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# Convalescent plasma may not be an effective treatment for severe and critically ill covid-19 patients: A Systematic Review & Meta-Analysis of Randomized Controlled Trials

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## ABSTRACT

**Background:** Convalescent plasma treatment for severe and critically ill Corona Virus Disease 2019 (COVID-19) patients remains controversial.

**Objective:** To evaluate the clinical improvement and mortality risk of convalescent plasma treatment in patients with severe and critically ill COVID-19 patients.

**Methods:** A literature search was conducted in the electronic databases for the randomized controlled studies about convalescent plasma therapy in severe and critically ill COVID-19 patients. Two reviewers independently extracted relevant data. The primary outcomes were clinical improvement and mortality risk of severe and critically ill COVID-19 patients that were therapied by convalescent plasma.

**Results:** A total of 14 randomized controlled trials with 4543 patients were included in this meta-analysis. Compared to control, no significant difference was observed for either clinical improvement (6 studies, RR 1.07, 95% CI 0.97 to 1.17,  $p = 0.16$ , moderate certainty) or mortality risk (14 studies, RR 0.94, 95% CI 0.85 to 1.03,  $p = 0.18$ , low certainty) in patients of convalescent plasma therapy group.

**Conclusion:** Convalescent plasma did not increase the clinical improvement or reduce the mortality risk in the severe and critically ill COVID-19 patients.

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## Introduction

COVID-19 infections are highly contagious, from December 2019 to February 2021, infected more than one hundred million people with almost 2 million deaths in 210 countries.<sup>1</sup> In addition,

the Epidemiology Working Group for NCIP Epidemic Response reported, 14% of patients would develop severe infections and suffer severe progressive pneumonia with multiple organ failure.<sup>2,3</sup> Unfortunately, there is still a lack of effective treatment for the COVID-19.

There are three phases involved in the progression of COVID-19. During the first phase, the virus replicates exponentially to cause tissue damage. In the second phase, the patients present with a hyper-inflammatory reaction, whereas in the third phase, the patient undergoes organ dysfunction and death.<sup>4</sup> Convalescent plasma was collected from the recovered individuals of COVID-19 infections.<sup>5</sup> Convalescent plasma can inhibit viral replication and regulate inflammation, thereby improving the prognosis of patients.<sup>6,7</sup> Some systematic reviews reported a reduction in the risk of death in patients with severe COVID-19 disease after convalescent plasma treatment.<sup>8,9</sup> However, these systematic reviews included observational studies or did not set clear diagnostic criteria for patients with severe infection.

**Abbreviations:** COVID-19, Corona Virus Disease 2019; SARS, Severe Acute Respiratory Syndrome; MERS, Middle East Respiratory Syndrome; RCT, Randomized Controlled Trials; PCR, Polymerase Chain Reaction; PaO<sub>2</sub>, arterial oxygen partial pressure; FiO<sub>2</sub>, Fraction of inspired oxygen; ICU, Intensive Care Unit; IQR, Interquartile-range; RoB, Risk of Bias; SD, Standard Deviation; GRADE, Grading of Recommendation's Assessment Development and Evaluation; CI, Confidence intervals; TSA, Trial Sequential Analysis; RR, Risk Ratio; MD, Mean difference; CP, Convalescent Plasma; IgG, Immunoglobulin G; FFP, Fresh frozen plasma

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At the same time, several recent RCT studies have reported that convalescent plasma does not significantly improve prognosis in patients with severe COVID-19 disease.<sup>7,10–12</sup> Therefore use of convalescent plasma for the severe COVID-19 infection treatment remains controversial.<sup>2,13</sup>

We aimed to perform a systematic review and meta-analysis to evaluate the efficacy of convalescent plasma therapy in patients with severe and critically ill COVID-19 patients.

## Methods

### Registration

The project was registered on the PROSPERO (CRD42021274365). We performed the meta-analysis and systematic review of the convalescent plasma transfusion therapy in severe and critically ill COVID-19 patients.

### Information sources

From inception till October 18, 2021, we conducted a thorough literature search in the following databases: PubMed, Cochrane Library, Web of Science, EMBASE. Besides, citations of previously published systematic reviews were also searched.

### Search strategy

The studies were searched using the keywords such as “COVID-19”, “severe acute respiratory syndrome coronavirus 2”, “2019-nCoV”, “SARS-CoV-2”, “coronavirus” “convalescent plasma,” “convalescent serum,” “Plasma immunoglobulins,” and so on. Table S1 shows the detailed search process.

### Literature inclusion criteria

Randomized controlled studies on convalescent plasma to treat severe and critically ill COVID-19 patients were included in this meta-analysis. However, prospective observational studies, retrospective studies, case reports, case series, and retrospective studies were excluded. Additionally, studies in which outcomes could not be extracted, studies containing many incomplete data, and/or duplicate studies were also excluded.

### Patient's inclusion criteria

- (1) Patients with confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) testing. There was no limitation of the PCR testing methods.
- (2) Pneumonia confirmed by chest imaging.
- (3) Clinical symptoms meet the definitions of severe or life-threatening COVID-19.
- (4) Severe COVID-19 Respiratory distress (Respiratory rate  $\geq$  30 breaths/min; resting-state oxygen saturation  $\leq$  94% on room air and requiring oxygen supplement; or arterial oxygen partial pressure (PaO<sub>2</sub>)/ fraction of inspired oxygen (FiO<sub>2</sub>)  $\leq$  300mmHg). Critical respiratory failure requiring mechanical ventilation, shock, or other organ failures (apart from the lung); requires monitoring intensive care unit (ICU).<sup>2,13</sup>

### Patient's exclusion criteria

- (1) Pregnancy or lactation
- (2) Blood component allergies

### Study Selection and Data Extraction

Two independent reviewers (Yang and Wang) performed a literature search and screening. In the case of inconsistencies in the data screening and extraction process, the conflicts were resolved using a group discussion and consultation with Professor Zheng RQ, a highly qualified COVID-19 treatment specialist. First, reviewers screened the literature titles and assessed the entire manuscript. Duplicate references were eliminated. After that, the following information was extracted from the studies: clinical improvement rate, mortality rate, 72h, 7th-day nucleic acid negative rate, oxygen support time, hospitalization, and discharge time. If there were several time points for clinical improvement, mortality, and discharge rate, we extracted the day closest to 28-day data. However, if data of 28-day could not be extracted, the data of 30-, 60- and 90-days were included in the analysis. At the same time, the patient's basic information was detracted: age, male, symptom onset to randomization, plasma usage control method, Plasma antibody titer, post-treatment patient antibody titer, etc. Finally, the data was converted to mean and standard deviation if reported as the median and interquartile range (IQR) for continuous variables.<sup>14,15</sup>

### Outcomes

Primary outcomes: symptoms improvement and mortality rate.

Secondary outcomes: 3-day and 7-day nucleic acid conversion rate, oxygen support duration, hospital stay duration, discharge rate.

### Risk of bias assessment and quality evaluation

All studies were assessed for risk of bias (RoB) using the Risk of Bias 2 (RoB2) tool.<sup>16</sup> Risks were classified as low, high, and unknown. Besides, a GRADE (Grading of Recommendations Assessment Development and Evaluation) evaluation was also performed.<sup>17</sup> However, more than five trials are required to study the outcomes to avoid the risk of publication biases. Therefore, we used funnel charts and Egger's test for published bias testing.

### Statistics

Two researchers carried out the data analysis. Mantel-Haenszel statistics and inverse variance models were used for the meta-analysis. Outcome data were analyzed by the Review Manager 5.3. The inverse variance model assessed the study weights. Relative risk was calculated for the result of dichotomous variables such as mortality. The mean, standard deviation (SD), and 95% confidence intervals (CI) for continuous variables were calculated. The  $\chi^2$  test, I<sup>2</sup>, was used to evaluate the homogeneity, where I<sup>2</sup>  $\geq$  50% represented high heterogeneity. For data with high heterogeneity, a random model was used. For the primary mortality outcomes, sequential research was conducted to evaluate if the sample size of the results was sufficient. In the trial sequential analysis (TSA), the required information size was based on a type I error of 5%, a beta of 20%, the proportion of participants in the control group with the outcome, and a relative risk reduction of 15% and 30%.

### Subgroup analysis and sensitivity analysis

Li et al. reported that convalescent plasma therapy was effective for severely infected, but not for critically ill patients.<sup>2</sup> Therefore, we performed the subgroup analysis for severe and critically ill patients for clinical improvement and mortality. Besides, to resolve the controversy regarding the literature about convalescent plasma therapy

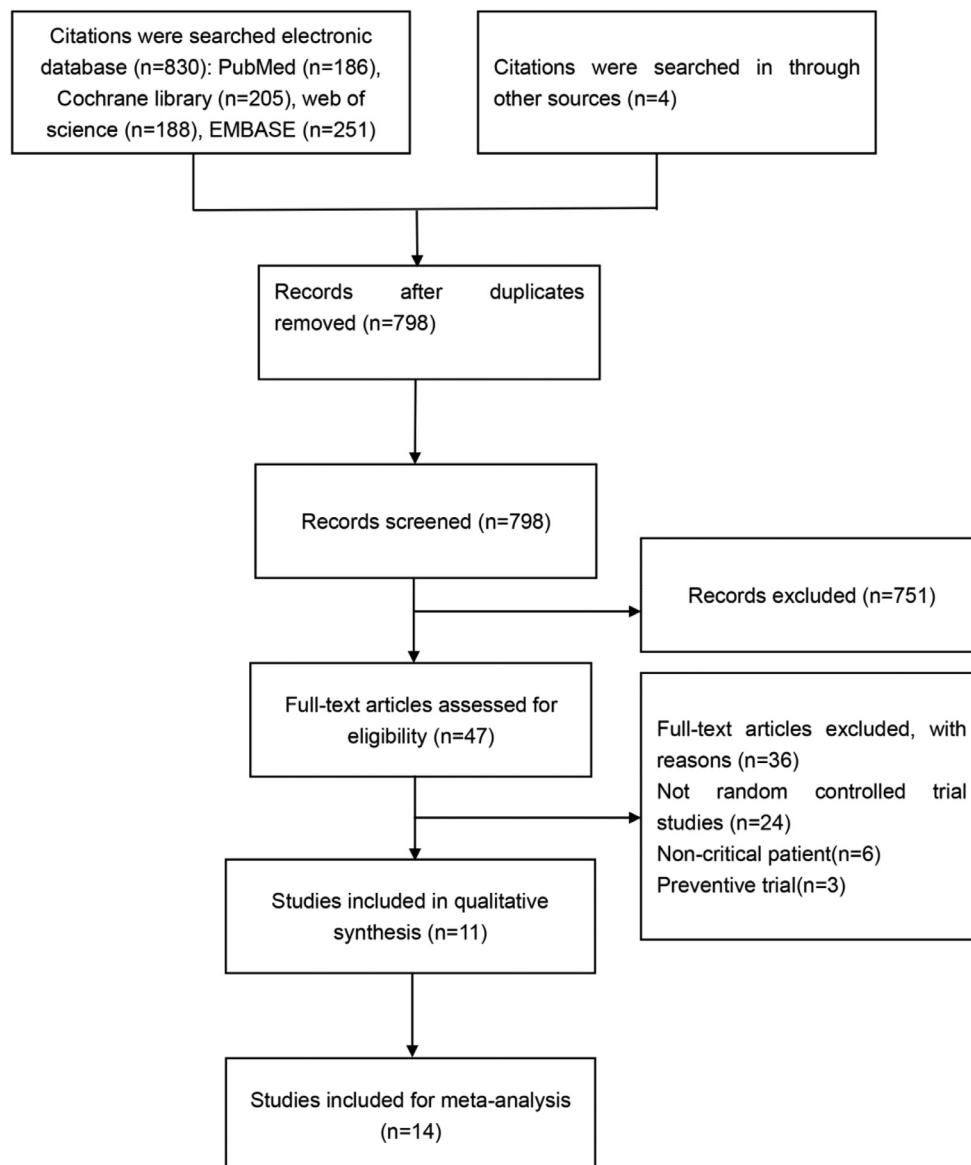


Fig. 1. Flow chart illustrating the study selection process.

for patients with severe COVID-19 infection, we performed a sensitivity analysis to assess the consistency of the results.

## Results

A total of 834 articles were retrieved. Only 830 studies had electronic data on PubMed, Embase, Web of SCI, and Cochrane Library, whereas 5 papers were retrieved in a previously published meta-analysis.<sup>18–22</sup> After that, 798 records were further processed after the removal of duplicates. After thoroughly reading the title and the abstract, unrelated literature on the convalescent plasma treatment of COVID-19 was excluded. After scrutinizing the studies based on the inclusion & exclusion criteria, a total of 14 randomized controlled trials and 4543 patients were included in the meta-analysis<sup>2,7,10–13,18–25</sup> (Fig. 1).

The included studies were conducted in China<sup>2</sup>, India<sup>21,23</sup>, Argentina<sup>11</sup>, Bahrain<sup>19</sup>, Iraq<sup>18,20</sup>, the United States<sup>25</sup>, Germany,<sup>24</sup> and Brazil<sup>12,13</sup>, Iran<sup>7</sup>, Netherlands<sup>10</sup>. Only 4 studies were on severe COVID-19 patients<sup>11,21,23,25</sup>, whereas ten studies included both the severe and critically ill COVID-19 patients.<sup>2,7,10,12,13,18–20,22,24</sup> Data of severe and critical patients were extracted separately in three trials.<sup>2,10,13</sup> Convalescent plasma therapy was compared to the

standard treatment in twelve studies.<sup>2,7,10–12,18,19,21–25</sup> In two trials, convalescent plasma was compared to the control plasma.<sup>13,20</sup> Anti-SARS-CoV-2 antibody titers were tested in all studies.<sup>2,7,10–13,18–25</sup> Characteristics of the included studies are shown in Table 1. Fig. 2 shows the details of the RoB of all studies. Table S2 shows the certainty of the obtained results.

## Primary outcomes

Compared to patients of control group, no significant difference in clinical improvement (6 studies, RR 1.07, 95% CI 0.97 to 1.17,  $p = 0.16$ , moderate certainty) (Fig. 3a) and mortality risk (14 studies, RR 0.94, 95% CI 0.85 to 1.03,  $p = 0.18$ , low certainty) (Fig. 4a) was observed for patients of convalescent plasma therapy group. There was no publication bias found in the clinical improvement (Egger's test,  $p = 0.154$ ) (Fig. 4b), but a publication bias was observed in the mortality risk (Egger's test,  $p = 0.009$ ) (Fig. 5b). We performed a sequential analysis for the mortality rate. A total of 4543 patients were included in our study, with an actual sample size of 4290 patients (Fig. 5). Outcome estimates were based on the following statistical indicators: the probability of type I error ( $\alpha = 0.05$ ), probability of type II error ( $\beta = 0.2$ ), relative risk reduction (RRR = 30%), and 15% event rate in

**Table 1**  
Characteristics of included studies.

| Trials                   | Country        | Participants                                                                                                                                                                                                                                                                     | Methods | Intervention                                                                                                                                                                                                                  | Convalescent Plasma                                                                                                                            | Remarks                                                                                                                                                                                                                          |
|--------------------------|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ling Li<br>2020          | China          | 103 COVID-19 patients, 45 severe patients, and 58 critical patients.<br>Age: CP group 70 (62–80) years<br>Control group 69 (63–76) years<br>Male: CP group 51.9%<br>Control group 64.7%<br>Symptom onset to randomization:<br>CP group 27 (22–39)<br>Control group 30 (19–38)    | RCT     | CP group: The transfusion dose of COVID-19 CP was approximately 4 to 13 mL/kg of recipient body weight.<br>Control group: Standard treatment                                                                                  | Only the plasma units with an S-RBD–specific IgG titer of at least 1:640 were used for this study                                              | /                                                                                                                                                                                                                                |
| Anup Agarwal<br>2020     | India          | 464 severe COVID-19 patients,<br>Age: CP group 52 (42–60) years<br>Control group 52 (41–60) years<br>Male: CP group 75%<br>Control group 77%<br>Symptom onset to randomization:<br>CP group 8 (6–11) days<br>Control group 8 (6–11) days                                         | RCT     | CP group: Received two doses of 200 mL of CP, transfused 24 hours apart, in addition to the best standard of care.<br>Control group: Standard treatment                                                                       | Nearly two thirds (n=161, 64%) of the donors had a neutralizing antibody titer of more than 1:20, with a titer of 1:40 (1:30–1:80)             | 348 (83%) had detectable neutralizing antibodies at enrolment.<br>The neutralizing antibody titer at enrolment was 1:90 (1:30–1:240).                                                                                            |
| V.A. Simonovich<br>2020  | Argentina      | 333 severe COVID-19 patients,<br>Age: CP group 62.5 (53–72.5) years<br>Control group 62 (49–71) years<br>Male: CP group 70.6%<br>Control group 61%<br>Symptom onset to randomization:<br>CP group 8 (5–10) days<br>Control group 8 (5–10) days                                   | RCT     | CP group: In patients weighing $\leq 70$ kg, 400 ml volume of CP will be transfused. In patients weighing $> 70$ kg, 600 ml volume of CP will be transfused at a rate of 5 to 10 ml/kg/h<br>Control group: Standard treatment | The total antibody titer goal in convalescent plasma was above 1:800 in all cases                                                              | At two days: CP group neutralizing antibody: 1:400 (1:200–1:1600)<br>control group neutralizing antibody: 1:400 (1:50–1:3200), $p < 0.05$                                                                                        |
| Leo Sekine<br>2021       | Brazil         | 160 severe and critical COVID-19 patients.<br>Age: CP group 59.0 (48.0–68.5) years<br>Control group 62.0 (49.5–68.0) years<br>Male: CP group 61.2%<br>Control group 55.0%<br>Symptom onset to randomization:<br>CP group $10.0 \pm 3.0$ days<br>Control group $9.8 \pm 3.2$ days | RCT     | CP group: Receive two infusions 48 hours apart of 300ml.<br>Control group: Standard treatment                                                                                                                                 | Antibody titers of Convalescent plasma were 1:320 (1:160–1:960). Five donors' convalescent plasma had lower than 1:80 (four 1:40 and one 1:20) | At 3-day: CP group neutralizing antibody: 1:5120 (1:2560–1:10240)<br>Control groups: 1:2560 (1:1920–5120) $p = 0.19$                                                                                                             |
| Max R. O'Donnell<br>2021 | USA and Brazil | 223 COVID-19 patients, 195 severe patients, and 28 critical patients.<br>Age $> 70$ : CP group 28%<br>Control group 29%<br>Male: CP group 64%<br>Control group 70%                                                                                                               | RCT     | CP group: a single unit of CP (~200–250 ml) was transfused.<br>Control group: a single unit of plasma.                                                                                                                        | There was a minimum anti–COVID-19 total IgG antibody titer of at least 1:400 in convalescent plasma                                            | /                                                                                                                                                                                                                                |
| Anwar M<br>2020          | Iraq           | 49 severe and critical COVID-19 patients.<br>Age: CP group $55.66 \pm 17.83$ years<br>Control group $47.82 \pm 15.36$ years<br>Duration of infection before inclusion in the study:<br>CP group $14.80 \pm 7.46$ days<br>Control group $16.57 \pm 5.99$ days                     | RCT     | CP group: 400 mL of frozen convalescent plasma were transfused.<br>Control group: Standard treatment                                                                                                                          | Only the donors with COVID-19 IgG index equal to or more than 1.25 were selected                                                               | CP group: 2 patients with weakly positive IgG, 8 patients with moderately positive, 11 patients with strongly positive IgG.<br>Control group: 21 patients with negative IgG, 7 patients with weakly positive IgG. ( $p < 0.05$ ) |

(continued on next page)

**Table 1** (Continued)

| Trials             | Country                       | Participants                                                                                                                                                                                                                                                                                         | Methods | Intervention                                                                                                                                                | Convalescent Plasma                                                                                                                                                     | Remarks                                                                                                                                                         |
|--------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Manaf A 2020       | Bahrain                       | 40 COVID-19 patients, 37 severe patients, and 3 critical patients.<br>Age: CP group $52.6 \pm 14.9$ years<br>Control $50.7 \pm 12.5$ group years<br>Male: CP group 85%<br>Control group 75%                                                                                                          | RCT     | CP group: The dosage of CP was 400 ml, given as 200 ml over 2h over 2 successive days.<br>Control group: Standard treatment                                 | /                                                                                                                                                                       | Patients who received early CP had a titer of 82 AU/ml (SD 23, SE 9.5, N = 6). Those who received CP after 3 days had a titer of 49 AU/ml (SD 58, SE 22, N = 7) |
| Körper, S 2021     | German                        | 105 severe and critical COVID-19 patients. 69 severe patients and 36 critical patients.<br>Age: CP group 59 (53–65) years<br>Control group 62 (55–66) years<br>Male: CP group 79.3%<br>Control group 67.3%<br>Symptom onset to randomization: CP group 7 (2–9) days<br>Control group 7 (5–10.5) days | RCT     | CP group: one transfusion unit each of CP was given on days 1, 3, and 5.<br>Control group: Standard treatment                                               | Low neutralizing units: median of neutralizing antibodies titer was 1:80.<br>High neutralizing units: median of neutralizing antibodies titer was 1:320                 | /                                                                                                                                                               |
| Bégin, P 2021      | Brazil, Canada, United States | 938 severe COVID-19 patients.<br>Age < 60 years: CP group 30.8%<br>Control group 69.2%<br>Age ≥ 60 years: CP group 69.2%<br>Control group 70.3%<br>Male: CP group 58.9%<br>Control group 60.1%<br>Symptom onset to randomization: CP group $8.0 \pm 3.8$ days<br>Control group $7.8 \pm 3.4$ days    | RCT     | CP group: Patients received 500 mL of convalescent plasma.<br>Control group: Standard treatment                                                             | In convalescent plasma, a threshold titer of > 1:160 or antibodies against the RBD of the COVID-19 spike protein using a threshold titer of > 1:100                     | /                                                                                                                                                               |
| Ray y 2020         | India                         | 80 severe COVID-19 patients.<br>Male: CP group 25%<br>Control group 32.5%<br>Age: Female $61.43 \pm 11.33$ years<br>Male $61.36 \pm 12.17$ years<br>Hospital admission to randomization: CP group $4.2 \pm 2.21$ days<br>Control group $3.85 \pm 2.63$ days                                          | RCT     | CP group: Patients received two consecutive doses of ABO-matched 200ml convalescent plasma on two successive days.<br>Control group: Standard treatment     | /                                                                                                                                                                       | The neutralizing antibody content of plasma was also not significantly different between the Control group and the CP group.                                    |
| Bajpai M 2020      | India                         | 29 severe and critically ill COVID-19 patients.<br>Age's group $48.1 \pm 9.1$ years<br>Control group $48.3 \pm 10.8$ year<br>Male: CP group 78.6%<br>Control group 73.3%                                                                                                                             | RCT     | CP group: Patients received ABO blood compatible 500 ml convalescent plasma in two divided doses on consecutive days.<br>Control group: Fresh frozen plasma | Antibody titers of the convalescent plasma donors ranged from 10 to 640.                                                                                                | An increasing rate of IgG antibody titer of patients of the CP group was more than the control group.                                                           |
| Pouladzadeh M 2021 | Iran                          | 60 severe and critically ill COVID-19 patients.<br>Male: CP group 53%<br>Control group 56.7%<br>Age ≤ 50 years: CP group 36.7%<br>Control group 40%<br>Age > 50 years: CP group 63.3%<br>Control group 60%                                                                                           | RCT     | CP group: Patients received 500 ml CP on admission day.<br>Control group: Standard treatment                                                                | donors patients showed the strong positive results of the COVID-19 IgG/IgM Quick Test (German) for neutralizing IgG antibodies and negative results for IgM antibodies. | /                                                                                                                                                               |

(continued on next page)

Table 1 (Continued)

| Trials                                                                                   | Country                                          | Participants                                                                                                                                                                                                                                                             | Methods | Intervention                                                                                                                                                                                    | Convalescent Plasma                                                                                                                    | Remarks |
|------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|---------|
| The REMAP-CAP Investigators 2021                                                         | Australia, Canada, United Kingdom, United States | 1987 severe and critically ill COVID-19 patients.<br>Male:CP group 67.4%<br>Control group 68.0%<br>Age: CP group 60.2±12.7 years<br>Control group 60.2±13.1 years<br>Hospital admission to randomization: CP group 1.8 (1.0-3.3) days<br>Control group 1.7 (0.9-3.5)days | RCT     | CP group: Patients receive high-titer ABO compatible convalescent plasma (total 123 volume approximately 550 +/- 150 ml) within 48 hours of randomization.<br>Control group: Standard treatment | High liter and low liter CP were received in CP group.                                                                                 | /       |
| Gharbharan A 2021                                                                        | The Netherlands                                  | 86 severe and critically ill COVID-19 patients.<br>Male:CP group 67%<br>Control group 77%<br>Age: CP group 63 (55–77) years<br>Control group 61 (56–70) years<br>Symptom onset to randomization: CP group 11 (6–16) days<br>Control group 9 (7–13) days                  | RCT     | CP group: Patients receive 300 mL CP on theadmission day and a second unit after five days.<br>Control group: Standard treatment                                                                | Donor with COVID-19-neutralizing antibodies confirmed by ELISA and having a COVID-19 PRNT and a PRNT50 titer of minimally 80 was used. |         |
| The IgM was also not significantly different between the Control group and the CP group. |                                                  |                                                                                                                                                                                                                                                                          |         |                                                                                                                                                                                                 |                                                                                                                                        |         |

CP: Convalescent Plasma; RCT: Randomized Controlled Trials; Ig, Immunoglobulin; SD: Standard Deviation; SE: Standard Error of Mean.

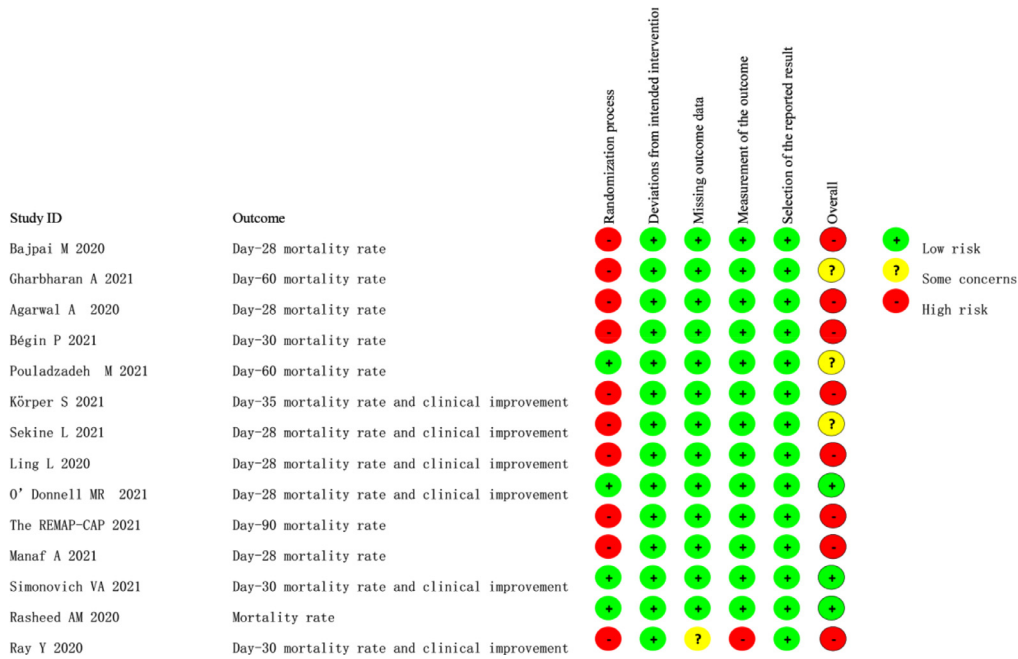


Fig. 2. Risk of bias summary. Review of authors' judgments on the risk of bias items in each included study.

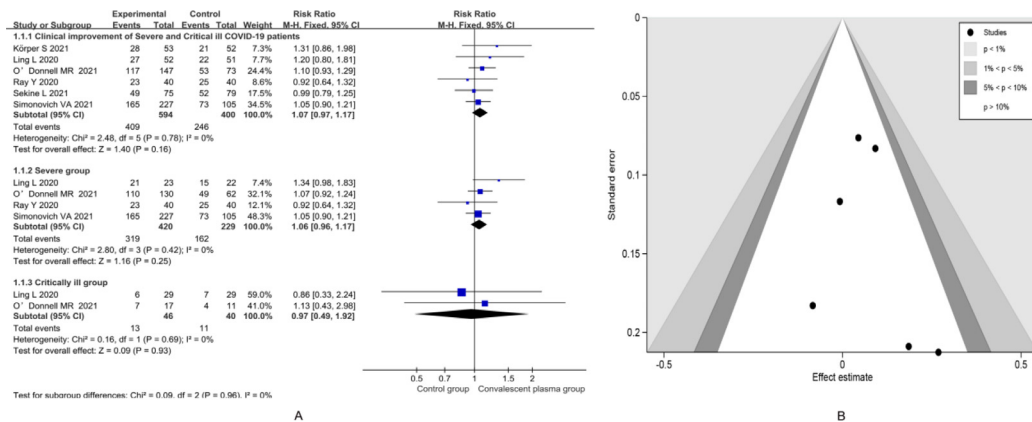


Fig. 3. A. Forest plot of the clinical improvement between the convalescent plasma therapy group and control group. M-H, Mantel-Haenszel; CI, confidence interval; RR, risk ratio. B. The funnel graph of clinical improvement.

the control group. The TSA results showed that the cumulative Z value neither crossed the traditional cut-off nor the TSA cut-off nor reached the required patient sample size.

### Secondary outcomes

#### Time of respiratory support

The Agarwal A, O'Donnell MR, reported the duration of respiratory support<sup>13,23</sup>, however, data on the time of respiratory support could not be converted to mean and SD. Therefore, we could not conduct a meta-analysis on the respiratory support timing. Compared to the control, time of respiratory support of convalescent plasma group patients was in concurrence with the findings of Agarwal A (median 9 days, IQR: 6 to 13 vs. 10 days, IQR:6 to 13,  $p = 0.7$ ) and O'Donnell MR (median 6 days, IQR: 3 to 16 vs. 7 days, IQR:3 to 11,  $p = 0.508$ ).<sup>13,23</sup> In addition, the studies by Sekine L et al. (median 11 days, minimum 0 days, maximum 21 days vs. median 7.5 days, minimum 0 days, maximum 22 days,  $p = 0.444$ )<sup>12</sup> and the REMAP-CAP investigators(OR 0.95, 95% CI 0.81 to 1.11,  $p > 0.05$ )<sup>22</sup>, reported that

patients in the convalescent plasma treatment group and control patients had no significant difference in the period without respiratory support.

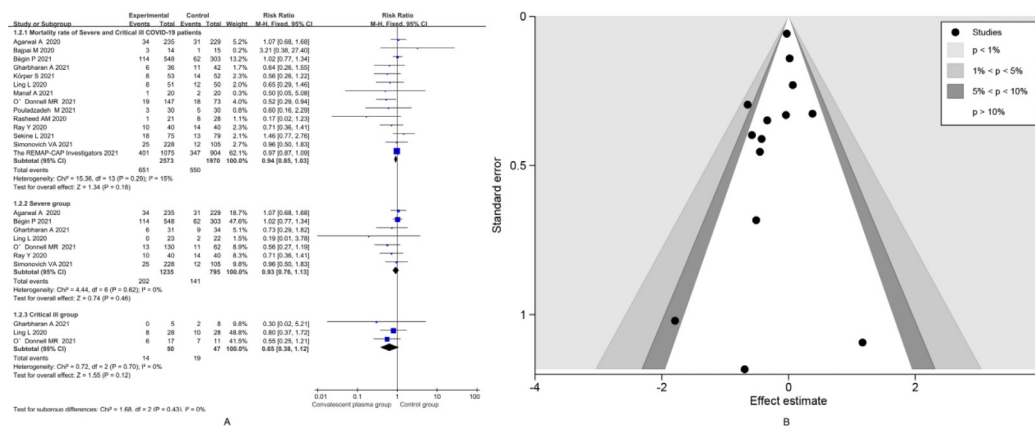
#### Time to hospital discharge

Even trials reported the time to hospital discharge<sup>2,7,11-13,19-24</sup>, however, the time to hospital discharge data could not be detracted, and no difference in time to hospital discharge was observed between patients in the convalescent plasma treatment with the control group ( $p > 0.05$ ).<sup>2,11,13,21,22,24</sup> Furthermore, the meta-analysis showed no differences in time to hospital discharge between patients in the convalescent plasma treatment and the control group (5 studies, MD -1.02 days, 95% CI -3.76 to 1.72,  $p = 0.47$ , very low certainty) (Fig. S1).

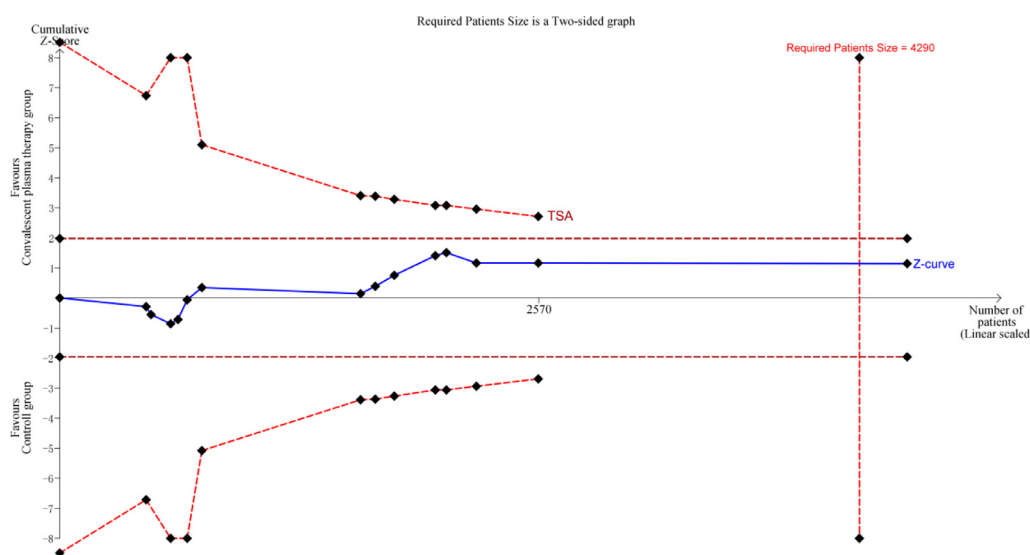
#### COVID-19 Nucleic Acid Negative Rate

Three trials reported negative nucleic acid rates at 72h and 7 days for COVID-19.<sup>2,12,23</sup> Two trials reported the rate of COVID-19 nucleic acid negative within 72h.<sup>2,23</sup> Two trials reported COVID-19 nucleic





**Fig. 4.** A. Forest plot of mortality between the convalescent plasma therapy group and the control group. M-H, Mantel-Haenszel; CI, confidence interval; RR, risk ratio. B. The funnel graph of mortality risk.



**Fig. 5.** Results of sequential analysis of mortality. TSA, trial sequential analysis.

acid negative rates within the 7 days.<sup>12,23</sup> However, no difference in COVID-19 nucleic acid negative rate at 72h (2 studies, RR 1.62, 95% CI 0.83 to 3.16,  $p = 0.16$ , very low certainty) and 7 days (2 studies, RR 1.19, 95% CI 1.00 to 1.40,  $p = 0.05$ , low certainty) between convalescent plasma therapy and control group patients (Fig. S2 & S3).

### Discharge rate

Five trials reported discharge rates<sup>2,11–13,24</sup>, however, no significant difference was observed in the discharge rate between patients in the convalescent plasma therapy and those in the control group (Five studies, RR 1.08, 95% CI 0.98 to 1.19,  $p = 0.14$ , moderate certainty) (Fig. S4).

### Subgroup analysis

We performed a subgroup analysis to investigate the effect of convalescent plasma therapy on clinical improvement and mortality rate in severe and critically ill COVID-19 patients. In the critically ill COVID-19 patients, convalescent plasma did not increase the rate of clinical improvement (two trials, RR 0.97, 95% CI 0.49 to 1.92,  $p = 0.93$ , very low certainty) or decrease the mortality risk (three trials, RR 0.65, 95% CI 0.38 to 1.12,  $p = 0.12$ , very low certainty) (Fig. 3 & 4). Similarly, in severe COVID-19 patients, convalescent plasma did not increase the

rate of clinical improvement (Four trials, RR 1.06, 95% CI 0.96 to 1.17,  $p = 0.25$ , moderate certainty) or reduce the mortality risk (seven trials, RR 0.93, 95% CI 0.76 to 1.13,  $p = 0.46$ , moderate certainty) (Fig. 3 & 4). Of note, there was a publication bias in the mortality risk parameter (Egger's test,  $p = 0.07$ ) (Fig. 4).

### Sensitivity analysis

There was a conflict for patients with severe COVID-19 infection in studies of Bégin P<sup>25</sup> and Agarwal A.<sup>23</sup> Therefore, a sensitivity analysis was performed to exclude studies of Bégin P<sup>25</sup> and Agarwal A.<sup>23</sup> However, the sensitivity analysis did not reveal any significant difference in mortality risk (12 studies, RR 0.92, 95% CI 0.83 to 1.02,  $p = 0.10$ , low certainty) (Fig. S5) between patients of the convalescent plasma therapy and standard treatment group. Moreover, there was a publication bias in the mortality risk parameter (Egger's test,  $p < 0.001$ ). In the critically ill COVID-19 patients, convalescent plasma did not decrease the mortality risk (three trials, RR 0.65, 95% CI 0.38 to 1.12,  $p = 0.12$ , very low certainty) (Fig. S5). Similarly, in severe COVID-19 patients, convalescent plasma did not reduce the mortality risk (five trials, RR 0.72, 95% CI 0.51 to 1.04,  $p = 0.08$ , moderate certainty) (Fig. S5).

## Discussion

Our study observed that convalescent plasma treatment for patients with severe and critically ill covid-19 infection could not increase the rate of symptomatic improvement or reduce the risk of death. Meanwhile, the convalescent plasma could not reduce the length of stay in the hospital or the time of oxygen support. Moreover, convalescent plasma did not significantly affect the 72h nucleic acid conversion rate and 30-day discharge rate. However, the therapy increased the 7-day nucleic acid conversion rate, though the increase was not statistically significant.

COVID-19 is a highly infectious disease with a high risk of death<sup>26</sup>, as the virus can invade multiple organs, causing acute respiratory distress syndrome, infectious shock, and multiple organ failure.<sup>27</sup> The lungs are the typical target organ. Besides, studies have reported a positive correlation between the severity of lung infections with the respiratory viral load.<sup>28</sup> Convalescent plasma reduces the viral infection rate by binding to the virus and removing pathogens through various pathways, such as complement activation and phagocytosis.<sup>29</sup> Moreover, in patients presenting with mild disease, early administration of convalescent plasma (within 3 days) significantly reduces the risk of progression to severe infection<sup>30</sup> and the risk of death.<sup>4</sup> However, a recent meta-analysis on mild, moderate, severe, and critically infected patients revealed that the convalescent plasma did not reduce mortality.<sup>31</sup>

The use of convalescent plasma in severely and critically ill patients remains controversial. Initially, Duan et al. recruited 10 patients with severe COVID-19 infection and treated them with convalescent plasma transfusions. The treatment resulted in a significant improvement in clinical symptoms, with a substantial decrease in the inflammatory parameters and an increase in the rate of nucleic acid conversion.<sup>32</sup> Subsequently, the FDA issued guidance on the use of convalescent plasma for the COVID-19 patients, citing convalescent plasma could be requested in emergencies for critically ill patients.<sup>33</sup> Further, O'Donnell MR et al. included 223 patients, where 150 were randomized to receive convalescent plasma and 73 to receive normal control plasma. The study found that the convalescent plasma did not improve clinical symptoms but reduced the risk of death in patients with severe infections.<sup>13</sup> Another meta-analysis including observational and retrospective studies concluded that convalescent plasma therapy reduces the risk of death in patients with severe infections.<sup>34,35</sup> However, recent RCT studies have shown that the use of convalescent plasma did not improve the prognosis of patients with severe disease.<sup>11,12,19,24,25</sup> Meanwhile, a study found that convalescent plasma had variable results in improving patient's clinical symptoms between severe and critical infections. Notably, the study showed that the treatment with convalescent plasma showed an increased clinical improvement in patients with severe COVID-19 ( $p < 0.1$ ).<sup>2</sup> In the meta-analysis, with subgroup analyses of severe and critically ill COVID-19 patients, convalescent plasma could decrease the mortality rate in severe COVID-19 patients<sup>36</sup>, however, the data was majorly extracted from the observational research.<sup>36</sup> The recent meta-analysis of Cao et al. also found that the convalescent plasma could decrease the mortality rate for severe or critical patients.<sup>37</sup> The meta-analysis results of Cao et al.<sup>37</sup> differ from our study, as they only analyzed 28-days mortality data. Still, most studies<sup>7,10,11,18,22,24,25</sup> reported a risk of death at 30-, 35-, 60-, and 90-days were not included in the analysis. Meanwhile, the meta-analysis of Cao et al.<sup>37</sup> did not define the diagnostic criteria for severe COVID-19 infection; thus, these two studies could not be included in the analysis. Of note, the sensitivity analysis showed that the convalescent plasma could not reduce the mortality risk, even though the studies of Agarwal A<sup>23</sup> and Bégin P<sup>25</sup> were excluded from the analysis. These results were similar to the study by Min et al., in which the subgroup of the RCT convalescent plasma did not reduce the mortality risk of patients with moderate and severe infections.<sup>2</sup>

Our study found that convalescent plasma in severe or critically ill patients did not improve the clinical symptoms or reduce the death risk. Our results concur with Gupta et al.,<sup>31</sup> and Janiaud et al.<sup>38</sup> However, we included only severe and critically ill patients for analyses. Of note, our study found that the convalescent plasma could increase the 7day nucleic acid conversion rate; however, the increase was not statistically significant. The observation needs to be validated further in a large sample size study.

## Limitations

This study had the following limitations: 1. We did not consider the effect of the new coronavirus variant on the results of this study. 2. Blood antibody titers following antibody infusion might affect the results. However, studies of adequate antibody titers in severe infections trials are relatively few to group them according to the antibody titers. 3. Control groups included standard care. This standard care was not a "standard" in the pandemic and got diversified depending on the resource availability in various international centers. 4. None of the included studies had a large cohort to power to detect the efficacy among diverse patient populations adequately.

## Conclusion

Convalescent plasma therapy in severe and critically ill COVID-19 patients does not increase clinical improvement and reduces the mortality risk. In addition, convalescent plasma does not lessen the time on oxygen therapy, the length of hospital stays, or increase the discharge rate of severe and critically ill COVID-19 patients. Convalescent plasma therapy in severe and critically ill COVID-19 patients requires further research.

## Declaration of Competing Interest

None.

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## Abbreviations

COVID-19, Corona Virus Disease 2019; SARS, Severe Acute Respiratory Syndrome; MERS, Middle East Respiratory Syndrome; RCT, Randomized Controlled Trials; PCR, Polymerase Chain Reaction; ICU, Intensive Care Unit; IQR, Interquartile-range; RoB: Risk of Bias; SD, Standard Deviation; GRADE, Grading of Recommendation's Assessment Development and Evaluation; CI, confidence intervals; TSA: Trial Sequential Analysis; RR, Risk Ratio; CP, Convalescent Plasma; IgG, Immunoglobulin G; FFP, fresh frozen plasma

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.hrtlng.2022.01.019](https://doi.org/10.1016/j.hrtlng.2022.01.019).

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