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REVIEW

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Systematic review and meta-analysis of randomised controlled trials testing the safety and efficacy of convalescent plasma in the treatment of coronavirus disease 2019 (COVID-19): Evidence-base for practise and implications for research

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Abstract

Background: Despite scientific advances, there is no effective medical therapy for coronavirus disease 2019 (COVID-19). This systematic review and meta-analysis aimed to evaluate the safety and efficacy of convalescent plasma therapy in COVID-19.

Methods: This review was carried out in accordance with Cochrane methodology including risk of bias assessment and grading of the quality of evidence. Only prospective clinical trials randomly assigning COVID-19 patients to convalescent plasma plus standard of care therapy (test arm) versus placebo/standard of care (control arm) were included. Two reviewers independently read each preprint/publication and extracted relevant data from individual studies. Data were pooled using the random-effects model and expressed as risk ratio (RR) with 95% confidence interval (CI).

Results: A total of 13 206 patients from 12 randomised controlled trials were included. There was no significant difference in clinical improvement rate (RR = 1.00, 95% CI: 0.98–1.02, $p = 0.96$) or time to clinical improvement (median difference of 1.08 days with 95% CI ranging from −0.15 to +2.30 days) between convalescent plasma versus placebo/standard of care therapy. The use of convalescent plasma was not associated with significantly reduced risk of death (RR = 0.81, 95% CI: 0.65–1.02, $p = 0.08$). Reassuringly, overall incidence of infusion-related serious adverse events was low (3.25%) and not significantly different (RR = 1.14, 95% CI: 0.93–1.40, $p = 0.22$) for convalescent plasma transfusion compared to placebo/standard of care therapy.

Conclusions: There is low to moderate certainty evidence that the addition of convalescent plasma to current standard of care therapy is generally safe but, does not result in any significant clinical benefit or reduction of mortality in COVID-19.

KEYWORDS
antibody, convalescent, coronavirus, plasma, randomised, therapeutics

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has engulfed over 200 countries since being declared a pandemic[1] by the World Health Organisation (WHO) and continues to grow exponentially in several parts of the world with over 140 million confirmed cases and 3 million deaths globally[2] by the time of this report. Over 150 medical and pharmacological therapies are currently being investigated in >1000 randomised controlled trials (RCTs) across the world with an

aim to generate high-quality evidence to inform and guide clinical practise during the ongoing pandemic.[3] However, even a year and half after it was initially described, COVID-19 is still largely managed empirically worldwide with few effective or proven therapies. Dexamethasone was the first drug to demonstrate significant reduction in mortality in COVID-19 patients requiring ventilatory support or supplemental oxygen.[4] Recently, remdesivir become the first drug to receive United States (US) Food and Drug Administration (FDA) approval for the treatment of hospitalised COVID-19 patients based on significant reduction in the duration of hospitalisation[5] for COVID-19 patients of varying disease severity. Amongst various other promising therapies, convalescent plasma[6,7] enriched in human antibodies against COVID-19 from recovered patients and humanised monoclonal antibodies[8] have received emergency use authorization (EUA) from US FDA till date.

The use of convalescent blood products (whole blood, plasma, serum, and isolates such as immunoglobulins and antibodies) collected from recovered patients to confer passive immunity in the recipients is not entirely new and has strong scientific rationale and historical precedence.[9,10] Convalescent plasma therapy is a passive antibody therapy that involves the transfusion of plasma rich in antibodies against a given pathogen to a susceptible individual for the purpose of preventing or treating an infectious disease. Efficacy of such therapy largely correlates with titres of anti-SARS-CoV-2 specific neutralising antibodies present in convalescent plasma.[7,10,11] In addition to the neutralising antibodies, other components in donor plasma such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, and pentraxins may also provide further benefit through their immunomodulatory effects and amelioration of systemic inflammatory response. [11] Convalescent plasma with neutralising antibodies has previously demonstrated clinical efficacy[9,10] against other virus-borne illnesses such as Ebola, human influenza A (H1N1), SARS, and Middle East respiratory syndrome (MERS). Over 50 RCTs are currently underway testing convalescent plasma against the present standard of care therapy in COVID-19 disease. However, many of these trials have limitation of numbers (small sample size) which would be inadequate to detect clinically meaningful and/or statistically significant differences, if any. Timely provision of COVID-19 convalescent plasma in resource-constrained settings poses significant logistic difficulties, challenges, and impediments in clinical trial accrual.[12,13] In addition, the unexpected presence of neutralising immunoglobulin G (IgG) antibodies against SARS-CoV-2 in recipients can even result in premature termination of the study, affecting statistical power and rigour. Given the context, a structured systematic review with appropriate statistical pooling of data in a direct comparison meta-analysis of all RCTs evaluating the safety and efficacy of convalescent plasma therapy in COVID-19 was necessary to create an evidence-base and facilitate rapid translation of research findings into clinical practise to inform and guide therapeutic decision-making globally.

2 | MATERIALS AND METHODS

This systematic review was carried out in accordance with Cochrane methodology for systematic reviews of interventional studies.[14] The analysis, interpretation, and reporting included a risk of bias assessment using the Cochrane Risk of Bias tool that assigns studies as having low, unclear, or high risk of bias. Quality of evidence and strength of recommendation was based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[15] that involves consideration of methodological quality, directness of evidence, heterogeneity, precision of effect estimates, and publication bias.

Literature search strategy: For the purpose of this systematic review, priority sources for retrieval of relevant studies included PubMed (https://pubmed.ncbi.nlm.nih.gov) and its curated version LitCOVID; National Library of Medicine database of clinical studies (https://clinicaltrials.gov); WHO International Clinical Trials Registry Platform (https://www.who.int/ictrp/en/); medRxiv (https://www.medrxiv.org); Cochrane living registry of COVID-19 studies (https://covid-19.cochrane.org) and Living mapping and living systematic review of Covid-19 studies (https://covid-nma.com). A systematic search of the medical literature (Table S1) without any language restrictions was conducted on 25 September 2020 and later updated from December 2020 through March 2021 in accordance with international guidelines. A reference list of selected articles was also screened for identifying additional potentially eligible studies.

Study eligibility: Only prospective clinical trials randomly assigning patients with COVID-19 infection to convalescent plasma plus standard of care therapy (test arm) versus placebo/standard of care therapy (control arm) were included. Given the lack of globally accepted standard of care therapy, this could vary across trials, but needed to be similar in both the arms within individual studies. Multi-arm trials were eligible if they directly compared convalescent plasma versus standard of care therapy, with appropriate arms being included in the meta-analysis. Trials allowing co-enrolment of patients across multiple studies were also eligible provided the co-interventions (concurrent medical treatment) were delivered similarly in each of the randomised arms. Emulated RCTs, quasi-randomised trials, propensity matched analyses, nonrandomised comparative studies, or observational studies were not considered in this review. Trials testing complementary and alternative medicines, traditional Chinese medicine, nutraceuticals, phytoceuticals, and herbal formulations were also ineligible.

Outcome measures: The selection of outcome measures for this systematic review was based on the outcome sets developed by WHO for research in COVID-19 hospitalised patients identified through COMET initiative (http://www.comet-initiative.org/Studies/Details/1538). The primary outcomes of interest included clinical benefit as measured on WHO[16] or similar ordinal scale and all-cause mortality. Clinical improvement was defined as becoming asymptomatic and/or discharged (achieving a score of 1 or 2 on the ordinal scale). Relevant endpoints included clinical improvement rate (CIR) on specified days (defined as proportion of patients with clinical improvement by Day7, Day14, Day28 of randomization), time-to-clinical improvement (TTCI), and death due to any cause by Day28 of randomization. Secondary outcomes included viral negativity rate on specified days (defined as proportion of patients with viral negativity on Day3, Day7, Day14 of randomization) and time to viral clearance based on COVID-19

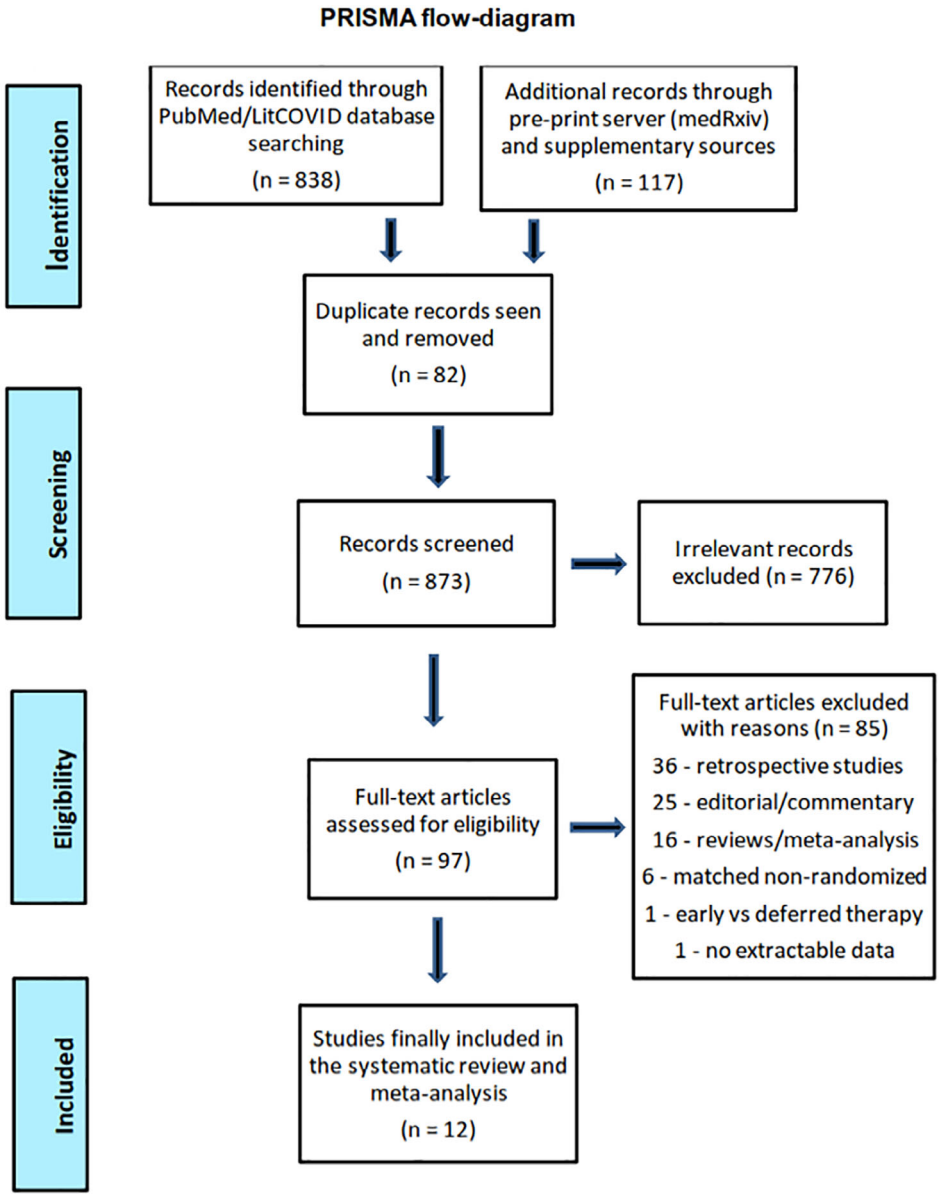

FIGURE 1 Flow-diagram of study selection and inclusion in the meta-analysis as per PRISMA guidelines

negativity as assessed by reverse transcriptase polymerase chain reaction (RT-PCR). In addition, safety outcomes included comparison of infusion-related serious adverse events between the two arms.

Data extraction and analyses: Two reviewers (BK and PT) independently read each preprint, publication, protocol, or any other available study report and extracted relevant data from individual primary studies. Discrepancy, if any, was resolved through consensus interpretation by a third reviewer (TG). In case of publication following a preprint report, data from the peer-reviewed article was used for statistical pooling. Extracted data included study characteristics (such as first author, publication year and journal), number of participants randomised, patient characteristics (severity of clinical presentation), intervention details (class and type of treatment), and outcome measures. For all dichotomous outcomes (CIR, viral negativity rate, adverse event rate, and mortality), the number of events of interest and the number of participants in each study arm were extracted per outcome. Data was pooled using the random-effects model and expressed as risk ratio (RR) with 95% confidence interval (CI). For continuous outcomes (TTCI and time to viral clearance), mean/median values with their dispersion as reported were extracted and expressed as difference in median time (in days) with 95% CI. Any p-value <0.05 was considered as statistically significant. Sensitivity analysis, subgroup analysis, and publication bias was also assessed as appropriate. All analyses were done using Review Manager (RevMan) version 5.3 & GRADE profiler (GRADEpro) version 3.6.1 (The Nordic Cochrane Centre, Cochrane Collaboration, 2008), Stata 14.0 (StataCorp LP, TX, USA) and R Studio. All data were reported in accordance with Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] No source of funding was involved in study conduct, data extraction and analysis, or reporting of results. The protocol is registered with the International Platform of Registered Systematic Reviews and Meta-analysis Protocols (INPLASY202090092).

TABLE 1 Baseline patient and disease characteristics in randomised controlled trials of convalescent plasma therapy in COVID-19

Author [reference] (study name)	Treatment arms	Patient numbers (N)	Disease severity	Median/mean age (years)	Comorbidity[a] (%)	Male patients (%)	Baseline swab positivity (%)
Agarwal A [18] (PLACID)	Convalescent plasma	235	Moderate disease	52	71.1%	75%	100%
	Standard of care	229		52	64.2%	77%	100%
AlQahtani M [19]	Convalescent plasma	20	Severe disease	52.6	35%	85%	100%
	Standard of care	20		50.7	45%	75%	100%
Avendano-Sola C [20] (ConPlas)	Convalescent plasma	38	Mild to moderate	61.3	52.6%	52.6%	68.4%
	Standard of care	43		60.3	27.9%	55.8%	79.1%
Bajpai M [21]	Convalescent plasma	14	Severe disease	48.1	Not known	78.6%	100%
	Fresh Frozen pasma	15		48.3	Not known	73.3%	100%
Gharbharan A [22] (ConCOVID)	Convalescent plasma	43	Moderate to severe	61	30%	67.4%	100%
	Standard of care	43		63	26%	76.7%	100%
Horby P [23] (RECOVERY)	Convalescent plasma	5795	Moderate to severe	63.6	55%	63%	96%
	Standard of care	5763		63.4	56%	66%	96%
Li L [24]	Convalescent plasma	52	Severe disease	70	29%	51.9%	100%
	Standard of care	51		69	27%	64.7%	100%
Libster R [25]	Convalescent plasma	80	Mild disease	76.4	86.2%	32.5%	100%
	Placebo	80		77.9	77.5%	42.5%	100%
O'Donnell M [26]	Convalescent plasma	150	Severe disease	60	37%	64%	100%
	Normal plasma	73		63	38%	70%	100%
Rasheed M [27]	Convalescent plasma	21	Severe to critical	55.7	47.6%	Not known	100%
	Standard of care	28		47.8	39.3%	Not known	100%
Ray Y [28]	Convalescent plasma	40	Severe disease	59	Not known	75%	100%
	Standard of care	40		61	Not known	67.5%	100%
Simonovich V [29] (PlasmAr)	Convalescent plasma	228	Severe disease	62.5	64.9%	71.6%	100%
	Placebo	105		62	64.8%	61%	100%

[a]Percentages represent either any morbidity or highest proportion of one morbidity as reported in each arm of individual studies.

TABLE 2 Summary efficacy and safety outcomes in RCTs comparing convalescent plasma versus placebo/standard of care therapy in COVID-19 included in the meta-analysis

Author [reference] (study name)	Treatment Arms	Patient numbers (N)	Day7 CIR (%)	Day14 CIR (%)	Day28 CIR (%)	TTCI (in days)	Day28 Mortality (%)	Day3 VNR (%)	Day7 VNR (%)	Infusion-related severe toxicity (%)
Agarwal A [18] (PLACID)	Convalescent plasma	235	75.2%	Not known	Not known	14	14.5%	42.9%	67.6%	1.3%
	Standard of care	229	65.7%	Not known	Not known	13	13.5%	36.6%	55%	0%
AlQahtani M [19]	Convalescent plasma	20	Not known	Not known	Not known	Not known	5%	Not known	Not known	0%
	Standard of care	20	Not known	Not known	Not known	Not known	10%	Not known	Not known	0%
Avendano-Sola C [20] (ConPlas)	Convalescent plasma	38	42.1%	76.3%	89.5%	8.5	0%	34.6%	50%	5.3%
	Standard of care	43	39.6%	86%	90.7%	9	9.3%	11.8%	26.5%	0%
Bajpai M [21]	Convalescent plasma	14	Not known	Not known	Not known	12.1	21.4%	Not known	Not known	0%
	Fresh frozen plasma	15	Not known	Not known	Not known	16.1	6.7%	Not known	Not known	0%
Gharbharan A [22] (ConCOVID)	Convalescent plasma	43	37.2%	55.8%	76.7%	12.5	13.9%	Not known	Not known	0%
	Standard of care	43	32.6%	51.2%	72.1%	13.5	25.6%	Not known	Not known	0%
Horby P [23] (RECOVERY)	Convalescent plasma	5795	Not known	Not known	66.4%	11	24%	Not known	Not known	3.3%
	Standard of care	5763	Not known	Not known	66.7%	11	24%	Not known	Not known	3%
Li L [24]	Convalescent Plasma	52	9.6%	32.7%	51.9%	28	15.7%	87.2%	Not known	1.9%
	Standard of care	51	9.8%	14.6%	43.1%	30	24%	37.5%	Not known	0%
Libster R [25]	Convalescent plasma	80	Not known	Not known	Not known	Not known	2.5%	Not known	Not known	0%
	Placebo	80	Not known	Not known	Not known	Not known	5%	Not known	Not known	0%
O'Donnell M [26]	Convalescent plasma	150	Not known	Not known	72%	5	12.6%	Not known	Not known	2.7%
	Normal plasma	73	Not known	Noy known	65.8%	7	24.6%	Not known	Not known	4.2%
Rasheed M [27]	Convalescent plasma	21	Not known	Not known	Not known	19.3	4.8%	Not known	Not known	0%
	Standard of care	28	Not known	Not known	Not known	23.4	28.6%	Not known	Not known	0%
Ray Y [28]	Convalescent plasma	40	9.5%	51.3%	75.7%	13	25%	Not known	Not known	Not known
	Standard of care	40	2.8%	41%	61.8%	17	35%	Not known	Not known	Not known
Simonovich V [29] (PlasmAr)	Convalescent plasma	228	21.2%	56.3%	74%	12	10.9%	Not known	Not known	5.7%
	Placebo	105	29.4%	55.1%	76.2%	12	11.4%	Not known	Not known	1.9%

Abbreviations: CIR, clinical improvement rate; COVID-19, coronavirus disease 2019; RCT, randomised controlled trials; TTCI, time to clinical improvement; VNR, viral negativity rate.

3 | RESULTS

The flow-diagram of study selection and inclusion in the meta-analysis as per the PRISMA guidelines is depicted in Figure 1. Detailed PRISMA cheque-list is also provided as online a Table S2. Systematic search of PubMed/LitCOVID identified 838 records with an additional 117 records being retrieved through supplementary search of other sources. After removing duplicates (n = 82) and excluding irrelevant/inappropriate records (n = 776) through rigorous screening all titles/abstracts, a total of 97 full-text articles (including preprints) were assessed for eligibility, of which 12 RCTs[18–29] were finally included and pooled in this systematic review and meta-analysis.

Description of included studies: Patient characteristics, treatment details, and relevant outcomes of all 12 RCTs randomly assigning COVID-19 patients to convalescent plasma plus standard of care therapy versus placebo/standard of care therapy are briefly summarised in Tables 1 and 2 respectively. These trials were conducted between February 2020 to January 2021 in various parts of the world ensuring good geo-ethnic representation. Patients included in these RCTs were largely representative of the typical COVID-19 patient population seen in routine clinical practise. Trials enrolled patients with wide range of severity ranging from mild/moderate illness to severe/critical and life-threatening disease with varying primary endpoints and outcome measures. Convalescent plasma was administered only once

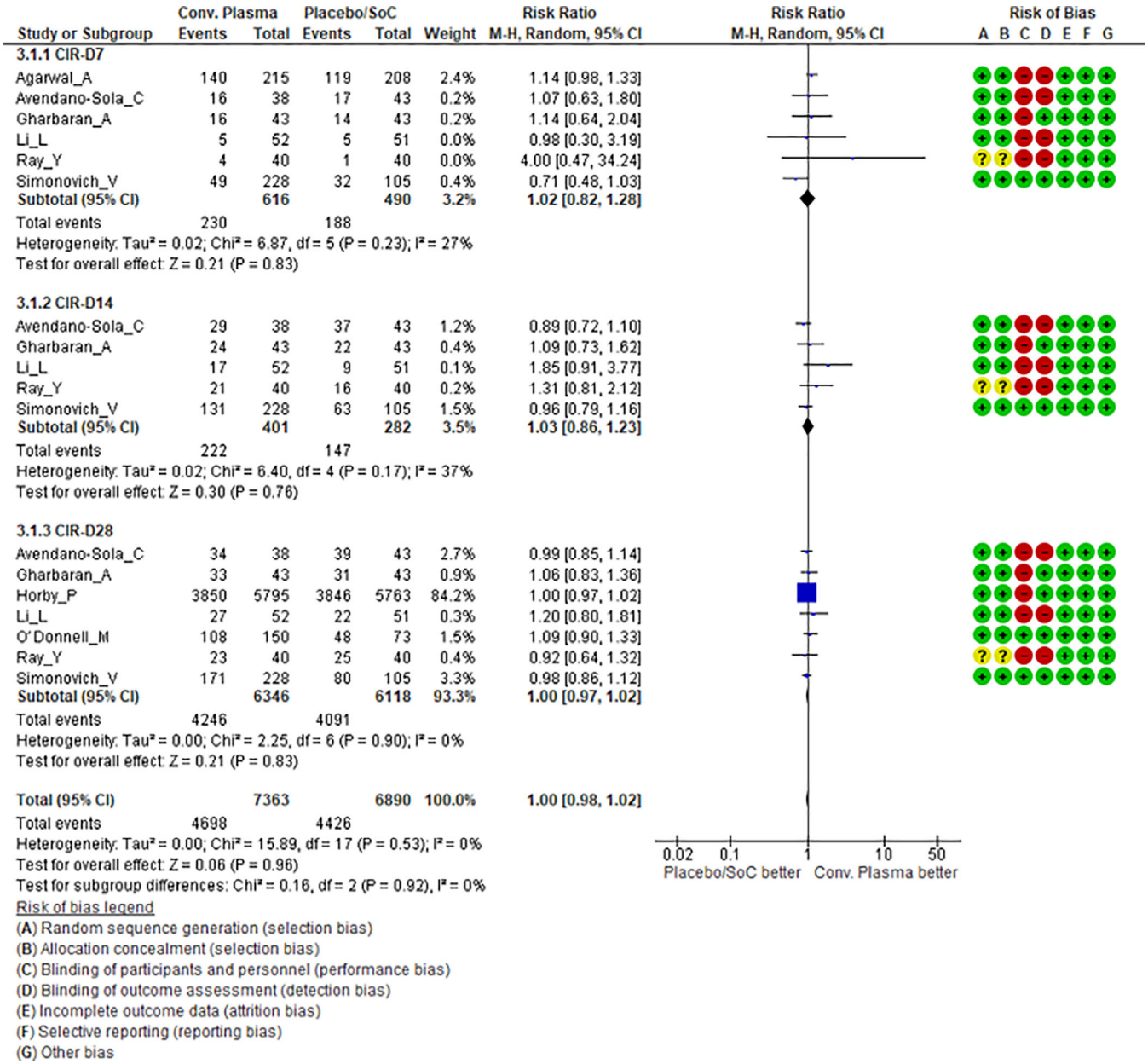

FIGURE 2 Forest plots including risk of bias in individual studies comparing convalescent plasma plus standard of care therapy versus placebo/standard of care therapy for clinical improvement rate (CIR) on specified days from randomization (Day7, Day14, Day28) and overall CIR in COVID-19

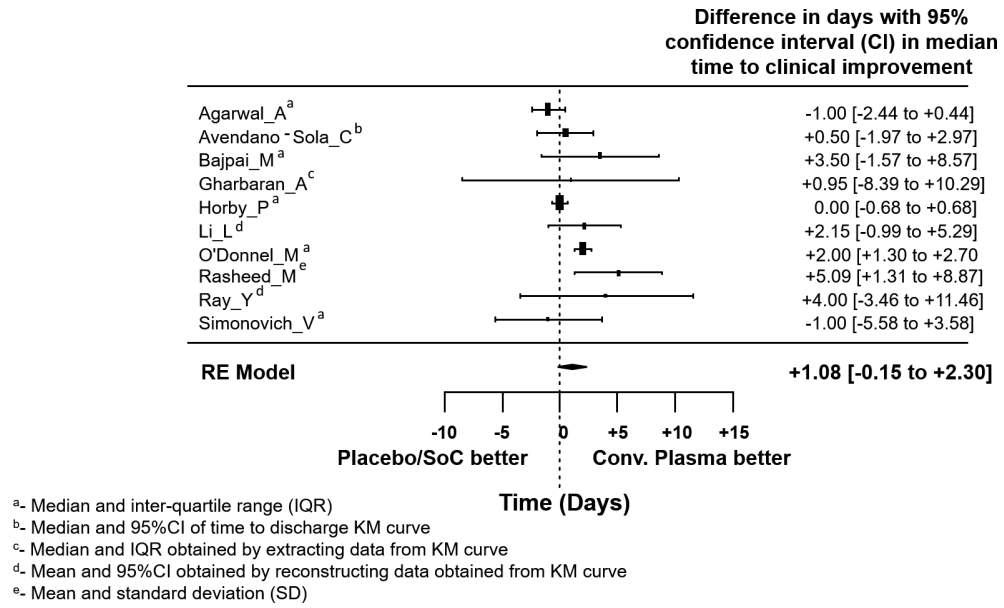

FIGURE 3 Median difference (in days) in time to clinical improvement (TTCI) between convalescent plasma plus standard of care therapy versus placebo/standard of care therapy in COVID-19

either using fixed dose of 250–500 ml[20,25–27,29] or 4–13 ml/kg body weight[24] or twice at a fixed dose of 200–275 ml given 12 to 24-h apart. [18,19,21,23,28] One trial[22] gave a single fixed dose of 300 ml convalescent plasma on day of inclusion but allowed a second such dose 5 days later in patients without clinical response and persistently positive RT-PCR. Only one trial[29] used convalescent plasma with very high neutralising antibody titres (minimum 1:800) while two other studies[23,26] used plasma with antibody titres >1:100 for transfusion. The standard of care though different in the included trials were in keeping with institutional protocols and national guidelines dictated by the best available evidence at the time and comprised of antimalarials (chloroquine, hydroxychloroquine), anti-virals (oseltamivir, lopinavir/ritonavir, remdesivir), broad-spectrum antibiotics (azithromycin), immunomodulators (steroids, tocilizumab, anakinra), traditional herbal medicines, and supportive care (oxygen inhalation and ventilatory support) as appropriate.

Evidence syntheses: There was no significant methodologic heterogeneity across the 12 included studies allowing statistical pooling of data from a total of 13 206 randomised patients in the meta-analysis. The addition of convalescent plasma to standard of care therapy was not associated with any significant or meaningful clinical benefit. There were no significant differences in rates of clinical improvement (Figure 2) between convalescent plasma plus standard of care therapy (test arm) versus placebo/standard of care therapy (control arm) either in terms of overall CIR (RR = 1.00, 95% CI: 0.98–1.02, $p = 0.96$) or CIR on Day7 (RR = 1.02, 95% CI: 0.82–1.28, $p = 0.83$); Day14 (RR = 1.03, 95% CI: 0.86–1.23, $p = 0.76$); and Day28 (RR = 1.00, 95% CI: 0.97–1.02, $p = 0.83$) respectively. Similarly, there was no significant difference in TTCI between the two arms (Figure 3) with a median difference of 1.08 days (95% CI: −0.15 to +2.30 days) favouring the convalescent plasma arm. The use of convalescent plasma was not associated with significantly reduced risk of death (Figure 4); RR of Day28 mortality was 0.81 (95% CI: 0.65–1.02, $p = 0.08$). Convalescent plasma however resulted in higher rates of viral clearance early after randomization, although based on a much smaller dataset comprising of just over 500 patients enrolled in three RCTs. Viral negativity rates both overall (RR = 1.55, 95% CI: 1.16–2.06, $p = 0.003$) and on Day3 (RR = 1.82, 95% CI: 1.02–3.23, $p = 0.04$) from randomization were higher in the convalescent plasma arm (Figure S3). Data regarding time to viral clearance was not reported consistently precluding statistically pooling of results. Reassuringly, the overall incidence of convalescent plasma transfusion-related serious adverse events was low with a weighted-mean pooled estimate of 3.25% (95% CI: 2.82–3.72%) confirming the safety of convalescent plasma transfusion. There was no significant difference (RR = 1.14, 95% CI: 0.93–1.22, $p = 0.22$) in treatment-related toxicity (Figure 5) between convalescent plasma plus standard of care therapy compared to placebo/standard of care therapy. Sensitivity analysis showed that no single trial was driving the results, inferences, and conclusions of the meta-analysis (Figure S4). Subgroup analysis stratified by disease severity (mild–moderate vs. severe-critical), timing of transfusion (early vs. later), sample size (small vs. large trials), and study design (open-label vs. placebo-controlled) suggested that the risk of dying was reduced with convalescent plasma transfusion in patients with more severe disease (RR = 0.62, 95% CI: 0.42–0.90, $p = 0.01$, 855 patients) and with early transfusion (RR = 0.51, 95% CI: 0.30–0.89, $p = 0.02$, 383 patients), based on much smaller patient numbers precluding definitive conclusions. A formal statistical analysis did not show any asymmetry in the funnel plot (Figure S5) indicating lack of significant publication bias.

Strength of recommendation: All RCTs[18-29] were of moderate to good quality with low risk of bias for most domains for the relevant outcomes of interest excepting high risk of performance and detection bias due to open-label nature of most included studies without placebo controls with lack of blinding of patients and/or physicians. Based on the above, there is low to moderate certainty evidence that the addition of convalescent plasma to standard of care therapy is not associated with significant clinical benefit or harm in patients with COVID-19 (Table 3).

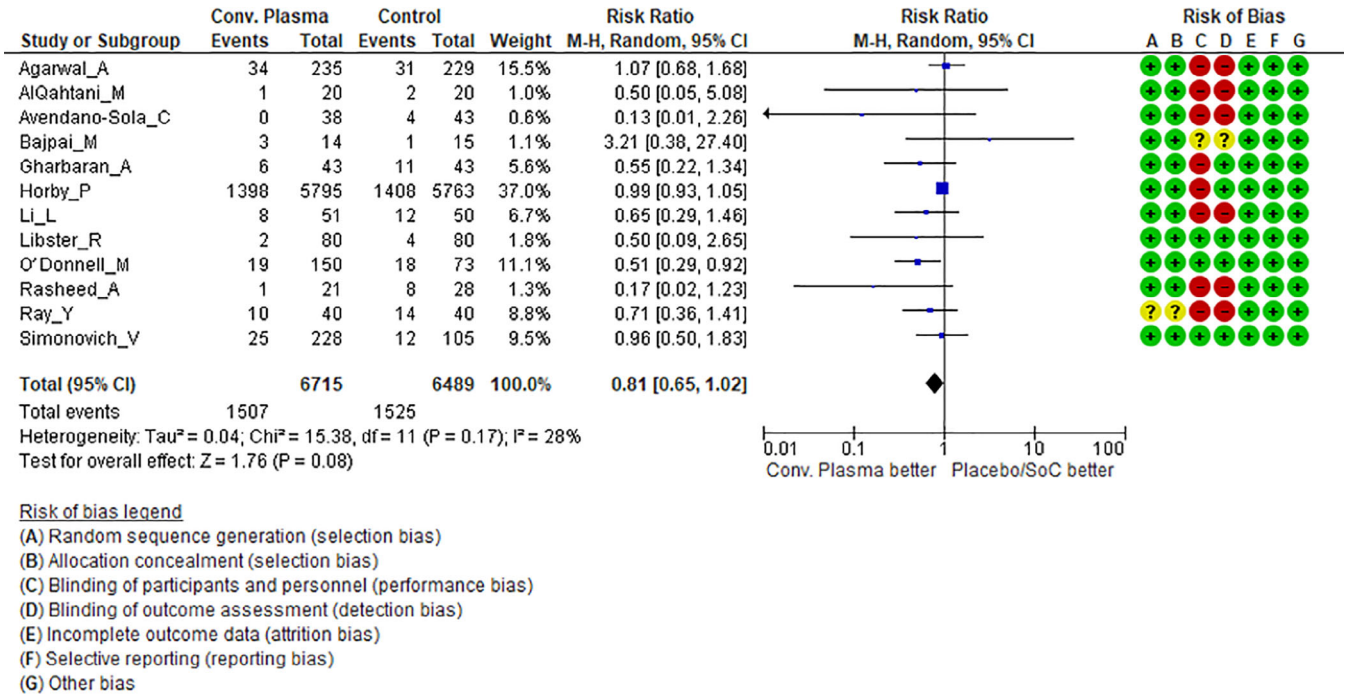

FIGURE 4 Forest plots including risk of bias in individual studies comparing convalescent plasma plus standard of care therapy versus placebo/standard of care therapy for all-cause mortality (by Day28 of randomization) in COVID-19

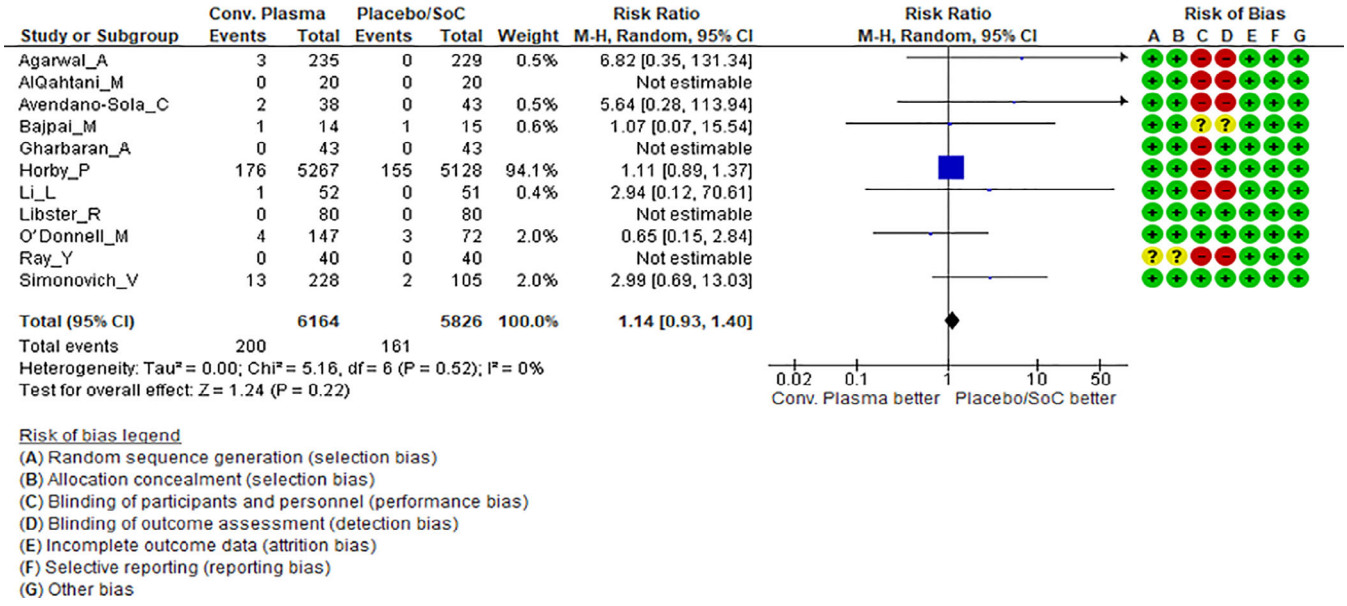

FIGURE 5 Forest plots including risk of bias in individual studies comparing convalescent plasma plus standard of care therapy versus placebo/standard of care therapy for infusion-related serious adverse events in patients with COVID-19

4 | DISCUSSION

The lack of an effective prophylactic and/or therapeutic agent against COVID-19 infection combined with strong scientific rationale and historical precedence demonstrating clinical benefit with convalescent plasma therapy in previous viral outbreaks[9,10] has prompted its widespread use hoping that this might be the magic potion for COVID-19 pandemic.[30]

Quite understandably, the use of convalescent plasma in COVID-19 infection has gained significant traction not only within the medical

TABLE 3 Summary of findings including relative effect and anticipated absolute effects with quality of evidence for benefits or harms of convalescent plasma therapy in COVID-19

Convalescent Plasma for COVID-19					
Outcomes	No of participants (studies) follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with convalescent plasma (95% CI)
Clinical improvement rate (Clinical)	14 253(8 studies)	⨁⨁⊖⊖LOW[a,b]due to risk of bias, imprecision	RR 1.00 (0.98 to 1.02)	Study population	
				642 CIR per 1000	0 fewer per 1000(from 13 fewer to 13 more)
				Moderate	
				542 CIR per 1000	0 fewer per 1000(from 11 fewer to 11 more)
Day28 mortality (Clinical)	13 206(12 studies)	⨁⨁⨁⊖MODERATE[b]due to imprecision	RR 0.81 (0.65 to 1.02)	Study population	
				235 per 1000	45 fewer per 1000(from 82 fewer to 5 more)
				Moderate	
				188 per 1000	36 fewer per 1000(from 66 fewer to 4 more)
Serious adverse events (Clinical)	11 990(11 studies)	⨁⨁⊖⊖LOW[a,b]due to risk of bias, imprecision	RR 1.14 (0.93 to 1.4)	Study population	
				28 per 1000	4 more per 1000(from 2 fewer to 11 more)
				Moderate	
				0 per 1000	-

Note: The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *GRADE Working Group grades of evidence*: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

Abbreviations: CI, confidence interval; RR: risk ratio.

[a]Most studies were open-label with no placebo-control resulting in potential performance bias.

[b]The 95% CI straddles the line of unity and increases/decreases the RR by more than 25% in several studies.

and scientific community across the globe but also within the lay public.[31] Despite lack of definitive evidence of efficacy, convalescent plasma was granted EUA by US FDA in late August 2020. Prior to this authorization, large scale clinical usage in the US was regulated through FDA's expanded access program,[32,33] that collected data on clinical outcomes and side effects in over 100 000 patients from 2700 hospitals across US in a span of 5 months (April to August 2020) and judged that convalescent plasma 'may be effective' and hence should be eligible for wider use under EUA. Safety data was derived from 20 000 patients initially and then over 35 000 hospitalised patients in the US which reported a very low incidence (<1%) of adverse events related to transfusion (circulatory overload, acute lung injury, severe allergic reactions), in the first few hours which was no different from standard blood/plasma transfusions.[32,33] Reassuringly, it largely eliminated concerns exacerbation of illness due to antibody-dependent enhancement. Further mining of this data suggests that patients who receive convalescent plasma early (within 3 days of their diagnosis) fared better than those who receive it later.[34,35] However, this observation has recently been challenged by a small RCT[33] that failed to report any significant benefit in the composite primary outcome of mechanical ventilation, hospitalisation for >14 days, or death in patients treated with upfront convalescent plasma at diagnosis compared to deferred therapy at further clinical deterioration for COVID-19 infection with an odds ratio (OR) of 0.95 (95% CI: 0.32–2.94, $p > 0.99$). There is some suggestion of a dose–response relationship, as those who receive plasma units with high titres of neutralising antibodies having lower mortality rate than patients receiving units with lower titres.[34,35] A minimum neutralising antibody titre in convalescent plasma needs to be determined to achieve desired efficacy yet maintain safe and sufficient supply[36] despite the negative impact of COVID-19 pandemic and resultant disruption of blood bank services.[37] The US FDA currently recommends anti-SARS-CoV-2 specific neutralising antibody titre >1:160 in donor plasma which corresponds to high efficacy based on the plaque reduction neutralisation test (PRNT) assay. It is now increasingly being recognised that evolutionary strain on the viral genome through the use of monoclonal

antibodies targeting the spike protein or convalescent plasma with low levels of neutralising antibodies for COVID-19 infection can potentiate immune escape allowing newer and novel mutations[38,39] with potential for increased infectivity, disease severity and even mortality. Consequent to the EUA, it has now become increasingly difficult to recruit patients on clinical trials evaluating convalescent plasma therapy clearly reflecting a missed opportunity to firmly establish its efficacy in COVID-19.[35]

An updated living Cochrane review[40] of convalescent plasma in COVID-19 involving 38 160 participants enrolled in 19 studies (two RCTs, eight nonrandomised controlled studies, and nine uncontrolled studies) reported an overall high risk of bias (due to study design, types of participants, and other previous or concurrent treatment) and concluded that the beneficial effects (improvement of clinical symptoms and reduction in mortality) or harms (severe/serious adverse events) of convalescent plasma therapy in patients with COVID-19 infection were very uncertain at the present time. More recently, Janiaud et al.[41] reported no significant clinical benefit (decrease in all-cause mortality, increase in rates of clinical improvement, or reduced length of hospitalisation) with convalescent plasma in COVID 19 infection compared to placebo/standard of care therapy in a pooled analysis of 1060 patients from four RCTs published in peer-reviewed journals, 316 patients from five RCTs posted on preprint servers and 10 406 patients from one RCT reported via press briefing. The summary risk ratio (RR) for all-cause mortality with convalescent plasma in the four peer-reviewed RCTs was 0.93 (95% CI: 0.63–1.38) with low certainty of the evidence due to imprecision. After adding results of six more RCTs (from preprints/press release), the summary RR was 1.02 (95% CI: 0.92–1.12) with moderate certainty of evidence. The authors further reported that limited data on clinical improvement, clinical deterioration, and serious adverse events showed no significant differences between the two treatments.

The current meta-analysis provides the most robust and best contemporary evidence regarding the safety and efficacy of convalescent plasma in the treatment of COVID-19 infection. The addition of convalescent plasma to the current standard of care therapy is not associated with statistically significant clinical improvement or reduction in mortality. Overall, the risk of infusion-related serious adverse events is quite low and not significantly different compared to placebo/standard of care therapy. The clinical significance of early viral negativity following convalescent plasma transfusion is unknown and its benefit when given early in the course of the disease and in patients with more severe disease should be considered exploratory findings from this meta-analysis based on much smaller cohort size for such analyses.

Strengths and limitations: Despite being the largest dataset (comprising over 13 000 patients) derived only from RCTs and pooled using modern meta-analytic methods, certain caveats and limitations remain. The efficacy of convalescent plasma largely correlates with high titres of neutralising antibodies in the donor plasma and lack/low-level of such antibodies in recipients. Only three RCTs transfused convalescent plasma with high titres of neutralising antibodies (measured quantitatively using the PRNT assay), while others did not mandate a quantitative estimation of such antibodies prior to transfusion. This was further confounded by the presence of anti-SARS-CoV-2 specific IgG antibodies in a significant proportion of convalescent plasma recipient patients even prior to transfusion in four studies. Detection of such neutralising IgG antibody was an exclusion criterion in only a single RCT, with other trials allowing such patients to be randomised. It is also hypothesized that early transfusion (within few days of symptom onset and/or disease of mild to moderate severity) of convalescent plasma is more effective than delayed/deferred transfusion (>7 days of symptom onset and/or severe to critical illness). However, most trials included patients somewhat late in the course of their illness with median time from symptom onset to transfusion being beyond 7 days in most studies. Four of the included RCTs were exploratory pilot studies with relatively small sample size and four others were terminated prematurely without achieving the specified target accrual further reducing statistical power and rigour. Only three of 12 included RCTs used placebo-controlled design, with remaining nine studies being open-label without blinding of patients/physicians with potential for performance and detection bias leading to downgrading of the quality of evidence. Finally, evidence synthesis and subgroup analyses were primarily based on data reported in preprints/publications without access to individual patient data which would be a more robust method to identify subgroups that might benefit with convalescent plasma transfusion.

Implications for research: Key considerations in clinical trials evaluating convalescent plasma for COVID-19 should include timing of administration relative to onset of disease, timing of donation relative to resolution of symptoms in the donor, severity of disease, pretransfusion serology, and antibody titres.[42,43] A scoping review[44] of registered clinical trials of convalescent plasma therapy for COVID-19 infection was conducted early in the course of the pandemic to provide a framework for accelerated synthesis of trial evidence. The review identified 48 such registered trials (29 controlled studies) projected to enrol over 5000 patients, combined analysis of which would be sufficient to determine meaningful improvements in mortality, intensive-care admission, or mechanical ventilation faster than any individual RCT determining effectiveness of convalescent plasma therapy. A more recent search of clinical trial registries identified 64 studies in 22 countries using convalescent plasma therapy for COVID-19 infection during an international survey.[45] Twenty of the 64 centres responded to the survey, of which only nine were RCTs, the remaining being single arm prospective case series. Only four RCTs planned to include over 400 patients (adequately powered) and only three RCTs were blinded (low risk of bias). The survey reported significant variability in donor antibody testing with no consensus towards an optimal cut-off of anti-SARS-CoV-2 IgG neutralising antibody titres in the donor plasma for transfusion.[45] Current trials of convalescent plasma therapy include patients with wide spectrum of COVID-19 illness (from mild to critical), have variable need for molecular evidence of viral infection, use nonstandardised intervention (differing antibody titres, dose, and timing), have no universally accepted standard of care (as comparator), are mostly open label without placebo control (such as normal plasma) with key differences in primary outcomes between trials.[46] It is conceivable that the treatment effect of convalescent plasma may differ by illness severity, by

dose in terms of volume, concentration of neutralisation antibody, and the risk of antibody dependent enhancement along with other adverse events during COVID-19 illness. The National Institutes of Health (NIH) COVID-19 treatment guidelines panel[47] recently stated that it cannot recommend convalescent plasma as a standard of care for treating COVID-19 at this time as currently the data are insufficient to recommend for or against its usage. Their report further states that prospective, well controlled, and adequately powered RCTs are needed to determine whether convalescent plasma and other passive immunotherapies are safe and effective in COVID-19.

Since the press release declaring closure of RECOVERY trial to recruitment on the convalescent plasma arm, three other RCTs, the REMAP-CAP (NCT02735707), CONCOR-1 (NCT04348656), and NIH-led C3PO study (NCT04355767) have issued public statements announcing cessation of recruitment based on reaching prespecified endpoints of statistical futility on interim analysis of available data. Many more RCTs of convalescent plasma including an ongoing large placebo-controlled trial of 1000 patients (PassITON)[48] are currently underway; an updated living pooled analysis[49] of yet unreported trials might further enhance the certainty of evidence and improve the strength of recommendation in the future.

The next generation of convalescent plasma trials should also determine desirable product attributes, optimal dose and timing of administration, as well as appropriate patient population for its usage.[46,50] All reported RCTs evaluating convalescent plasma in COVID-19 till date have included only hospitalised adults with mild/moderate to severe/critical disease, excepting one study conducted in the outpatient setting for elderly patients with milder disease to prevent symptomatic worsening. If the main mechanism of action of convalescent plasma is through virus neutralisation, it would possibly be most efficacious when used very early in the course of the disease and/or even for prophylaxis in high-risk individuals.[50] In addition, there may be specific groups who are more likely to benefit such as those with impaired immune responses secondary to an immunocompromised state (inherited or acquired immunodeficiency, cancer patients, transplant recipients on suppressive medication) leading to delayed viral clearance.[50] Continuous monitoring of pooled international trials of convalescent plasma for COVID-19 hospitalised patients (COMPILE) project is presently pooling individual patient data from RCTs of convalescent plasma in real-time[49] under a shared regulatory and statistical framework (http://nyulmc.org/compile). A similar initiative from the European Union COVID-19 convalescent plasma platform (https://www.euccp.dataplatform.tech.ec.europa.eu/) could be considered to further strengthen the evidence-base.

5 | CONCLUSIONS

There is low to moderate certainty evidence that the addition of convalescent plasma to current standard of care therapy is generally safe with low risk of transfusion-associated serious adverse events but does not result in significant clinical benefit or reduction of mortality in patients with COVID-19 infection. An updated meta-analysis including other ongoing large RCTs of convalescent plasma therapy may help improve this evidence-base in the future.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Tejpal Gupta: Conceptualization, methodology, analysis, and writing–original draft. **Sadhana Kannan**: Methodology, literature search strategy, and analysis. **Babusha Kalra**: Data curation and writing–review & editing. **Prafulla Thakkar**: Data curation and writing–review & editing.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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