	-0.88	0.541
Duration of invasive mechanical ventilation		
Randomization	1.80	0.323
Detsky quality score	-1.08	0.477
Sample size	-1.08	0.477
Men	-2.59	0.234

is effective and safe without developing drug resistance; therefore, it may play an important role in the treatment of COVID-19, especially in critically ill patients. Future large randomized controlled trials are needed to explore the specific regimen and efficacy of TPE and to determine how TPE affects the clinical course of COVID-19 and its mechanisms.

This study met most of the methodological criteria recommended for systematic reviews and meta-analyses (Liberati et al., 2009). However, some limitations need to be considered when interpreting the results of this study. First, some included trials had small sample sizes, which may have reduced the power of the results. Second, most included trials were non-randomized. Finally, this meta-analysis was not patient-level, so the results should be considered provisional.

Conclusions

The addition of TPE significantly reduced mortality in hospitalized patients with moderate-to-critical COVID-19. Plasma exchange therapy should be considered for COVID-19, especially in critically ill patients.

Conflict of interest

The authors have no competing interests to declare.

Funding

None.

Data availability statement

Extracted data are available on request to the corresponding author.

Ethical approval

Not applicable.

Contributors

All authors, led by DH, were involved in the concept and protocol design of the meta-analysis. JQ and GW screened the titles and abstracts and extracted data from the articles. JQ was primarily responsible for statistical analyses. DH was primarily involved in the interpretation of the quality data. All authors contributed to interpreting the results. GW and DH accessed and verified the data. All authors contributed to the writing of the article and approved its submission. DH was responsible for the decision to submit the article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2022.06.014](https://doi.org/10.1016/j.ijid.2022.06.014).

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