SYSTEMATIC REVIEW

Convalescent Plasma—A Light at the End of the Tunnel: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Soumya Sarkar[1], Puneet Khanna[2], Akhil K Singh[3]

Abstract

In the absence of a definitive therapy during this ongoing unprecedented crisis, coronavirus disease-2019 (COVID-19) pandemic, convalescent plasma transfusion (CPT) has shown some promising results. This review summarizes the existing evidence of the efficacy of CPT in COVID-19 patients based upon scientific publications to date.

We have included only the randomized controlled trials (RCTs) through an extensive screening of electronic databases up to July 31, 2021.

In 19 RCTs, with a total of 16,476 COVID-19 patients we found low-quality evidence of significant reduction in mortality (odds ratio (OR) = 0.80; 95% confidence interval (CI): 0.66–0.96, I^2 = 40%), better clinical outcome when applied <7 days (OR = 2.13, 95% CI 1.28–3.53, I^2 = 0%), and improved viral clearance (OR = 2.6, 95% CI: 1.3–5.45, I^2 = 74%). Meta-regression analysis found that as a covariate, intubation on admission (p = 0.007) had a significant impact. However, there was any significant reduction neither in duration for clinical improvement (MD = −0.79, 95% CI: −2.76–1.18, I^2 = 98%), nor in total period of hospital stay (MD = 0.02, 95% CI: −0.75–0.78, I^2 = 81%).

Early application of CPT is still relevant in reducing morbidity and mortality in critically ill patients and is too early to write it off as a potential therapeutic modality for COVID-19 patients.

Keywords: Convalescent plasma, Coronavirus disease 2019, Meta-analysis, Randomized controlled trial, SARS-CoV-2.

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Introduction

In the absence of definitive therapy for the novel coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the US Food and Drug Administration (FDA) approved the use of convalescent plasma therapy (CPT) in COVID-19 patients under the emergency investigational new drug category.[1]

Traditionally during epidemics, the CPT has been tried in patients whose critical condition is refractory to supportive care.[2] The plasma is procured from a recently recovered person from a viral illness, which is supposed to have the maximum levels of polyclonal antibodies directed against the virus.[3]

The passive immune therapy has evolved from convalescent whole blood, convalescent plasma, pooled human immunoglobulin, and polyclonal or monoclonal antibodies, to the current practice of plasma collected by apheresis.[4] The practice of using blood products from recovered patients as a therapeutic agent was way back in the late 1800s. CPT has been effectively used since the Spanish influenza pandemic in 1915–1917,[5] severe acute respiratory syndrome (SARS) in 2003,[6] influenza A (H1N1) in 2009,[7] avian influenza A (H5N1),[8] and even in viral hemorrhagic fever-like Ebola.[3]

The CPT seems to be a promising option, with some early promising results on the improvement of clinical symptoms and reduction in mortality. However, the clinical evidence in this regard is still inconclusive and contradictory. Thus, the purpose of this review is to analyze the current evidence of the efficacy and safety of convalescent plasma therapy in COVID-19 patients. We have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines.

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Methods

Search Strategy

The authors PK and SS independently searched the major electronic databases (PubMed, MEDLINE, and Embase), Google Scholar (https://scholar.google.com), and preprint platforms medRxiv (https://www.medrxiv.org) from January 1, 2020, to July 31, 2021, with the following keywords: "COVID-19" OR "SARS-CoV-2" AND "plasma" OR "convalescent plasma" AND "Randomized Controlled trials" OR "RCT."

Inclusion and Exclusion Criteria

The RCTs over CPT in COVID-19 patients published in the English language were included. Our primary outcome of interest was mortality and viral clearance was the secondary outcome (PRISMA flow diagram).

Controlled clinical trials, comparative cohort studies, and case–control studies—cross-sectional studies with a control group on convalescent plasma therapy for COVID-19 patients were excluded.

Study Selection

Initially, SS and PK screened every available abstract separately after the removal of the duplications for excluding the irrelevant articles. After that, the full texts of the potential studies were examined. Disagreements were consulted with AKS.

Data Extraction

SS and PK extracted the data of the first author, year of publication, type of study, place, sample size, details of the intervention and control groups, mortality, clinical improvement, and viral clearance by using a preconceived data extraction sheet individually.

Risk of Bias Assessment

PK and SS assessed the potential bias in every selected study individually with the Risk of Bias (RoB) 2.0 tool after resolving the difference of opinion with the consultation of AKS.

Quality of the Evidence

PK and AKS evaluated the quality of evidence independently by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.

Data Synthesis

We used the Review Manager version 5.4 for conducting this meta-analysis along with subgroup analyses based upon severity and administration time of CPT, and the comprehensive meta-analysis version 3 for conducting meta-regression analysis. We calculated the odds ratio (OR) with 95% confidence interval (CI) according to the Cochrane Handbook for Systematic Reviews of Interventions. Statistical heterogeneity was assessed with the I^2 >50%, indicating substantial heterogeneity. A funnel plot was used to assess publication bias.

Results

Basic Characteristics

A total of 19 studies out of 1,337 identified publications were included after satisfying the inclusion criteria and 9 of them were preprints (Flowchart 1; Table 1).

Meta-analysis

Mortality

A significant reduction in mortality among COVID-19 patients with CPT (OR = 0.80; 95% CI: 0.66–0.96, I^2 = 40%) was found in 19 RCTs (n = 1,409 patients) (Fig. 1).

In subgroup analysis, though the impact of CPT on mortality among critically ill patients (OR = 0.68; 95% CI: 0.52–0.88, I^2 = 59%) was significant, the patients with mild (OR = 1.00; 95% CI: 0.75–1.35, I^2 = 0%) or moderate illness (OR = 0.70; 95% CI: 0.27–1.83, I^2 = 46%) showed no additional benefit.

Flowchart 1: PRISMA-2009 flow diagram

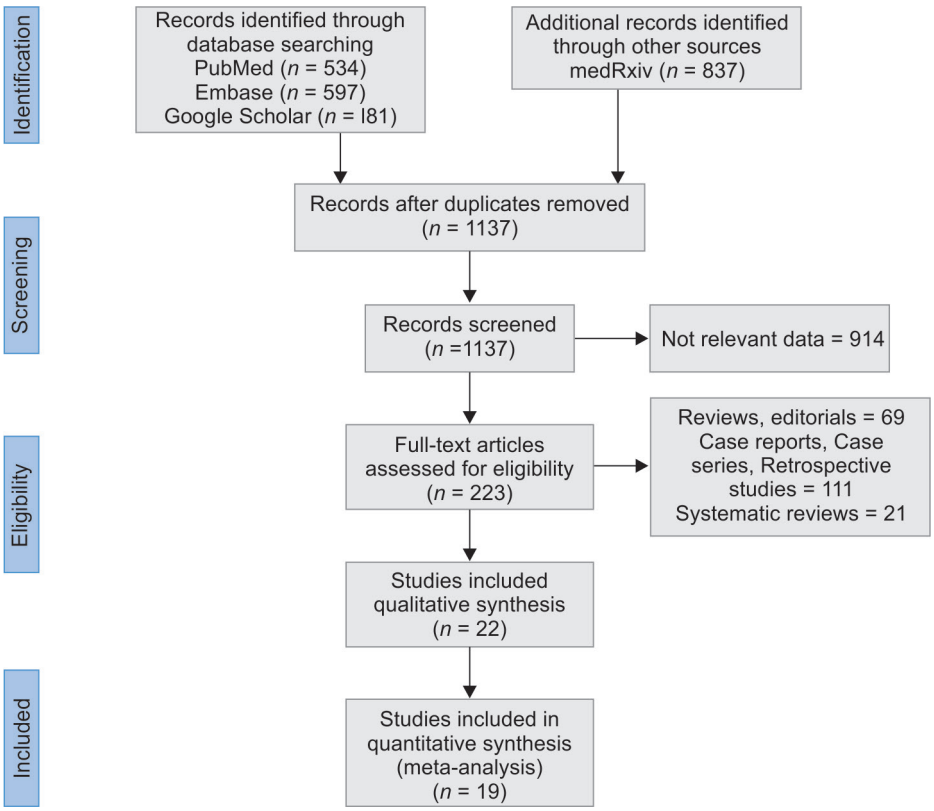


Table 1: Characteristics of the included studies

Sl. No.	*Studies, Year*	*DOI, PMID*	*Type of study, center*	*Country*	*Study population*	*Dosage of CP*	*Titer*	*Initiation time*	*Condition of the patients*	*Outcome*
1.	Agarwal et al., 2020	DOI: 10.1136/bmj.m3939, PMID: 33093056	Open-label RCT, MC	India	464	Two doses of 200 mL of CP, 24 hours apart	>1:80	6 days (IQR 3–11 days)	Moderately ill	CP was not beneficial for preventing the mortality
2.	AlQahtani et al., 2020	DOI: 10.1038/s41598-021-89444-5, PMID: 33976287	Open-label RCT, SC	Bahrain	40	200 mL over two successive days	Not specified	<3 ($n = 6$), >3($n = 7$)	Moderately ill	Fewer patients required ventilation for a shorter duration
3.	Bajpai et al., 2020	DOI: 10.1101/2020.10.25.20219337	Open-label RCT, SC	India	29	500 mL plasma in two divided doses on consecutive days	>1:80	3	Severely ill	CP resulted in rapid improvement in respiratory parameters and shortened time to clinical recovery, without any significant reduction in mortality
4.	Gharbharan et al., 2020	DOI: 10.1038/s41467-021-23469-2, PMID: 34045486	Open-label RCT, MC	Netherlands	86	300 mL	>1:80	10 days (IQR 6–15)	Severely ill	No statistically significant differences in mortality (or improvement in the day-15 disease severity was observed when the study was suspended
5.	Libster et al., 2020	DOI: 10.1056/NEJMoa2033700, PMID: 33406353	Open-label RCT, MC	Argentina	160	250 mL	>1:1,000	Within 72 hours	Mild COVID-19	Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill-infected older adults reduced the progression of COVID-19
6.	Li et al., 2020	DOI: 10.1001/jama.2020.10044, PMID: 32492084	Open label RCT, MC	China	103	4–13 mL/kg	>1:640	27 days (IQR, 22–39)	Severely ill	No significant improvement in time to clinical improvement within 28 days in severe or life-threatening COVID-19 patients until the early termination of the trial
7.	Rasheed et al., 2020	PMID: 32920571	Open-label RCT, MC	Iraq	49	400 mL	Not specified	14.80 + 7.46	Critically ill	CP lowered death rate from 28% in control group to 4.8%
8.	Ray et al., 2020	DOI: 10.1101/2020.11.25.20237883	Open-label RCT, SC	India	80	200 mL on two successive days	Not specified	4.2 ± 2.21	Severely ill	Significantly improved hypoxia, reduction in hospital stay in severe COVID-19 patients with ARDS
9.	Simonovich et al., 2020	DOI: 10.1056/NEJMoa2031304, PMID: 33232588	Open-label RCT, MC	Argentina	333	500 mL (IQR, 415–600)	1:3,200 (IQR 1:800–1:3,200)	8 days (IQR, 5–10)	Severely ill	No significant difference in overall mortality between the patients treated with convalescent plasma
10.	Sola et al., 2020	DOI: 10.1101/2020.08.26.20182444	Open-label RCT, MC	Spain	81	250–300 mL	1:292 (IQR 238–451)	8 days	Not specified	Patients assigned to CP had a lower rate of worsening at 15 days than patients receiving standard care
11	Ali et al., 2021	DOI: 10.1016/j.eclinm.2021.100926, PMID: 34109306	Open-label RCT, SC	Pakistan	50	(0.15, 0.20, 0.25, 0.30 gm/kg)	Not specified	8.0 ± 3.0	Critically ill	The hyperimmune anti-COVID-19 intravenous immunoglobulin derived from CP reduces mortality and morbidity in critically ill COVID-19 patients

Table 1: *(Contd)*

12	CONCOR, 2021	DOI: 10.1101/2021.06.29.21259427	Open-label RCT, MC	Canada, USA, Brazil	851	500 mL	>1:160	8 (IQR, 5–10)	Mild COVID-19	No significant difference in terms of mortality; frequency of intubation was found with CP in comparison with the hospitalized COVID-19 patients, received standard care
13	Gonzalez et al., 2021	DOI: 10.1101/2021.03.28.21254507	Open-label RCT, SC	Mexico	165	200 mL over 2 hours, for 2 days	Not specified	Not specified	Severely ill	Both CP and IVIG had similar outcomes in terms of hospitalization duration or mortality in COVID-19 patients
14	Guerrero et al., 2021	DOI: 10.1097/CCM.0000000000005066, PMID: 33870923	Open-label RCT, SC	USA	74	480 mL	1:526 (1:359–1:786)	9 (IQR, 6–18)	Moderately ill	The overall 90-day mortality was lower in CP group in comparison with standard plasma group (27 vs 33%; $p = 0.63$). The outcome is more significant in intubated patients at admission
15	Körper et al., 2021	DOI: 10.1101/2021.05.10.21256192	Open-label RCT, MC	Germany	105	837 mL (IQR 738–872 mL)	1:160 (IQR 1:80–1:320)	7 days	Critically ill	The CPT-recipient COVID-19 patients had a median time of 26 days for clinical improvement and 31 days for discharge from hospital in comparison with the control group (66 days and 51 days, respectively). Significant benefit is noted in CP with higher neutralizing antibodies
16	O'Donnell et al., 2021	DOI: 10.1172/JCI150646, PMID: 33974559	Open-label RCT, MC	USA, Brazil	223	250 mL	1:160 (IQR 1:80–1:320)	9 days	Severely ill	CP was associated with significantly reduced mortality (OR 0.44, 95% CI 0.22–0.91, $p = 0.034$)
17	Pouladazdeh et al., 2021	DOI: 10.1007/s11739-021-02734-8, PMID: 33837906	Open-label RCT, SC	Iran	60	500 mL	Not specified	Not specified	Critically ill	CP posses immunomodulatory, antiviral role for avoiding the cytokine storm and improving the 8-point WHO severity score
18	Recovery Collaborative Group, 2021	DOI: 10.1101/2021.03.09.21252736	Open-label RCT, MC	UK	11,558	550 mL	≥1:100	9 days	Critically ill	High-titer CP did not improve survival in COVID-19 patients
19	REMAP-CAP, 2021	DOI: 10.1101/2021.06.11.21258760	Open-label RCT, MC	Australia, Canada, UK, USA	1,979	550 ± 150 mL	≥1:160	Not specified	Severely ill	The mortality was 37.3% in CP group, and 38.4% in control group

CP, convalescent plasma; SC, single center; MC, multicenter; RCT, randomized controlled trial; IQR, inter-quartile range; ARDS, acute respiratory distress syndrome; IVIG, intravenous immune globulin

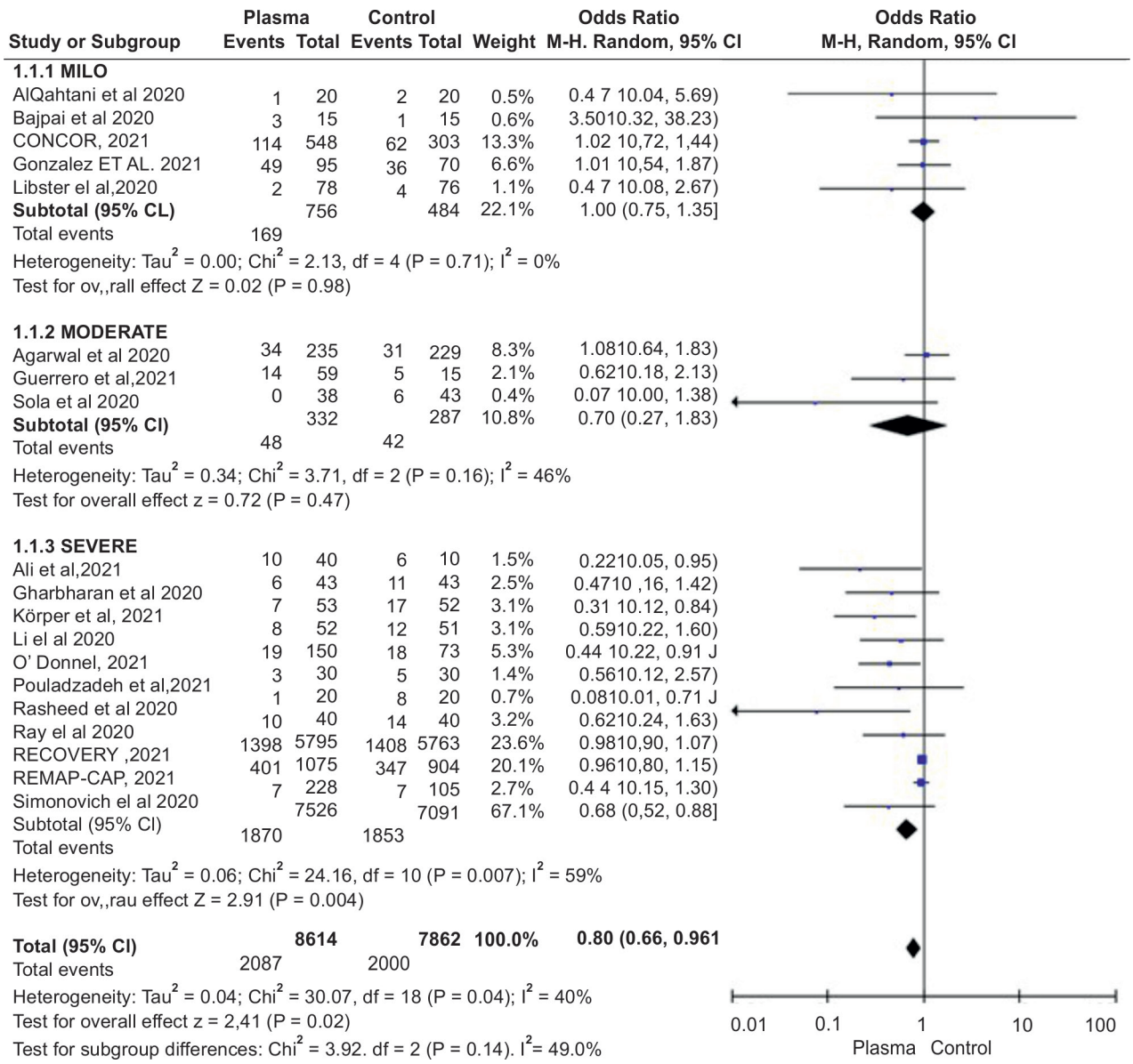


Fig. 1: The efficacy of convalescent plasma therapy on mortality in COVID-19 patients

Clinical Improvement

Thirteen RCTs with 13,320 patients indicated that no statistically significant clinical improvement (OR = 1.27, 95% CI 1–1.61, $I^2 = 45\%$) in CPT-recipient COVID-19 patients in comparison with patients who received standard care (Fig. 2A).

However, in a subgroup analysis of five studies ($n = 369$) where CPT was applied <7 days of symptoms, there are significantly higher odds for clinical improvement (OR = 2.13, 95% CI 1.28–3.53, $I^2 = 0\%$).

Viral Clearance

Viral clearance was assessed in four RCTs ($n = 631$). Significant clearance of viral shedding (OR = 2.66, 95% CI 1.3–5.45, $I^2 = 74\%$) was found in CPT-recipient COVID-19 patients. However, the result is highly heterogeneous (Fig. 2B).

Period for Clinical Improvement and Hospital Stay

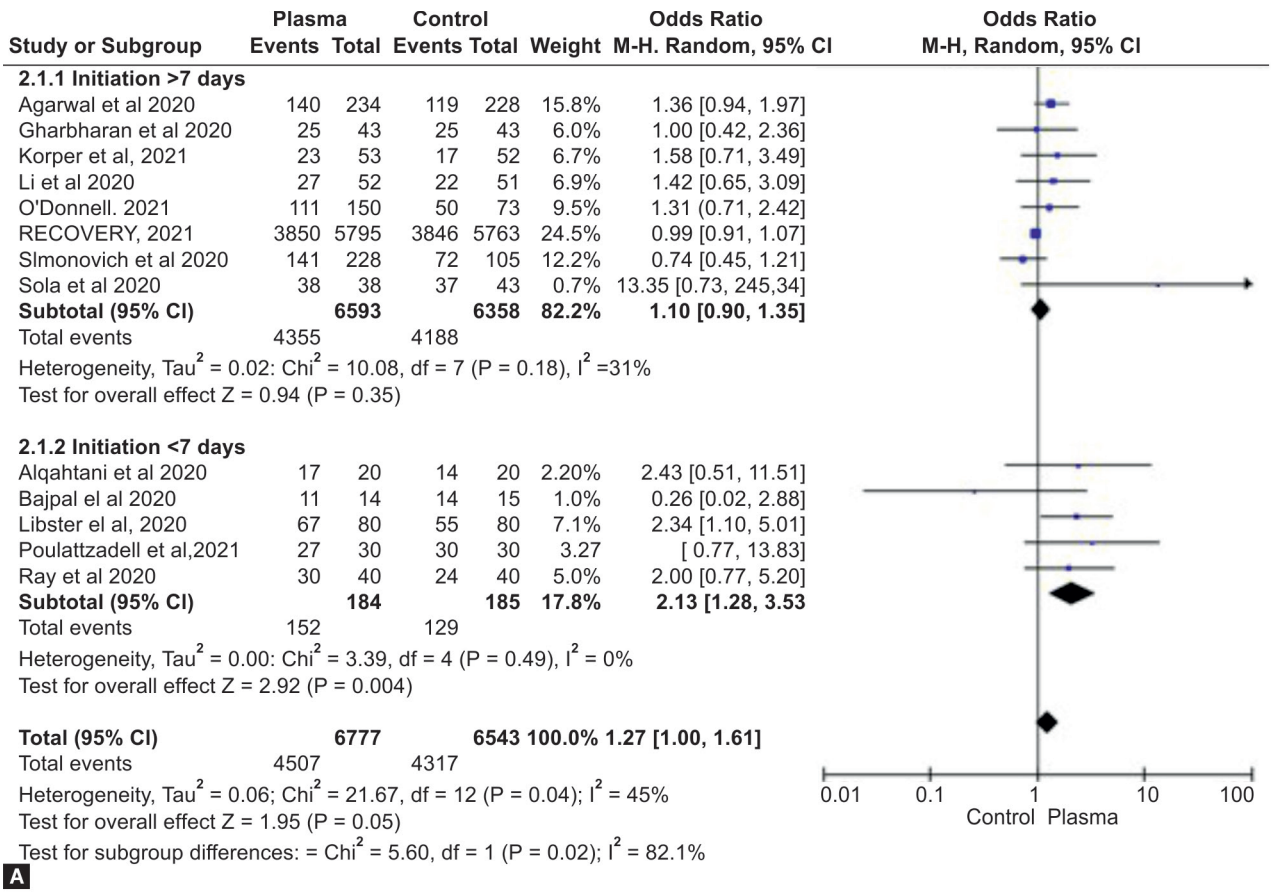
The CPT recipients showed a significant reduction neither in duration for clinical improvement (MD = −0.79, 95% CI: −2.76–1.18, $I^2 = 98\%$; $n = 354$) (Fig. 2C) nor in overall period for hospital stay (MD = 0.02, 95% CI: −0.75–0.78, $I^2 = 81\%$; $n = 1,208$) (Fig. 2D).

Meta-regression

Meta-regression analysis found that the association between CPT and mortality in COVID-19 patients was influenced only by intubation status on admission ($p = 0.007$) (Fig. 2E), but not by volume ($p = 0.676$), titer ($p = 0.464$), concomitant use of steroid ($p = 0.650$), tocilizumab ($p = 0.864$), remdesivir ($p = 0.524$), presence of preexisting lung disease ($p = 0.236$), and diabetes ($p = 0.151$).

Publication bias for the studies on COVID-19 mortality was assessed. The funnel plot indicates that a publication bias is likely as few smaller studies were associated with large effects (Supplemental Fig. 1).

Supplemental Figs 1A and B: (A) Funnel plot of the included studies for assessment of publication bias; (B) ROB-2 assessment for the included randomized controlled trials



Figs 2A and B: (A) The impact of convalescent plasma therapy on clinical improvement in COVID-19 patients; (B) The effect of convalescent plasma therapy on viral clearance in COVID-19 patients

Discussion

We have identified low-quality evidence with variability that the lower odds of mortality along with better clearance of viral shedding in COVID-19 patients who received the convalescent plasma therapy. (Table 2)

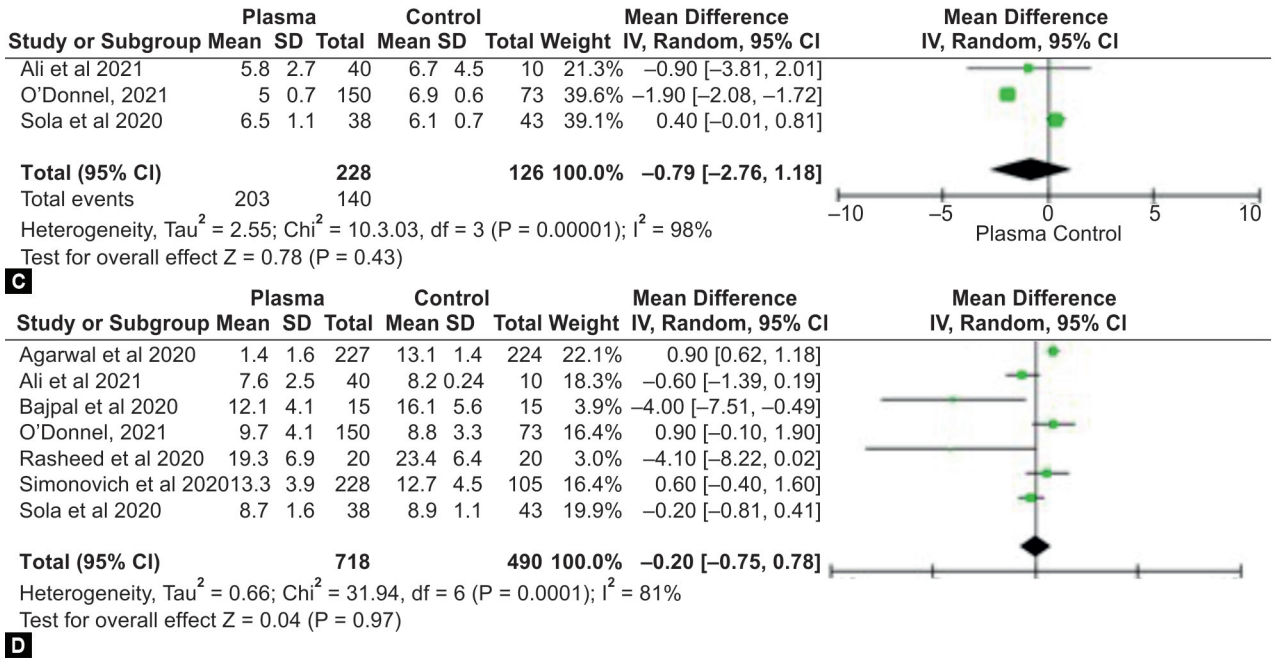
Similarly, a recent systematic review also found a significant reduction of mortality (risk ratio (RR) = 0.57, 95% CI 0.44–0.74, I^2 = 0%) in nine controlled studies with severely and critically ill COVID-19 patients.[9]

Previously, Sarkar et al.[10] also found low-quality evidence of reduced mortality (OR 0.44; 95% CI 0.25–0.77), and better clearance of viral shedding (OR, 11.29; 95% CI, 4.9–25.9) among CPT-recipient COVID-19 patients, in two RCTs and five matched cohort studies.

Another recent systematic review also reported a significant decrease in viral loads and improvement in clinical symptoms within 3–26 days post-CPT for the management of COVID-19.[11]

However, a living systematic review reported very low-quality evidence of no beneficial effect of CPT in reducing all-cause mortality at hospital discharge [RR 0.89, 95% CI 0.61–1.31] in one RCT and three controlled non-randomized studies of interventions, respectively.[12]

Another meta-analysis on efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections also found very low-quality noninformative results about complete recovery (OR 1.04, 95% CI 0.69–1.64), the period of hospital stays (mean difference–1.62, 95%



Figs 2C and D: (C) The impact of convalescent plasma therapy on duration for clinical improvement in COVID-19 patients; (D) The impact of convalescent plasma therapy on the period of hospital stays in COVID-19 patients

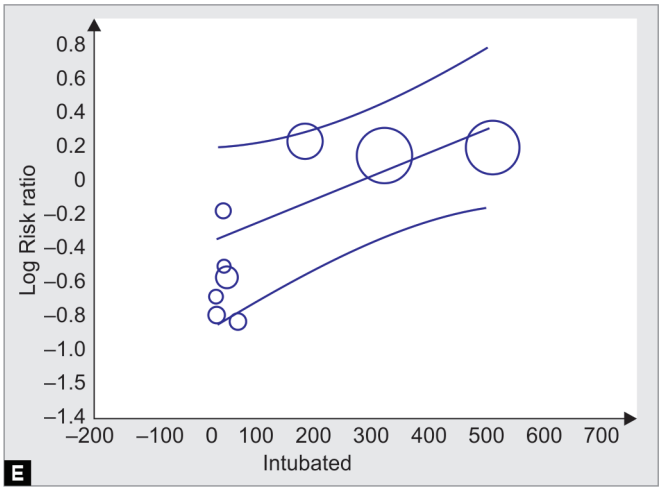


Fig. 2E: Meta-regression analysis showed that the association between convalescent plasma therapy and mortality was influenced by intubation status

CI –3.82–0.58), and viral clearance on day 3 (RR 1.07, 95% CI 0.58–1.8) and day 7 (RR 1.32, 95% CI 0.97–1.81).[13]

A recent systematic review and meta-analysis on severe acute respiratory infections of viral etiology reported that though the observational studies indicate a decline in mortality with CPT (OR 0.36, 95% CI 0.23–0.56, p <0.00001), the RCTs have not found any significant benefit for reducing the mortality (OR 0.82; 95% CI 0.57–1.19; $p = 0.30$).[14]

Rajendran et al.[15] also could not provide any opinion regarding the efficacy of CPT in COVID-19 due to paucity in quantitative synthesis for their systemic review. Similarly, another recent meta-analysis of 10 RCTs also reported that in comparison with standard care, CPT did not reduce the all-cause mortality (RR: 1.02; 95% CI 0.92–1.12).[16]

We found an earlier administration of CPT is associated with better odds for favorable outcomes. Similarly, a number of recent studies[17,18] also echoed that while early application of CPT is beneficial in critically ill COVID-19 patients, late CPT is futile. However, another recent RCT reported no significant reduction of mortality rate (OR 3.04, 95% CI 0.54–17.2, $p = 0.25$), and the requirement for mechanical ventilation (OR 3.04, 95% CI 0.54–17.2, $p = 0.25$) is associated with early administration of CPT in comparison with the deferred patients. But it has to be noted that only 43.3% of the patients of the deferred group received CPT.[19]

A decline in per capita CPT, since late 2020 following the publication of several negative RCTs and meta-analyses resulted in approximately 29,000–36,000 excess deaths in the USA. Apart from the reaffirmation of the FDA for the Emergency Use Authorization for early CP with the adequate amount of antibodies in hospitalized patients again in February 2021, the guidelines of American Association of Blood Banks and Brazil also emphasized the early use of CP with high content of specific antibody.[20]

Strengths and Limitations

Our study is a comprehensive review using only RCTs for assessing the efficacy of CPT in COVID-19 patients using data from the COVID-19 studies and may be considered at the moment as the prime evidence for decision-making.

Although in the present scenario, the efficacy of CPT in COVID-19 patients is debatable; this meta-analysis provides a signal of benefit in COVID-19 patients. However, the findings are heterogeneous and of low-quality evidence. A significant variation regarding methodology, the timing of initiation, optimal dosage, and neutralizing antibody titer, and concomitant therapy have been noted across the studies.

Table 2: GRADE evidence profile of COVID-19 studies

Outcome	No. of participants			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence (GRADE)	Relative effect
	Total no.	Intervention	Control							
Mortality	16,476	8,614	7,862	Yes	No	No	No	None	Low ⊕⊕⊖⊖	OR 0.80 (95% CI 0.66–0.96)
Clinical improvement	13,320	6,777	6,543	Yes	No	No	Yes	None	Very low ⊕⊖⊖⊖	OR 1.27 (95% CI 1–1.61)
Viral clearance	631	316	315	Yes	No	No	No	None	Low ⊕⊕⊖⊖	OR 2.66 (95% CI 1.3–5.45)
Duration for clinical improvement	354	228	126	Yes	No	No	Yes	None	Very low ⊕⊖⊖⊖	MD = −0.79 (95% CI: −2.76 to 1.18)
Period of hospital stay	1,208	718	490	Yes	No	No	Yes	None	Very low ⊕⊖⊖⊖	MD = 0.02 (95% CI: −0.75 to 0.78)

CI, confidence interval; COVID-19, coronavirus disease-2019; GRADE, grading of recommendations assessment, development, and evaluation; MD, mean difference; OR, odds ratio

Conclusion

In conclusion, as the COVID-19 pandemic progresses, there is a desperate need for definitive treatment. Till the development of an effective treatment or vaccine, CPT seems to be a safe and effective option and the current evidence regarding the use of CPT in COVID-19 patients is encouraging. It is too early to write it off as a potential therapeutic modality for COVID-19 patients.

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