



Convalescent Plasma in the Treatment of Severe COVID-19: A Systematic Review and Meta-Analysis

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Abstract

Background: COVID-19 is a public health emergency of international concern. Its incidence rates and mortality are very high; however, so far, an effective drug treatment remains unknown. Based on the role of convalescent plasma therapy in previously identified viral pneumonias, patients with severe COVID-19 have been given this therapy. This systematic review and meta-analysis aimed to summarize the clinical evidence regarding the efficacy and safety of convalescent plasma therapy in the treatment of severe COVID-19.

Methods: PubMed, Embase, Ovid, China Knowledge Network, China Biomedical, VIP Chinese Sci-tech Journal, Wanfang Database, and the International Clinical Trials Registry Platform were searched up to 21 June 2020, to identify clinical studies and registered trials on the use of convalescent plasma in the treatment of critically ill patients with COVID-19. Stata 13.0 was used to perform Meta-analysis. All records were screened as per the protocol eligibility criteria.

Results: Nineteen clinical reports regarding convalescent plasma in the treatment of severe COVID-19 were included. Through systematic analysis, convalescent plasma was found to yield some efficacy on severe COVID-19 and had almost no obvious adverse reactions.

Conclusion: Convalescent plasma therapy seems to yield some efficacy among patients with severe COVID-19 and almost no obvious adverse reactions were found. However, at present, the clinical evidence is insufficient, and there is an urgent need for support from high-quality clinical trial data.

Keywords: Coronavirus disease (COVID-19); SARS-CoV-2; Convalescent plasma; Pneumonia

Introduction

Coronavirus disease (COVID-19) is a public health emergency of international concern. According to the official website of WHO, as of 10

CEST of June 20, 2020, 8,525,042 people had been infected with COVID-19 and 456,973 related deaths had occurred worldwide. With the rap-



id increase in the number of confirmed cases worldwide, the number of deaths had increased at an even faster rate (1). Due to the high mortality rate of severe COVID-19, it is very important to institute effective treatment for critically ill patients. However, so far, there is no clear, effective, and proven drug treatment.

Convalescent plasma therapy has been used for more than 100 years and played a role during various viral infectious disease pandemics. A meta-analysis showed that the use of convalescent plasma, serum, or hyperimmune globulin may be effective in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe acute respiratory infection due to influenza viruses, it can reduce the associated mortality, and is safe (2). Convalescent plasma with antibody titer $\geq 1:80$ was effective in the treatment of Middle East respiratory syndrome coronavirus (MERS-CoV) infection (3).

According to previous studies on viruses similar to SARS-CoV-2, including SARS and MERS viruses, convalescent plasma may be effective in the treatment of severe COVID-19. To seek evidence regarding convalescent plasma in the treatment of severe cases, the present paper systematically evaluated the evidence from a literature review.

Methods

Literature inclusion criteria

We assessed studies including randomized controlled trials, clinical controlled trials, cohort studies, case-control studies, case series studies, and case reports about the use of plasma therapy among convalescent COVID-19 patients. There was no restriction on language.

The participants were critically ill patients diagnosed with COVID-19. The diagnostic methods could be based on the guidelines of COVID-19 published in various countries.

As intervention, the treatment group included convalescent plasma, and conventional therapy

was unlimited. The treatment of the control group was unlimited. The outcome indicators included clinical efficacy, survival rate, mortality, viral load, antibody titer, and adverse reactions.

Exclusion criteria

We excluded other pieces of literature that did not meet the inclusion criteria, such as non-clinical reports, reviews, inconsistent research objectives, inconsistent intervention measures, and duplicate literature.

Data extraction

According to the pre-established data extraction table, the literature data were extracted and a unified data table was established using Excel 2013 (Microsoft Corp., Redmond, WA, USA), including author, year of publication, sample size, sex, age, underlying diseases, plasma therapy information, intervention measures, observation indicators, and clinical outcomes.

Data processing

The mortality and the negative rate of PCR data were analyzed by Meta-analysis using Stata 13.0.

Results

According to the inclusion and exclusion criteria, 19 clinical reports were retrieved.

Clinical report

Literature screening

According to the predetermined retrieval scheme, we searched the literature, and read the titles and abstracts. We initially excluded literature that did not meet the inclusion criteria, read the full text of the remaining literature, and excluded retrospective studies, duplicate studies, studies with inconsistent intervention measures, non-controlled studies, and other pieces of literature. Finally, 19 studies were included (Fig. 1).

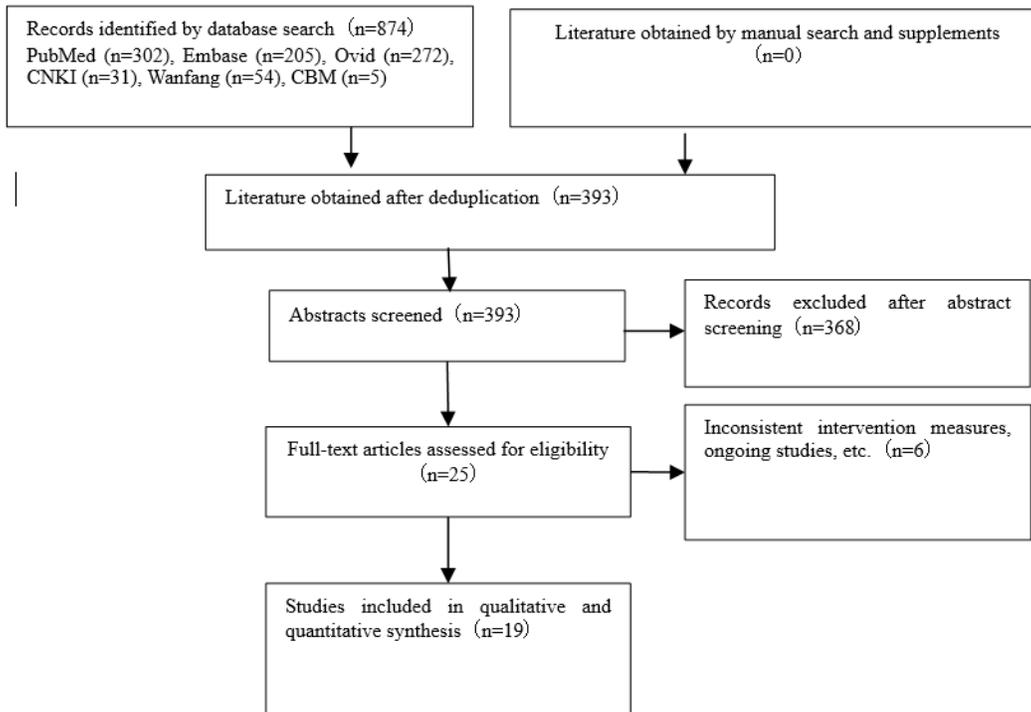


Fig. 1: PRISMA flow chart of study selection

Efficacy and safety of convalescent plasma in the treatment of COVID-19

Thus far, 19 clinical reports have been published on the use of convalescent plasma in the treatment of COVID-19(4-22), including those emanating from China, USA, South Korea and Turkey. Among the 146 patients who reported the clinical efficacy, the oldest was 100 years old and the youngest was 19 yr old. The most common complications of these patients were essential hypertension, cardio-cerebrovascular diseases, diabetes, and so on. The majority of patients received mechanical ventilation, while almost simultaneously else antiviral treatment including remdesivir, hydroxychloroquine, abidol, ribavirin or peramivir, and so on. According to the needs of the disease, they also received different antibacterial or antifungal treatments, hormone treatments, albumin, immunoglobulin, and other immune agent treatments. The clinical effect was evaluated after transfusion by assessing clinical

symptoms, chest images or CT, nucleic acid detection, viral antibody level, blood leukocyte count, lymphocyte count, interleukin-6 (IL-6) levels, C-reactive protein (CRP) levels, disease prognosis, and so on. Most patients showed improvement in symptoms after transfusion; the inflammation had resolved on chest imaging or CT, viral nucleic acid test results returned negative, antibody titer increased, white blood cell and lymphocyte counts normalized, IL-6 and CRP levels decreased.

Some studies (5, 11, 15, 20) reported mortality. Baseline characteristics (age, gender, severity of the diseases, and so on) of patients between convalescent plasma treatment group and control group in these four studies showed no significant differences. The mortality rate of the treatment group was lower than control group, and the difference was significant (RR=0.59,95% CI (0.37,0.94), $P<0.05$) (Fig. 2).

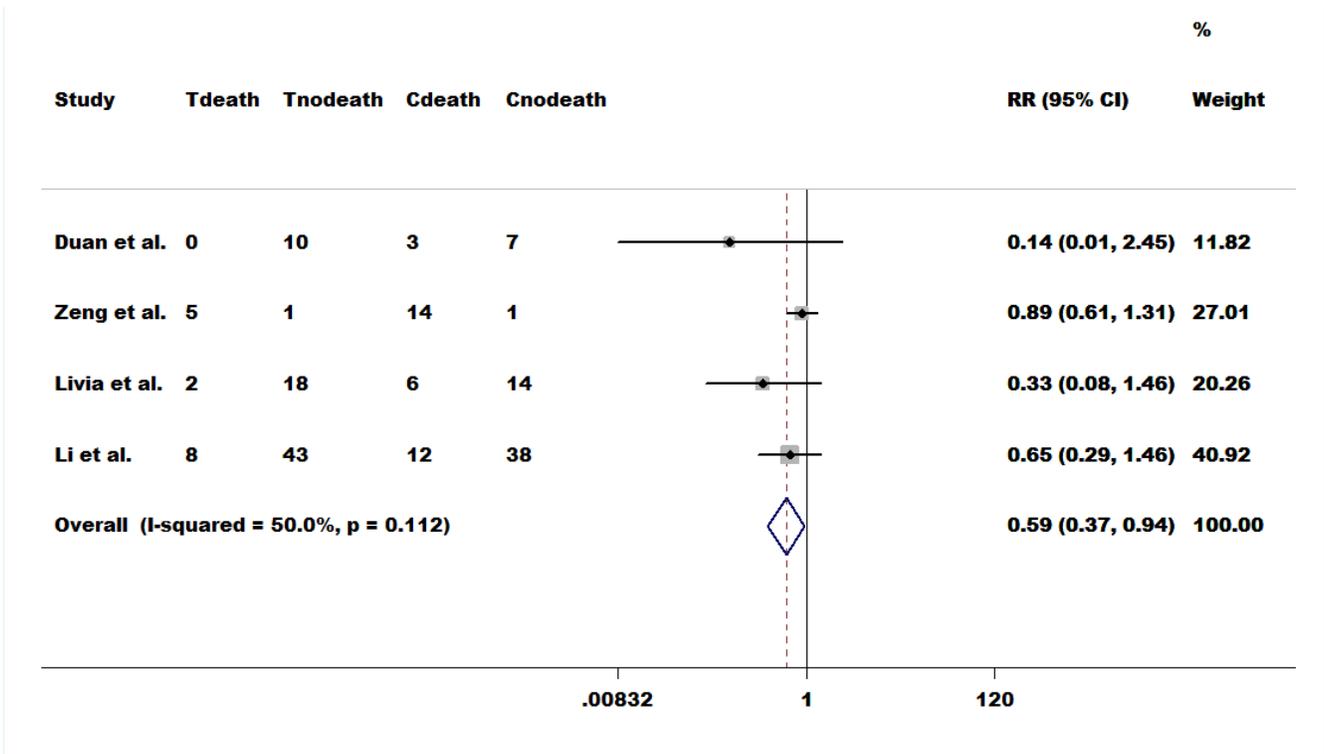


Fig. 2: Meta-analysis of the mortality of convalescent plasma therapy

Zeng et al. (11) and Li et al. (15) reported the negative rate of PCR. Meta-analysis showed that the negative rate of the treatment group was

higher than control group, and the difference was significant (RR=2.55, 95% CI (1.76,3.70), $P<0.05$) (Fig. 3).

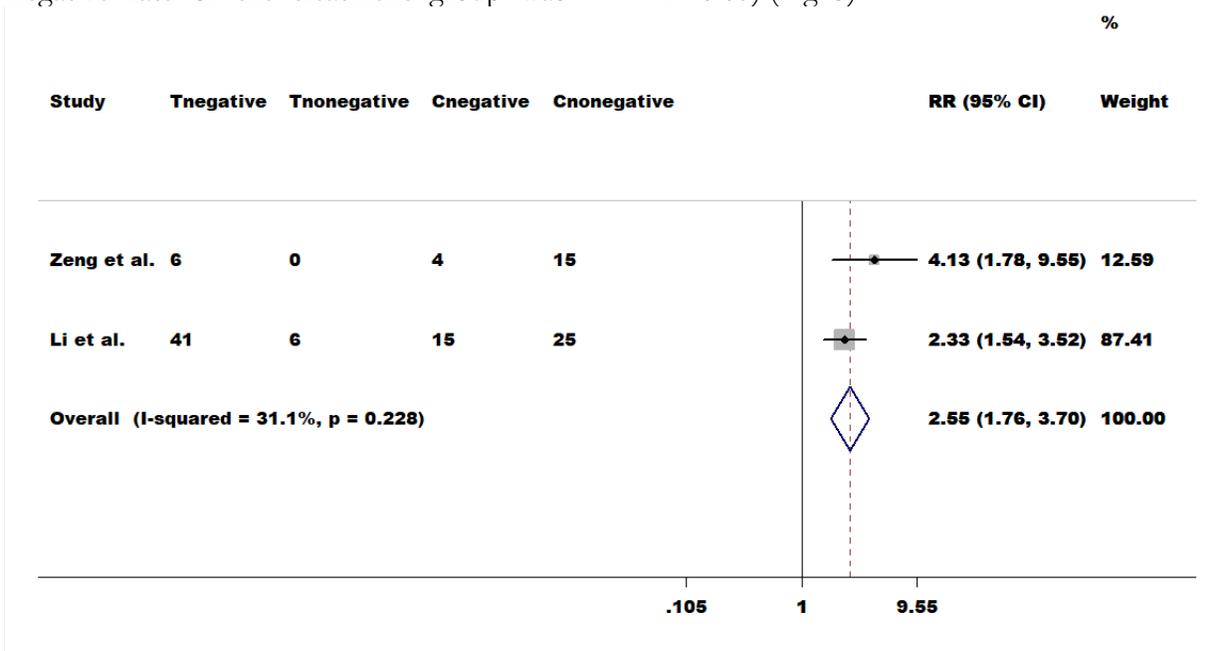


Fig. 3: Meta-analysis of the negative rate of PCR

In a study, the average time of plasma transfusion was 21.5 d after the onset of the disease in 5 patients who died (11), and the effect of transfusion within 14 d of disease onset of 3 patients were better than that observed more than 14 d after onset of 1 patient, suggesting that plasma transfusion should be carried out as early as possible among patients with severe disease (5).

In some studies, the specific requirements of plasma titer in convalescence were put forward (4-6,15,17,19,22). The titer of antibody was higher than 1:160-1:1000. In another studies, the age that requirements for blood donors were put forward was 18-67 yr old (5,6,8,10,14,15). Suggesting that the titer of plasma antibody should be as high as possible and the donors should be as young as possible.

Analyzed some key safety metrics after transfusion of ABO compatible human COVID-19 convalescent plasma in 5,000 hospitalized adults with severe or life-threatening COVID-19, the

incidence of all serious adverse events (SAEs) in the first four hours after transfusion was <1%, including mortality rate (0.3%)[1]. Of the 36 reported SAEs, there were 25 reported incidences of related SAEs, including mortality (n=4), transfusion-associated circulatory overload (n=7), transfusion-related acute lung injury (n=11), and severe allergic transfusion reactions (n=3). However, only 2 (of 36) SAEs were judged as definitely related to the convalescent plasma transfusion by the treating physician. These early indicators suggest that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19.

The use of convalescent plasma in the treatment of patients with severe COVID-19 seemed to yield some efficacy and almost no serious adverse reactions were found. However, these results were limited by the use of antiviral, hormone, and other treatments; and the low level of clinical evidence. (Table 1 and 2).

Table 1: Summary of general information of patients in clinical reports

<i>Author and time of publication</i>	<i>Country/region</i>	<i>Sample size</i>	<i>Sex</i>	<i>Age or Median Age (yr)</i>	<i>Underlying diseases</i>
Li et al.,April 2020	China, Qingdao	1	Female	79	Epilepsy
Duan et al.,March 2020	China, Wuhan	10	4 females 6 males	52.5	4 patients had cardio-cerebrovascular disease and essential hypertension
Shen et al.,March 2020	China, Shenzhen	5	3 males 2 females	36-73	1 patient with hypertension complicated with mitral regurgitation
Zhang et al.,March 2020	China, Dongguan, Xiangtan, Zhongshan	4	2 males 2 females	31-73	1 patient with hypertension 1 patient with COPD 1 patient with hypertension and chronic renal failure 1 pregnant woman
Ahn et al.,April 2020	Korea	2	1 female 1 male	67-71	1 patient with hypertension
Ye et al.,April 2020	China, Wuhan	6	3 males 3 females	28-75	1 patient with Sjogren's syndrome
Zhang et al. April 2020	China, Nanjing	1	Female	64	Hypertension and diabetes
Zeng et al.,April 2020	China,Zhengzhou	6	5 males 1 female	61.5	1 patient with diabetes 1 patient with hypertension 1 patient with cardiovascular disease
Dai et al.,March 2020	China, Qinghai	3	3 males	Young and middle-aged	1 patient had hypertension and hyperglycemia
Li et al.,June 2020	China, Wuhan	52	27 males 25 females	70	29 patients with hypertension 14 patients with Cardiovascular disease 11 patients with Cerebrovascular disease 8 patients with hepatopathy 3 patients with cancer 2 patients with nephropathy
Jonathon Anderson et al., May 2020	USA, Nashville, Tennessee	1	1 female	35	Pregnant, diabetes, asthma, obesity

Eric Salazar et al., May 2020	USA, Houston, Texas	25	11 males 14 females	51(19-77)	10 patients with diabetes 9 patients with hypertension 5 patients with Hyperlipidemia 4 patients with gastrointestinal reflux disease
Ma et al., April 2020	China, Ningxia	1	1 male	66	Not described
Kong et al., May 2020	China, Wuhan	1	1 male	100	hypertension, abdominal aortic aneurysm, cerebral infarction, prostate hyperplasia, and complete loss of cognitive function
Michael J Joyner et al., June 2020	USA	5000	3153 males 1824 females 23 others	62.3 (18.5-97.8)	/
Olgu Erkin Çınar et al., May 2020	Turkey	1	1 male	55	MDS/ RAEB-1 disseminated systemic tuberculosis kidney disease
Livia Hegerova et al., June 2020	USA, Washington, Seattle	20	Not described	60(29-95)	12 patients with hypertension 9 patients with diabetes 4 patients with obesity
Xu et al., June 2020	China, Jiangsu Changzhou	1	1 male	65	/
Xiao et al., May 2020	China, Jiangxi Nanchang	6	4 males 2 females	69.3±2.9	3 patients with hypertension

Table 2: Summary of Efficacy and Adverse Reactions of Convalescent Plasma Therapy in Clinical Reports

<i>Author and time of publication</i>	<i>Use of convalescent plasma therapy</i>	<i>Prognosis</i>	<i>Adverse reactions</i>	<i>Remarks</i>
Li et al., April 2020	200ml	Improvement	None	/
Duan et al., March 2020	200ml	3 patients were discharged 7 patients had improved	One patient had fleeting facial erythema	cohort study
Shen et al., March 2020	400ml, Continuous transfusion	4 cases of ARDS resolved 3 cases were weaned off mechanical ventilation 1 patient did not require ECMO 3 were discharged 2 were in stable condition	Not described	antibody titer >1:1000
Zhang et al., March 2020	200–300ml each time, a total amount of 200–2400ml	3 patients improved and discharged 1 patient transferred to unisolated ICU	No serious adverse reactions	Pregnant woman experienced a stillbirth
Ahn et al., April 2020	Plasma was transfused twice at intervals of 12 hours	Improvement	None	No evaluation of antibody titer in convalescent plasma
Ye et al., April 2020	200ml, 1–3 times	Improvement	None	1 case was negative of pharyngeal swab test 1 patient was asymptomatic
Zhang et al., April 2020	200 ml	Improvement	None	
Zeng et al., April 2020	200–600 ml	5 patients died, no SARS-CoV-2 was detected 1 patient was cured	None	cohort study
Dai et al., March 2020	50 ml, every two days, 100 ml in total	2 patients had improved.	Not described	antibody titer was undetectable
Li et al., June 2020	4 to 13 mL/kg, 200–300mL	27 patients had improved 8 patients had died	1 patient developed chills and rashes 1 patient presented with shortness of breath, cyanosis, and severe dyspnea	RCT
Jonathon Anderson et al., May 2020	1 unit	Improvement	no further issues after discharge	continuing antenatal care
Eric Salazar et al., May 2020	300ml, 1 patient received a second transfusion	19 patients had improved 3 patients remained unchanged 2 patients had deteriorated 1 patient had died	1 patient developed a morbilliform rash	/
Ma et al., April 2020	400ml	Improvement	Not described	/

Kong et al., May 2020	100ml,twice	Improvement	Not described	IgG titer >1:640
Michael J Joyner et al., June 2020	/	/	Mortality:4 TACO:7 TRALI:11 Severe allergic transfusion reaction:3	/
Olgu Erkin Çınar et al., May 2020	200ml,twice	Improvement	None	IgG titer of 5.1
Livia Hegerova et al., June 2020	Not described	9 patients had discharged 2 patients had died	None	cohort study
Xu et al., June 2020	Not described	Improvement	None	/
Xiao et al., May 2020	200~500 mL(4~5 mL/kg)	Improvement	Not described	cohort study IgG titer >1:160

Discussion

Convalescent plasma therapy yields some efficacy among patients with severe COVID-19 and almost no obvious adverse reactions were found. However, the clinical evidence is insufficient and there is an urgent need for support from high-quality clinical trial data. In addition, special attention should be paid to the indications, contraindications, selection criteria of donors, and storage and transfusion procedures for plasma therapy. At present, under the condition that there is no effective treatment for patients with severe COVID-19, some countries have put forward some guidelines based on the clinical experience regarding convalescent plasma therapy in the treatment of SARS, MERS, and severe avian influenza.

Epstein Jay et al. (23) compiled a document approved by the Global Blood Safety Working Group of the International Society of Blood Transfusion and reported that as a possible treatment for COVID-19, factors such as pre-screening and pre-donation testing of donors, qualification criteria of whole blood or plasma donors and collection standards should be taken into account when preparing and transfusing COVID-19 convalescent plasma. From January 27th to Apr 1st, 2020, China has successively issued guidelines for the diagnosis and treatment of COVID-19 (the trial version and the fourth to seventh editions)(24-27), "COVID-19 Convalescent Plasma Clinical Treatment Plan (trial first and second editions)"(28), "Further strengthening COVID-19 convalescent plasma treatment work plan"(29), and "Severe COVID-19: A series of guidelines for the diagnosis and treatment of crit-

ical and severe cases (trial second edition)"(30). The scope of application of plasma therapy for COVID-19 in the convalescent stage has been revised continuously. Convalescent plasma therapy should be considered for severe cases and critically ill patients under certain conditions, for patients with rapid disease progression, and convalescent plasma containing novel coronavirus antibody should be used in the treatment of early COVID-19. It can be considered as a choice for specific treatment. The titer of protective antibody in convalescent plasma should be measurable. The recommended dosage of transfusion in two stages is 200–500 ml (4–5 ml/kg body weight) and clear requirements have been put forward in three aspects: target task, work measures, and work requirements. On March 24, 2020, the United States Federal Drug Administration approved a clinical study of convalescent plasma in the treatment of COVID-19 (31). The guidelines for the diagnosis and treatment of COVID-19 issued by the National Institutes of Health (32) on Apr 21, 2020 point out that there are not enough data to recommend the use of recovered plasma or hyperimmune globulin for the treatment of COVID-19 (level of evidence: IIIA). Despite a good historical record, few controlled trials had assessed the efficacy of convalescent plasma, largely due to its emergent use during epidemics (33). Data on the use of convalescent plasma therapy be collected and mined from ongoing clinical studies. Based on the severity of the situation in Italy, convalescent plasma therapy would be regarded as "empirical". A donor diagnosed with COVID-19, based on virology, should fully recover within at least 14 d, and a titer of at least 1:320 is recommended (34).

Conclusion

In the clinical trials conducted under the guidance of normative documents in various countries or regions, the existing reported clinical data show that convalescent plasma therapy seems to yield some efficacy among patients with severe COVID-19 and almost no obvious adverse reactions were found. However, the level of clinical evidence is low due to the small sample size, as well as the influence of antiviral, hormonal, and other treatments. Therefore, this clinical treatment modality should be used cautiously in patients with severe COVID-19 when there is a lack of high-quality clinical trial data. The principle of early treatment should be followed when using it. The correlation between the plasma dose and therapeutic effect of plasma therapy in the treatment of COVID-19 cannot be confirmed. Follow-up clinical trials of plasma therapy for COVID-19 should pay attention to the differences in implementation of treatment (dose, frequency, timing, etc.) and the influence of donor plasma standards, and adopt randomized controlled studies as far as possible to arrive at conclusions that are more accurate.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare no conflict of interest.

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