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Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19

A Systematic Review and Meta-analysis

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IMPORTANCE Convalescent plasma is a proposed treatment for COVID-19.

OBJECTIVE To assess clinical outcomes with convalescent plasma treatment vs placebo or standard of care in peer-reviewed and preprint publications or press releases of randomized clinical trials (RCTs).

DATA SOURCES PubMed, the Cochrane COVID-19 trial registry, and the Living Overview of Evidence platform were searched until January 29, 2021.

STUDY SELECTION The RCTs selected compared any type of convalescent plasma vs placebo or standard of care for patients with confirmed or suspected COVID-19 in any treatment setting.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data on relevant clinical outcomes, trial characteristics, and patient characteristics and used the Cochrane Risk of Bias Assessment Tool. The primary analysis included peer-reviewed publications of RCTs only, whereas the secondary analysis included all publicly available RCT data (peer-reviewed publications, preprints, and press releases). Inverse variance–weighted meta-analyses were conducted to summarize the treatment effects. The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation.

MAIN OUTCOMES AND MEASURES All-cause mortality, length of hospital stay, clinical improvement, clinical deterioration, mechanical ventilation use, and serious adverse events.

RESULTS A total of 1060 patients from 4 peer-reviewed RCTs and 10 722 patients from 6 other publicly available RCTs were included. The summary risk ratio (RR) for all-cause mortality with convalescent plasma in the 4 peer-reviewed RCTs was 0.93 (95% CI, 0.63 to 1.38), the absolute risk difference was −1.21% (95% CI, −5.29% to 2.88%), and there was low certainty of the evidence due to imprecision. Across all 10 RCTs, the summary RR was 1.02 (95% CI, 0.92 to 1.12) and there was moderate certainty of the evidence due to inclusion of unpublished data. Among the peer-reviewed RCTs, the summary hazard ratio was 1.17 (95% CI, 0.07 to 20.34) for length of hospital stay, the summary RR was 0.76 (95% CI, 0.20 to 2.87) for mechanical ventilation use (the absolute risk difference for mechanical ventilation use was −2.56% [95% CI, −13.16% to 8.05%]), and there was low certainty of the evidence due to imprecision for both outcomes. Limited data on clinical improvement, clinical deterioration, and serious adverse events showed no significant differences.

CONCLUSIONS AND RELEVANCE Treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes. The certainty of the evidence was low to moderate for all-cause mortality and low for other outcomes.

Editorial

Supplemental content

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Patients with COVID-19 have frequently been treated with convalescent plasma (ie, plasma from persons who have recovered from SARS-CoV-2 infection), but the clinical evidence of benefits or harms is limited.[1] Preliminary reports indicating that convalescent plasma is well tolerated with low risk of adverse events[2] led to Emergency Use Authorization in the US in August 2020.[3] Despite the large number of clinical trials being conducted since the start of the pandemic, only a few have been published in peer-reviewed journals and some have posted preliminary results on preprint servers.

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) platform trial is by far the largest clinical trial on COVID-19 treatments, and has provided important evidence for several promising treatments, including dexamethasone,[4] hydroxychloroquine,[5] lopinavir-ritonavir,[6] and azithromycin.[7] The part of the trial investigating treatment with convalescent plasma was halted based on the recommendation of the RECOVERY data monitoring committee. Communicated as a press release on January 15, 2021, the preliminary reported results based on data from 10 406 patients indicate no significant association of a benefit with convalescent plasma in reducing all-cause mortality compared with standard of care (risk ratio [RR], 1.04; 95% CI, 0.95-1.14).[8]

Given the previously reported clinical trials and this recent announcement,[8] a systematic review and meta-analysis was conducted to summarize and assess all published evidence from randomized clinical trials (RCTs) on the association between treatment with convalescent plasma compared with standard of care or placebo on clinical outcomes in patients with COVID-19.

Key Points

Question Is treatment with convalescent plasma associated with improved clinical outcomes?

Findings In a meta-analysis of 4 peer-reviewed and published randomized clinical trials including 1060 patients with COVID-19 treated with convalescent plasma vs control, the risk ratio for mortality was 0.93 and after the addition of 6 unpublished randomized clinical trials and 10 722 patients, the risk ratio for mortality was 1.02; neither finding was statistically significant. No significant associations with benefit were shown for hospital length of stay, mechanical ventilation use, clinical improvement, or clinical deterioration.

Meaning Among patients with COVID-19, treatment with convalescent plasma compared with control was not associated with improved survival or other positive clinical outcomes.

Methods

This review has been reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis.[9]

Search Strategy and RCT Selection

Two reviewers (P.J. and C.A.) systematically searched PubMed (using peer-review of electronic search strategies[10]), the Cochrane COVID-19 trial registry, and the Living Overview of Evidence platform for all published RCTs as of January 29, 2021, aiming to assess the benefits and harms of convalescent plasma to treat patients with COVID-19. Search strategies were designed with terms related to convalescent plasma and COVID-19 along with standard RCT filters (eMethods in the Supplement).

In addition, we searched for press releases presenting results of RCTs assessing convalescent plasma. Peer-reviewed publications, preprints, and press releases were eligible for inclusion. There were no restrictions on language or geographic region.

The selected RCTs included patients with suspected or confirmed SARS-CoV-2 infection randomly allocated to receive convalescent plasma, placebo together with standard of care, or only standard of care. The RCTs were included regardless of the level of plasma titer (ie, low or high antibody titer) or health care setting. The RCTs aimed at preventing the occurrence of COVID-19 were excluded.

Outcomes

The outcomes were all-cause mortality at any time point, length of hospital stay, number of patients with clinical improvement or deterioration, number of patients requiring mechanical ventilation, and number of patients experiencing serious adverse events.

Data Extraction and Risk of Bias Assessment

We extracted the following information for each RCT: trial design characteristics (randomization procedure and blinding), descriptions of the experimental and control groups, baseline characteristics of the patients, eligibility criteria for plasma donors, and trial location. High antibody titer was defined in this meta-analysis as S-protein receptor-binding domain-specific IgG antibody titer of 1:640 or higher or serum neutralization titer of 1:40 or higher. For each outcome, we collected either the number of events for the convalescent plasma and control groups or the effect size and corresponding 95% CI (only hazard ratios [HRs] were consistently reported for length of hospital stay). Data on outcomes (F.E. and M.H.) and characteristics (A.M.S. and V.G.) were extracted independently by 2 reviewers.

For each RCT, 2 reviewers (A.M.S. and V.G.) independently assessed the risk of bias for all-cause mortality, mechanical ventilation use, and length of hospital stay using version 2 of the Cochrane Risk of Bias Assessment Tool (low risk, some concerns, or high risk of bias).[11] We also used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[12] to assess the certainty of the evidence for the summarized outcomes regarding the treatment effect of convalescent plasma on patients with COVID-19.

Disagreements among reviewers were discussed with a third reviewer (P.J.) until a consensus was reached.

Statistical Analyses

The primary analysis included only RCTs published in peer-reviewed journals. A secondary analysis included all the RCTs (peer-reviewed, preprints, and information from the press release for the RECOVERY trial).

For outcomes with available data (all-cause mortality, length of hospital stay, and mechanical ventilation use), we conducted meta-analyses to summarize the treatment effects using RRs and HRs when applicable. The treatment effects for clinical improvement, clinical deterioration, and serious adverse events were not summarized due to inconsistent definitions of these outcomes and insufficient reporting of relevant details. When possible (based on the available data), we also estimated and summarized the treatment effects across the RCTs on an absolute risk difference scale.

We conducted inverse variance-weighted random-effects meta-analyses using the Paule and Mandel τ^2 estimator for heterogeneity.[13] We applied the Hartung-Knapp adjustment[14] to account for uncertainties due to large variations in sample size and in the number of outcome events across the RCTs. Heterogeneity across the RCTs was described using the I^2 and τ^2 metrics.[15]

We conducted sensitivity analyses to assess the robustness of the results using the following meta-analytic models: Sidik-Jonkman τ^2 estimator (instead of the Paule and Mandel estimator), the profile likelihood model, and the inverse variance-weighted fixed-effects model.

All tests were 2-sided and statistical significance was based on the 95% CIs excluding the null. All analyses were conducted using R version 3.6.2 meta and metafor packages (R Foundation for Statistical Computing).

Results

A total of 4357 records were identified in databases, registries, and other sources. There were 4 RCTs published in peer-reviewed journals[16-19] and 5 RCTs published as preprints[20-24] that were included. In addition, press releases were identified for 2 RCTs (the RECOVERY trial[8] and the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP][25]) but only the reported results from the RECOVERY trial[8] (NCT04381936) were included, stating 1873 deaths among 10 406 patients randomized (eFigure 1 in the Supplement).

Of the 10 included RCTs, 3 were conducted in India, 2 in Argentina, and 1 each in Bahrain, China, the Netherlands, Spain, and the UK (**Table 1**). Five RCTs were terminated early; 2 were terminated early due to futility (Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease [ConCOVID; NCT04342182][22] and RECOVERY [NCT04381936][8]) and 3 were terminated early due to slow recruitment (Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients [ConPlas-19; NCT04345523],[23] ChiCTR2000029757,[19] and NCT04479163).[16] There were 2 double-blind RCTs (NCT04479163 and Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia [PlasmAr; NCT04383535]),[18] whereas the other 8 were open-label RCTs.

From the 4 RCTs published in peer-reviewed journals, there were 1060 patients (595 randomized to convalescent plasma and 465 to placebo together with standard of care or only standard of care). From the 5 RCTs published as preprints, there were 316 patients (155 randomized to convalescent plasma and 161 to placebo together with standard of care or only standard of care). From the RECOVERY trial, there were 10 406 patients (the number of patients randomized per group was not reported in the press release information).

Of the 10 RCTs, 9 included only patients with confirmed SARS-CoV-2 infection but the RECOVERY trial included those with either confirmed or suspected SARS-CoV-2 infection. Only 1 RCT included outpatients, 5 included inpatients requiring supplemental oxygen, and 4 included inpatients regardless of need for supplemental oxygen (Table 1). Patients were administered a single convalescent plasma transfusion in 5 of the RCTs and were administered 2 transfusions 24 hours apart in the other 5 RCTs (Table 1). Of the 10 RCTs, high plasma titer was used in 4, low titer was used in 1, a minimum plasma titer cutoff was not used in 3, and it was unclear in 2 (Table 1). Six RCTs used donated plasma from men, nulliparous women, or women testing negative for HLA antibodies (this type of description was not reported for 4 RCTs: RECOVERY [NCT04381936], NCT04479163, ChiCTR2000029757, and ConPlas-19 [NCT04345523]). Only 3 RCTs (PlasmAr [NCT04383535], NCT04356534, and PLACID [CTRI/2020/04/024775]) reported the COVID-19 severity of plasma donors.

Detailed information on patient characteristics were available for 9 of the 10 RCTs (**Table 2**). The mean age of patients was younger than 70 years and they were typically male (≤80%); these generalizations did not apply to NCT04479163. Comorbidities at randomization were common when reported in the trials and only 2 RCTs reported the concurrent treatments at randomization.

Risk of Bias

The risk of bias for mortality, length of hospital stay, and mechanical ventilation use was deemed low for 7 of the 10 RCTs. For 2 of the RCTs, the risk of bias was classified as having some concerns (NCT04356534 and ConPlas-19 [NCT04345523]) and for 1 RCT it was deemed high (Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease [PICP19; CTRI/2020/05/025209]; **Figure 1**). Loss to follow-up was less than 10% when reported in 9 RCTs (data were unavailable for the RECOVERY trial).

The RECOVERY trial was deemed as having probably low risk of bias based on the trial protocol and published information for other treatments assessed by the trial (Figure 1).[4-6,26,27]

Data Availability

Mortality was assessed in all 10 RCTs and for 8 of the trials it was assessed between 15 to 30 days after randomization (1 RCT assessed mortality at 60 days and 1 RCT did not report length of follow-up; eTable 1 in the Supplement). Length of hospital stay was assessed in 7 RCTs; 3 used medians or means (1 published in a peer-reviewed journal and 2 published as preprints), 1 used HRs (published as a preprint), and 3 used both medians and HRs (2 published in peer-reviewed journals and 1 published as a preprint). The need for mechanical ventilation use was reported in 5 RCTs (3 peer-reviewed and 2 preprints). Data on clinical deterioration and

Table 1. Characteristics of the 10 Trials

	Trial registration No. (study acronym)[a]									
	ChiCTR 2000029757[19]	NCT 04479163[16]	NCT 04383535 (PlasmAr)[18]	CTRI /2020/04/ 024775 (PLACID)[17]	NCT 04345523 (ConPlas-19)[23]	NCT 04346446 (ILBS-COVID-02)[21]	NCT 04356534[20]	NCT 04342182 (ConCOVID)[22]	CTRI /2020/05/ 025209 (PICP19)[24]	NCT 04381936 (RECOVERY)[8]
Publication format	Journal	Journal	Journal	Journal	Preprint	Preprint	Preprint	Preprint	Preprint	Press release
Peer-reviewed	Yes	Yes	Yes	Yes	No	No	No	No	No	No
No. included	103	160	333	464	81	29	40	86	80	10 406
No. planned for inclusion	200	210	333	452	278	40	40	426	80	20 000
Setting	Hospitalized	Outpatient	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized	Hospitalized
Oxygen supplementation	All patients	None	Some patients	All patients	Some patients	All patients	All patients	Some patients	All patients	Some patients
Plasma titer[b]	High	High: >1:1000	High: ≥1:800 (RBD)	No minimum	High: ≥1:80 neutralizing	No minimum	No minimum	Low: ≥1:400 RBD	Unclear	Unclear
Dose description	Single transfusion of 4-13 mL/kg	Single transfusion of 250 mL	Single transfusion of 5-10 mL/kg (minimum, 400 mL; maximum, 700 mL)	Two transfusions of 200 mL administered 24 h apart	Single transfusion of 250-300 mL	Two transfusions of 500 mL administered 24 h apart	Two transfusions of 200 mL administered 24 h apart	Single transfusion of 300 mL[c]	Two transfusions of 200 mL administered 24 h apart	Two transfusions of 275 mL (±75 mL) administered 24 h apart
Treatment since symptom onset	Any time	≤72 h	Any time	Any time	≤12 d	≤3 d	≤14 d	Any time	≤14 d	Any time
Type of control	Standard of care	Placebo and standard of care	Placebo and standard of care	Standard of care	Standard of care	Placebo and standard of care	Standard of care	Standard of care	Standard of care	Standard of care

Abbreviations: ConCOVID, Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease; ConPlas-19, Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients; PICP19, Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease; PlasmAr, Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia; RBD, receptor-binding domain; RECOVERY, Randomized Evaluation of COVID-19 Therapy.

[a] Three of the trials did not have study acronyms (only trial registration numbers) and ILBS-COVID-02 and PLACID did not have expansions in the original publications.

[b] High was defined in this meta-analysis as S-protein RBD–specific IgG antibody titer of 1:640 or higher or serum neutralization titer of 1:40 or higher.

[c] The COVIDAR IgG test was used to determine the dose.

Table 2. Patient Baseline Characteristics in 9 Trials

	Trial registration No. (study acronym)[a]								
	ChiCTR 2000029757[19]	NCT04479163[16]	NCT04383535 (PlasmAr)[18]	CTRI/2020/04/024775 (PLACID)[17]	NCT04345523 (ConPlas-19)[23]	NCT04346446 (ILBS-COVID-02)[21]	NCT04356534[20]	NCT04342182 (ConCOVID)[22]	CTRI/2020/05/025209 (PICP19)[24]
No. of patients randomized									
Convalescent plasma group	52	80	228	235	38	14	20	43	40
Control group[b]	51	80	105	229	43	15	20	43	40
Age, median (IQR), y									
Convalescent plasma group	70 (62-80)	76.4 (8.7)[c]	62.5 (53-72.5)	52 (42-60)	60.5 (46-74)	48.1 (9.1)[c]	52.6 (14.9)[c]	61 (56-70)	NR
Control group[b]	69 (63-76)	77.9 (8.4)[c]	62 (49-71)	52 (41-60)	58 (51-73)	48.3 (10.8)[c]	50.7 (12.5)[c]	63 (55-77)	NR
Sex, No. (%)									
Convalescent plasma group									
Male	27 (52)	26 (32)	161 (71)	177 (75)	20 (53)	11 (79)	17 (85)	29 (67)	30 (75)
Female	25 (48)	54 (68)	67 (29)	58 (25)	18 (47)	3 (21)	3 (15)	14 (33)	10 (25)
Control group[b]									
Male	33 (65)	34 (42)	64 (61)	177 (77)	24 (56)	11 (73)	15 (75)	33 (77)	27 (67)
Female	18 (35)	46 (58)	41 (39)	52 (23)	19 (54)	4 (27)	5 (25)	10 (23)	13 (33)
Type of mechanical ventilation use at randomization, No. (%)[d]									
Invasive									
Convalescent plasma group	14 (28)	0	0	0	0	0	0	5 (12)	0
Control group[b]	11 (22)	0	0	0	0	0	0	8 (19)	0
Noninvasive									
Convalescent plasma group	21 (41)	0	0	0	0	0	0	NR	0
Control group[b]	23 (46)	0	0	0	0	0	0	NR	0
Comorbidities at randomization, No. (%)									
Hypertension									
Convalescent plasma group	29 (56)	62 (78)	111 (49)	92 (39)	20 (53)	0	5 (25)	11 (26)	NR
Control group[b]	27 (53)	52 (65)	48 (46)	81 (35)	12 (28)	0	5 (25)	11 (26)	NR
Diabetes									
Convalescent plasma group	9 (17)	23 (29)	40 (18)	113 (48)	12 (32)	0	7 (35)	13 (30)	NR
Control group[b]	12 (24)	13 (16)[e]	21 (20)	87 (38)	5 (12)	0	9 (45)	8 (19)	NR
Cardiac disease									
Convalescent plasma group	14 (27)	14 (18)[e]	8 (4)	15 (6)	6 (16)	0	2 (10)	9 (21)	NR
Control group[b]	12 (24)	7 (9)[e]	3 (3)	17 (7)	9 (21)	0	2 (10)	11 (26)	NR

(continued)

Table 2. Patient Baseline Characteristics in 9 Trials (continued)

	Trial registration No. (study acronym)[a]								
	ChiCTR 2000029757[19]	NCT04479163[16]	NCT04383535 (PlasmAr)[18]	CTRI/2020/04/024775 (PLACID)[17]	NCT04345523 (ConPlas-19)[23]	NCT04346446 (ILBS-COVID-02)[21]	NCT04356534[20]	NCT04342182 (ConCOVID)[22]	CTRI/2020/05/025209 (PICP19)[24]
Pulmonary disease[f]									
Convalescent plasma group	NR	5 (6)	32 (14)	8 (3)	2 (5)	0	3 (15)	12 (28)	NR
Control group[b]	NR	8 (10)	7 (7)	7 (3)	8 (19)	0	0	11 (26)	NR
Chronic kidney failure									
Convalescent plasma group	2 (4)	1 (1)	10 (4)	8 (3)	2 (5)	0	1 (5)	1 (2)	NR
Control group[b]	4 (8)	3 (4)[e]	4 (4)	9 (4)	2 (5)	0	1 (5)	6 (14)	NR
Cancer									
Convalescent plasma group	3 (6)	4 (5)	27 (12)	1 (<1)	NR	0	NR	5 (12)	NR
Control group[b]	0	2 (2)	14 (14)	0	NR	0	NR	3 (7)	NR
Liver disease									
Convalescent plasma group	5 (10)	0	NR	0	NR	NR	0	1 (2)	NR
Control group[b]	5 (10)	0	NR	0	NR	NR	0	0	NR
Risk factors at randomization, No. (%)									
Smoker[g]									
Convalescent plasma group	NR	13 (16)	107 (47)	19 (8)	NR	NR	0	NR	NR
Control group[b]	NR	10 (12)	43 (41)	18 (8)	NR	NR	0	NR	NR
Body mass index >30[h]									
Convalescent plasma group	NR	4 (5)	104 (46)	16 (7)	NR	NR	NR	NR	NR
Control group[b]	NR	8 (10)[e]	52 (50)	17 (7)	NR	NR	NR	NR	NR

Abbreviations: ConCOVID, Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease; ConPlas-19, Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients; NR, not reported; PICP19, Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease; PlasmAr, Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia.

[a] Three of the trials did not have study acronyms (only trial registration numbers) and ILBS-COVID-02 and PLACID did not have expansions in the original publications. Only 3 trials reported concurrent treatments at randomization. Of 81 patients in ConPlas-19, 70 (86.4%) received hydroxychloroquine, 50 (61.7%) received azithromycin, and 46 received (56.8%) corticosteroids. Of 103 patients in ChiCTR2000029757, 85 (82.5%) received antiviral drugs, 77 (74.8%) received antibacterial or antibiotic drugs, and 37 (35.9%) received corticosteroids. Of 333 patients in PlasmAr, 9 (2.7%) received corticosteroids. Information on patient baseline characteristics were not available for the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial because the results were communicated as a press release.

[b] Placebo together with standard of care or only standard of care.

[c] Reported as mean (SD).

[d] Categorized according to what was reported in the trial reports.

[e] The denominator was 79 patients.

[f] Includes chronic obstructive pulmonary disease, asthma, and tuberculosis.

[g] Includes current and former smokers.

[h] Calculated as weight in kilograms divided by height in meters squared.

Figure 1. Risk of Bias Assessments for the Outcomes of All-Cause Mortality, Length of Hospital Stay, and Mechanical Ventilation Use

Risk of bias domain (assessments for the effect of assignment to intervention)	Trial registration No. or study acronym									
	ChiCTR2000029757[19]	NCT04479163[16]	PlasmAr[18]	PLACID[17]	ConPlas-19[23]	ILBS-COVID-02[21]	NCT04356534[20]	ConCOVID[22]	PICP19[24]	RECOVERY[8]
1. Randomization process	Low	Low	Low	Low	Some concerns	Low	Some concerns	Low	Some concerns	Low
2. Deviations from the intended interventions	Low	Low	Low	Low	Low	Low	Low	Low	Some concerns	NA
3. Missing outcome data	Low	Low	Low	Low	Low	Low	Low	Low	Low	NA
4. Measurement of the outcome	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
5. Selection of the reported result	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Overall risk of bias	Low	Low	Low	Low	Some concerns[a]	Low	Some concerns[a]	Low	High risk[b]	Probably low risk[c]

Three of the trials did not have study acronyms (only trial registration numbers) and ILBS-COVID-02 and PLACID did not have expansions in the original publications. ConCOVID indicates Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease; ConPlas-19, Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients; NA, not available; PICP19, Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease; PlasmAr, Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia; RECOVERY, Randomized Evaluation of COVID-19 Therapy.

[a] There was no detailed information reported regarding (1) the randomization process or (2) the concealment of randomized assignment.

[b] There was no detailed information reported regarding (1) the randomization process, (2) the concealment of randomized assignment, (3) the flow of patients through the trial, and (4) possible deviations from the intended interventions due to the open-label setting of the trial.

[c] The results were communicated as a press release. The assessment of this trial considered the study protocol and publications reporting results from other treatment groups of the trial.[4-6,26,27]

clinical improvement were available in 5 RCTs (3 peer-reviewed and 2 preprints) and 3 RCTs reported data on serious adverse events (1 peer-reviewed and 2 preprints).

Association of Convalescent Plasma With Clinical Outcomes

In the primary analysis including only peer-reviewed RCTs, the mortality in patients receiving convalescent plasma was 11.6% (69/595) and 12.7% (59/465) in control patients. The summary RR for all-cause mortality with convalescent plasma was 0.93 (95% CI, 0.63 to 1.38; P = .60) and the absolute risk difference was −1.21% (95% CI, −5.29% to 2.88%). There was no significant between-trial heterogeneity (I^2 = 0%; τ^2 = 0 [95% CI, 0 to 1.35]) (**Figure 2**A). In the RECOVERY trial, the reported 28-day mortality rates were 18% with convalescent plasma and 18% for usual care (control).

Across the 10 RCTs, the summary RR for all-cause mortality with convalescent plasma was 1.02 (95% CI, 0.92 to 1.12]; P = .68). There was no significant between-trial heterogeneity (I^2 = 0%; τ^2 = 0 [95% CI, 0 to 0.86]). In this meta-analysis of the 10 RCTs for all-cause mortality, the RECOVERY trial accounted for 90.2% of the weight and 88.3% (10 406/11 782) of the patients (Figure 2). The results of the sensitivity analyses were consistent with the main results (eTable 2 in the Supplement).

The 4 peer-reviewed RCTs showed no significant associations between treatment with convalescent plasma and reductions in length of hospital stay (summary HR, 1.17 [95% CI, 0.07 to 20.34], P = .61 for analysis of 436 patients) or mechanical ventilation use (summary RR, 0.76 [95% CI, 0.20 to 2.87], P = .35 for analysis of 957 patients) (Figure 2). The absolute risk difference for mechanical ventilation use was −2.56% (95% CI, −13.16% to 8.05%). Similar results were observed for the peer-reviewed and preprint RCTs for length of hospital stay (HR, 1.07 [95% CI, 0.79 to 1.45], P = .87 for analysis of 603 patients) and for mechanical ventilation use (RR, 0.81 [95% CI, 0.42 to 1.58], P = .88 for analysis of 1026 patients; Figure 2). The absolute risk difference for mechanical ventilation use was −2.21% (95% CI, −8.94% to 4.51%) (eFigure 2 in the Supplement).

For clinical improvement and clinical deterioration, the RRs were not summarized across RCTs due to inconsistent definitions and insufficient reporting of relevant details for these outcomes (eTable 1 and eFigure 3 in the Supplement). Of the 5 RCTs (3 peer-reviewed and 2 preprints) that reported such data, none demonstrated statistically significant clinical deterioration or improvement in patients who received convalescent plasma compared with the control group and the 95% CIs were wide (eFigure 3 in the Supplement).

No meta-analysis was conducted on serious adverse events due to inconsistencies in the reporting. PlasmAr (NCT04383535), ConPlas-19 (NCT04345523), and ConCOVID (NCT04342182) were the RCTs that reported data on serious adverse events (eFigure 4 in the Supplement); 60 serious adverse events were reported for the 309 patients in the convalescent plasma groups and 26 serious adverse events were reported for the 191 patients in the control groups. Even though ConCOVID (NCT04342182) included all-cause mortality in its definition of serious adverse events and 17 patients died, only plasma-related serious adverse events were reported (with 0 events). Similarly, PLACID (CTRI/2020/04/024775) and NCT04356534 reported recording serious adverse events including all-cause mortality but no clear data were shown.

The Certainty of the Evidence

For the primary analysis that only included the 4 RCTs published in peer-reviewed journals, the certainty of the evidence (using GRADE) for mortality was low due to very serious imprecision concerns regarding the wide 95% CI for the summary RR, which would be compatible with substantial benefit or harm. For the secondary analysis that included all 10 RCTs (published in peer-reviewed journals, published as preprints, and the RECOVERY trial), the concern regarding imprecision was reduced and the certainty of the evidence was rated as moderate (eTable 3 in the Supplement).

For length of hospital stay and mechanical ventilation use, the certainty of the evidence was rated as low for peer-reviewed trials only and when considering all publicly available trials due to very serious imprecision concerns (wide 95% CIs for the summary RR estimates; eTable 3 in the Supplement).

Discussion

In this meta-analysis that included 4 RCTs published in peer-reviewed journals for the primary analysis and an additional 6 RCTs not published in peer-reviewed journals (5 preprints and 1 press release) for the secondary analysis, treatment with convalescent plasma compared with placebo in combination with standard of care or only standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes among patients with COVID-19.

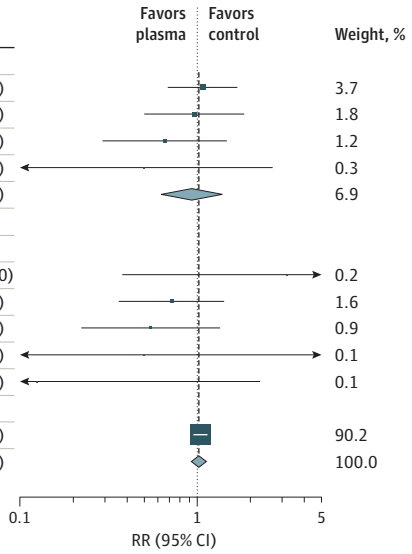
The certainty of the evidence on all-cause mortality was low when only the peer-reviewed trials were included and then moderate when the evidence from the RCTs published as preprints and the RECOVERY trial was added. The evidence was largely dominated by the RECOVERY trial, which accounted for 90.2% of the weight in the meta-analysis, although the pooled results from the 4 peer-reviewed trials were similar. The results from the RECOVERY trial published as a press release warrant cautious interpretation until the trial results are fully analyzed and reported in a peer-reviewed journal.

There also was no significant association of convalescent plasma with benefits on other patient-relevant clinical outcomes, including reduction in the length of hospital stay or mechanical ventilation use; however, summarized sample sizes were considerably smaller (range, 603-1026 patients) than for all-cause mortality (11 782 patients). Data on clinical improvement or deterioration were limited and inconclusive due to the use of inconsistent definitions for the outcomes and insufficient reporting of the relevant details for these outcomes. Similarly, the safety of convalescent plasma regarding serious adverse events could not be reliably assessed because only 3 RCTs reported data and there were inconsistencies in the definitions used. Although it was identified during the literature search, the press release for the REMAP-CAP trial[25] was not

Figure 2. Association of Convalescent Plasma With All-Cause Mortality, Length of Hospital Stay, and Mechanical Ventilation Use in Peer-Reviewed Trials and Non–Peer-Reviewed Trials (Preprints and the RECOVERY Trial)

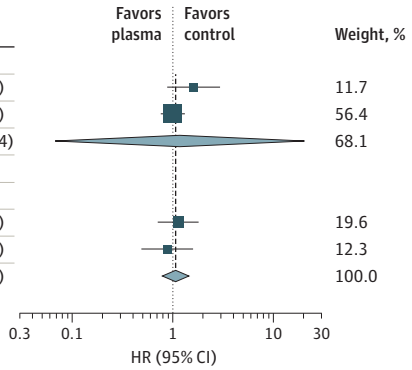
A All-cause mortality

Trial	Events, No./total: Plasma	Control	RR (95% CI)	Weight, %
Studies published in peer-reviewed journals				
PLACID[17]	34/235	31/229	1.07 (0.68-1.68)	3.7
PlasmAr[18]	25/228	12/105	0.96 (0.50-1.83)	1.8
ChiCTR2000029757[19]	8/52	12/51	0.65 (0.29-1.47)	1.2
NCT04479163[16]	2/80	4/80	0.50 (0.09-2.65)	0.3
Summary for peer-reviewed studies			0.93 (0.63-1.38)	6.9
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .65$				
Studies published as preprints				
ILBS-COVID-02[21]	3/14	1/15	3.21 (0.38-27.40)	0.2
PICP19[24]	10/40	14/40	0.71 (0.36-1.41)	1.6
ConCOVID[22]	6/43	11/43	0.55 (0.22-1.34)	0.9
NCT04356534[20]	1/20	2/20	0.50 (0.05-5.08)	0.1
ConPlas-19[23]	0/38	4/43	0.13 (0.01-2.26)	0.1
Study published as press release				
RECOVERY[8]	NA/NA	NA/NA	1.04 (0.95-1.14)	90.2
Summary for all studies			1.02 (0.92-1.12)	100.0
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .48$				
Test for overall effect: $P = .68$				



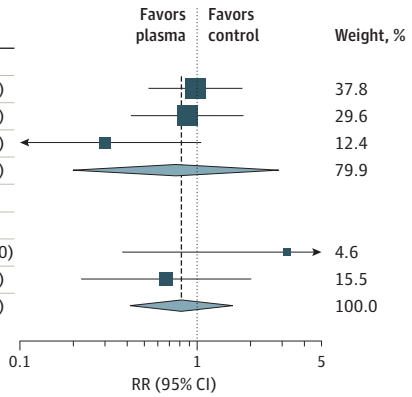
B Length of hospital stay

Trial	Events, No./total: Plasma	Control	HR (95% CI)	Weight, %
Studies published in peer-reviewed journals				
ChiCTR2000029757[19]	NA/52	NA/51	1.61 (0.88-2.95)	11.7
PlasmAr[18]	NA/228	NA/105	1.00 (0.76-1.32)	56.4
Summary for peer-reviewed studies			1.17 (0.07-20.34)	68.1
Heterogeneity: $I^2 = 49\%$, $\tau^2 = 0.0559$, $P = .16$				
Studies published as preprints				
ConPlas-19[23]	NA/38	NA/43	1.13 (0.71-1.80)	19.6
ConCOVID[22]	NA/43	NA/43	0.88 (0.49-1.59)	12.3
Summary for all studies[a]			1.07 (0.79-1.45)	100.0
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .48$				
Test for overall effect: $P = .55$				



C Mechanical ventilation use

Trial	Events, No./total: Plasma	Control	RR (95% CI)	Weight, %
Studies published in peer-reviewed journals				
PLACID[17]	19/235	19/229	0.97 (0.53-1.79)	37.8
PlasmAr[18]	19/228	10/105	0.87 (0.42-1.82)	29.6
NCT04479163[16]	3/80	10/80	0.30 (0.09-1.05)	12.4
Summary for peer-reviewed studies			0.76 (0.20-2.87)	79.9
Heterogeneity: $I^2 = 29\%$, $\tau^2 = 0.1194$, $P = .25$				
Studies published as preprints				
ILBS-COVID-02[21]	3/14	1/15	3.21 (0.38-27.40)	4.6
NCT04356534[20]	4/20	6/20	0.67 (0.22-2.01)	15.5
Summary for all studies[a]			0.81 (0.42-1.58)	100.0
Heterogeneity: $I^2 = 11\%$, $\tau^2 = 0.0559$, $P = .34$				
Test for overall effect: $P = .44$				



Three of the trials did not have study acronyms (only trial registration numbers) and ILBS-COVID-02 and PLACID did not have expansions in the original publications. Hartung-Knapp adjustment was used for the random-effects model and the Paule-Mandel estimator was used for τ^2. The weight percentages correspond to the secondary analysis for all studies. ConCOVID indicates Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease; ConPlas-19, Convalescent Plasma Therapy vs SOC for the Treatment of COVID-19 in Hospitalized Patients; HR, hazard ratio; NA, not available; PICP19, Passive Immunization With Convalescent Plasma in Severe COVID-19 Disease; PlasmAr, Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia; RECOVERY, Randomized Evaluation of COVID-19 Therapy; RR, risk ratio.

[a] Includes only the studies shown that were published in peer-reviewed journals or as preprints.

included because it did not present quantitative results. However, according to their reported preliminary analysis including 912 participants requiring intensive care unit support, treatment with convalescent plasma did not show a beneficial effect on the number of days requiring intensive support or on mortality. The REMAP-CAP preliminary findings are consistent with

our summarized results and, given the relatively small sample size of REMAP-CAP compared with the RECOVERY trial,[8] the data would likely not change our interpretation.

Difficulties in synthesizing evidence across COVID-19 trials because of heterogeneous outcome measures were anticipated by Zarin and Rosenfeld[28] who identified 351 unique descriptions for outcome measures among 232 trials registered until June 2020, including 14 unique ordinal scales. Besides precluding a meaningful overview, unnecessary variation in outcome measures makes precise conclusions more challenging. To aid the development of uniform outcome measurement across trials, core outcome sets involving patients may be a fruitful way forward.[29]

Limitations

This study has several limitations. First, 3 of the 10 RCTs had some concerns or high risk of bias. However, those 3 RCTs only contributed to 1.8% of the weight of the meta-analysis on all-cause mortality, which was highly dominated by data from the RECOVERY trial. Although access to full publication of the results was not yet available, the mortality results from the RECOVERY trial appear likely to be at low risk of bias and without a specific reason to downgrade the certainty of evidence based on previously published treatment group results and the RECOVERY trial protocol.[4-6,26,27]

Second, the reporting of clinical outcomes, other than all-cause mortality, for RECOVERY was insufficient and inconsistent regarding the use of definitions and relevant details across its COVID-19 treatment trials.

Third, the data were too limited to perform meaningful subgroup analyses. The observations reported in the literature regarding a benefit with early high-titer plasma[1] administration in observational studies call for further analyses based on individual patient data such as the Continuous Monitoring of Pooled International Trials of Convalescent Plasma for COVID-19 Hospitalized Patients (COMPILE) project.[30]

Fourth, except for 1 RCT with outpatients,[16] all patients were hospitalized with or without oxygen supplementation, indicative of moderate to critical COVID-19. The generalizability of the results to patients with milder COVID-19 is unclear.

Fifth, the primary focus of this meta-analysis was on published RCTs. There are many ongoing trials (>100) assessing convalescent plasma that are at risk of being terminated early or never published, but a collaborative meta-analysis of all these data is underway.[31]

Conclusions

Treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes. The certainty of the evidence was low to moderate for all-cause mortality and low for other outcomes.

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REFERENCES

1. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al; Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis*. 2015;211(1):80-90. doi:10.1093/infdis/jiu396

2. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc*. 2020;95(9):1888-1897. doi:10.1016/j.mayocp.2020.06.028

3. US Food and Drug Administration. FDA issues Emergency Use Authorization for convalescent plasma as potential promising COVID-19 treatment, another achievement in administration's fight against pandemic. Published August 24, 2020. Accessed January 27, 2021. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment

4. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med*. Published online July 17, 2020. doi:10.1056/NEJMoa2021436

5. Horby P, Mafham M, Linsell L, et al; RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med*. 2020;383(21):2030-2040. doi:10.1056/NEJMoa2022926

6. Horby PW, Mafham M, Bell JL, et al. Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2020;396(10259):1345-1352. doi:10.1016/S0140-6736(20)32013-4

7. Horby P, Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19—preliminary report. *medRxiv*. Published online June 22, 2020. doi:10.1101/2020.06.22.20137273

8. RECOVERY Trial. Press release: RECOVERY trial closes recruitment to convalescent plasma treatment for patients hospitalised with COVID-19. Published January 15, 2021. Accessed January 27, 2021. https://www.recoverytrial.net/news/statement-from-the-recovery-trial-chief-investigators-15-january-2021-recovery-trial-closes-recruitment-to-convalescent-plasma-treatment-for-patients-hospitalised-with-covid-19

9. Page M, McKenzie J, Bossuyt P, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *MetaArXiv*. Published online September 14, 2020. doi:10.31222/osf.io/v7gm2

10. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS: peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016;75:40-46. doi:10.1016/j.jclinepi.2016.01.021

11. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898

12. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD

13. Langan D, Higgins JPT, Simmonds M. Comparative performance of heterogeneity variance estimators in meta-analysis: a review of simulation studies. *Res Synth Methods*. 2017;8(2):181-198. doi:10.1002/jrsm.1198

14. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14:25. doi:10.1186/1471-2288-14-25

15. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

16. Libster R, Pérez Marc G, Wappner D, et al; Fundación INFANT–COVID-19 Group. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med*. Published online January 6, 2021. doi:10.1056/NEJMoa2033700

17. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P; PLACID Trial Collaborators. Convalescent plasma in the management of moderate COVID-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ*. 2020;371:m3939. doi:10.1136/bmj.m3939

18. Simonovich VA, Burgos Pratx LD, Scibona P, et al; PlasmAr Study Group. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med*. Published online November 24, 2020. doi:10.1056/NEJMoa2031304

19. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA*. 2020;324(5):460-470. doi:10.1001/jama.2020.10044

20. AlQahtani M, Abdulrahman A, Almadani A, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. *medRxiv*. Published online November 4, 2020. doi:10.1101/2020.11.02.20224303

21. Bajpai M, Kumar S, Maheshwari A, et al. Efficacy of convalescent plasma therapy compared to fresh frozen plasma in severely ill COVID-19 patients: a pilot randomized controlled trial. *medRxiv*. Published online October 27, 2020. doi:10.1101/2020.10.25.20219337

22. Gharbharan A, Jordans CCE, Geurtsvankessel C, et al. Convalescent plasma for COVID-19: a randomized clinical trial. *medRxiv*. Published online July 3, 2020. doi:10.1101/2020.07.01.20139857

23. Avendaño-Solà C, Ramos-Martinez A, Muñez-Rubio E, et al. Convalescent plasma for COVID-19: a multicenter, randomized clinical trial. *medRxiv*. Published online September 29, 2020. doi:10.1101/2020.08.26.20182444

24. Ray Y, Paul SR, Bandopadhyay P, et al. Clinical and immunological benefits of convalescent plasma therapy in severe COVID-19: insights from a single center open label randomised control trial. *medRxiv*. Published online November 29, 2020. doi:10.1101/2020.11.25.20237883

25. European Union Recover Project. Press release: REMAP-CAP: international trial of SARS-CoV-2 convalescent plasma pauses enrollment of critically ill COVID-19 patients. Published online January 11, 2021. Accessed February 1, 2021. https://www.recover-europe.eu/press-release-international-trial-of-sars-cov-2-convalescent-plasma-pauses-enrollment-of-critically-ill-covid-19-patients/

26. RECOVERY Trial. Randomised evalution of COVID-19 therapy (RECOVERY protocol). Accessed January 27, 2021. https://www.recoverytrial.net/files/recovery-protocol-v12-1-2020-12-16.pdf

27. Horby PW, Roddick A, Spata E, et al. Azithromycin in hospitalised patients with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv*. Published online December 14, 2020. doi:10.1101/2020.12.10.20245944

28. Zarin DA, Rosenfeld S. Lack of harmonization of coronavirus disease ordinal scales. *Clin Trials*. Published online December 15, 2020. doi:10.1177/1740774520972082

29. Marshall JC, Murthy S, Diaz J, et al; WHO Working Group on the Clinical Characterisation and Management of COVID-19 Infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192-e197. doi:10.1016/S1473-3099(20)30483-7

30. Petkova E, Antman EM, Troxel AB. Pooling data from individual clinical trials in the COVID-19 era. *JAMA*. 2020;324(6):543-545. doi:10.1001/jama.2020.13042

31. Janiaud P, Axfors C, Saccilotto R, Hemkens L, Schmitt A. COVID-evidence: a living database of trials on interventions for COVID-19. Published online April 1, 2020. Last updated August 19, 2020. Accessed February 17, 2021. https://osf.io/gehfx