

Safety and efficacy of convalescent plasma as a therapy for SARS-CoV-2: A systematic review and meta-analysis

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Abstract

Background and Aims: The safety and efficacy of convalescent plasma therapy (CPT) in SARS-CoV-2 is promising but intriguing due to heterogeneity of published studies. We conducted this systematic review and meta-analysis of convalescent plasma use in COVID-19 to identify its safety and efficacy.

Material and Methods: We comprehensively searched the databases - PubMed, Web of Science, Embase, and the Cochrane Library for journal papers published between December 2019 and January 2021 about the use of CPT in SARS-CoV-2, and performed a meta-analysis using random effects models and assessed the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: Of 1529 records, 11 studies were eligible (five RCTs, two nonrandomized intervention trials, three prospective observational, and one retrospective), and all were conducted in confirmed patients of SARS-CoV-2. Out of the 11 studies, four investigated the effect of CPT on mortality, three on symptom alleviation, five on duration of hospital stay, four on time to discharge, three on the effect on viral clearance, three on the improvement in antibody titers, two on oxygen requirement, and two on adverse events. The pooled estimate for relative risk of death from SARS-CoV-2 was no different after CPT than control (RR: 0.87, 95% CI: 0.69, 1.10), ($p = 0.426$) but the relative risk of clinical improvement of symptoms was better after CPT (RR: 1.61, 95% CI: 0.97, 2.70). There was earlier hospital discharge after CPT over control (RR: 1.49, 95% CI: 0.79, 2.80), improved viral clearance (RR: 1.95; 95% CI: 1.07, 3.53), and quicker detection of antibody titer (RR: 1.95; 95% CI: 1.07, 3.53). No difference was observed for adverse effects between CPT and control (RR: 0.92.; 95% CI: 0.63, 1.35).

Conclusion: CPT appears to be a safe and promising treatment in moderate to severe SARS-CoV-2 leading to faster clinical improvement, reduced oxygen requirement, early hospital discharge, and quicker emergence of protective antibodies despite having no mortality benefit.

Keywords: SARS-CoV-2, convalescent plasma, meta-analyses

Introduction


The outbreak of SARS-CoV-2 has inflicted a heavy casualty worldwide and the end doesn't seem anywhere near. Till date nearly 123 million patients are affected and 2.7 million deaths have been reported worldwide. Many old and new drugs have

been tried so far with variable success, although any definitive cure is still elusive.^[1,2]

Convalescent plasma therapy (CPT) involves collection of antibody-rich blood from SARS-CoV-2 recovered patients and its transfusion to affected patients. The neutralizing antibodies present in the blood bind to the viruses and prevent their entry into the host cell. They stimulate immune phagocytosis by the

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host cells leading to the killing of viruses. This therapy has been used earlier during Spanish flu pandemic of 1918 and thereafter during the outbreaks of SARS, MERS, and Ebola viruses. Three systematic reviews consisting of 13 studies (both observational and clinical trials) have so far reported its benefit in SARS-CoV-2, whereas two meta-analyses have found no advantages.^[3-5] Although FDA has approved its use for SARS-CoV-2, the specific treatment criteria are unknown. Most studies included in the earlier systematic reviews and meta-analyses possessed more weaknesses than strengths. The main weakness of the studies were in the lack of uniformity in CPT, inclusion of more patients with severe disease, wide variability in the dosing and timing of CPT, dearth of information about the viral load prior to CPT, and limited data about the neutralizing antibody titers following CPT.

This systematic review and meta-analyses were conducted to emendate the previous deficiencies and investigate the effects of CPT in SARS-CoV-2, and also unearth the key determinants of this treatment.

Method

Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review was registered in PROSPERO database (CDR 42021274135). The following databases - PubMed, Web of Science, Embase, and the Cochrane Library were comprehensively searched for journal papers published between December 2019 and January 2021, using the keywords “convalescent plasma,” “SARS-CoV-2,” “COVID-19,” “plasma,” “serum,” “immune,” and the related words for publications. Articles published in English language only were searched for analysis. Additionally, the references for selected studies were searched to identify other studies. Following the removal of duplicate entries, a three-stage screening process was adopted to identify eligible studies through the detailed examination of each title, abstract, and full text. Two reviewers independently screened the titles and abstracts of the retrieved citations and then assessed the full-text manuscripts that were considered potentially eligible. In case of disagreement between the two reviews with respect to fulfilment of inclusion criteria, the third reviewer acted as arbitrator.

Study selection

All studies fulfilled the following criteria: i) the population of interest was patients with confirmed diagnosis of SARS-CoV-2 for any age or sex, ii) randomized controlled trials (RCTs), non-randomized single-arm intervention studies, prospective observational studies, retrospective studies were eligible, iii) the intervention measure was CPT therapy, iv) there

was reporting of at least two outcomes of interest (mortality, symptom alleviation, hospital length of stay, antibody levels, viral load, effect on oxygen requirement, and v) reporting of adverse events. Only studies in English language were chosen.

The exclusion criteria were: i) reviews, case series, case reports, clinical guidelines, and expert consensus, ii) animal or *in vitro* studies, (iii) studies for which the full text was not available, and iv) studies with insufficient data on clinical information.

Data extraction

The studies retrieved during the searches were screened against the eligibility criteria and those meeting the criteria were included. Data was extracted from the eligible studies using a template by two independent authors and validated by a third. The following information was extracted: authors and country of the study, study design, number of participants, patients condition, time of administration, titers and dosages of CP, concomitant therapy, conclusion of authors, adverse events (AEs), and other results.

Risk of bias assessment

Two researchers independently assessed the potential bias for each selected study. The third researcher was consulted for resolving any difference of opinion. The ‘Risk of Bias’ 2.0 tool was used to assess the randomized clinical trials, which includes five domains: ‘randomization process,’ ‘deviations from intended interventions,’ ‘missing outcome data,’ ‘measurement of the outcome,’ and ‘selection of the reported results.’ The ‘Risk of Bias in Nonrandomized studies (ROBINS-I)’ was applied to assess the risk of bias in nonrandomized studies of interventions. It comprised seven domains: ‘bias due to confounding,’ ‘selection of participants,’ ‘classification of intervention,’ ‘deviations from intended interventions,’ ‘missing data,’ ‘measurement of outcomes’ and ‘selection of the reported results.’ The NIH quality assessment toll was used to assess the risk of bias in observational studies. Each domain was judged as ‘low,’ ‘moderate,’ ‘serious,’ and ‘critical.’ For every criterion, risk of bias was classified as ‘high,’ ‘unclear,’ or ‘low.’

Quality of the evidence

Two researchers independently assessed the quality of evidence by using the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE)’ tool. The GRADE was used to create a ‘Summary of findings’ table. The quality of evidence of each outcome is classified as ‘high,’ ‘moderate,’ ‘low,’ or ‘very low.’

Statistical analysis

The statistical software of SPSS was used for analyses. One researcher entered the data, and two researchers checked their accuracy. For dichotomous outcomes, the number of events

and total number of participants in two groups were recorded. Fixed-effects model was used if the result of the Q test was not significant ($p > 0.1$). The odds ratio (OR) and the RR with 95% confidence intervals (CIs) were assessed for all studies. A Chi-square test with a significance level at $P \leq 0.05$ was used to assess heterogeneity of treatment effects between trials. The I² statistic was used to quantify possible heterogeneity (I² statistic: 30–60% represented moderate heterogeneity, 75–100% considerable heterogeneity). If heterogeneity was above 80%, the potential causes were explored through sensitivity and subgroup analyses. If no reason for heterogeneity could be found, meta-analysis was not conducted. Subgroup analyses were performed if appropriate based on the data retrieved.

Result

Using the predefined key words, the initial literature search revealed 1529 studies from various databases. After pruning the results as per the inclusion and exclusion criteria, a total of 11 studies were selected for analysis as is shown in the PRISMA chart [Figure 1]. The studies included five randomized control studies, two nonrandomized interventional

studies, three prospective observational studies, and one retrospective observational study. The study characteristics are displayed under relevant headings [Table 1]. A “Summary of findings” table was also created using the GRADE tool, which was used to assess the quality of evidence [Table 2].

Study inclusion and characteristics

Out of the 11 studies, four studies investigated the effect of CPT on mortality after both moderate and severe COVID. A total of three studies investigated the effect of CPT on symptom alleviation, five studies investigated the effect on duration of hospital stay, four studies on time to discharge after COVID admission, three studies on the effect on viral clearance, three studies on the improvement in antibody titers, two studies on oxygen requirement, and two studies on adverse events.

Risk of bias within the studies

The risk of bias was low in two studies (two randomized controlled studies), moderate in six studies (three randomized controlled studies, two nonrandomized interventional studies, one prospective observational study), and high in three studies (two prospective observational studies, one retrospective observational study) [Table 3].

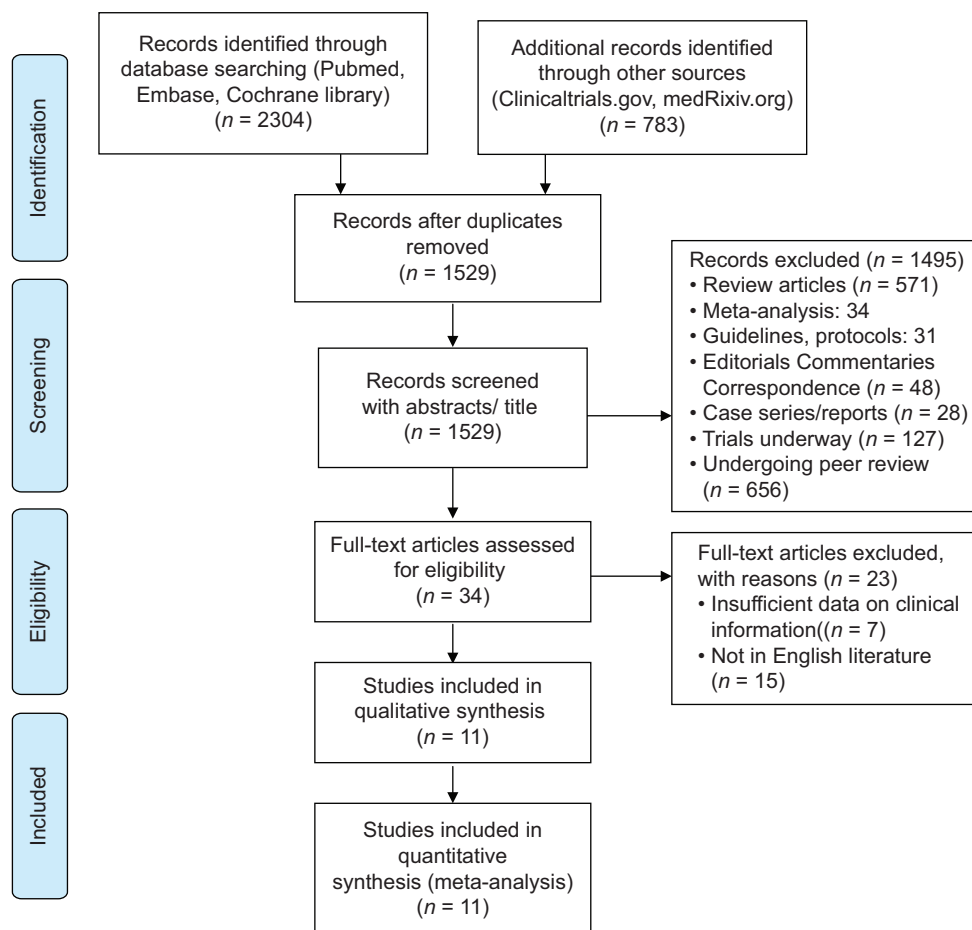


Figure 1: PRISMA

Table 1: Study characteristics

Authors and country	Design	Number of participants (n)	Criteria for enrolment	Time of CPT	Dosage and titers of CPT	Concomitant therapy	Conclusion	Adverse events (AEs) and other remarks
Duan K et al. China	Multi-center pilot observational study	20	Adults >18 years with severe COVID-19 infection, Respiratory distress (RR ≥30 beats/min, SpO ₂ <93% at rest, PaO ₂ :FiO ₂ ≤300 mmHg	Mean time from disease onset to CP transfusion=16.5 days	200 ml with the neutralizing antibody titers above 1:640 and transfused within 4 hours	Antiviral, Steroids, Antibiotics, Antifungal, anticoagulants	Potential benefit reduced viral load, better clinical outcomes	No serious adverse reactions
Abolghasemi H et al. Iran	Nonrandomized multi-center RCT	189	Confirmed COVID-19 with lung involvement on imaging with symptoms viz. dyspnea, respiratory rate ≥20/min, fever and cough, SPO ₂ ≤93% on room air, ≤7 days since disease onset	Within 3 days of hospital admission.	500 ml, repeat transfusion if no improvement occurs after 24 hours.	Antivirals, hydroxychloroquine, antiinflammatory agents	CPT is safe and effective for COVID-19 with improved patient survival & significantly reduced hospitalization and need for intubation	No serious adverse events
Ling Li et al. China	Open-label, multicenter, randomized clinical trial	103	Severe COVID-19 infection with respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation).	17.4 days (Median)	4 to 13 ml/kg of body weight: 10 ml for the first 15 minutes, then increased to 100 ml/hour	Antiviral, Antibacterial, steroids, human immunoglobulin, Chinese herbal medicines	No significant improvement in time to clinical improvement after 28 days, Early termination of trial	2 patients developed adverse reactions. One case of definite nonsevere allergic transfusion reaction or a probable nonsevere febrile nonhemolytic transfusion. The second patient had severe transfusion associated dyspnea
4. Rasheed et al. Iraq	Randomized controlled trial	49	Critically ill COVID-19 patients, (adults ≥18 year, SpO ₂ <90% in resting state, on O ₂ or mech vent)	Within first 3 days of ICU admission	400 mL single dose	Hydroxychloroquine, Azithromycin, Oxygen therapy, Methylprednisolone, Antibiotics, Anticoagulants	CPT is effective when donors with high level of SARS-CoV2 antibodies are selected and when recipients are in the early stage of disease illness	No serious adverse reaction. Single case of mild allergic reaction
5. Simonovich et al., Argentina	Double-blind, placebo-controlled, multicenter trial	333	Severe Covid-19 (radiological confirmed pneumonia, plus one of the following SaO ₂ <at rest and ambient air, PaO ₂ :FiO ₂ <300, SOFA or modified SOFA score of two or more points above baseline	Symptom onset to enrolment=8 days (IQR=5-10 days)	Median dose - 500 ml (IQR: 415-600) Median titer=1:3200 (IQR: 1:800-1:3200)	Glucocorticoids, Antivirals, Tocilizumab, Ivermectin, Hydroxychloroquine	No differences observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo.	No significant differences in incidence or severity of adverse events. Five patients in test group developed non-hemolytic febrile reactions

Contd...

Table 1: Contd...

Authors and country	Design	Number of participants (n)	Criteria for enrolment	Time of CPT	Dosage and titers of CPT	Concomitant therapy	Conclusion	Adverse events (AEs) and other remarks
Gharbharan et al. Netherlands	Multicenter open-label randomized clinical trial	86	Adults > 18 years with positive RT-PCR test in last 96 hours.		300 mL neutralizing titers of at least 1:80. Second dose after 5 days in patients without a clinical response and a persistently positive RT-PCR	Chloroquine, Azithromycin, Antivirals, Tocilizumab	Most COVID-19 patients already have high neutralizing antibody titers at hospital admission. Screening for antibodies and prioritizing convalescent plasma to risk groups with recent symptom onset will be key to identifying patients that may benefit from convalescent plasma.	No serious adverse events
7. Agarwal et al. BMJ October 2020, India	Open label, parallel arm, phase II, multicenter, randomized controlled trial.	Total=464 (Test=235 vs. Control=229)	Adults > 18 years age with moderate covid-19, PaO ₂ /FIO ₂ : 200-300 mm Hg or a respiratory rate >24/min, SpO ₂ ≤93% on room air)	Not mentioned	Two doses of 200 mL convalescent plasma, transfused 24 hours apart, levels of neutralizing antibodies not measured	Antivirals, antibiotics, immunomodulators, supplemental oxygen	Convalescent plasma was not associated with a reduction in progression to severe covid-19 or all cause mortality. This trial has high generalizability and approximates convalescent plasma use in real-life settings with limited laboratory capacity. <i>A priori</i> measurement of neutralizing antibody titres in donors and participants might further clarify the role of convalescent plasma in the management of covid-19	One patient in each group developed minor adverse events (pain at the infusion site, chills, nausea, bradycardia, and dizziness)
8. Liu et al. Nature Medicine November 2020 USA	Retrospective, propensity score-matched case-control study	Total=39. Retrospectively propensity-score matched to control patients (1:2 to 1:4)	severe or life-threatening COVID-19 at admission	Median time from admission to transfusion=4 days (range 0-7 days)	Not mentioned	Corticosteroids, Azithromycin, Interferential Antivirals, IL-6 inhibitors	Convalescent plasma is potentially effective against COVID-19, but adequately powered, randomized controlled trials are needed.	No serious transfusion-associated adverse events,
9. Li et al. JAMA, August 2020, China	Open-label, multicenter, randomized clinical trial	Total=103 (Test=52 vs. Control=51)	Adults > 18 years, with positive PCR within 72 hours of admission with Severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring		4 to 13 mL/kg	Antiviral, Antibacterial Steroids, Human immunoglobulin, Chinese herbal medicines	Among patients with severe or life-threatening COVID-19, convalescent plasma therapy did not result in a statistically significant improvement in time to clinical improvement within	Two participants reported transfusion-related adverse events following convalescent plasma transfusion. One patient in the severe COVID-19 group nonsevere allergic

Contd...

Table 1: Contd...

Authors and country	Design	Number of participants (n)	Criteria for enrolment	Time of CPT	Dosage and titers of CPT	Concomitant therapy	Conclusion	Adverse events (AEs) and other remarks
10. Zeng <i>et al.</i> 2020	Observational, prospective	N=6	mechanical ventilation) COVID-19 infection	21.5 days (median)	8 ml/kg	Antiviral, Steroids, anticoagulants	28 days. Interpretation is limited by early termination of the trial	transfusion reaction, other patient, who was in the life-threatening severe transfusion associated dyspnea. No side-effects
11. Liu <i>et al.</i> 2020	Observational, prospective	N=23	COVID-19 and respiratory failure COVID-19, respiratory failure, On HFNC/NIV	12 days (median)	300 ml	Steroids, anticoagulants	Five out of six died; no benefit Eight died; 15 survived; mortality benefit ($P=0.03$)	Mild allergic reaction in three patients

Mortality outcomes

The pooled estimate for relative risk of death from COVID was not statistically different after CPT than control (RR: 0.87, 95% CI: 0.69, 1.10), ($p = 0.426$). The mortality outcomes were influenced by the studies of Zeng *et al.*^[6] (RR: 0.89, 95% CI: 0.61, 1.31, 38.04%) and Abolghasemi *et al.*^[7] (RR: 0.61; 95% CI: 0.34, 1.10; 15.72% for severely ill COVID patients. However, Duan *et al.*^[8] found mortality benefit with CPT (RR: 0.65; 95% CI: 0.29, 1.46; 8.59%) in patients having moderate to severe disease. All the studies had low risk of bias. Additionally, Abolghasemi *et al.* found the risk of endotracheal intubation to be 7% in CPT as against 20% in the control group, although the study was not powered to detect such difference.^[7] CPT was found to be cost effective as well. [Figure 2] Among others, Li *et al.* and Agarwal *et al.*^[9] failed to observe any difference in the 28-day mortality after CPT.^[10]

Clinical improvement

The pooled estimate for relative risk of clinical improvement of symptoms was better after CPT than control (RR: 1.61, 95% CI: 0.97, 2.70). Some studies considered both clinical and microbiological recovery. All the studies investigating symptomatic improvement with CPT showed a positive association. Li *et al.* (RR: 1.85; 95% CI: 0.91, 3.77; 22.92%) and Simonovich *et al.* (RR: 2.10; 95% CI: 1.66, 2.66; 37.47%) showed improvement in both moderately and severely ill patients whereas Agarwal *et al.* (RR: 1.16; 95% CI: 1.02, 1.33; 39.61%) found benefit in moderately ill patients.^[9,11] However, there was significant heterogeneity between the studies ($I^2 = 90.9\%$, $P < 0.0001$) [Figure 3]. Rasheed *et al.*^[12] demonstrated a decreased recovery time for the critically ill COVID-19 patients who received CP.

Discharge from hospital

The pooled estimate showed a relative risk for earlier discharge after CPT over control (RR: 1.49, 95% CI: 0.79, 2.80). This was most notable in the studies by Zeng *et al.*^[6] (RR: 2.50; 95% CI: 0.18, 33.83; 5.14%) and Abolghasemi *et al.*^[7] (RR: 3.47; 95% CI: 1.40, 8.62; 22.04%) where early discharge was noted in severely ill patients after CPT. It was also observed by Li *et al.*^[10] (RR: 1.42; 95% CI: 0.90, 2.24; 33.41%) in severely ill patients. However, the same was not reported by Simonovich *et al.* (RR: 0.90; 95% CI: 0.76, 1.06; 39.41%). There were significant heterogeneity among the four studies ($I^2 = 78.1\%$ $P = 0.003$) [Figure 4].^[11]

Viral clearance

CPT improved viral clearance in all studies (RR: 1.95; 95% CI: 1.07, 3.53). Zeng *et al.*^[6] demonstrated increased clearance in severely ill patients (RR: 3.30; 95% CI: 1.47, 7.42; 23.78%) whereas Li *et al.*^[10] (RR: 2.33; 95% CI:

Table 2: Summary of findings using the GRADE tool for quality assessment

Outcome	Illustrative comparative study		Relative effect (95% CI)	Number of participants in CP (studies)	Quality of evidence across the studies (GRADE)	Comments
	Assumed risk (SC)	Corresponding risk (CP)				
Death (total all cause) after treatment	Moderate to severely ill patients 22.02 per 100	67.96 per 100	0.87 (.69-1.10)	407 (4)	Low to moderate ⊙⊙	The end points are 28 days mostly. Studies are open level.
Improvement of symptoms (WHO 6 points ordinal scale for breathlessness) after treatment	Moderate to severe ill 50.74 per 100	76.19 per 100	1.61 (.97-2.70)	462 (3)	Moderate ⊙⊙⊙	No blinding in one study.
Improvement in detectable antibody titer (third day)	Moderate to severe ill 57.08 per 100	73.94 per 100	1.61 (.97-2.70)	501 (3)	Moderate to High ⊙⊙⊙	Wide CI. One open level study.
Improvement in requirement of O ₂ support	Moderate to severe ill 14.03 per 100	80.01 per 100	1.08 (.92-1.27)	317 (2)	Low to moderate ⊙⊙	Either open level or partial blinding
Viral clearance after treatment	Moderate to severe ill 50 per 100	72.56 per 100	1.95 (1.07-3.53)	226 (2)	Low to moderate ⊙⊙	Open level study
Hospital stays in days after treatment	Moderate to severely ill 8.45±1.87-13.5±1.33	4.52±2.35-14.25±1.5	0.11 (-.01-.24)	591 (4)	Low to moderate ⊙⊙	Dissociation of results between severely and moderately ill.
Early discharge (within 5-28 days of CP treatment)	Moderate to severely ill 39.34 per 100	48.75 per 100	1.49 (.89-2.80)	400 (4)	Low ⊙	Incongruence of results because of methodological difference.
Adversity in course after treatment	Moderate to severely ill 15.26 per 100	11.85 per 100	0.92 (.63-1.35)	388 (2)	High ⊙⊙⊙⊙	Deterioration of symptoms.

Table 3: Risk of bias assessment

Authors	Type of study	Risk of Bias
Kai Duan <i>et al.</i>	Prospective, observational	High
Hassan	Nonrandomized	Moderate
Abolghasemi <i>et al.</i>	Interventional	Moderate
Ling Li <i>et al.</i>	Multicenter, RCT	Moderate
Rasheed <i>et al.</i>	Multicenter, RCT	Low
Simonovich <i>et al.</i>	Multicenter, RCT	Moderate
Gharbharan <i>et al.</i>	Multicenter, RCT	Moderate
Agarwal <i>et al.</i>	Multicenter, RCT	Low
Liu <i>et al.</i>	Retrospective, observational	High
Li <i>et al.</i>	Nonrandomized RCT	Moderate
Zing <i>et al.</i>	Prospective, observational	Moderate
Liu <i>et al.</i>	Prospective, observational	High

1.54, 3.52; 35.2%) and Agarwal *et al.*^[9] (RR: 1.23; 95% CI: 1.04, 1.46; 41.02%) in both moderate and severely ill patients. Significant heterogeneity was found between these studies ($I^2 = 83.9\%$ $P = 0.002$) [Figure 5]. Both Li *et al.* and Agarwal *et al.* showed significantly faster conversion from positive to negative RT PCR in the CPT group over control. In the study by Li *et al.*, the sero-negative conversion was 72 hours in the severe disease group, whereas the same was on day seven of enrolment in the study by Agarwal *et al.*^[9,10]

Antibody titer

The pooled estimate for relative risk of detectable antibody titer was higher after CPT than control (RR 1.44, 95% CI: 0.72, 2.88). Significant improvement in titers was seen in severely ill patients by Rasheed *et al.* (RR 3.33; 95% CI: 1.84, 6.03; 28.98%) and in moderate to severe patients by Simonovich *et al.* (RR: 1.38; 95% CI: 1.03, 1.85; 34.59%).^[11,12] Study by Agarwal *et al.* showed no improvement in detectable antibody titers in moderately severe patients (RR 0.78; 95% CI: 0.68, 0.88; 36.43%). Significant heterogeneity was found between these studies ($I^2 = 94\%$ $P < 0.0001$) [Figure 6].^[9]

Simonovich and colleagues observed higher antibody titers on day 2 of CP transfusion, but no significant difference was noted at day seven or day 14. Agarwal *et al.*^[9] did not find any difference altogether in the level of antibody titers and suggested no benefit of CP transfusion on protective antibody levels.^[11,12]

Requirement of oxygen

A decreased oxygen requirement was seen after CPT in severely ill patients by Abolghasemi *et al.*^[7] (RR: 1.17;

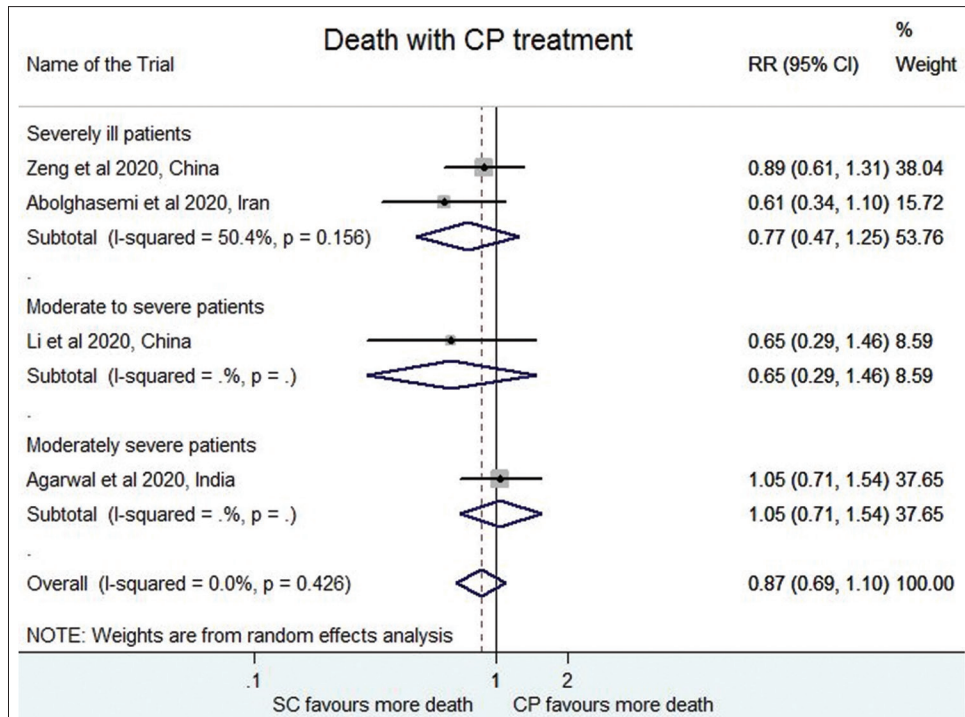


Figure 2: Mortality outcome after Convalescent Plasma Therapy. CP = Convalescent plasma SC = Standard of care RR = Relative Risk

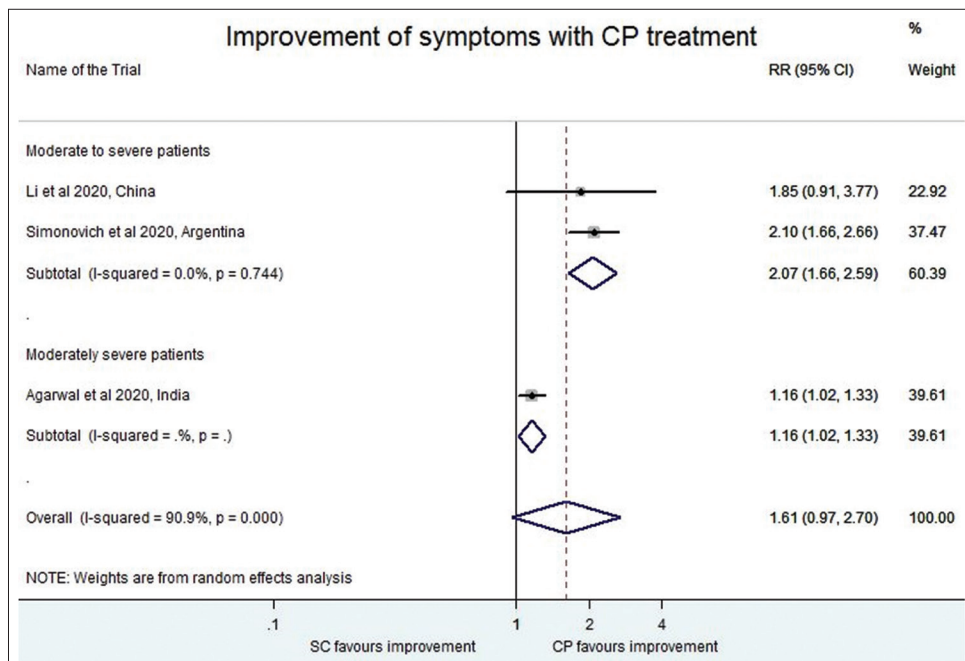


Figure 3: Clinical improvement with Convalescent plasma therapy. CP = Convalescent plasma SC = Standard of care RR = Relative Risk

95% CI: 1.03, 1.32; 51.51%). Simonovich and workers showed no decrease in Oxygen requirement in moderate to severe patients (RR: 0.99; 95% CI: 0.86, 1.14, and 48.49%). The overall pooled estimate for relative risk of requirement of oxygen support showed no difference with CPT (RR: 1.08, 95% CI: 0.92, 1.27).^[11] The heterogeneity between these two studies was not significant ($I^2 = 67.2%$,

$P = 0.081$) [Figure 7]. Agarwal *et al.* demonstrated no difference in the average inspired oxygen requirement between the different trial arms.^[9]

Adverse effects

The occurrence of adverse effects following CPT transfusion was assessed in various studies [Table 4]. No difference was observed in the pooled estimate of RR for adverse effects

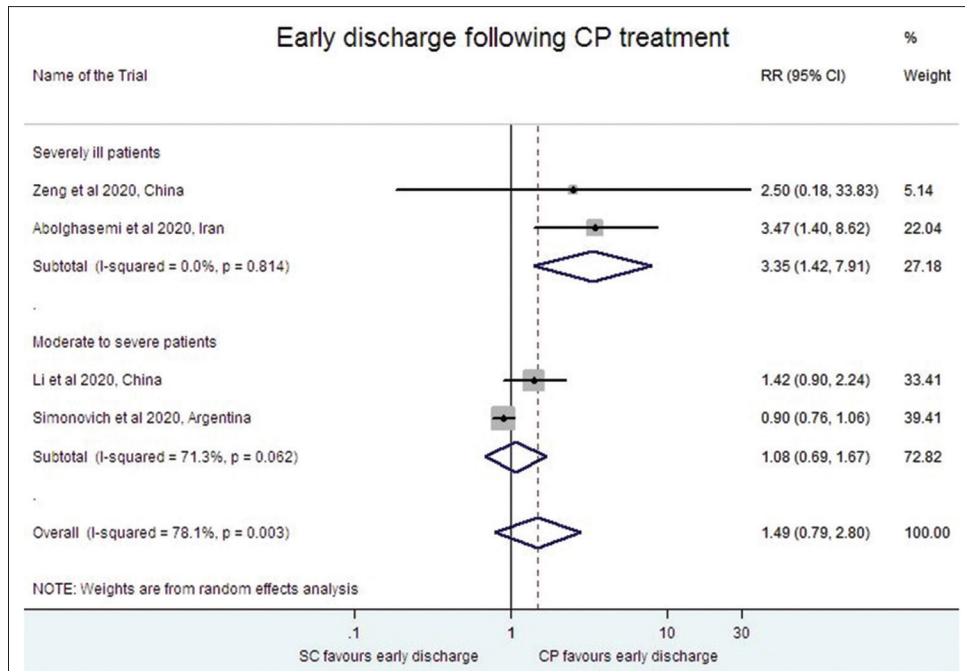


Figure 4: Discharge from hospital after Convalescent Plasma Therapy. CP = Convalescent plasma SC = Standard of care RR = Relative Risk

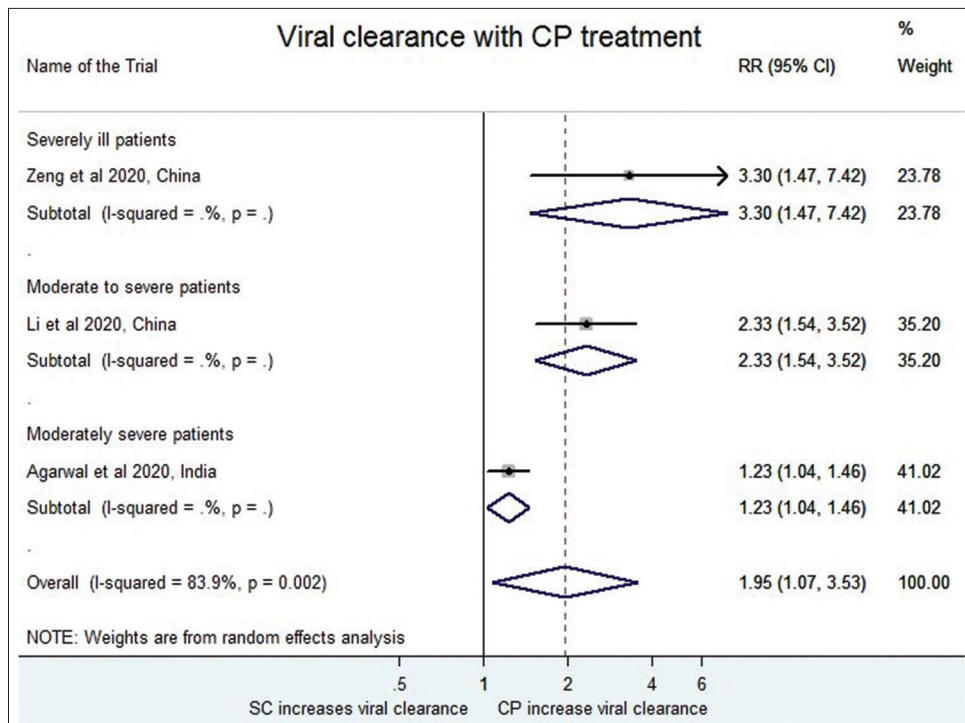


Figure 5: Viral clearance after Convalescent Plasma Therapy. CP = Convalescent plasma SC = Standard of care RR = Relative Risk

following CPT and control arm (RR: 0.92.; 95% CI: 0.63 1.35). Both Simonovich *et al.* (RR: 0.88, 95% CI: 0.42, 1.82; 26.81%) and Agarwal *et al.* (RR: 0.94; 95% CI: 0.61, 1.47; 73.19%) found insignificant difference in the incidence of adverse events in moderate to severe and moderately severe COVID-19 patients, respectively. No heterogeneity was observed in the studies ($I^2 = 0.0\%$, $P = 0.854$)^[9,11] [Figure 8].

Discussion

Our meta-analysis did not find any evidence of mortality benefit in SARS-CoV-2 following CPT. A similar systematic review and meta-analysis on severe acute respiratory syndrome (SARS) reported high-mortality benefit (OR, 0.25; 95% CI, 0.14 to 0.45; $I^2 = 0\%$) in comparison to

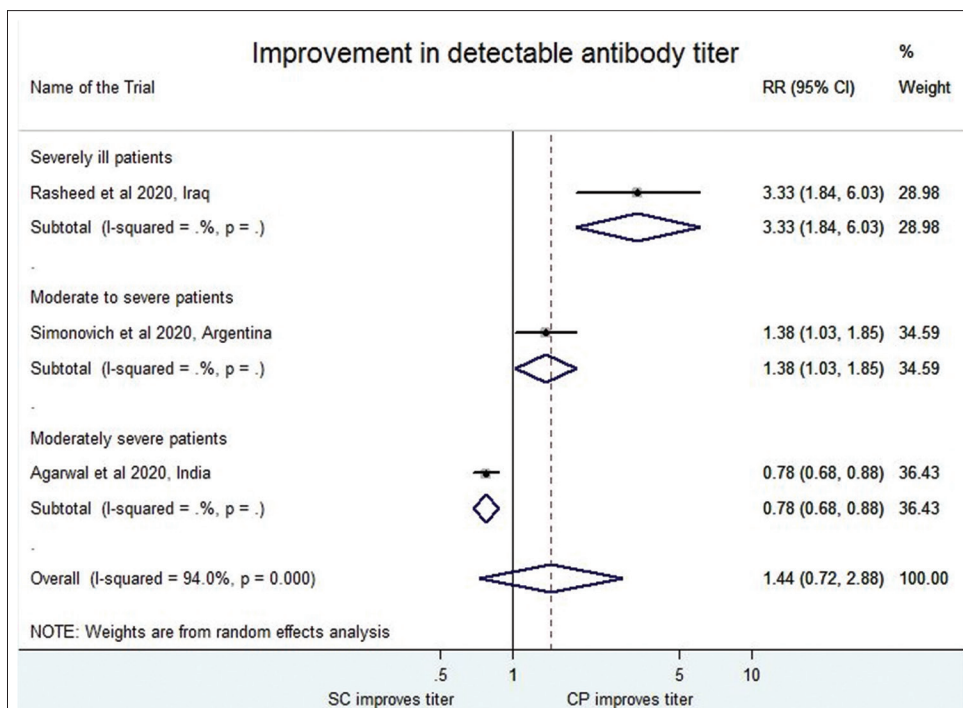


Figure 6: Antibody titer after Convalescent Plasma Therapy. CP = Convalescent plasma SC = Standard of care RR = Relative Risk

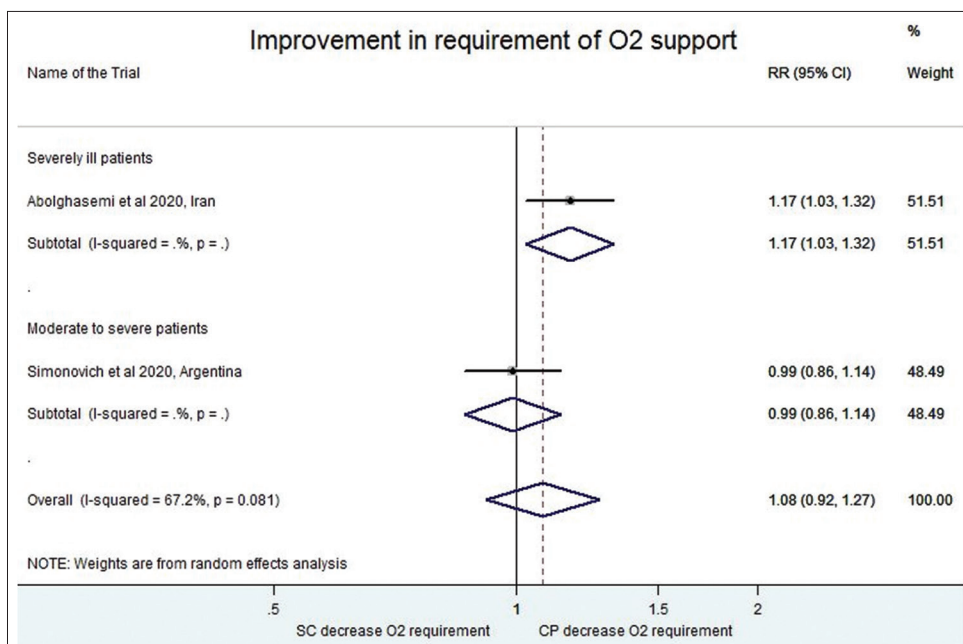


Figure 7: Effect on oxygen requirement after Convalescent Plasma Therapy. CP = Convalescent plasma SC = Standard of care RR = Relative Risk

placebo or no therapy.^[13] But, the said meta-analysis lacked information about the donor status and the severity of illness in the recipients. Another recent systematic review on CPT in SARS-CoV-2 patients reported mortality benefit with CPT, but relied heavily on case reports and case series, and not on observational studies or clinical trials. They were also unable to explain the variable efficacy of CPT in SARS-CoV-2 due to paucity of quantitative information.^[3]

Most of the earlier systematic reviews were based on low quality evidence, whereas our review has moderate quality of evidence. This has been possible in our review due to assessment of bias risk for all determinants, unlike other studies. Another systematic review that failed to elicit any mortality benefit of CPT but concluded it as safe considered the increased oxygen requirement as detrimental to patient safety in the absence of pulmonary involvement. However, the studies demonstrated

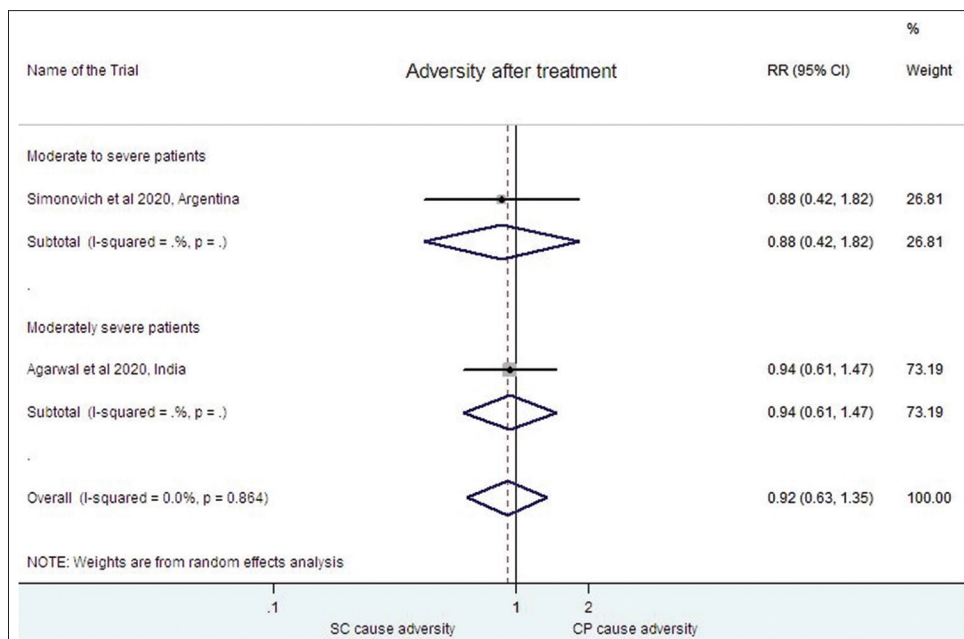


Figure 8: Adverse effects after Convalescent Plasma Therapy. CP = Convalescent plasma SC = Standard of care RR = Relative Risk

Table 4: Adverse events after CPT

Events	Incidence
Skin rash (Red rash)	1/20 (Rasheed <i>et al.</i> , 2020); 1/10 (Duan <i>et al.</i> , 2020);
Serious events (anaphylaxis, other allergic reaction)	54/228(CP) and 19/105(SC) (Simonovich <i>et al.</i> , 2020)
Transfusion-related adversity (pain, chill, nausea, bradycardia, dizziness)	5/235 (Agarwal <i>et al.</i> , 2020); 2/52 (Li <i>et al.</i> , 2020); 1/115 (Abolghasemi <i>et al.</i> , 2020)
No serious events	Liu <i>et al.</i> , 2020; Gharbharan <i>et al.</i> , 2020; Zeng <i>et al.</i> , 2020

significant increase in the requirement of oxygen in many patients with extrapulmonary involvement. The same effect was not weighed separately through discrimination tests. But, the most important factor was that the meta-analysis was based upon the CPT use on other severe viral respiratory infections also and the conclusions drawn about SARS-CoV-2.^[14]

We were also able to gather evidence with regard to early clinical improvement and faster viral clearance after CPT unlike other reviews. Another systematic review reported a significant decrease in viral loads and improvement in clinical symptoms within three to 26 days posttransfusion. But, they included patients with very high volume of plasma transfusion. It is known that too much plasma volume can dilute the concentration of the therapeutic drugs and affect recovery, which can delay viral clearance.^[15] Most of the earlier meta-analyses failed to limit the volume of plasma transfusion because of high heterogeneity. Moreover, the criteria of donor being symptom free for 14 days after recovery from SARS were not reviewed in many meta-analyses.

Our review found no difference in the oxygen requirement of patients undergoing CPT as against control, and the evidence was moderate. There was no heterogeneity among the studies. But the fact that CPT improves the host microenvironment and promote endogenous repair by inhibiting the overactive immune system can raise expectation about reduced oxygen requirement. Our review suggests the involvement of more complex mechanisms in the genesis of hypoxemia, which CPT alone may fail to redress.

The lack of adverse effects found low evidence in our meta-analysis that is similar to other reviews and meta-analyses because mild allergic reactions that are very common after CPT are excluded by majority of studies. There can be diagnostic dilemma for effects like fever, chills, circulatory overload, and so on, which are common during natural progression of SARS-CoV-2.^[16,17]

Limitations

Our meta-analysis has several limitations. First, certain outcome variables like clinical improvement, duration of hospital stay, discharge from hospital, and viral clearance showed considerable heterogeneity (I² statistic: 75–100%). So, defining the source of heterogeneity as clinical, methodological, or statistical is important to substantiate these findings.

Second, we did not weigh the criteria for donor selection before CPT and therefore the level of protection achieved in the recipient varied with changing titers in the donor plasma during CPT. This can also influence mortality besides affecting symptomatic clinical improvement. In other words,

conclusive evidence was lacking in these aspects. Lastly, our review relied on evidences collected from moderate to severe patients, and mild to moderate patients were missed. Much evidence accounts for timely and effective administration of CPT in mild SARS-CoV-2 resulting in early recovery and discharge sparing time, effort, and resources for other cases. A detailed subgroup analysis of moderate and severe cases can account for more details.

Conclusions

CPT appears to be a safe and promising intervention in the management of moderate to severe SARS-CoV-2 till date. Despite lacking evidence for any mortality benefit, it can result in faster clinical improvement, diminished oxygen requirement, shorter hospital stay, and earlier discharge thereby sparing resources and manpower for sick patients. Being safe and possessing high ability for viral clearance, its predictability can be used to treat SARS-CoV-2 in severe patients. However, donor selection and timing of CPT administration can be decisive.

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Conflicts of interest

There are no conflicts of interest.

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