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Convalescent plasma as a potential management option in COVID-19: a critical review of randomized controlled registered trials

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Abstract. **Currently, there is no approved antiviral agent to treat COVID-19. The management is based on reducing the virus spread in communities, providing supportive treatment to patients, and recently receiving immunization. In this critical review, we focus on randomized and controlled clinical trials.**

ClinicalTrials.gov, Chinese Clinical Trial Registry (ChiCTR), Japan Primary Registries Network (JPRN), the Australian New Zealand Clinical Trials Registry (ANZCTR), and six other Clinical Trials Registers were searched. Only randomized controlled trials covering treatment or prevention with convalescent plasma in COVID-19 patients were included. Data were extracted into summary tables. The matrix developed was used to identify common themes and compare primary and secondary outcomes of each trial against other parameters/characteristics of the trial. Microsoft Excel was used to create grids of numbers, texts and analysis using various formulae. A total of 3109 trial registry entries were identified, and 44 fulfilled the inclusion and exclusion criteria of the study. The majority of trials (n= 42, 95%) explored the therapeutic potential; only two examined prevention use. The trial's outcome measures varied and were 59 primary (median:1, IQR, 0) and 267 secondary measure outcomes (median: 6, IQR, 8). While 17 studies were recruiting for Phase 1 or 2, the remaining 16 studies were in Phase 2, and 3 and 11 studies had no phases. The total number of participants in these studies was 9432, including control groups (median: 120, IQR, 211). This review provides an overall analysis of clinical trials currently available from seventeen countries and highlights critical issues that we can learn from these trials based on available information.

Key Words:
COVID-19, Convalescent plasma, Ongoing clinical trials, Controlled studies, Critical review.

Introduction

Early in December 2019, a novel coronavirus (COVID-19) outbreak started in the Hubei province and its capital Wuhan of China and caused a global pandemic. The number of patients confirmed to have the disease has exceeded 149 million from more than 221 countries, and the number who died is over 3,148,845 (up to 27 of April 2021). Coronaviruses were identified in the 1960s and recently identified in two outbreaks severe acute respiratory syndrome (SARS) in 2003 and the Middle East Respiratory Distress (MERS-CoV) in 2012. The current severe acute respiratory syndrome coronavirus-2 (COVID-19) caused by SARS-CoV-2 is the most recently identified. The management of COVID-19 is based on reducing the virus spread in the communities and providing supportive treatment to patients, and recently, by mass immunization. Several medications have been identified in the management of patients which are beyond the scope of this review[1-3]. Antibodies play a critical role in the protection of the immune system against infection and providing passive immunity to prevent and treat bacterial and viral infections. The use of serum therapy dated back to 1892 and proved to be useful in treating bacterial and viral infections including diphtheria, pneumococcus, measles and mumps diseases[4,5]. Furthermore, specific immune globulins were found useful in several viral infections, including hepatitis B virus, cytomegalovirus, respiratory syncytial virus and Junin virus (Argentine hemorrhagic fever)[6,7]. During the first half of the 20th century, convalescent plasma has been used to treat many bacterial and viral outbreaks based on this concept. These infections include measles[8], polio[9], pneumococcus, Hemophilus influenzae type B (Hib) and Menin-

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gococcal meningitis. In 1918 influenza pandemic, serum from recovered patients was the primary therapy used for treating ill patients[4,10,11], and also used in treating patients admitted with severe SARS-CoV, influenza A H1N1[12], and MERS-CoV infections[13,14] during the outbreaks in 2003, 2009, and 2012, respectively[12,15]. Also, in treating patients infected with the Western African Ebola virus during the 2013-2016 epidemic[16,17]. Currently published studies on the use of convalescent plasma in treating COVID-19 are mostly small studies, or case reports, have no proper controls or randomized. They reported a reduction in virus level, improvement in chest radiologic images, or clinical improvement of patients[18-22]. In addition, most studies were not consistent in their outcomes, and several variables such as preparation of convalescent plasma, titres of anti-SARS-CoV-2 antibodies, therapeutic dosage and frequency of administration could have contributed to these variabilities, making it difficult to make conclusions.

Therefore, with these limitations in mind, this critical review aims at studying worldwide clinical trials from ten clinical trial registries of the United States, China, Japan, Australia and New Zealand, Hong Kong, Republic of Korea, Iran, the Netherlands, Germany, and the European Union. The search focused on the potential use of convalescent plasma in the prevention or treatment of COVID-19. These clinical trials are run by major centres in these countries and are well-funded and aimed to present evidence-based answers to questions raised about the feasibility of using convalescent plasma. This review provides an analysis of the ongoing clinical trials and an overall critical analysis these studies. It also aims at identifying homogenous studies that can be included in meta-analysis when the results become available and published.

Materials and Methods

Study Design

This review comprises randomized-controlled clinical trials. It covers the registry of ongoing clinical trials in ten registries - NIH National Insti-

Table I. Sum of the registries searched for randomized-controlled clinical trials on the use of convalescent plasma in treatment and prevention of COVID-19.

No	Registry	Country	URL
1	US National Library of Medicine ClinicalTrials.gov	The United States	https://clinicaltrials.gov
2	Chinese Clinical Trial Registry (ChiCTR)	China	http://www.chictr.org.cn/searchprojen.aspx
3	Japan Primary Registries Network (JPRN)	Japan	https://dbcentre3.jmacct.med.or.jp/JMACTR/App/JMACTRS02/JMACTRS02.aspx?kbn=4
4	Australian New Zealand Clinical Trials Registry (ANZCTR)	Australia and New Zealand	https://www.anzctr.org.au
5	HKU Clinical Trial Registry (HKUCTR)	Hong Kong	http://www.hkuctr.com/search
6	Clinical Research Information Service (CRiS), Republic of Korea	Republic of Korea	http://cris.nih.go.kr/cris/en/search/basic_search.jsp
7	Iranian Registry of Clinical Trials (IRCT)	Iran	https://www.irct.ir
8	The Netherlands National Trial Registry (NTR)	The Netherlands	https://www.trialregister.nl/trials
9	German Clinical Trials Register (DRKS)	Germany	https://www.drks.de/drks_web/
10	The European Union (EU) Clinical Trials Register	European Union	https://www.clinicaltrialsregister.eu/ctr-search/search

tutes of Health Clinical Trials (Clinicaltrials.gov), Chinese Clinical Trial Registry (ChiCTR) (http://www.chictr.org.cn/enIndex.aspx), and eight others summarized in Table I and indicating the country and the URL of each registry. The search was conducted for countries that do not speak English as their first language, the English version of the websites for their registry were used.

Identifying the Relevant Studies

These registers were searched using the following keywords, "COVID-19", "Convalescent plasma", "SARS-CoV-2", "Plasma", "Globulin", Hyperimmune serum", "COVID", "Therapeutic", "Control", "Controlled", Randomised", "Randomized" and "Prevention"[23]. Studies non-randomized, non-controlled, observational, retrospective, cohort prospective, or case studies were not included. Also, studies that were withdrawn, cancelled, or terminated were not included.

Study Selection

The author and a research assistant examined the outcomes of the search for trials utilizing the use of convalescent plasma, collected from patients who had recovered from COVID-19 with documentation of infection and recovery, and used in treating participants or preventing COVID-19. The evaluation was checked by each researcher independently to ensure accuracy in collecting information[24].

Charting the Data

For each identified study, the following data were collected by each research independently: (i) Title of the trial, (ii) Trial ID number, (iii) Recruiting status, and started day, and anticipated study completion, (iv) Age range of eligible participants, (v) Intervention, dosage, rout of administration, frequency, manufacturing method, if stated, and control treatment, (vi) Number of participants anticipated by the study- intervention and control groups, if stated, (vii) Study type and study design, (viii) Primary and secondary outcome outcomes, and (ix) Sponsor, institute/hospital handling the trial, and country of origin[25]. The data were extracted into summary tables. The matrix developed was used to identify common themes and compare primary and secondary outcomes of each trial against other parameters/characteristics of the trial.

Statistical Analysis

The data collected from these clinical studies were analyzed by the author and two research assistants independently. We used Microsoft Excel to create grids of numbers, texts and analysis using various formulae. The analysis explored the characteristics of included studies, methods used in trials, including controlled *vs.* non-controlled studies, therapeutic *vs.* preventive trials, primary and secondary outcomes, Phases completed in the trial and potential studies that can contribute to a future meta-analysis. We evaluated details on the analysis and comparison of the results obtained. The analysis aimed at facilitating knowledge synthesizes to come with a meaningful understanding of findings. We discussed differences in the assessment made by the researchers a meeting to explore each supportive evidence until we reached a consensus. The agreement between evaluators measured by the degree of inter-rater agreement using the Cohen kappa coefficient was also carried out using SPSS software (SPSS Inc., Armonk, NY, USA)[26].

Ethics Statement

The study does not involve human participants. It is a review of registered trials on convalescent plasma. The information is available on the websites of different registered clinical trials. The study does not include confidential or personal information. The College of Medicine recommended no need for ethics review.

Patient and Public Involvement

Patients and the public were not involved in this study.

Results

Clinical Trials and Selection Process

A total of 44 clinical trials are identified and included in this study. These include 32 trials from Clinicaltrials.gov, six trials from ChiCTR, four trials from IRCT, one from each of NTR and EU Clinical Trials Register. A total of 215 trials were identified. After exclusion of duplicates (n=23), trials not matching the inclusion criteria (n=143), and studies that were withdrawn or terminated (n=5), a total of 44 records were included in this review. The trials not matching the inclusion criteria included: non-randomized (n=62), observational studies (n=27), prospective or retrospective cohort studies (n=9), case reports and case series reports (n= 11), and trials not yet recruiting (n=34). ***Figure 1*** summarizes the clinical trials identified from each international center, trials that were excluded, and the finalization of studies included in this review. ***Appendix I*** summarizes the details of each trial included in this review.

Characteristics of Included Clinical Trials

The 44 studies included a total of 9432 participants including control (median: 120, IQR, 211) and the number varied from 15 to 1200 participants. While 17 studies are recruiting for Phase 1 or 2, the remaining 16 studies are in Phase 2 and 3 and eleven studies have no phases in their design. The studies from China started early in 2020; in February (n=4), and March (n=2). Other studies started in March (n=1), April (n=14), May (n=17), and June (n=6). Not all trials are expected to be completed in 2020, only 19 trials, while 13 trials are expected to be completed early in 2021, one in May 2022, and another by the end of April 2023. The remaining trials (n= 10) did not indicate a date of completion. The age of participants varied, the majority of clinical trials included ages from both sexes from 18 years old and older (n=35). However, two studies only included participants aged 65 years and older (the study number NCT04374526 from Italy, and the study number NCT04479163 from Argentina). A study from Iran (number IRCT20200310046736N1) focused on participants at the age of 20-45 years old, and an American study (number NCT04442191) recruited participants at the age of 40 and older. Only one study recruited participants at the age of 12 months and older (study number NCT04361253 from the United States).

Countries and Institutes/Universities Involved

Nearly all clinical trials included in this article were conducted in one country. The United States is conducting over one fourth of these studies (n=11), Argentine, South America, Mexico, Brazil (n=7), China (n=6), Iran (n=4), Italy (n=3), and two studies from each of France, Spain, the Netherlands, and India, and one trial from each of Denmark, Germany, Russia, El Salvador, and Bahrain. The total number of institutes and hospitals involved in these 44 clinical trials are 159 (median: 1, IQR, 2) and the numbers of institutes/hospitals involved in one trial varied from 1 to 31. Major institutes/hospitals that lead or contributed to these clinical trials are Johns Hopkins University, University of Pennsylvania, Brooklyn Hospital, Weill Cornell Medical Center, Bloomberg Foundation, Department of Defense, National Institute of Allergy and Infectious Diseases, Columbia University Irving Medical Center, in the United States. Hospital San Vicente Fundación, and Hospital San Vicente Fundación, the Republic of Colombia, South America. Centenario Hospital Miguel Hidalgo Aguascalientes, Mexico. University of Sao Paulo, General Hospital São Paulo, Brazil. Sinopharm Wuhan Blood Products Co., Ltd., Wuhan, and Institute of Blood Transfusion, Chinese Academy of Medical Sciences, Wuhan, Hubei, China. Birjand University of Medical Sciences, Birjand, South Khorasan, Iran. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy. SMIT, Saint Antoine hospital, Paris, France. Hospital Clínico Universitario Lozano Blesa Zaragoza, Aragón, Spain. Erasmus Medical Center Rotterdam, Zuid-Holland, and NoordWest Ziekenhuisgroep Alkmaar, the Netherlands. Max Healthcare Institute Limited, India. Aalborg University Hospital Aalborg, and Aarhus University Hospital Arhus, Denmark, and DRK-Bluspendedienst Baden-Württemberg – Hessen gGmbH. Germany.

Methods Used in the Trials

All trials included in this study are randomized controlled studies. However, the design of these trials varied significantly in several aspects. For example, not all studies were blinded, only 14 trials were masked (2 quadruple-masked, one single-blinded and 11 double blinded). The remaining 25 are non-masked, and five trials did not state. Studies that are quadruple-masked are blinding participants, care provider, investigator and outcome assessor. The control used in these trials also varied significantly. Most studies provided "best standard care" or "routine care as per their institute" to the control patients (n=23). Others used standard fresh plasma (n=6), or plasma collected before December 31, 2019 (n=3), humane immunoglobulin (n=1) or plasma from a random donor (n=1) in the control group. Other studies used normal saline (n=4), albumin 5% infusion (n=1), or lactated ringer solution (n=2) in the control group. Treating the control group with medications to compare the outcomes with those of the intervention group treated with convalescent plasma has also been used. For example, standard therapy hydroxychloroquine (400 milligrams each 12 hours for 10 days) in the trial number NCT04332835 and treatment of patients with pneumonia due to SARS-CoV-2 with conventional therapy (Azithromycin and hydroxychloroquine and 20% albumin in Hartman solution) in the trial number NCT04405310. Information about convalescent plasma manufacturing, neutralizing antibody titres, dosage, or frequency of administration were not provided in the majority of trial. The dosage varied from 200 ml/

day for three days as in (NCT04374526), 200-250 ml with neutralizing antibody titres >1:320 as in (NCT04373460), 400 ml/day as a single dose as in (NCT04381858), or 600 ml as a single dose as in (NCT04345289). The neutralizing antibody titres were >1:64 containing two specific antibodies as in (NCT04442191). Only two of these trials were investigating the prevention role of convalescent plasma (trials number NCT04390503 and NCT04479163), while the remaining 42 trials are exploring the therapeutic role of convalescent plasma.

The studies also varied significantly in their primary outcome and secondary outcome measures. A total of 59 primary outcomes (median: 1, IQR, 0) is targeted, while the secondary outcome measures of the 44 trials are 267 (median: 6, IQR, 8). Seven studies have no secondary outcome measures in their design. The primary outcome measures included (1) Assessing survival, severity of clinical disease caused by COVID-19 or outcomes at time point when convalescent plasma is administrated compared to a control group (for example, NCT0434599, NCT04345991, NCT04397757), (2) Assessing the preventive effects of administrating convalescent plasma on close contacts (for example, NCT04390503), (3) Assessing the prevention of severity of COVID-19 when convalescent plasma administrated at an earlier stage to elderly patients (for example, NCT04479163), (4) Assessing safety and effectiveness of convalescent plasma (for example, NCT04388410, NCT04374487, NCT04345289, ChiCTR2000030929), (5) Assessing the efficiency of convalescent plasma in critically ill COVID-19 patients (for example, NCT04359810, NCT04346446, NCT04342182, ChiCTR2000029757, ChiCTR2000030010, ChiCTR200030627), (6) Assessing effects of convalescent plasma to limit complications caused by COVID-19 (for example, NCT04421404, NCT04364737), (7) and Comparing convalescent plasma with other treatments used in patients with COVID-19, such as immunoglobulins, or drug treatment of COVID-19 (for example NCT04381858, NCT04366245, NCT04392414, IRCT20200413047056N1, IRCT20200404046948N1, NCT04383535, NCT04332835, NCT04405310). The secondary outcomes covered related detailed points/issues mostly related to primary outcomes.

The Degree of Agreement Between Assessors

The inter-rater agreement between assessors had an overall kappa score in the range of 0.821-0.862.

Discussion

This study shows that the number of randomized controlled clinical trials on the role of convalescent plasma in COVID-19 management is increasing; nearly all started in the first half of 2020. However, there is no harmony in the design of intervention and control arms across these clinical trials, making it challenging to design a meta-analysis study based on findings. For example, there are differences in the severity of COVID-19 when patients are treated and the timing of treatment with convalescent plasma varied. Also, information about the dose used, the manufacturer, and the antibody titres are not consistent, and in several trials, such information is lacking. These concerns should be considered by designers of meta-analysis studies when results become available. Reviewers and editors should also check these areas when meta-analysis studies are submitted for consideration for publication. The neutralizing antibody titres was not stated by the majority of trials. Although, it is important to ensure that these trials are consistent with the US Food and Drug Administration (FDA) recommendations of titres >1:160[27].

Recently, the use of convalescent plasma to treat critically ill patients with severe COVID-19 infection has been approved by the FDA. The recommendation is to use convalescent plasma only in patients with severe COVID-19 infection and life-threatening emergency. Severe disease means the presence of dyspnea, respiratory rate of ≥30 breaths per minute, blood oxygen saturation ≤93%, ratio of the arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300, or lung infiltrates >50% within 24 to 48 hours[27]. Research on the use of convalescent plasma showed contradictory results. While one study concluded a low-quality evidence that convalescent plasma may offer minimal or no beneficial effect in treating COVID-19[28], another study showed that convalescent plasma could be life-saving and form an alternative therapy to treating critical COVID-19 patients with diabetes mellitus[29]. A recent Cochrane systematic review on the convalescent plasma in patients with COVID-19 showed that some studies reported improvement in clinical symptoms in at least some participants. However, the overall evidence is low regarding the effect of convalescent plasma in reducing clinical symptoms[30]. Duan et al[31] reported ten severe patients with confirmed COVID-19 enrolled in a prospective study and given one dose

of 200 ml of convalescent plasma with neutralizing antibody titers above 1:640 and also received maximal support and antiviral agents. After convalescent plasma treatment, the clinical symptoms improved, together with improved oxyhemoglobin saturation within three days.

A recently published randomized multicenter randomized clinical trial examined the efficacy and adverse effects of convalescent plasma therapy in patients with COVID-19 infection. The study was carried out in seven centers in Wuhan, China. The study design comprised an intervention group treated with standard treatment plus convalescent plasma (n=52), and a control group was given standard treatment only (n=51). Both groups were standardized for disease severity. The study showed that there were no significant differences between the two groups within 28 days (the target of the study). Therefore, the interpretation of the results was limited because of the early termination of the trial[32].

Therefore, it appears from the currently available studies that the use of convalescent plasma in patients with COVID-19 necessitates large clinical trials to provide evidence about the clinical use of convalescent plasma in patients with COVID-19.

Current clinical trials included in this paper covered both sexes and several targeted participants at the age of 18 and older. Not all clinical trials were blinded. One was single-blinded, eleven were double-blinded, and two were quadruple-masked. These studies had a total number of participants of 45, 2493, and 1310, respectively. In single-blinded trials the subjects are unaware of which group they have been assigned, while in double-blinded, neither the subjects nor the investigators are aware of the treatment assigned to each group until the end of the study. Therefore, blinding aim at reducing information bias or beliefs about treatment effects. It helps to ensure treat participants assigned to the intervention and control treatment same throughout the trial and objectively evaluate the outcomes of the trial[33]. A meta-analysis of empirical studies showed an odds ratio of 0.86 (95% confidence interval 0.74-0.99) demonstrating that the lack of blinding leads to overestimated treatment effects[34].

The countries leading these trials are mainly the United States, where over one-fourth of the trials are carried out. Other countries include South America, Argentina, Mexico, and Brazil, China, Iran and European countries (France, Spain, the Netherlands, Denmark, and Germany), India, Russia, and Bahrain. The studies with a larger number of participants were those conducted in the United States (total =3335, median:200, IQR,450, range 30-1200), while the trials from Iran had the smallest number of participants (total=180, median: 52.5, IQR,37.5, range 15-60). This information may provide a base for comparison when meta-analysis studies are considered. However, several other parameters should be checked when preparing a meta-analysis including differences in the doses, titres of antibodies, and frequency of treatment. Also, the timing of treatment and the severity of the COVID-19.

Several studies discussed the possible mechanisms by which convalescent plasma could work in COVID-19 disease. The mechanisms underlying the effects of convalescent plasma in patients with SARS-CoV and SARS-CoV-2 can be summarized as follows. Firstly, neutralization and antiviral effects. Convalescent plasma neutralizing antibodies play a role in the clearance of the virus. These neutralizing antibodies bind to spike 1-receptor binding protein (s1-RBD), S1-N-terminal domain and S2, which inhibit virus entry and limiting virus amplification[35]. Other mechanisms promoting the work of neutralizing antibodies include complement activation[36], phagocytosis, and antibody-dependent cellular cytotoxicity. Specific immunoglobulins such as IgM and IgG add to the work of neutralizing antibodies and contribute to antiviral mechanisms. In patients recovering from SARS infection, these specific immunoglobulins become of highest concentration on day nine after infection for IgM, and in the second week for IgG[37,38].

Secondly, immunomodulation by amelioration of severe inflammation. In COVID-19 overactivation of the immune system, also known as a cytokine storm. This response is derived by IL-1ß, IL-2, IL-6, IL-17, IL-8, and TNF-œ, causing pulmonary injury, fibrosis, and reduced pulmonary oxygenation. On this basis, it is believed that convalescent plasma interferes with these changes and ameliorate the inflammatory response associated with the infection.

Thirdly, mechanisms involving inhibition of the complement cascade C3a and C5a, limiting the formation of immune complexes. There is evidence that complement activation contributes to systematic inflammation and migration of neutrophils and causing lung injuries[39]. Therefore, convalescent plasma could act by limiting the inflammatory cascade and minimizing tissue and lung injuries induced by the complement activation and activated inflammatory changes.

Also, convalescent plasma modulates the balance between CD4+/CD8+ T cells and reduce the antigenic presentation of T cells via the modulation and inhibition of dendritic cells. These mechanisms suggest that convalescent plasma may act using several mechanisms to induce an anti-inflammatory effect in patients with an acute viral infection such as COVID-19. This study also shows that the use of convalescent plasma in the prevention of COVID-19 was limited and not well-addressed. The preventive use of convalescent plasma has been shown in small studies[40,41]. In the first study, Gharbharan et al 2020[40] in a randomized trial from the Netherlands compared the use of convalescent plasma with standard therapy in hospitalized patients with COVID-19. The trial was halted prematurely because the majority of patients were found to have baseline neutralizing antibody titres that were comparable to donor levels. The study may suggest that hospitalized patients may not benefit from plasma-treatment if they have high baseline neutralizing titres. Therefore, patients that have no such high titres levels may benefit from convalescent plasma when receiving treatment at earlier stages; and should be investigated in large trials if such treatment could reduce the progress of the disease. A second descriptive study from China involving sex patients confirmed to have COVID-19 who were treated with convalescent plasma. The effectiveness of the intervention was determined by alleviation of the clinical picture, radiological changes, and laboratory changes. The study reported clinical improvement and other parameters of the six patients, and they did not require ICU treatment. The study claim that convalescent plasma ameliorates COVID-19 severity and complications. However, the number of patients in the study was too small, no control group, nor randomization[41]. Therefore, the results do not provide strong evidence for the ameliorating effects of convalescent plasma. Randomized controlled studies with large number of patients are needed to assess the value of convalescent plasma and provide evidence[42,43].

Strengths and Limitations of This Study

This study is not without limitations. This area is rapidly changing. Therefore, the addition of new clinical trials to a clinical trial registry and changes in the status and number of participants after the collection of data is expected. Second, although the registries have been searched by using several keywords and using several approaches, the filter of most registries is not sensitive enough, and we have to search the outcomes manually to identify clinical trials fitting with the study inclusion criteria. Third, not all information needed, as per the study protocol, are provided in a few studies. This study, however, presents a critical analysis of current registered randomized controlled trials in the use of convalescent plasma in the prevention and as a therapy for COVID-19.

Conclusions

This critical review on registered randomized controlled clinical trials on the convalescent plasma in the prevention and treatment of COVID-19 highlights the current status of ongoing clinical trials. It presents a stimulus and a guide for writing meta-analysis once the results from these trials become available, particularly masked studies with a more significant number of participants and the control group receiving routine management care for COVID-19. The review highlights the lower number of trials examining the preventive role of convalescent plasma. Also, it highlights the need for sufficient power and definition of disease severity in the studies to be included in a meta-analysis, particularly regarding age, sex, disease severity, primary and secondary outcome measures, time of intervention, as well as the dose, frequency of treatment and antibody titers used in convalescent plasma to treat patients with SARS-CoV-2 infection.

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Contributors

SAA has created the idea of the review, the design, and conception of the review. SAA collected the data, conducted data analysis, created tables and appendices, wrote and edited the manuscript.

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Conflict of Interests

The author declares no conflict of interest.

Patient Consent for Publication
Not required.

Data Availability
Data sharing not applicable. All data available have been included in the manuscript.

Supplementary Material
The content has been supplied by the authors.

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