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Plasma convalescent decrease mortality in COVID-19 patients: a systematic review and meta-analysis

A. YUWONO SOEROTO[1,2], A. PURWIGA[2], A. ALAM[3], D. PRASETYA[1,4]

[1]Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin Hospital, Bandung, Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin Hospital, Bandung, Indonesia
[3]Division of Infectious Disease, Department of Child Health, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin Hospital, Bandung, Indonesia
[4]Division of Hematology and Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin Hospital, Bandung, Indonesia

Abstract. – OBJECTIVE: To investigate the role of Convalescent Plasma (CP) in reducing mortality of COVID-19 patients.

MATERIALS AND METHODS: A systematic literature search was conducted from PubMed, Embase, Medrxiv, and Google Scholar from April and finalized in December 2020 using the following terms: covid-19, convalescent plasma, cp, ccp, copla. The studies were screened, extracted, and evaluated by two authors independently. Comparative retrospective or prospective studies with a control group were included. Mortality was defined as the outcome of interest. Research articles not published in the English language, not available in full text, review articles, no measured outcome of interest were excluded from this study.

RESULTS: Eighteen studies were included in this meta-analysis. There were 5658 patients with 2092 patients treated with CP and 3536 patients as a control group. Forest plot showed CP use was associated with decreased mortality with OR = 0.64 (95% CI 0.49 to 0.84, p<0.001) and heterogeneity (I2)= 27.62%. Few patients experienced an adverse event, but no fatal case was reported.

CONCLUSIONS: Convalescent plasma is effective in reducing mortality of severe and critical COVID-19 with tolerable adverse effects.

Key Words:
COVID-19, Convalescent plasma, Mortality.

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which started in Wuhan, China, has become a significant concern worldwide. By December 21, there had been 75,704,857 confirmed cases and 1,690,061 deaths globally[1]. To date, there is no specific recommended treatment for SARS-CoV-2 infection[2]. The National Institutes of Health (NIH) includes blood-derived products such as CP and SARS-CoV-2 immunoglobulin as immune-based therapy for COVID-19 adjuvant treatment. However, NIH neither recommends their use due to insufficient data[3].

Convalescent plasma has been used to treat several previous emerging viral infections, such as SARS, middle east respiratory syndrome (MERS), Ebola, and avian flu. It is evident that the plasma has the potential to increase survival rates in patients with SARS, MERS, Ebola, and avian flu[4-6]. COVID-19 has a high mortality rate, especially in those with older age and comorbid diseases, such as diabetes mellitus (DM type 2), hypertension, and obesity[7,8]. A study conducted by Bloch et al[9] showed that CP decreases the viral load and improves survival rates in COVID-19 patients. A recent study[10] showed CP might reduce 14 days of follow-up mortality in severe or critically ill COVID-19 patients. Based on limited existing evidence, CP may be a promising treatment option for SARS-COV-2 infection. This meta-analysis aims to investigate the role of CP in reducing mortality of COVID-19 patients.

Materials and Methods

Literature Search

A systematic literature search was conducted from PubMed, Embase, Medrxiv, and Goo-

Corresponding Author: Arto Yuwono Soeroto, MD; e-mail: aysoeroto@yahoo.co.id

gle Scholar using the following keywords: ("COVID-19" or "SARS-COV-2") AND ("Convalescent" or "Plasma" or "CP" or "CCP" or "Copla"). The following filter was also applied in the search system, including human subject, observational study, English, clinical trial. Hand searching and manual search were also performed to include all relevant published articles. The systematic literature research was performed from April to December 2020. The identical results were removed using Endnote X9.01 for Windows. The reporting was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Study Selection and Eligibility Criteria

Comparative retrospective or prospective studies with a control group were included. Mortality was defined as the outcome of interest. Research articles not published in the English language, not available in full text, review articles, no measured outcome of interest were excluded from this study.

Data Extraction

Data extraction was performed using standardized forms that include generic information (first author, year, place), sample size, study design, age, and gender. Additional data consisting of the severity of the disease, time of CP infusion, CP doses, antibody titers, adverse event, comorbidities (HTN, DM, and obese), concomitant treatment were also extracted. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of each included study. Screening of title and abstract, full-text screening, data extraction, and quality assessment were performed by two authors (AYS and AP) independently.

Statistical Analysis

Stata version 16 was used for data collection and meta-analysis. The effect size for the outcome of interest was reported as odds ratio (OR) using restricted maximum likelihood (REML) with a random effect model despite heterogeneity. Statistical significance was set at ≤ 0.05 with a two-tailed hypothesis. A funnel plot was drawn to evaluate the publication bias when there are at least ten included studies. A further test for funnel plot asymmetry using Egger's test was conducted when publication bias was indicated. Subgroup analysis was performed based on type of study, COVID-19 severity, time of CP infusion, and mortality at follow-up.

Results

Study Selection

The electronic database's initial search yielded 792 records (PubMed, Embase, MedRxiv, and Google Scholar) and 18 records from hand-searching. A total of 524 records were included after the duplicate was removed. Included records were screened by title and abstract and yield 112 records. The remaining articles were assessed thoroughly for eligibility criteria. Eighteen studies were included in this meta-analysis. The selection process is shown in Figure 1.

Study Characteristics

There were 5658 patients with 2092 patients treated with CP and the remaining 3536 patients as a control group. The median age was ranged from 52.5-70 years. Males (62.9%) were more frequent compared to female patients. Most studies were controlled clinical trials (61.2%). Most studies (77.7%) reported the volume of convalescent plasma used. The most widely CP volume used ranges from 200-400 ml, given once. Five studies reported 2-4 times following the first dose depending on consideration such as no improvement and other clinical judgments. Neutralizing antibody titers were reported in 66.6% of the studies. The neutralizing antibody titers used range from $\geq$1:80 to $\geq$1:1350. The timing of plasma infusion varied between the studies included. Most studies (44.4%) provide plasma infusions $\leq$14 days after the onset of symptoms, followed by >14 days (27.7%), time of infusion was not reported (27.7%). Mortality in the included study had several definitions, including mortality (38.8%), $\leq$14 days of follow-up (16.6%), 14 to 28 days of follow-up (33.3%), and 28-60 days of follow-up (11.1%). Most studies (61.1%) had high-quality assessments (NOS score $\geq$6). The primary characteristics of the study are shown in Table I.

Forest Plot and Subgroup Analysis

The meta-analysis (Figure 2) conducted from 18 studies showed CP use was associated with decreased mortality with OR = 0.64 (95% CI 0.49 to 0.84, $p<0.001$) and heterogeneity (I^2) = 27.62%. Subgroup analysis were performed based on four categories: type of study, COVID-19 severity, time of CP infusion, and mortality. In subgroup analysis, CP was associated with decreased mortality in CCTs, severe to critically-ill, time of infusion ($\leq$14 days and >14 days), and mortality at end of follow-up subgroup. The subgroup analysis is shown in Table II.

Table I. Characteristics of included studies.

No	Author, Place (Design)	Samples	Age	Male (%)	CP Group	Control Group	Measured Outcome	Quality Assessment
1	Hegerova et al 2020[27] US (CCTs)	40 (20 *vs*. 20) Matched by age, comorbidities, SOFA Score, and Severity of illness All patients had severe or life-threatening COVID-19	60 (Matched). Median	N/A	One unit of CP. Dose and antibody titers N/A The majority of patients received azithromycin (60%), hydroxychloroquine (55%), or multiple combinations The time of CP infusion was not defined No adverse events with CP were reported	Half of control patients received remdesivir	Mortality at 7 days follow-up (2/20) *vs* (5/20) Mortality at 14 days follow-up (2/20) *vs* (6/20)	5
2	Li et al 2020[28] China (RCTs)	103 (52 *vs*. 51) All patients had severe or life-threatening COVID-19	70 (70 *vs*. 69) Median	58.2 (51.9 *vs*. 64.7)	One unit of CP with median median volume of 200 ml. Antibody titers using S-RBD–specific IgG titer of at least 1:640 and standard treatment (same as in the control group) CP was given at least 14 days after the onset of symptoms in most cases One patient experienced fever and rash. The other experienced severe dyspnea and cyanosis. Both improved with supportive care	Standard treatment consisted of symptomatic control and supportive care for COVID-19. Possible treatments included antiviral medications, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications	Mortality at 28 days follow-up (8/51) *vs*. (12/50).	7
3	Agarwal et al 2020[29] India (RCTs)	464 (235 *vs*. 229) All patients had moderate COVID-19	N/A (52 *vs*. 52)	76.2 (75 *vs*. 77)	Two doses of 200 mL convalescent plasma, transfused 24 hours apart with antibody titers > 1:1280 and standard treatment The time of CP infusion was not defined One patient experienced a minor adverse event such as pain at the infusion site, chills, nausea, bradycardia, and dizziness.	Standard treatment (antivirals, broad-spectrum antibiotics, immunomodulators, supportive management)	Mortality at 28 days follow-up (44/235) *vs*. (41/229)	6
4	Xia et al 2020[10] China (CCTs)	1568 (138 *vs*. 1430) matched All patients had severe or critical COVID-19	63 (65 *vs*. 63) Median	50.8 (55.8 *vs*. 50.3)	One dose of plasma ranged 200 – 1200 ml with antibody titers N/A and standard treatment (not specified) The time of CP infusion was not defined No adverse events with CP were reported	Control got standard treatment (not specified)	Mortality at 14 days follow-up (3/138) *vs*. (59/1400)	5

Table I. *(Continued).* Characteristics of included studies.

No	Author, Place (Design)	Samples	Age	Male (%)	CP Group	Control Group	Measured Outcome	Quality Assessment
5	Zeng et al 2020[18] China (CCTs)	21 (6 *vs*. 15) All patients had critical COVID-19	N/A (61.5 *vs*. 73) Median	76.1 (83.3 *vs*. 73.3)	The median volume of plasma infused was 300 ml with antibody titers N/A. Standard treatment not mentioned CP was given at a median of 21.5 days after the first detection of viral shedding No adverse events with CP were reported	Standard treatment not mentioned	Mortality (5/6) *vs*. (14/16)	4
6	Liu et al 2020[21] US (CCTs)	195 (39 *vs*. 156) All patients had severe to life-threatening COVID-19	N/A (55 *vs*. N/A) mean	N/A (66 *vs*.	Two doses of approximately 250 ml plasma infused over 1-2 hours with antibody titers ≥ 1:320. Standard treatment not mentioned The median time between admission and transfusion was 4 days (The median duration of symptoms before initial presentation was 7 days) No serious adverse events with CP were reported	Standard treatment not mentioned	Mortality at 21 days follow-up (5/39) *vs*. (38/156)	6
7	Chen et al 2020[22] China (CCTs)	29 (19 *vs*. 10) All patients had severe to critically COVID-19	N/A (55 *vs*. 53) Median	55.1 (58 *vs*. 60)	One dose of plasma ranged 200 – 1200 ml with antibody titers >1:160 and standard treatment The time of CP infusion was not defined One patient experienced an evanescent facial red spot	Standard treatment (antivirals, steroids, and traditional Chinese medicine)	Mortality (0/19) *vs*. (3/10)	5
8	Gharbharan et al 2020[30] Netherlands (RCTs)	86 (43 *vs*. 43) Most patient (84%) in the CP group had WHO severity score ≥4 Most patients (88%) in the control group had WHO severity score ≤2	63 (63 *vs*. 61) Median	72 (77 *vs*. 67)	Received one or two doses of 300 ml plasma with antibody titers ≥ 1:80 and standard treatment same as in the control group. The second dose was given after 5 days of the first infusion for patients without clinical response and persistent positive RT-PCR CP was given on average 30 days after the onset of symptoms No serious adverse events with CP were reported	Standard treatment (azithromycin, chloroquine, lopinavir/ritonavir, tocilizumab, anakinra)	Mortality at 60 days of follow-up (6/43) *vs*. (11/43)	6

Table continued

Table I. ***(Continued).*** Characteristics of included studies.

No	Author, Place (Design)	Samples	Age	Male (%)	CP Group	Control Group	Measured Outcome	Quality Assessment
9	Abolghasemi et al 2020[31] Iran (CCTs)	189 (115 *vs*. 74) Matched age, gender, HTN, DM. All patients included had some or all of the disease clinical symptoms such as shortness of breath (dyspnea), respiratory frequency ≥ 20/min, fever and cough	55.3 (55.4 *vs*. 56.8) Mean	55 (58.3 *vs*. 50)	One dose of 500 mL plasma with antibody titers cut-off index >1.1 and standard treatment same as in the control group. The second dose may be given after 24 hours of the first infusion for patients without improvement. CP was given at least after 7 days after the onset of symptoms No adverse events with CP were reported	Standard treatment (antiviral including Lopinavir/Ritonavir, Hydroxychloroquine, and an anti-inflammatory agent)	Mortality (17/115) *vs*. (18/74)	6
10	Duan et al 2020[23] China (CCTs)	20 (10 *vs*. 10) Matched by age, gender, severity All patients had severe COVID-19	52.5 Median (matched)	60 (matched)	One dose of 200 ml plasma with antibody titers >1:640 and standard treatment same as in the control group CP was given at a median of 16.5 days after the onset of symptoms No serious adverse events with CP were reported	Standard treatment (antivirals, antibiotics, antifungals, steroids)	Mortality (0/10) *vs*. (3/10)	5
11	Rasheed et al 2020[24] Iraq (RCTs)	49 (21 *vs*. 28) Matched by age, gender. Severity N/A All patients had critically ill COVID-19	55.4 Mean	57.1	One dose of 400 ml plasma with IgG index ≥1.25 and standard treatment same as in the control group CP was given at a mean of 14.8-19.3 days after the onset of symptoms One patient experienced mild skin redness and itching after 1 hour of CP admission	Standard treatment (azithromycin, hydroxychloroquine, methylprednisolone, oxygen support)	Mortality (1/21) *vs*. (8/28)	6
12	Salazar et al 2020[19] US (CCTs)	387 (136 *vs*. 251) Matched by age, sex, BMI, comorbidities All patients had severe or life-threatening COVID-19	N/A	N/A	One or two units of plasma transfused within 72 hours of admission with an anti-RBD IgG titer ≥1:1350 (80% probability of antibody titers ≥1:160) and standard treatment Time of CP infusion was categorized into ≤72 and >72 hours of admission The adverse event was not reported	Standard treatment (mostly with tocilizumab, steroids, antivirals, azithromycin)	Mortality at 28 days of follow-up (7/136) *vs*. (25/251)	6

Table continued

Table I. ***(Continued).*** Characteristics of included studies.

No	Author, Place (Design)	Samples	Age	Male (%)	CP Group	Control Group	Measured Outcome	Quality Assessment
13	Simonovich et al 2020[32] Argentina (RCTs)	333 (228 *vs*. 105) All patients had severe COVID-19	N/A (62.5 *vs*. 62) Median	67.5 (70.6 *vs*. 61)	One dose of 500 ml (median) plasma with minimum antibody titers>1:400 The median time from the onset of symptoms to enrollment in the trial was 8 days The overall incidence of adverse events (OR, 1.21; 95% CI, 0.74 to 1.95)	Placebo. Placebo defined as normal saline in addition with standard treatment (antivirals, glucocorticoid)	Mortality at 30 days of follow-up (25/228) *vs*. (11/105)	7
14	Altuntas et al 2020[33] Turkey (RCTs)	1776 (888 *vs*. 888) Matched by age-gender, comorbidity, and other COVID-19 treatments All patients had severe or critically ill COVID-19	N/A (60 *vs*. 61) Median	70.3 (69.4 *vs* 71.4)	The plasma volume and antibody titers were not reported Time of CP infusion was categorized into ≤5, 6-10, 11-15, 16-20, and >20 days from onset of symptoms to infusion The adverse event was not reported	Favipravir, lopinavir + ritonavir, hydroxychloroquine, high dose vitamin C, azithromycin (matched with CP group)	Mortality (219/888) *vs*. 246 *vs*. 888)	5
15	Avendano-Sola et al 2020[34] Spain (RCTs)	77 (38 *vs*. 39) Patients with either radiographic evidence of pulmonary infiltrate or clinical evidence plus SpO2 ≤94% on room air, and within 12 days from the onset of symptoms (fever or cough). Patients with mechanical ventilation were excluded from the study	59 (N/A)	54.3 (N/A)	One does of 250 – 300 ml plasma with antibody titers >1:80 and standard treatment same as in the control group CP was given at a median of 8 days between the onset of symptoms and randomization No adverse event related to CP infusion was reported	Standard treatment (not specified)	Mortality at 15 days of follow up (0/38) *vs*. (4/39)	6

Table continued

Table I. ***(Continued).*** Characteristics of included studies.

No	Author, Place (Design)	Samples	Age	Male (%)	CP Group	Control Group	Measured Outcome	Quality Assessment
16	Perotti et al 2020[35] Italy (CCTs)	69 (46 *vs*. 23) All patients had moderately to severely compromised respiratory function according to Berlin score	N/A (63 *vs*. N/A)	N/A (61 *vs*. N/A)	One to three dose of 250 – 300 ml plasma with antibody titers at least ≥1:80 and standard treatment CP was given at a mean ranged from 2 – 29 days after the onset of symptoms. Five serious adverse events occurred in four patients including chills and fever, subsegmental pulmonary embolism, anaphylaxis/hypersensitivity, TRALI, urticaria	Standard treatment	Mortality at 7 days of follow-up (3/46) *vs*. (7/23)	6
17	Omrani et al 2020[36] Qatar (CCTs)	80 (40 *vs*. 40) All patients had severe COVID-19 infection	53.5 (47.5 *vs*. 55.5)	83.6 (85 *vs*. 87.5)	One does of 400 ml plasma standard therapy. with antibody titers N/A and standard treatment CP was given at a median of 7 days after the onset of symptoms and ICU admission CP appeared to be safe and was not associated with excess adverse events	Standard treatment (supportive care, hydroxychloroquine, azithromycin, and /or lopinavir-ritonavir)	Mortality at 28 days of follow-up (1/40) *vs*. (5/40)	6
18	Rogers et al 2020[37] US (CCTs)	241 (64 *vs*. 177) Matched among all variables examined except corticosteroid use All patients had severe COVID-19	61 (61 *vs*. 61)	54.8 (57.8 *vs*. 53.7)	The volume of plasma and antibody titers N/A and standard treatment CP was given at a median of 7 days after the onset of symptoms Two patients experienced TRALI and one patient experienced TACO	Standard treatment (not specified). Matched except corticosteroid use	Mortality (8/64) *vs*. (28/177)	5

Data presented as total (CP group vs. control group). CP: Convalescent plasma; US: United States; CCTs: Controlled Clinical Trials; RCTs: Randomized Controlled Trials; HTN: Hypertension; DM: Diabetes Mellitus Type 2; IMV: Invasive mechanical ventilation; OR: Odds Ratio; CI: Confidence Interval; TRALI: Transfusion-related Acute Lung Injury; TACO: Transfusion-associated Circulatory Overload N/A: Not available

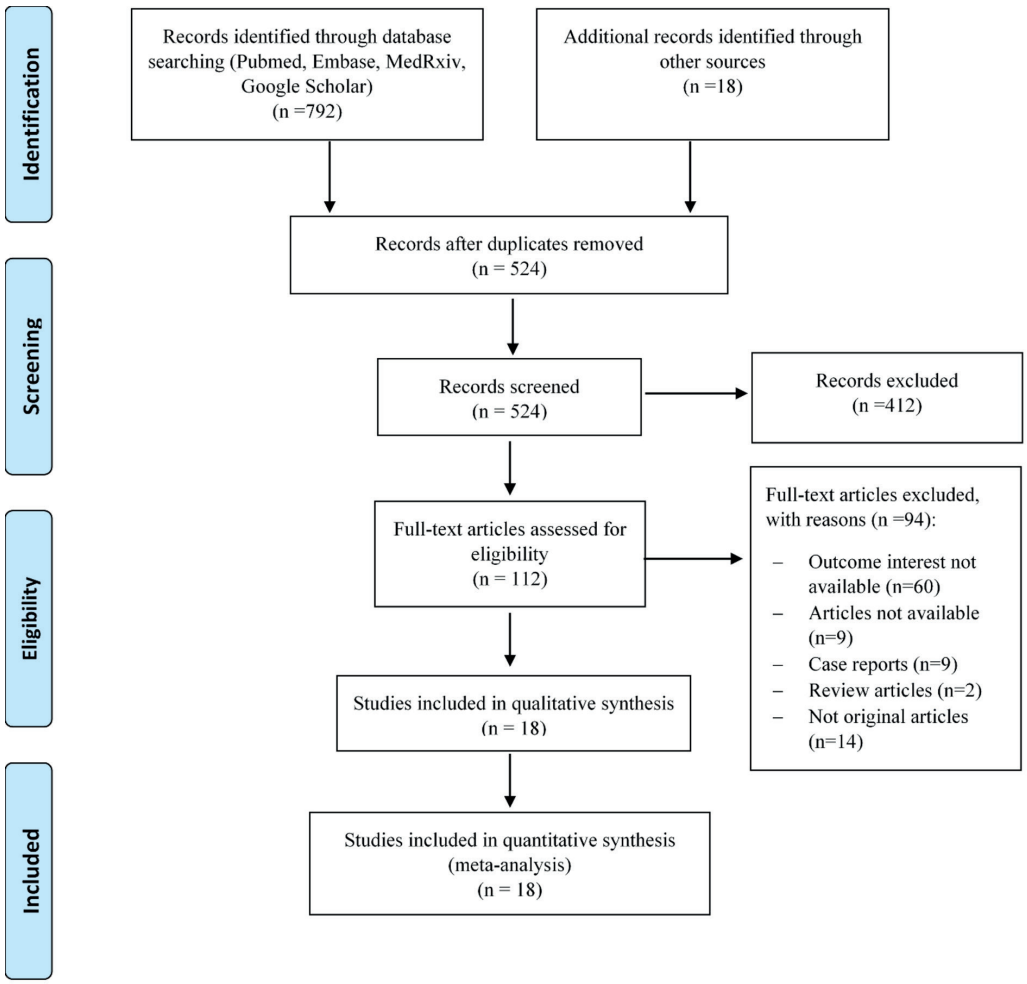

Figure 1. PRISMA Flowchart.

Publication Bias

The funnel plot graph showed an asymmetrical non-inverted funnel that may indicate the presence of publication bias. Thus, a more formal evaluation of the small study effect using Egger's test was conducted. Egger's test showed $p<0.001$ indicated that there was evidence of a small-study effect (Figure 3).

Discussion

Our meta-analysis from 18 studies showed CP use was associated with decreased mortality with OR = 0.64 (95% CI 0.49 to 0.84). Although the use of CP seems promising, the evidence is still limited. Subgroup analysis from RCTs studies showed there was no difference in mortality between CP and the control group. The variation in protocols and lack of standardization from one study to another also could influence the results. Most studies in RCTs (85.7%) provide the neutralizing antibody titers used with ranges ≥1:80 to ≥1:1280. While in CCTs only 45.4% of studies provided the neutralizing antibody titers used with ranges ≥1:320 to ≥1:1350. The time of CP infusion was also varied between RCTs and CCTs studies. In comparison between RCTs and CCTs studies, CP was given in ≤14 days (42.8% *vs.* 45.4%) followed by >14 days (28.5% *vs.* 27.2%) after the onset of symptoms, and not specified (28.5% *vs.* 27.2%). Besides, known comorbid and concomitant treatment also may play a role. All these differences may explain why different results were obtained between RCTs and CCTs.

Convalescent plasma mediates its effect by a variety of mechanisms. Neutralizing antibodies

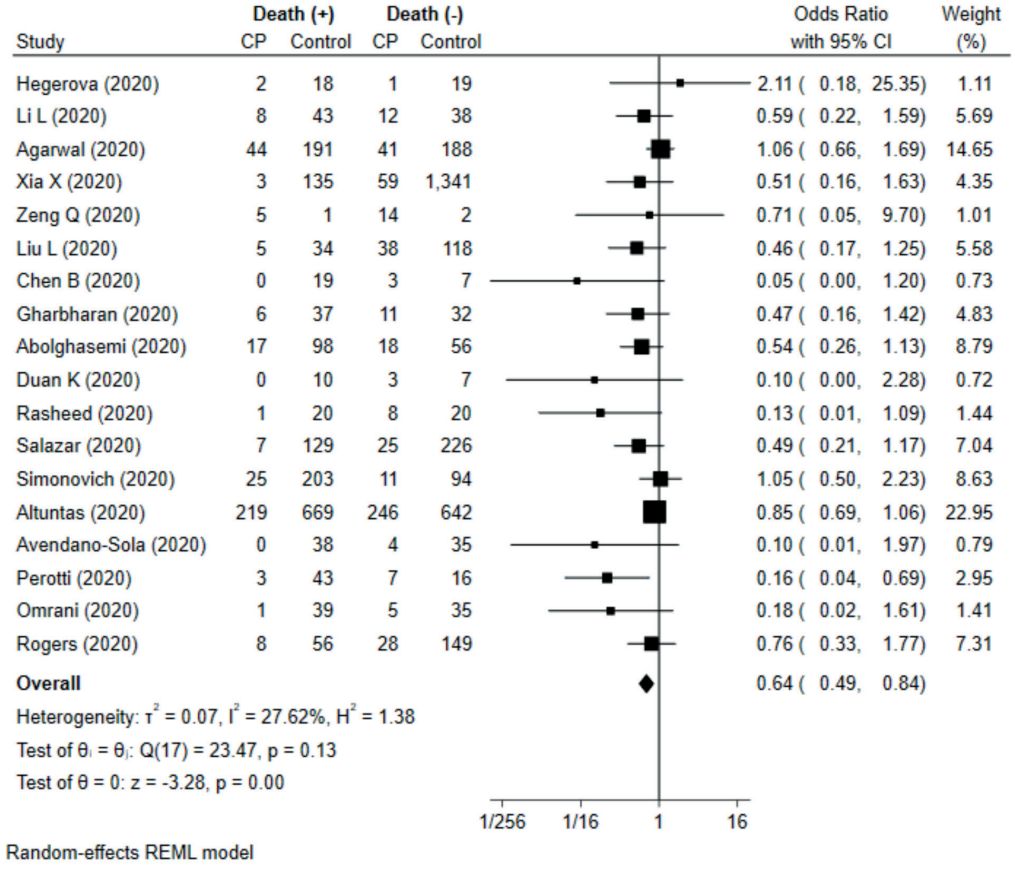

Figure 2. The Forest plot showed CP use was associated with decreased mortality.

Table II. Subgroup analysis.

Overall and subgroup analysis	Number of Studies	Pooled RR (95% CI)	*p*-value	Publication Bias[d]
Total	18	0.64 (0.49-0.84)	0.001	<0.001
Type of Study				
RCTs	7	0.85 (0.71-1.02)	0.07	0.03
CCTs	11	0.48 (0.34-0.70)	<0.001	0.18
COVID-19 Severity				
At least moderate (based on WHO criteria)[a]	5	0.51 (0.26-1.02)	0.057	0.004
Severe to critically ill, life threatening	13	0.68 (0.51-0.91)	<0.0001	<0.0001
Time of Infusion after the onset of symptoms				
≤14 days	8	0.61 (0.43-0.86)	0.004	0.06
>14 days	5	0.28 (0.13-0.61)	0.001	0.47
Not specified	5	0.87 (0.72-1.05)	0.14	0.38
Mortality				
≤14 days follow-up	3	0.42 (0.14-1.31)	0.13	0.37
14 to 28 days of follow-up	6	0.60 (0.36-1.00)	0.052	0.009
28 to 60 days of follow-up	2	0.78 (0.37-1.67)	0.52	-
Not specified[c]	7	0.65 (0.43-0.99	0.04	0.01

RCTs: Randomized Clinical Trials; CCTs: Controlled Clinical Trials; WHO: World Health Organization. [a]For studies that included inclusion criteria based on clinical manifestations instead of severity, we defined new severity classification according to WHO; [b]from mean or median; [c]Mortality from the retrospective study (end of follow-up); [d]Publication bias was assessed using Egger's Test.

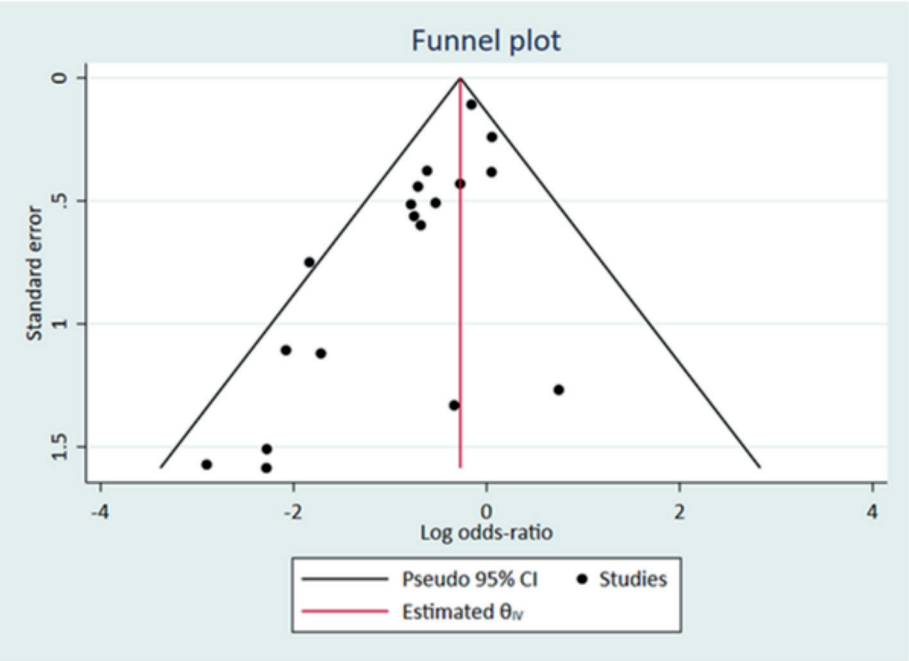

Figure 3. The funnel Plot showed an asymmetrical non-inverted funnel. Egger's test was conducted with $p<0.001$.

may attach to the virus and prevent its interaction with the angiotensin-converting-enzyme 2 (ACE-2) receptor, which provides immunomodulation. Other mechanisms, such as complement activation, phagocytosis, and antibody-dependent cellular toxicity, may also contribute[9,11,12]. Neutralizing antibodies bind directly and interfere with viral replication. Their antiviral function does not depend on host immune cells[13]. Thus, CP may be useful in immunocompromised patients.

Convalescent plasma must contain high antibody titers to neutralize the virus effectively. Also, plasma collecting timing is crucial since it affects the antibody titers. Plasma convalescent should be collected 14 days or more after resolving symptoms in which the antibody titers are high[14,15]. The United States FDA suggests a minimum titer of 1:160 is sufficient for effective response[16]. In our meta-analysis, the neutralizing antibody titers used range from ≥1:80 to ≥1:1350. Subgroup analysis based on neutralizing antibody titers used cannot be performed due to wide variation used. This large variation may have contributed to the results found.

From the previous SARS-CoV-1 pandemic, CP is more beneficial if given early (<14 days of symptoms)[17]. One of included studies by Zeng et al[18] also showed CP administration at the median of 21 days did not reduce mortality. However, the neutralizing antibody titer in study is unknown. A study by Salazar et al[17] found that convalescent plasma can significantly reduce mortality in severe or critically ill patients, especially if given within 72 hours of admission with titer >1:1350[19]. The primary immune response for most acute viral infections usually occurs 10-14 days after infection followed by clearance. Later, clinical worsening occurs as a result of the inflammatory process or immune response, not direct injury from the virus itself[17]. Thus, administration of CP after the peak of viral load may not be beneficial because the immune response triggered by the virus is already high.

Siddiqi et al[20] proposed that COVID-19 can be classified into three stages: stage 1 (mild), stage 2 (moderate), and stage 3 (severe). The viral loads tend to peak within the first week of disease onset. In the second week, elevated immune responses trigger cytokine storms, which can be reduced by CP. Therefore, CP should be given in the early course of the disease or as a prophylaxis[5,9]. Several studies[21-24] showed CP decreases mortality in patients with severe to critically ill COVID-19. Our review showed CP was more effective in reducing mortality in patients with severe to critically ill compared to moderate COVID-19 ($p<0.0001$ *vs.* $p=0.057$, respectively). Antibody titers may play an important role in determining the efficacy of

CP. It should be high enough to elicit the curative effect through several mechanism[25].

The adverse effect associated with CP infusion is classified into known and theoretical[26]. The known risk includes allergy/anaphylaxis, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and unintended infection[12]. The risk of blood-borne pathogens is small. The theoretical risk includes antibody-dependent enhancement (ADE). Our meta-analysis showed that seven patients experienced serious adverse effects, such as subsegmental pulmonary embolism anaphylaxis, TRALI, and TACO. As shown in Table I, some patients experienced mild adverse effects such as fever, chills, nausea, rash, evanescent facial red spot, itching, and pain at site infusion. Overall, the adverse event was observed within two to six hours after the plasma transfusion. No antibody dependent enhancement was reported. However, there were two studies[19,33] included in this review did not specify whether they observe the adverse event or not.

Our review shows wide variation among CP volume, neutralizing antibody titers, and time of CP infusion from the onset of symptoms in included studies which may influence the results. CP seems to be more beneficial in reducing mortality in severe to critically ill COVID-19 patients. Optimal neutralizing antibody titers should be investigated to elicit maximum CP therapeutic effect. However, our study cannot determine the role of antibody titers due to wide variation in studies. Another limitation is an asymmetrical non-inverted funnel plot that may indicate the possibility of publication bias.

Conclusions

Convalescent plasma is effective in reducing mortality of severe and critical COVID-19 with tolerable adverse effects.

Conflict of Interest

The authors declare that there they have no conflict of interest regarding the publication of this paper.

Consent for Publication

The authors declare that this manuscript is original, has not been published before, and is not currently being considered for publication.

Funding Statement

The author(s) received no funding for this work.

Ethics Approval

Not applicable. No ethical approval will be needed because data from previously published studies in which informed consent was obtained by primary investigators will be retrieved and analysed.

Competing Interest Statement

The authors have declared that no competing interests exist.

Author's Contributions

Arto Yuwono Soeroto (AYS), Aga Purwiga (AP), Anggraini Alam (AA), and Dimmy Prasetya (DP) conceived and designed the study. AA and DP acquire the data. AYS and AP performed data extraction and interpreted the data. AYS and AP performed the statistical analysis. All authors contributed to the writing of the manuscript

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Acknowledgment

Not applicable.

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