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Systematic Literature Review: Could Plasma Convalescent Prevent Death on COVID-19?

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A B S T R A C T

The COVID-19 pandemic is still a global health problem, and the lack of effective and efficient treatment standards is one of the causes of the high morbidity and mortality rates. One approach often used in various cases of COVID-19 is convalescent plasma therapy. The administration of convalescent plasma is one of the treatment options that are often used in cases of COVID-19 with mild, moderate, severe, chronic, and critical symptoms. The article review aims to analyze how convalescent plasma transfusion in various cases of COVID-19 can prevent death and improve clinical outcomes. The PRISMA flowchart is applied to filter the literature that meets the inclusion criteria: published articles with experimental or observational research discussing the use of convalescent plasma in COVID-19 patients; published January 2020 - March 2021. We conducted article searches through PubMed, Google Scholar, and Science Direct. Assessment of the quality of the articles using the EPHPP form, and we chose ten articles. The results of the qualitative analysis prove that convalescent plasma administration in various COVID-19 cases significantly reduces viral load, clinical improvement and prevents death in mild, moderate, and severe COVID-19s, but for terminal or critical cases, it does not show significant results. The success rate of convalescent plasma therapy is determined by the high antibody titer in plasma donors, the distance between its administration and the onset of symptoms, and the patient's baseline condition before plasma administration. Based on these results, further research is needed to determine the standard dose and method of administration of convalescent plasma referring to the varied baseline conditions of patients.

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1. INTRODUCTION

At the end of 2019, the Chinese government announced a novel coronavirus pneumonia (NCP) case caused by the 2019-novel coronavirus (2019-nCoV) (Gil *et al.*, 2020). The name NCP was replaced by COVID-19, while SARS-CoV-2 was replaced 2019-nCoV by the International Committee on Taxonomy of Viruses and WHO (Zhang *et al.*, 2020). Global data on the number of confirmed cases and deaths from COVID-19 have steadily climbed, prompting WHO to declare it a global health emergency (Zhang *et al.*, 2020). New cases of COVID-19 reached 103 million in February 2021, with 2.2 million deaths; these numbers suggest a global decrease trend (Garibaldi *et al.*, 2021). However, British authorities reported infection with a new variant of SARS-CoV-2 in early 2021, which is more virulent, more readily transferred, and reduces the effectiveness of the vaccination used by the United Kingdom government (Hacisuleyman *et al.*, 2021). The SARS-CoV-2 delta variant development was linked to an increase in confirmed cases and deaths in India by the end of March 2021. This variant had been identified in 43 countries spanning six continents (Lopez Bernal *et al.*, 2021).

Numerous of registered clinical studies are currently underway, the vast majority of which are testing antiviral medications, anti-inflammatory or immunosuppressive therapies, and antibody therapy (Mehta *et al.*, 2020; Nasrallah *et al.*, 2020). In a randomized controlled investigation, remdesivir, an RNA polymerase inhibitor, was shown to be effective against SARS-associated coronavirus, and certain COVID-19 recoveries require less time (Beigel *et al.*, 2020; Gil *et al.*, 2020). Remdesivir, an RNA polymerase inhibitor, is an antiretroviral, was proven to be effective against SARS-associated coronavirus in a randomized controlled study, certain COVID-19 recoveries take less time (Beigel *et al.*, 2020). Furthermore, dexamethasone has recently been demonstrated to decrease mortality in oxygen-treated patients, particularly intubated patients (Horby *et al.*, 2021). Efforts to prevent COVID-19 through the development of numerous vaccinations have been made; however, these efforts have not been successful in reducing COVID-19 morbidity and mortality since the emergence of the Delta variant. As a result, although several preventive and therapeutic techniques are being researched, supportive therapy is the main treatment for COVID-19.

Convalescent plasma (CP) therapy has been used to treat patients during previous outbreaks of COVID-19. The administration of CP is still controversial due to the lack of research data that can prove the effectiveness and efficiency of CP in COVID-19 cases. Several studies have shown that CP can improve the outcome of COVID-19 patients, but several studies have stated that there is no significant improvement and differences. Meanwhile, despite the limitations imposed by the Emergency Use Authorization (EUA) law and the ability to be used in clinical trials, various COVID-19 treatment centers use CP in clinical practice (Rejeki *et al.*, 2021). Based on the principle of passive immunization, the administration of convalescent plasma (CP) from donors of COVID-19 patients who have been proclaimed cured is a viable alternative for COVID-19 prevention and therapy because it is widely available. Giving CP containing neutralizing antibodies / NAb will bind to the epitope on the outer surface of the virus particle, preventing virus invasion and replication (Salazar *et al.*, 2020). Another pathway of administering CP is by antibody-dependent cellular cytotoxicity and/or phagocytosis (Dai, Gu and Hao, 2020). CP treatment may potentially have immunomodulatory effects by increasing macrophage activation and avoiding systemic hyperinflammation, often known as a "cytokine storm." The results of a serial case study on the administration of CP in COVID-19

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demonstrate its prospective role in improving disease manifestations, suppressing viral replication, and elevating levels of antibodies (Mair-Jenkins *et al.*, 2015; Ingraham *et al.*, 2020).

However, the previous studies have various weaknesses and limitations to be generalized in the population and become a reference for establishing CP as standard therapy for COVID-19. Related to the lack of data, WHO opens opportunities for researchers to explore CP associated with the method of administration, dosage, donor requirements, conditions of patients who meet the requirements for administration, and side effects. These results will be the basis for researchers to conduct clinical trials and ultimately produce a standard guideline used by medical personnel in dealing with COVID-19 cases. Based on these phenomena and conditions, The authors would like to undertake a systematic literature study on the administration of CP to COVID-19 patients.

2. METHOD

This systematic review implemented the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocols (Peng, Rhind and Beckett, 2021). PRISMA diagrams help authors develop structured and transparent articles in systematic review articles and meta-analyses (Permana *et al.*, 2020).

Searching Strategy

The authors selected articles published between January 2020 until March 2021 using several keywords: COVID-19 OR SARS-CoV-2 AND convalescent plasma from relevant databases such as PubMed, Google Scholar, and Science Direct. All papers that covered the administration of convalescent plasma or CP in the treatment of COVID-19 were eligible, including experimental (true experimental, quasi-experimental, pre-experimental study), observational (cohort, case-control/retrospective study, and cross-sectional study), and full-text articles. This study's inclusion criteria:

1. The study population was all COVID-19 patients with mild, moderate, or severe symptoms.
2. The intervention was CP administration.
3. The result's outcome mentioned comparison before-after CP treatment or comparison between the CP treatment group with or without a control group.

Article Screening

The screening procedure begins with a thorough assessment of article titles to eliminate article duplication. Then we evaluated the title and abstract to see if they were related to the study's goals; if they were, the complete article was examined by two reviewers separately. The reviewers reached a consensus with the other reviewers to resolve rating disputes. The data extraction procedure, covered in another sub-chapter, employs the same method and strategy (Peng, Rhind and Beckett, 2021).

Data Extraction and Study's Critical Appraisal

The authors compiled the data extraction for the selected articles by creating a table that included the author's name, country of origin, research period, population or research respondents, CP dose and

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time of administration, use of other drugs, respondent's condition before CP administration, results, and side effects of CP administration.

The Effective Public Health Practice Project (EPHPP) equipment tools are used by researchers to critically evaluate each quantitative research publication (experimental study, quasi-experimental study, and observational study) that meets the inclusion requirements. Study design, sample selection, confounder identification and treatment, outcomes blinding between participants and assessors, data collecting procedures and analysis, withdrawals, and dropouts, are all areas where EPHPP is used to evaluate the quality of a study in three categories: strong, moderate, and weak. The authors used the six-component ratings to get the overall rating of each study. A good rating was awarded to those with no weak evaluations and at least four strong reviews. Moderate was defined as having four or fewer strong reviews and one or fewer weak reviews. Those who obtained two or more poor reviews were categorized as weak (Peng, Rhind and Beckett, 2021).

The assessor team will review the results of the EPHPP assessment on all papers to determine the significant elements that will serve as a reference for evaluating the usage of articles in this literature study (Long, French and Brooks, 2020; Peng, Rhind and Beckett, 2021).

3. RESULTS

Searching Result

Researchers used three primary search platforms in this study: PubMed, Google Scholar, and Science Direct., to find 1934 publications using the search methods stated before. The first phase in the selection process filtered duplicate articles and full-text documents that are not accessed and purchased for then the authors acquired 1423 documents. We made the second step selection by evaluating the relevancy of the article's title and abstract, selecting 350 documents. The third step evaluation used inclusion criteria, and there were 16 document articles. The final step in the selection process was the assessment of articles using EPHPP equipment tools and discussion among the assessor members, resulting in the acquisition of 10 article papers. This study's PRISMA flow diagram is shown below in figure 1:

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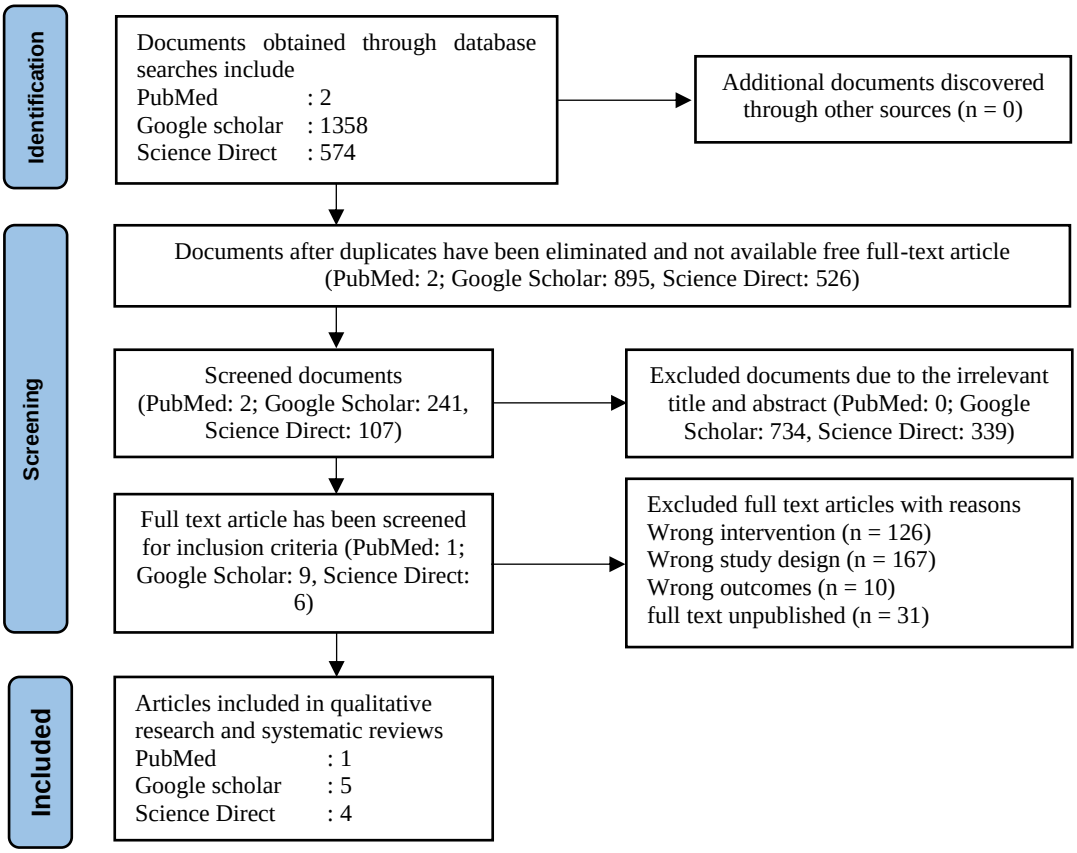

Figure 1. PRISMA Diagram Flow

Critical Appraisal Result

The initial critical appraisal is performed independently by two reviewers. A discussion procedure is followed if there are discrepancies in the assessment to create a final critical appraisal result. The reviewers examined the manuscript on six components: probability sampling, design of the study, confounding variables, blinded, data gathering, and dropout or withdrawal. The following table shows the outcomes of the EPHPP appraisal criticism in table 1:

Table 1. EPHPP Critical Appraisal Result

Authors	BS	SD	CO	BL	DC	DO/WD	Result
Duan et.al	S	M	S	M	S	S	S
Li et al.	S	S	S	M	S	S	S
Salazar et al	S	S	M	M	S	S	S
Wu et al	S	M	S	M	S	S	S
Salazar et al	S	S	M	M	S	S	S
Libster, et al	S	S	S	S	S	S	S
Alsharidah et. al.	S	M	S	M	S	S	S
Maor et al	S	M	S	M	S	S	S
Omrani, et al.	S	M	S	M	S	S	S
Rejeki et al	S	M	S	M	S	S	S

BS (bias selection); SD (study design); CO (confounders); BL (blinding method); DC (data collection & analysis); DO/WD (drop out/ withdrawal); S (strong); M (moderate) and W (weak

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Based on the critical appraisal result to all document's articles, there were ten substantial articles. Each study has weaknesses, most of which are related to the double-blind research method, and just one of the ten studies employs it.

Articles Included in the Systematic Review

This systematic review includes original research consisting of clinical trial studies (pre-experimental, non-randomized control trials, and randomized control trials) and analytical observational studies (cohort/prospective studies and case-control/retrospective studies). One article features a clinical trial with a pre-experimental/ pilot research design. One study with a non-randomized control trial design; 2 research with a randomized controlled trial design; There are three cohort/prospective studies and two retrospective/ case-control studies. Based on the critical appraisal evaluation of articles that meet the inclusion criteria, there are ten articles presented in the table 2 below:

Table 2. Description of Articles

Author, & Study Periode	Study Design & Study Population	CP Dosage & Administrated Day	Other Treatment	Status During CP	Outcome	Side Effect
Duan et al (Duan, Liu, C. Y. Li, *et al*., 2020) China January - February 2020	A pilot clinical trial using ten patients with severe COVID-19: 3 patients with Hypertension, one patient with cardiovascular and cerebrovascular disease, six patients without comorbidities. The median age patients in this research were 52.5 years	CP dosage: 1 x 200 mL CP with a neutralizing activity of greater than 1:640. CP Administration: 11-20 days after the first symptoms onset	All patients received antiviral, six patients received antibiotics, three patients received antifungal, six patients using corticosteroid and oxygen support	All patients on this study admitted to the ICU, with following O_2 supplementation: High-flow oxygen support (n = 5), ventilators (n = 3), Low-flow nasal cannula oxygen support (n = 2); none (n = 2)	1) SARS CoV-2 patients who received CP before the 14th day of symptoms had significant improvements. 2) Clinical symptoms improved within three days 3) Improvement in radiological examination within seven days 4) two patients transitioned from ventilators to high-flow oxygen, one patient stopped high-flow oxygen support, and one patient was converted to intermittent oxygenation 5) At 7 days following CP delivery, all patients' viral load was negative.	One patient showed red spot after administration of CP.

Table 2. Description of Articles *(Continue)*

Author, & Study Periode	Study Design & Study Population	CP Dosage & Administrated Day	Other Treatment	Status During CP	Outcome	Side Effect
Rejeki et al. (Rejeki *et al.*, 2021) Indonesia May until July 2020	A nonrandomized clinical trial with ten patients with confirmed COVID-19 by RT PCR, median age 56.6 years.	CP dosage: 3 ml/kg BW; 3 doses with interval two days on each dose CP administration: Median time from first symptoms until CP administration was 25 days	All patients received antiviral drugs and other supportive therapy based on Indonesian Government Guidelines	Five patients have moderate symptoms, and five patients have severe symptoms. The severity of symptoms was made based on Siddiqi & Mehra standard and WHO guidelines	All patients with moderate illness and two severe illness patients showed improvement 1 -3 days after first dose of CP. 1) Increasing CT value 2) Seven patients showed negative result of RT PCR and three patients remained positive at the end of trial (4 weeks)	There is no major events related CP administration
Libster, et al. (Libster *et al*., 2021) Argentina June until October 2020	Randomized double blind control trial 160 patients with median age 77.2 years); confirmed COVID-19, divided into two groups:	CP dosage: 250 ml of CP with an IgG titter more than 1:1000 CP administration 72 hours following the onset of the	all patients received no drugs other than CP in the treatment group and placebo in the control group	Patients had mild symptoms and having comorbid conditions (any chronic illness and metabolic diseases)	The treatment of high-titer convalescent plasma against SARS-CoV-2 to infected older persons within 72 hours of the start of mild illness decreased the escalation of COVID-19 to severe symptoms	No adverse effects were observed

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	80 patients received CP 80 patients received placebo	first signs of illness				
Li et al. (Li *et al.*, 2020) China February – April 2020	Randomized Clinical Trial: 103 patients with median age were 70 years and met the inclusion criteria and were split into two groups: (1) The group that received standard therapy and CP administration (2) A group with standard treatment, without CP therapy	The mean dose of convalescent plasma 1x 200 ml with IgG titter minimum 1:640 CP Administration: 14 days after the the onset of the disease	Antiviral drugs, antibacterial drugs, steroids, human immunoglobulin, Chinese herbal remedies, and other treatments	All responders were hospitalized, and there were 2% of patients who did not require oxygen support, 29-30% who did, 41-46 % who used non-invasive ventilation (non-invasive high flow oxygenation), and 22-17.5 % who used invasive mechanical ventilation in the two study groups.	There were no significant clinical improvements between groups with CP and standard therapy groups. There was no significant difference between the two groups regarding death within 28 days and time to hospital discharge. At 24, 48, and 72 hours following convalescent plasma treatment, there was a higher negative SARS-CoV-2 PCR testing rate, indicating that convalescent plasma treatment was associated with antiviral efficacy in COVID-19 patients.	Following a CP transfusion, one patient exhibited adverse reactions and a slight fever. Another patient complained of shortness of breath.
Salazar et al., (Salazar, Paul A. Christensen, Graviss, *et al.*, 2020) USA March – July 2020	Cohort study propensity score matched: 387 patients with severe and/or critical illness COVID-19. Patient's aged 18 - 80 years. This study comparing 136 patients with CP treatment and 251 patients using standard regiment without CP therapy	CP dosage: 76 % respondent received one dose of CP (1 x 200 ml) & 90% with titter IgG ≥ 1: 1350; and 24 % received double doses of CP & 95% with titter IgG ≥ 1: 1350 CP Administration: 1) Within 72 hours after admission. 2) More than 72 hours after admission. 3) Within 72 hours of admission with titer ≥ 1350	Standard regiment for covid 19 patients	Respondents' characteristics: utilize invasive mechanical ventilation, high flow ventilation, low flow ventilation, and no supplemental oxygen.	1) Although the difference was not statistically significant, the transfused patients had a lower risk of dying within 28 days than the propensity score-matched controls. 2) Patients who got a CP transfusion during 72 hours after being admitted to the hospital with IgG titer was more significant than 1:1350 (high titer). Had a significantly lower death rate. 3) According to multivariate research, patients who were not administered with convalescent plasma had a greater probability of dying within 28 days (regardless of titter or timing).	No adverse effect of CP administration

Table 2. Description of Articles *(Continue)*

Author, & Study Periode	**Study Design & Study Population**	**CP Dosage & Administrated Day**	**Other Treatment**	**Status During CP**	**Outcome**	**Side Effect**
Alsharidah et. al. (Alsharidah *et al.*, 2021). Kuwait May to June 2020	Study design prospective multicentre interventional study with median age 54 years and divided two groups: 1. Group with CP 135 patients 2. Group control with standard treatment 233 patients	CP dosage: 79.3 % patients received 2 units CP (2 x 200 ml) and 20.7 % patients received 1 unit of CCP (1 x 200-400 ml) CP administration: 24 hours after the admission	Antibiotics and heparin without any antiviral drugs	In the two study groups there were patients with moderate and severe manifestations	1) CP treatment significantly improved clinical outcomes in moderate and severe patients. 2) The administration of CP to two clinical groups (moderate and severe disease) resulted in a considerable reduction in fatality rates.	No adverse effects were observed
Maor et al. (Maor *et al.*, 2020) Israel April until May 2020	Prospective cohort study: 49 patients confirmed COVID-19 with median age 64 years, divided into two groups: 1. 30 patients received low level titter Ab	CP dosage: 2 x 200 ml with median titter IgG was 1:160 CP administration: The median time from PCR diagnosis to the median time administration of CP was 10 days after PCR	Patients involved in the study received standard therapy, but none received remdesivir	The two groups consisted of patients with moderate cases (O_2 saturation less than 93 % at room air) and severe COVID-19 with a minimum one criteria such as severe pneumonia /shock using hemodynamic support/ using mechanical	1) When compared to low-titter CP, high-titter CP has been proven to dramatically improve clinical and laboratory conditions in COVID-19 individuals with moderate and severe disease. 2) High titters of CP have also been demonstrated to be effective and efficient when given to patients 10 days following diagnosis.	No major side effect, only one patient has rash and recover after antihistamine therapy

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	2. 19 patients received high titter Ab	confirmed diagnosis		ventilation/ O_2 saturation less than 90 % at room air		
Salazar et al. (Salazar, Paul A Christensen, Graviss, *et al*., 2020) USA March until September 2020	A cohort study on COVID-19 patients who were observed for 60 days after hospital, patients aged 18-80 years admission which was divided into two groups: 1. The case group was 341 covid 19 patients 2. The control group consisted of 594 covid 19 Both groups have been selected according to the matching criteria to minimize confounding factors.	CP dosage: 79 % received one dose of 300 ml CP, and 91 % patients received titter IgG 1:1350. CP Administration: (1) Administering CP within 72 hours of being hospitalized. (2) Administering CP more than 72 hours after being hospitalized	All patients received standard therapy such as remdesivir azithromycin, steroid, hydroxychloroquine, ribavirin, and tocilizumab	The patients' conditions varied; some did not require oxygen supplementation, while others required low flow oxygen, high flow oxygen, and mechanical ventilation.	There were significantly different on: 1) mortality in CP group was lower than control. 2) Clinical improvement 3) Regardless of plasma titter, transfusion later in hospitalization or later in the disease course (e.g., after intubation) had no meaningful advantage on mortality. 3) The negative RT PCR results in the group that received CP transfusion for seven days of observation were significantly higher than the control group without CP transfusion	5 patients experienced side effects of skin rash. One patient experienced shortness of breath, which improved with diphenhydramine. One patient experienced shortness of breath due to fluid overload improved with furosemide administration.
Wu et al. (Wu *et al.*, 2020): China January to April 2020	Retrospective observational study: Twenty-seven respondents were positive for COVID-19 for a long time with coexisting chronic diseases. The median age was 64 years. Patients were divided into 2 groups: 15 respondents in the early negative (EN) & 12 respondents in late negative (LN) group.	CP dosage: Both groups received 1 x 400 ml in each group with a titter >1:160 CP administration: 40 days after first symptoms in the EN group and 45 days after the first symptoms on the LN group	Received broad-spectrum antibiotic therapy, ribavirin, lopinavir, favipiravir	Nineteen patients didn't require oxygen treatment, 3 patients need nasal catheter oxygen therapy, 5 patients use mechanical ventilation, and 1 patient required Extracorporeal membrane oxygenation	EN group has median length hospitalization (37 days) shorter than LN (52 days) There was no significant difference in pulmonary radiographic improvement between 2 groups The median viral load in the EN group was lower than the LN group significantly in 3,5-, and 7-days observation Total patients' death within 60 days on LN group (3) was higher than EN group (0)	No adverse effects were observed

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Table 2. Description of Articles *(Continue)*

Author, & Study Periode	Study Design & Study Population	CP Dosage & Administrated Day	Other Treatment	Status During CP	Outcome	Side Effect
Omrani, et al. (Omrani *et al.*, 2021). Qatar April until June 2020	Non-Randomized retrospective study 80 COVID-19 confirmed patients, median aged 53.5 years, median BMI 27.4; divided into two groups: 40 patients with CP and standard therapy 40 patients with standard therapy without CP	CP dosage: A total of 400 cc of compatible convalescent plasma was given to each patient. Median titter IgG 1 :160 CP administration: 10 days (median value) after the first onset of symptoms	Most patients received antiviral, antibiotic, steroid and 91.2 % patient received tocilizumab.	All patients used in this study have several criteria such as: 86.2 % patients using mechanical ventilation, all patients at least have one of the following comorbidities (DM and hypertension) Most patients have an infiltrate on their lungs based on CT radiographic.	There were no significant differences on observation 28 days: Respiratory improvement and duration of respiratory improvement Patients discharged alive from ICU within 28 days. Viral load All-cause mortality within 28 days Viral clearance within 28 days after the first onset	No major side effects have been reported using convalescent plasma.

4. DISCUSSION

According to the findings of a systematic literature review, eight study articles stated that CP transfusion provided benefits for mild, moderate, severe, and persistent cases of COVID-19 (Maor *et al.*, 2020; Alsharidah *et al.*, 2021). However, according to two studies, CP administration did not result in significant clinical improvement (Li *et al.*, 2020; Omrani *et al.*, 2021). After delivering CP to COVID-19 patients, the global results in eight articles reported that significantly reduce mortality, length of hospital stay, clinical manifestations, and viral load. The success in these studies could be associated with characteristics of study participants (age and comorbidity disease), the initial condition of study subjects (using supplemental oxygen or not, and the type of oxygen support), disease severity (mild, moderate, severe, or critical illness), the content of transfused antibody levels, and time of CP administration after first onset or hospitalization.

Convalescent plasma, or CP, provides both passive and rapid antibody-mediated protection, including anti-SARS-COV-2 antibodies (Al-Riyami, 2021). CP provides neutralizing antibodies directed against the SARS-Cov-2 membrane spike protein. This membrane spike protein will mediate viral and ACE2 receptor binding to the host cell surface. Complement activation, antibody-dependent cellular toxicity, and phagocytosis can all be inhibited by CP treatment, minimizing the inflammatory cascade (Franchini and Liumbruno, 2021). CP also has anti-coagulation factors, natural antibodies, defensins, pentraxins, and other undefined proteins(Choi, 2020; Psaltopoulou *et al.*, 2020; Briggs *et al.*, 2021; Franchini, Glingani, and Liumbruno, 2021).

Neutralizing antibodies play a critical function in eliminating viruses and preventing viral illness. The success of this medication was linked to the concentration of neutralizing antibodies in CP. Other antibodies, including IgG and IgM, are found in plasma, but they do not affect the virus's replication. Plasma-transferred IgG neutralizes cytokines like IL-6 and TNF, suppressing the inflammatory response. After receiving CP, participants' IgG and IgM titers grew time-dependent. By interacting with viruses, antibodies could decrease virus entrance into cells and boost viral clearance via antibody-dependent phagocytosis or antibody-dependent cellular toxicity. In excessively inflammatory conditions, passive immunity provided by COVID-19 CP may minimize the inflammatory cascade triggered by pathogenic antibodies, as well as the cellular

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damage generated by complement cascade activation (Rojas *et al.*, 2020; Bloch, 2021; Franchini, Glingani and Liumbruno, 2021)**.** Even though CP has several action methods, it is most effective because it contains anti-SARS-CoV-2 antibodies, which block the virus from entering cells and multiplying. CP's antiviral action is thus proportional to the quantity of antibodies present. The more neutralizing antibodies in the plasma, the better it stops viral reproduction (Franchini and Liumbruno, 2021).

COVID-19 has a poor prognosis due to several factors, including being over the age of 65 years; complaining of shortness of breath; having comorbidities (heart disease, respiratory problems, and diabetes); a decreased lymphocyte count and an increased neutrophil/lymphocyte ratio; elevated LDH, AST, bilirubin procalcitonin; and elevated inflammatory markers (CRP, IL-6, serum IL-6); and the presence of endothelial abnormality and angiogenesis (Zhou *et al.*, 2021). The first consideration is the characteristics of the study's respondents, such as their age, comorbidities, degree of illness, and oxygen supplementation. The respondents' ages ranged from 18 to 80 years, with median values ranging from 52.5 to 77 years. Two articles used respondents' median age of 70 without mentioned about comorbidity (Li *et al.*, 2020) and 77.2 years with comorbidities in all respondents (Libster *et al.*, 2021). Four articles mentioned that almost all participants have at least one comorbidity. Three articles didn't mention comorbidity. Two articles mentioned that respondents' conditions varied; some had comorbidities, while others did not (using the propensity score-matched method).

Antibody titer level is also thought to influence COVID-19 clinical progress. The dose of CP administration varied across the ten articles in this study, with three articles mentioning the administration of 400 ml (administered a single dose of 400 ml or double dose of 200 ml for a total of 400 ml); one article giving one dose of 300 ml, one article using a double dose of 250 ml; two studies using a single dose of 250 ml; and one study using a triple dose of 3 mL/BW. Based on these dosages, the CP dose varies from at least 200 ml to the maximum of 400 - 500 ml CP. Median IgG titers administered to patients or respondents vary between 1:160 until 1: 1350 (three articles used 1:160; two articles apply 1: 640; two articles apply 1:1350; only one article applies 1: 1000; one article didn't mention the titter of IgG on CP donors). The prior study of Maor et al. with multivariate analysis stated that administration of CP with antibody titer factors had a dominant influence among other variables. Antibody titers above four can significantly improve all conditions of COVID-19 patients (marked by staying alive, not using mechanical ventilation, symptoms being mild or moderate during the 14-day observation period) (Maor *et al.*, 2020). Administration of CP with a high titer of anti-spike protein receptor-binding domain more than or equal to 1: 1350 significantly suppressed mortality throughout 28 days of observation (Salazar, Paul A. Christensen, Graviss, *et al.*, 2020). The FDA has also determined that the standard neutralizing antibody titer for CP donors for COVID-19 was ≥ 1:160 (Barone and DeSimone, 2020). Maor et al.'s research demonstrated that the improvement in the result is related to the Ab titer administered to the patient (dose-dependent) (Maor *et al.*, 2020). These research's results suggested that the neutralizing antibodies were a consequence of a short-term humoral immune response, and hence plasma of recently recovered individuals should be more beneficial (Duan, Liu, C. Li, *et al.*, 2020).

Another element influencing the efficacy of CP therapy is the time of administration. The

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timeline for delivering CP between ten articles differs from one another, based on the median value of the period between the first onset of illness and the administration of CP, the shortest median value was 72 hours, and the longest was 45 days. If the administration is based on the hospital admission range to CP administration, the fastest range was 24 hours, and the longest range was 72 hours following hospital admission. CP administration is carried out within 72 hours (using Youden index analysis revealed that the cut point of transfusion is 44 hours) after being hospitalized, demonstrating a significant improvement in outcomes (Salazar, Paul A Christensen, Graviss, *et al.*, 2020). The severity of illness impacted the effectiveness of CP therapy (Tirnea *et al.*, 2021); mild and moderate COVID-19 patients improved faster than severe COVID-19 patients, and severe COVID-19 patients had a better outcome than life-threatening COVID-19 patients. Another study stated that giving CP to critically ill patients of COVID-19 did not significantly reduce the mortality rate (Luchsinger *et al.*, 2020).

Two articles studies produced contradictory results that the administration of CP did not significantly improve clinical outcomes, mortality, or length of hospital stay, but it has a potent antiviral effect (Li *et al.*, 2020; Omrani *et al.*, 2021). Several factors could alter these outcomes, including a limited sample size, and the researchers ended the study observation prematurely. The limited-time of the trial follow-up may have prevented observing clinical outcomes in patients with severe disorders, particularly life-threatening COVID-19, as they may take longer to show significant improvement. The trial was probably underpowered to find a clinically significant advantage of convalescent plasma treatment. Another issue that influenced the results was the length of time between the onset of the first symptoms and the randomization process and delivery of CP in the research, which made it difficult to determine whether the improvement was due to CP or the administration of other medications. Patient clinical improvement can also be influenced by clinician decisions and other non-standardized therapies, impacting patient outcomes (Li *et al.*, 2020; Omrani *et al.*, 2021). In the research of Omrani et al. using respondents who use mechanical ventilation (86.2%) and have a chronic disease, the median age of respondents is 53.5 years and has a BMI above the normal standard of 27.4, with a neutralizing antibody titer with a median value of 1:160. The characteristics of respondents with severe-life threatening COVID-19 and the administration of CP with a low antibody titer could be factors that caused no significant difference after CP administration. In the study of Li et al., factors such as a short observation time, a small sample size, and a long delay between CP administration and the beginning of symptoms all contributed to no significant differences in the respondents' results. On the other hand, CP therapy decreased viral load significantly (negative RT PCR results) at 24, 48, and 72 hours following CP administration (Li *et al.*, 2020).

In the study conducted by Maor et al. and Wu et al. using a CP dose with the same median neutralizing antibody titer (median 1: 160) (Maor *et al.*, 2020; Wu *et al.*, 2020) as Omrani et al. but the results of Maor et al. and Wu et al. showed significant improvement. These different outcomes may be due to the patients' different general conditions (severe and life-threatening symptoms did not dominate the respondent's condition). Maor et al. used two different titer antibodies and found that administering IgG titers above 4 resulted in considerably better outcomes than administering IgG titers below 4, and CP should be transfused ten days after the onset of first symptoms (Maor *et al.*, 2020).

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These systematic reviews reveal that the author detected no serious side effects in CP administration. Four studies reported side effects with CP administration, while the other six studies did not identify any negative effects. In one study, at least only one respondent and a maximum of seven respondents suffered side effects from CP treatment. Although CP is beneficial, its administration carries several concerns, including spreading a pathogenic microorganism and extensive lung injury in critically ill patients. Another uncommon concern is antibody-dependent infection enhancement, occurring at sub-neutralizing concentrations and inhibiting innate antiviral mechanisms, allowing logarithmic intracellular virus development (Duan, Liu, C. Li, *et al.*, 2020). CP transfusion-related adverse reactions also induce febrile, allergic, dyspnea, hypotensive, hemolytic event, septic reactions, and circulatory overload (Li *et al.*, 2020). The clinical manifestations among the ten respondents who suffered side effects such as rash or red patches on the skin in seven respondents; mild fever in one respondent; and shortness of breath in two respondents due to an allergic reaction and fluid overload. All negative reaction after CP administration treatable and does not lead death. Overall, this review article found no reports on pulmonary harm or infection enhancement

The current systematic literature study had certain limitations. First, other than the CP transfusion, the patients got conventional care in nine articles. Despite the uncertainty about the medications' efficacy, all patients got antiviral treatment. As a result, the idea that these antiviral medications could help patients' recovery or synergize with CP's therapeutic impact cannot be ruled out. Furthermore, some patients were given corticosteroid medication, which may interfere with immune response and cause virus clearance to be delayed. Only one article mentioned that the control group only received a placebo, and the treatment group received CP administration only, the procedure can be applied because all selected respondents have mild COVID-19 symptoms (Libster *et al.*, 2021). The research by Libster et al. was the only study that apply double blinds in its research design, whereas other studies utilized open labels since the baseline conditions of respondents used ranged from moderate to critical disease, making double blinds challenging to apply. The diversity of doses (the volume, the administration procedure, and antibody titer) of CP between studies is additionally a drawback during this study, so an efficient and efficient standardized CP dose is required in every case of COVID-19 (a mild, moderate, severe, persistent, and critical illness).

5. CONCLUSIONS

Based on the systematic review results in this study, we can conclude that CP administration has benefits in mild, moderate, severe, and persistent COVID-19 patient outcomes, including decreased viral load, length of hospitalization, and use of oxygen supplements, markers of inflammation, and mortality. However, its use in terminal/critical phase cases does not show significant results, so further studies are needed. The positive response to CP administration is directly proportional to the patient's baseline condition before CP administration, the antibody titer contained in the plasma, the distance between the administration and the onset of symptoms, or the beginning of hospitalization (the shorter, better the outcome). CP administration should be done carefully and with the proper procedure, and monitoring should be done to ensure that there are no negative side effects for the patient. The existence of differences in CP doses, antibody

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titers, and the applied transfusion procedures requires a consensus on the standard of administering CP in various COVID-19 cases.

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