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Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review (Review)

Valk SJ, Piechotta V, Chai KL, Doree C, Monsef I, Wood EM, Lamikanra A, Kimber C, McQuilten Z, So-Osman C, Estcourt LJ, Skoetz N

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[Intervention Review]

Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review

Sarah J Valk[1,2a], Vanessa Piechotta[3b], Khai Li Chai[4c], Carolyn Doree[5], Ina Monsef[3], Erica M Wood[4], Abigail Lamikanra[6], Catherine Kimber[5], Zoe McQuilten[4], Cynthia So-Osman[7,8], Lise J Estcourt[9], Nicole Skoetz[10]

[1]Jon J van Rood Center for Clinical Transfusion Research, Sanquin/Leiden University Medical Center, Leiden, Netherlands. [2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands. [3]Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [4]Transfusion Research Unit, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia. [5]Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. [6]Clinical, Research and Development, NHS Blood and Transplant, Oxford, UK. [7]Sanquin Blood Bank, Amsterdam, Netherlands. [8]Erasmus Medical Centre, Rotterdam, Netherlands. [9]Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK. [10]Cochrane Cancer, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[a]contributed equally. [b]contributed equally. [c]contributed equally

Contact address: Lise J Estcourt, lise.estcourt@nhsbt.nhs.uk, lise.estcourt@ndcls.ox.ac.uk.

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ABSTRACT

Background

Convalescent plasma and hyperimmune immunoglobulin may reduce mortality in patients with respiratory virus diseases, and are currently being investigated in trials as a potential therapy for coronavirus disease 2019 (COVID-19). A thorough understanding of the current body of evidence regarding the benefits and risks is required.

Objectives

To assess whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19.

Search methods

The protocol was pre-published with the Center for Open Science and can be accessed here: osf.io/dwf53

We searched the World Health Organization (WHO) COVID-19 Global Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, Centers for Disease Control and Prevention COVID-19 Research Article Database and trials registries to identify ongoing studies and results of completed studies on 23 April 2020 for case-series, cohort, prospectively planned, and randomised controlled trials (RCTs).

Selection criteria

We followed standard Cochrane methodology and performed all steps regarding study selection in duplicate by two independent review authors (in contrast to the recommendations of the Cochrane Rapid Reviews Methods Group).

We included studies evaluating convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, irrespective of disease severity, age, gender or ethnicity.

We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)) and studies evaluating standard immunoglobulins.

Data collection and analysis

We followed recommendations of the Cochrane Rapid Reviews Methods Group regarding data extraction and assessment.

To assess bias in included studies, we used the assessment criteria tool for observational studies, provided by Cochrane Childhood Cancer. We rated the certainty of evidence using the GRADE approach for the following outcomes: all-cause mortality at hospital discharge, improvement of clinical symptoms (7, 15, and 30 days after transfusion), grade 3 and 4 adverse events, and serious adverse events.

Main results

We included eight studies (seven case-series, one prospectively planned, single-arm intervention study) with 32 participants, and identified a further 48 ongoing studies evaluating convalescent plasma (47 studies) or hyperimmune immunoglobulin (one study), of which 22 are randomised.

Overall risk of bias of the eight included studies was high, due to: study design; small number of participants; poor reporting within studies; and varied type of participants with different severities of disease, comorbidities, and types of previous or concurrent treatments, including antivirals, antifungals or antibiotics, corticosteroids, hydroxychloroquine and respiratory support.

We rated all outcomes as very low certainty, and we were unable to summarise numerical data in any meaningful way. As we identified case-series studies only, we reported results narratively.

Effectiveness of convalescent plasma for people with COVID-19

The following reported outcomes could all be related to the underlying natural history of the disease or other concomitant treatment, rather than convalescent plasma.

All-cause mortality at hospital discharge

All studies reported mortality. All participants were alive at the end of the reporting period, but not all participants had been discharged from hospital by the end of the study (15 participants discharged, 6 still hospitalised, 11 unclear). Follow-up ranged from 3 days to 37 days post-transfusion. We do not know whether convalescent plasma therapy affects mortality (very low-certainty evidence).

Improvement of clinical symptoms (assessed by respiratory support)

Six studies, including 28 participants, reported the level of respiratory support required; most participants required respiratory support at baseline. All studies reported improvement in clinical symptoms in at least some participants. We do not know whether convalescent plasma improves clinical symptoms (very low-certainty evidence).

Time to discharge from hospital

Six studies reported time to discharge from hospital for at least some participants, which ranged from four to 35 days after convalescent plasma therapy.

Admission on the intensive care unit (ICU)

Six studies included patients who were critically ill. At final follow-up the majority of these patients were no longer on the ICU or no longer required mechanical ventilation.

Length of stay on the ICU

Only one study (1 participant) reported length of stay on the ICU. The individual was discharged from the ICU 11 days after plasma transfusion.

Safety of convalescent plasma for people with COVID-19

Grade 3 or 4 adverse events

The studies did not report the grade of adverse events after convalescent plasma transfusion. Two studies reported data relating to participants who had experienced adverse events, that were presumably grade 3 or 4. One case study reported a participant who had moderate fever (38.9 °C). Another study (3 participants) reported a case of severe anaphylactic shock. Four studies reported the absence

of moderate or severe adverse events (19 participants). We are very uncertain whether or not convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence).

Serious adverse events

One study (3 participants) reported one serious adverse event. As described above, this individual had severe anaphylactic shock after receiving convalescent plasma. Six studies reported that no serious adverse events occurred. We are very uncertain whether or not convalescent plasma therapy affects the risk of serious adverse events (very low-certainty evidence).

Authors' conclusions

We identified eight studies (seven case-series and one prospectively planned single-arm intervention study) with a total of 32 participants (range 1 to 10). Most studies assessed the risks of the intervention; reporting two adverse events (potentially grade 3 or 4), one of which was a serious adverse event. We are very uncertain whether convalescent plasma is effective for people admitted to hospital with COVID-19 as studies reported results inconsistently, making it difficult to compare results and to draw conclusions. We identified very low-certainty evidence on the effectiveness and safety of convalescent plasma therapy for people with COVID-19; all studies were at high risk of bias and reporting quality was low.

No RCTs or controlled non-randomised studies evaluating benefits and harms of convalescent plasma have been completed. There are 47 ongoing studies evaluating convalescent plasma, of which 22 are RCTs, and one trial evaluating hyperimmune immunoglobulin. We will update this review as a living systematic review, based on monthly searches in the above mentioned databases and registries. These updates are likely to show different results to those reported here.

PLAIN LANGUAGE SUMMARY

Plasma from people who have recovered from COVID-19 to treat individuals with COVID-19

Background

Coronavirus (COVID-19) is a highly infectious respiratory illness caused by a new strain of virus. The outbreak has spread rapidly on a global scale. People infected with this virus may not show signs of the disease, others may develop symptoms, including fever, cough, shortness of breath and sore throat. In some people the infection is more severe and can cause severe breathing difficulties, leading to hospitalisation, admission to intensive care or death. Currently, no vaccine or specific treatment is available.

People who have recovered from COVID-19 develop natural defences to the disease in their blood (antibodies). Antibodies are found in part of the blood called plasma. Plasma from blood donated from recovered patients, which contains COVID-19 antibodies, can be used to make two preparations. Firstly, convalescent plasma, which is plasma that contains these antibodies. Secondly, hyperimmune immunoglobulin, which is more concentrated, and therefore contains more antibodies.

Convalescent plasma and hyperimmune immunoglobulin have been used successfully to treat other respiratory viruses. These treatments (given by a drip or injection) are generally well-tolerated, but unwanted effects can occur.

What did we want to find?

We wanted to know whether plasma from people who have recovered from COVID-19 is an effective treatment for people with COVID-19, and whether this treatment causes any unwanted effects.

Our methods

We searched major medical databases for clinical studies on treatment with convalescent plasma or hyperimmune immunoglobulin for people with COVID-19. Studies could be conducted anywhere in the world and include participants of any age, gender or ethnicity, with mild, moderate or severe COVID-19.

COVID-19 is spreading rapidly, so we needed to answer this question quickly. This meant that we shortened some steps of the normal Cochrane Review process - only one review author extracted data from studies and assessed study quality; normally two review authors would do this.

Key results

We included eight completed studies, with 32 participants who received convalescent plasma. None of the studies randomly allocated participants to different treatments (randomised trials produce the best evidence). None of the studies included a group of people who did not receive convalescent plasma, as a comparison group.

All participants in the studies were alive at the end of follow-up, but not all had been discharged from hospital. Follow-up varied from 3 to 37 days after treatment with convalescent plasma.

Six studies used the level of breathing support that participants required as a measure of recovery. Breathing support included oxygen therapy, mechanical ventilation and the need for a special machine that oxygenates the blood. All six studies reported clinical improvement in at least some of their participants, but it remains uncertain whether this improvement was related to convalescent plasma, another treatment, or the natural progression of the disease.

Six studies reported time to discharge from hospital for some of their participants, all of whom received convalescent plasma. The time to discharge ranged from 4 to 35 days after convalescent plasma treatment.

Six studies included participants with severe COVID-19. Most had improved at final follow-up, but this improvement may have been due to another treatment, the natural progression of the disease or convalescent plasma treatment.

Two participants reported unwanted effects related to convalescent plasma. One participant developed a fever, and a second participant experienced anaphylactic shock (severe allergic reaction) early on in the transfusion.

Certainty of the evidence

Our certainty (confidence) in the evidence was very limited because the studies were not randomised and did not use reliable methods to measure their results. Furthermore, they had only a small number of participants, who received various treatments alongside convalescent plasma, and some had underlying health problems.

Conclusion

We are very uncertain whether plasma from people who have recovered from COVID-19 is an effective treatment for people with COVID-19. The completed studies we found were poor quality and their results could be related to the natural progression of the disease, other treatments that the participants received, or to convalescent plasma. However, our searches found 48 ongoing studies: 47 evaluating convalescent plasma and 1 evaluating hyperimmune immunoglobulin, of which 22 are randomised. We will update this review with their results when these studies are completed.

BACKGROUND

Description of the condition

The clinical syndrome coronavirus disease 2019 (COVID-19) is a new, rapidly emerging zoonotic infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; WHO 2020a). On 11 March 2020, the World Health Organization (WHO) declared the current COVID-19 outbreak a pandemic, with the outbreak resulting in almost 3.5 million cases and over 239,000 deaths worldwide (WHO 2020b; WHO 2020c). Although there are similarities with historic coronavirus epidemics, with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) responsible for 813 and 858 deaths respectively, the scale and impact of the COVID-19 pandemic presents unprecedented challenges to health facilities and healthcare workers all over the world (WHO 2007; WHO 2019).

With a preliminary hospitalisation rate of 12.3 patients per 100,000 population in the USA, COVID-19 has taken a toll on healthcare capacity, and especially on intensive care unit (ICU) capacity (CDC 2020a). Early reports of the case fatality rate suggest that it ranges between of 0.7% to 4%, with higher rates also reported (WHO 2020a; WHO 2020c). However, these numbers should be interpreted with great care due to the data pertaining to the early emergency response, which due to shortage of test kits has led to selective testing of people with severe disease, underreporting of cases and delays from confirmation of a case to time of death (Kim 2020). The median incubation period of SARS-CoV-2 was reported to be five days, with 97.5% of cases developing symptoms within 11.5 days of infection (Lauer 2020). Common signs and symptoms can include fever, dry cough, fatigue and sputum production (WHO 2020a). Other, less commonly reported signs and symptoms are shortness of breath, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhoea, haemoptysis and conjunctival congestion (WHO 2020a). Of the reported cases, 80% are estimated to have a mild or asymptomatic course of infection, and an estimated 5% of cases are admitted to the ICU with acute respiratory distress syndrome (ARDS), septic shock or multiple organ failure, or both (Team 2020; WHO 2020a). A risk factor for developing infection and progressing to severe disease is old age, with people aged over 80 years at highest risk of mortality. Other risk factors are cardiovascular disease, obesity, hypertension, diabetes, chronic respiratory disease, cancer and compromised immune status (Chen 2020; Huang 2020; Liang 2020; WHO 2020a; Wu 2020a).

SARS-CoV-2 is a positive-sense, single-stranded RNA (ribonucleic acid) virus with a large RNA genome. Although not much is known about the specific mechanisms underlying severe disease in COVID-19, there are indications that the virus is capable of inducing an excessive immune reaction in the host, with highly activated but decreased numbers of $CD4^+$ and $CD8^+$ T cells detected in the peripheral blood of people with COVID-19 (Xu 2020). Early reports also showed that people critically ill with COVID-19 frequently exhibit a hypercoagulable state and endothelial inflammation, which is hypothesised to lead to the high burden of thromboembolic events seen in this population (Driggin 2020). Preliminary reports into the pathophysiology of SARS-CoV-2 have further indicated that the observed decrease in human angiotensin-converting enzyme 2 (ACE2) activity may play a role in causing the rapid deterioration of patient lung function (Tolouian 2020; Van de Veerdonk 2020). ACE2 is a protein that functions as the receptor facilitating entry of SARS-CoV-2 into the host cell, and is most abundant on type II alveolar cells in the lungs.

Description of the intervention

Convalescent plasma, convalescent serum and hyperimmune immunoglobulin prepared from convalescent plasma, are interventions that have been used in the past to treat conditions when no vaccine or pharmacological interventions were available. Diphtheria, pneumococcal pneumonia, hepatitis A and B, mumps, polio, measles and rabies are conditions where convalescent plasma has been shown to be effective (Eibl 2008).

A systematic review has shown that convalescent plasma may have clinical benefit for people with influenza and SARS (Mair-Jenkins 2015). This systematic review included observational studies and randomised controlled trials (RCTs) investigating the use of convalescent plasma, serum or hyperimmune immunoglobulin for treating severe acute respiratory infections of laboratory-confirmed or suspected viral aetiology, and included investigations with patients of any age and sex. Control interventions consisted of sham, or placebo, therapy and no therapy. The authors concluded that, although the included studies were generally small and of low quality, with a moderate to high risk of bias, the use of convalescent plasma may reduce mortality and appears safe (Mair-Jenkins 2015). The authors also suggested that the effectiveness of convalescent plasma in reducing hospital length of stay is dependent on early administration of the therapy, and use as prophylaxis is more likely to be beneficial than treating severe disease. However, the optimal timing and dosage of convalescent plasma therapy is unknown.

There is conflicting evidence about the effect of convalescent plasma or hyperimmune immunoglobulin for treating severe acute respiratory infections. Studies investigating the effectiveness of hyperimmune immunoglobulin for influenza have been contradictory, with some RCTs showing effectiveness (Hung 2013), whereas others show no benefit (Beigel 2017; Beigel 2019; Davey 2019).

Although convalescent plasma is generally thought to be a safe and well-tolerated therapy, adverse events can occur. Limited information is available about specific adverse events related to convalescent plasma therapy, but symptoms that have been reported are similar to those for other types of plasma blood components, including fever or chills, allergic reactions, and transfusion-related acute lung injury (TRALI; Beigel 2019; Chun 2016; Luke 2006). Furthermore, the transfer of coagulation factors present in plasma products is potentially harmful for people with COVID-19, who are already at an increased risk of thromboembolic events (Driggin 2020). Plasma transfusions are also known to cause transfusion-associated circulatory overload (TACO). TACO and TRALI are especially important to consider, because COVID-19 patients with comorbidities, who might be eligible for experimental treatment with convalescent plasma therapy, are at an increased risk of these adverse events. There are risk-mitigation strategies that can be implemented to prevent TRALI. These include limiting donations from female donors, especially those with a history of pregnancy, and screening of donors for antibodies that are implicated in TRALI (Otrock 2017). In addition to the aforementioned adverse events, transfusion-transmitted infections, red blood cell alloimmunisation and haemolytic transfusion reactions have also been described following plasma transfusion, although they

are less common (Pandey 2012). Pathogen inactivation can be implemented to decrease the risk of transmitting infections by transfusion (Rock 2011).

When compared to convalescent plasma, hyperimmune immunoglobulin has the advantage of preventing transfer of potentially harmful coagulation factors that are present in plasma products. The amount and antibody concentration can be more accurately dosed compared to convalescent plasma, and hyperimmune immunoglobulin can be prepared in a consistent manner (Hung 2013). Not many studies have reported on adverse events of hyperimmune immunoglobulin, but the safety profile of standard intravenous immunoglobulin is known and the adverse events reported here are also likely to occur in hyperimmune immunoglobulin therapy. Common adverse events of intravenous immunoglobulin that occur immediately after administration are: infusion site pain; swelling and erythaema; and immediate systemic reactions, such as head and body aches, chills and fever (Stiehm 2013). Other, less common early adverse reactions to immunoglobulin therapy are pulmonary complications, such as pulmonary embolism, pulmonary oedema and pleural effusion, with TRALI also reported (Baudel 2020; Stiehm 2013). Anaphylactic and anaphylactoid reactions to immunoglobulin therapy are rare (Brennan 2003; Stiehm 2013). Delayed adverse events of immunoglobulin therapy, which occur within hours to days of initiation of immunoglobulin therapy, are persistent headaches (common), aseptic meningitis, renal failure, thromboembolic events, and haemolytic reactions (Sekul 1994; Stiehm 2013). Transmission of infectious agents has been described after administration of intravenous immunoglobulin, but this risk is considered to be low (Stiehm 2013). Other, severe adverse events that occur late after administration are lung disease, enteritis and dermatological disorders (Stiehm 2013).

A theoretical risk related to virus-specific antibodies, which are transferred with convalescent plasma and hyperimmune immunoglobulin administration, is antibody-dependent enhancement of infection (Morens 1994). Here, virus-binding antibodies facilitate the entry and replication of virus particles into monocytes, macrophages and granulocytic cells and thereby increase the risk of more severe disease in the infected host. Although antibody-dependent enhancement has not been demonstrated in COVID-19, it has been seen with previous coronavirus infections when the antibodies given targeted a different serotype of the virus (Wan 2020; Wang 2014). A mechanism for antibody-dependent enhancement in COVID-19 has recently been proposed, with non-neutralising antibodies to variable S domains potentially enabling an alternative infection pathway via Fc receptor-mediated uptake (Ricke 2020). Antibody-dependent enhancement is therefore a potentially harmful consequence of convalescent plasma and hyperimmune immunoglobulin therapy for COVID-19.

In summary, the benefits of the intervention, both for convalescent plasma or hyperimmune immunoglobulin, should be carefully considered in view of the risks of adverse events.

How the intervention might work

Convalescent plasma contains pathogen-specific neutralising antibodies, which can neutralise viral particles, and treatment with convalescent plasma or hyperimmune immunoglobulins confers passive immunity to recipients. The duration of conferred protection can differ depending on the timing of administration, ranging from weeks to months after treatment (Casadevall 2020).

By neutralising SARS-CoV-2 particles, early treatment with convalescent plasma is postulated to increase the patient's own capacity to clear the initial inoculum (Casadevall 2020; Robbins 1995). This could lead to a reduction in mortality and fewer hospitalised patients progressing to the ICU. Furthermore, convalescent plasma may reduce the length of ICU stay in critically ill patients (Mair-Jenkins 2015), thus helping to lift pressure from global healthcare systems and increasing ICU capacity.

Preliminary evidence in humans and rhesus macaques has shown that reinfection with SARS-CoV-2 is not likely, with most (but not all) patients who recovered from COVID-19 producing sufficient amounts of neutralising antibodies to protect against reinfection (Bao 2020; Wu 2020b). This implies that convalescent plasma from people who have recovered from SARS-CoV-2 infection is capable of conferring passive immunity. A recently reported case series also indicated sufficient neutralising antibody titres in convalescent plasma to neutralise SARS-CoV-2 in five COVID-19 patients, who all recovered after treatment (Shen 2020). It is important to note, however, that research in other coronavirus species has shown that immunity may not be long-lasting, with two to three years of protection estimated from work with SARS and MERS (Mo 2006; Payne 2016). Furthermore, there are indications that the severity of infection has an impact on antibody titres, with less severe disease leading to lower neutralising antibody response in people with SARS and COVID-19 (Ho 2005; Zhao 2020).

Why it is important to do this review

There is a clear, urgent need for more information to guide clinical decision-making for COVID-19 patients. Pharmacological interventions have not yet proven to be effective, and current treatment consists of supportive care with extracorporeal membrane oxygenation in severe cases and oxygen supply in mild cases (CDC 2020b; WHO 2020d). A vaccine could aid in inducing immunity in the population and preventing transmission to those who are at risk for severe disease, but no vaccine is currently available, although multiple candidate vaccines are in development. Until these vaccines are available and distributed, convalescent plasma is a potential therapy for COVID-19 patients. Convalescent plasma, and hyperimmune immunoglobulin to a certain extent, can be prepared and made rapidly available by blood banks and hospitals when enough potential donors have recovered from the infection, using readily available materials and methods (Bloch 2020). However, its safety and efficacy are not well characterised, and there are costs associated with pursuing the use of convalescent plasma for treatment of COVID-19.

A multitude of clinical trials investigating the safety and effectiveness of convalescent plasma or hyperimmune immunoglobulins have been announced, and their results will need to be interpreted with care. Thus, there needs to be a thorough understanding of the current body of evidence regarding the use of convalescent plasma for people with COVID-19, and an extensive review of the available literature is required.

OBJECTIVES

To assess whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19.

METHODS

Criteria for considering studies for this review

Types of studies

The protocol for this review was registered with the Center for Open Science (Piechotta 2020).

As planned at the protocol stage, we included prospective non-comparative study designs (e.g. case series), because there was no evidence from randomised controlled trials (RCTs), non-randomised studies of interventions (NRSIs), and only one prospective observational study available (please find further explanations in Appendix 1). We followed the suggestions specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), as far as possible, and applied the methodology outlined in the following sections. We considered studies including one or more participant(s) with coronavirus disease 2019 (COVID-19).

We included full-text publications, abstract publications, and results published in trials registries, if sufficient information was available on study design, characteristics of participants, interventions and outcomes. We did not apply any limitation with respect to the length of follow-up.

Types of participants

We included individuals with a confirmed diagnosis of COVID-19, with no age, gender or ethnicity restrictions.

We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)). We also excluded studies including populations with mixed virus diseases (e.g. influenza), unless the trial authors provided subgroup data for people with COVID-19.

Types of interventions

We included the following interventions.

- Convalescent plasma from people who recovered from SARS-CoV-2 infection
- Hyperimmune immunoglobulin therapy

We did not include studies on standard immunoglobulin.

In future updates we plan to include the following comparisons for studies with a control arm.

- Convalescent plasma versus standard care or placebo
- Convalescent plasma therapy versus control treatment, for example, drug treatments (including but not limited to hydroxychloroquine, remdesivir). Co-interventions will be allowed, but must be comparable between intervention groups.
- Convalescent plasma therapy versus hyperimmune immunoglobulin
- Hyperimmune immunoglobulin versus standard care or placebo
- Hyperimmune immunoglobulin versus control treatment, for example, drug treatments (including but not limited to hydroxychloroquine, remdesivir). Co-interventions will be allowed, but must be comparable between intervention groups.

Types of outcome measures

We evaluated core outcomes as pre-defined by the Core Outcome Measures in Effectiveness Trials Initiative for Covid-19 patients (COMET 2020).

Primary outcomes

Effectiveness of convalescent plasma for people with COVID-19

- All-cause mortality at hospital discharge
- Time to death

Secondary outcomes

Effectiveness of convalescent plasma for people with COVID-19

- Improvement of clinical symptoms, assessed by need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days:
  - oxygen by mask or nasal prongs
  - oxygen by non-invasive ventilation (NIV) or high-flow
  - intubation and mechanical ventilation
  - mechanical ventilation plus high-flow oxygen
  - extracorporeal membrane oxygenation (ECMO)
- 30-day and 90-day mortality
- Time to discharge from hospital
- Admission on the ICU
- Length of stay on the ICU

Safety of convalescent plasma for people with COVID-19

- Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions)
- Number of participants with serious adverse events

Timing of outcome measurement

For time-to-event outcomes, such as mortality, discharge from hospital, and improvement of clinical symptoms, we included outcome measures representing the longest follow-up time available.

We included all other outcome categories for the observational periods that the study publications reported. We included those adverse events occurring during active treatment and had planned to include long-term adverse events as well. If sufficient data had been available, we planned to group the measurement time points of eligible outcomes, for example, adverse events and serious adverse events, into those measured directly after treatment (up to seven days after treatment), medium-term outcomes (15 days after treatment) and longer-term outcomes (over 30 days after treatment).

Search methods for identification of studies

We searched for studies in all languages in order to limit language bias. However, we prioritised articles in languages that our review team could accommodate (these are English, Dutch, German, French, Italian, Malay and Spanish). We did not seek translators for this version of the review. We tagged all references in additional languages as 'awaiting classification' and will seek translators via Cochrane TaskExchange in an update of this review.

Electronic searches

We designed and tested search strategies for electronic databases according to methods suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019), CD developed them and Cochrane Haematology's Information Specialist (IM) peer reviewed them. In this emerging field, we expected that at least the abstract would be in English. If studies are published in other languages than those our review team could accommodate (English, Dutch, German, French, Italian, Malay and Spanish), we plan to involve Cochrane TaskExchange to identify people within Cochrane to translate these studies for an update of this review.

As publication bias might influence all subsequent analyses and conclusions, we searched all potential relevant trials registries in detail to detect ongoing as well as completed studies, but not yet published studies. Nowadays, it is mandatory to provide results at least in the trials registry. In case results were not published elsewhere, we had planned to extract and analyse these data. However, no outcome data have yet been added to the trials registries (also stated in Differences between protocol and review).

We searched the following databases and sources, from 1 January 2019 to 23 April 2020.

- Databases of medical literature
  - WHO COVID-19 Global Research Database (search.bvsalud.org/global-research-on-novel-coronavirus-2019-ncov/advanced/?lang=en), searched 23 April 2020; Appendix 2
  - MEDLINE (Ovid, 1 January 2019 to 23 April 2020), Appendix 3
  - Embase (Ovid, 1 January 2019 to 23 April 2020), Appendix 4
  - PubMed (for epublications ahead of print only; searched 23 April 2020), Appendix 5
  - Center for Disease Control and Prevention COVID-19 Research Article Database (www.cdc.gov/library/researchguides/2019novelcoronavirus/databasesjournals.html; downloaded 22 April 2020), Appendix 6
  - Cochrane COVID-19 Study Register (covid-19.cochrane.org; searched 23 April 2020), Appendix 7
- Trials registries and registry platforms to identify ongoing studies and results of completed studies
  - ClinicalTrials.gov - COVID-19 Subset (clinicaltrials.gov/ct2/results?cond=COVID-19; searched 23 April 2020), Appendix 8
  - WHO International Clinical Trials Registry Platform (ICTRP) - COVID-19 Subset (www.who.int/ictrp/en); searched 23 April 2020), Appendix 9

Searching other resources

In an update of this rapid review we plan to:

- handsearch the reference lists of all identified studies, relevant review articles and current treatment guidelines for further literature; and
- contact experts in the field, drug manufacturers and regulatory agencies in order to retrieve information on unpublished studies.

Data collection and analysis

Selection of studies

Two out of four review authors (SJV, KLC, VP, NS) independently screened the results of the search strategies for eligibility for this review by reading the abstracts using Covidence software. We coded the abstracts as either 'retrieve' or 'do not retrieve'. In the case of disagreement or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Two review authors assessed the full-text articles of selected studies. If the two review authors were unable to reach a consensus, they consulted a third review author to reach a final decision.

We documented the study selection process in a flow chart, as recommended in the PRISMA statement (Moher 2009), and show the total numbers of retrieved references and the numbers of included and excluded studies. We list all articles that we excluded after full-text assessment and the reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management

One review author (SJV or KLC) performed all data extractions and assessments. Two other review authors (VP, NS) verified the accuracy and (where applicable) the plausibility of extractions and assessment.

One review author (VP or NS) assessed eligible studies obtained in the process of study selection (as described above) for methodological quality and risk of bias, the other review author verified the 'Risk of bias' assessment.

One review author (SJV or KLC) extracted data using a customised data extraction form developed in Microsoft Excel (Microsoft Corporation 2018); please see Differences between protocol and review). Another review author (NS) verified the accuracy and (where applicable) the plausibility of extractions and assessment. We conducted data extraction according to the guidelines proposed by Cochrane (Li 2019). If the review authors were unable to reach a consensus, we consulted a third review author (VP).

We collated multiple reports of one study so that the study, and not the report, is the unit of analysis.

We extracted the following information.

- General information: author, title, source, publication date, country, language, duplicate publications
- Quality assessment: study design, confounding, definition of risk estimates, selection bias, attrition bias, detection bias, reporting bias
- Study characteristics: trial design, setting and dates, source of participants, inclusion/exclusion criteria, comparability of

groups, treatment cross-overs, compliance with assigned treatment, length of follow-up

- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, disease, severity of disease, additional diagnoses, previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
- Interventions: convalescent plasma therapy or hyperimmune immunoglobulin therapy, concomitant therapy, duration of follow-up
  * For studies including a control group: comparator (type)
- Outcomes
  * Effectiveness of convalescent plasma for people with COVID-19:
    - ☐ all-cause mortality at hospital discharge
    - ☐ time to death
    - ☐ improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days
    - ☐ 30-day and 90-day mortality
    - ☐ time to discharge from hospital
    - ☐ admission on the ICU
    - ☐ length of stay on the ICU
  * Safety of convalescent plasma for people with COVID-19:
    - ☐ number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
    - ☐ number of participants with serious adverse events

Assessment of risk of bias in included studies

If RCT data had been available, we had planned to use the Risk of Bias 2.0 (RoB 2) tool to analyse the risk of bias in the underlying study results (Sterne 2019). If non-randomised studies of interventions (NRSIs) data had been available, we had planned to use the Risk Of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool (Sterne 2016). Please refer to Appendix 1 for detailed information regarding how we had planned to assess the risk of bias of RCTs and NRSIs.

Non-controlled, prospectively planned studies

As specified in the Types of studies section we only included non-controlled prospective studies because we did not identify any controlled studies.

One review author (VP or NS) assessed eligible studies for methodological quality and risk of bias (using the 'Risk of bias' assessment criteria for observational studies tool provided by Cochrane Childhood Cancer (see Table 1; Mulder 2019). A second review author (VP or NS) verified the accuracy and the plausibility. Any 'Risk of bias' judgements were performed and presented per outcome per study.

The quality assessment strongly depends upon information on the design, conduct and analysis of the trial. The two review authors (VP, NS) resolved any disagreements regarding the quality assessments by discussion, in case of disagreement they would have consulted a third review author (SJV or KLC).

We assessed the following domains of bias.

- Internal validity
  * Unrepresentative study group (selection bias)
  * Incomplete outcome assessment/follow-up (attrition bias)
  * Outcome assessors unblinded to investigated determinant (detection bias)
  * Important prognostic factors or follow-up not taken adequately into account (confounding)
- External validity
  * Poorly defined study group (reporting bias)
  * Poorly defined follow-up (reporting bias)
  * Poorly defined outcome (reporting bias)
  * Poorly defined risk estimates (analyses)

For every criterion, we made a judgement using one of three response options.

- High risk of bias
- Low risk of bias
- Unclear risk of bias

Measures of treatment effect

Please refer to Appendix 1 for information regarding how we had planned to measure the treatment effects of RCTs and NRSIs.

Uncontrolled studies

For uncontrolled studies we did not carry out an analysis using quantitative data from indirect controls, as we are aware of the difficulties of indirect comparisons of participant groups with varying baseline characteristics, especially in the absence of individual patient data. Because authors of one-arm, non-comparative studies, often discuss their findings using information from other intervention and observational studies as implicit controls, we discussed our findings extensively in the context of what is known about the outcome of 'comparable' patients receiving other experimental treatments but not convalescent plasma therapy or hyperimmune immunoglobulin therapy. We did not meta-analyse the data but provided information from individual studies within tables.

Unit of analysis issues

As we identified uncontrolled studies only, meta-analysis was not appropriate. Instead, we narratively described and presented results per study in tables.

Please refer to Appendix 1 for information regarding how we had planned to combine studies with multiple treatment groups.

Dealing with missing data

Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data, which we will need to take into account: at study level, at outcome level and at summary data level (Higgins 2019b). In the first instance, it is of the utmost importance to differentiate between data 'missing at random' and 'not missing at random'.

We will request missing data from the study authors in an update of this review. If, after this, data are still missing, we will have to make explicit assumptions of any methods the included studies used. For example, we will assume that the data were missing at random or

we will assume that missing values had a particular value, such as a poor outcome.

Assessment of heterogeneity

As we identified uncontrolled studies only, meta-analysis was not appropriate. Instead, we narratively described and presented results per study in tables.

Please refer to Appendix 1 for information regarding how we had planned to assess heterogeneity.

Assessment of reporting biases

As mentioned above, we searched trials registries to identify completed studies that have not been published elsewhere, to minimise or determine publication bias.

In an update of this review, we intend to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test (Sterne 2019), for meta-analyses involving at least 10 studies. We will consider $P < 0.1$ as significant for this test.

Data synthesis

Please refer to Appendix 1 for information regarding how we had planned to synthesise data from RCTs and NRSIs.

We did not meta-analyse data from uncontrolled trials, as there might be no additional benefit in meta-analysing data without a control group. We reported outcome data of each included trial within tables.

As data did not allow quantitative assessment, we presented outcome data individually per study within tables.

Subgroup analysis and investigation of heterogeneity

In an update of this review, we plan to perform subgroup analyses of the following characteristics.

- Age of participants (divided into applicable age groups, e.g. children; 18 to 65 years, 65 years and older)
- Severity of condition
- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression)

We will use the tests for interaction to test for differences between subgroup results.

Sensitivity analysis

In an update of this review, we will perform only one sensitivity analysis for the following.

- 'Risk of bias' assessment components (low risk of bias versus high risk of bias)

To assess the influence of study quality on an outcome, we will perform sensitivity analyses per outcome, comparing studies with at least one domain of high risk of bias to those without high risk of bias.

- Influence of completed, but not published studies
- Influence of premature termination of studies

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the following outcomes (please find the rationale for the amendment of graded outcomes in the Differences between protocol and review).

- All-cause mortality at hospital discharge
- Time to death
- Clinical improvement (assessed by need for respiratory support) at the following time points
  - 7 days post-convalescent plasma transfusion
  - 15 days post-convalescent plasma transfusion
  - 30 days post-convalescent plasma transfusion
- Grade 3 and 4 adverse events
- Serious adverse events

We used GRADEpro GDT software to create an 'evidence profile'. We will also use the GRADEpro GDT software to create a 'Summary of findings' table, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* when results of controlled trials are available (Schünemann 2019).

RESULTS

Description of studies

Results of the search

We identified 1267 potentially relevant references. After removing duplicates, we screened 1039 references based on their titles and abstracts, and we excluded 956 references that were irrelevant because they did not meet the prespecified inclusion criteria. We evaluated the remaining 83 references and screened the full texts, or, if these were not available, abstract publications or trials registry entries. Of these, we classified two studies as awaiting classification for this review (Qiu 2020; Tu 2020).

We identified 56 potentially eligible studies within 57 citations: eight completed studies (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), and 48 ongoing studies (ChiCTR2000029757; ChiCTR2000029850; ChiCTR2000030010; ChiCTR2000030039; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030841; ChiCTR2000030929; ChiCTR2000031501; EUCTR2020-001310-38; IRCT20151228025732N53; IRCT20200310046736N1; IRCT20200325046860N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; NCT04264858; NCT04292340; NCT04321421; NCT04327349; NCT04332380; NCT04332835; NCT04333251; NCT04333355; NCT04338360; NCT04340050; NCT04342182; NCT04343261; NCT04343755; NCT04344535; NCT04345289; NCT04345523; NCT04345679; NCT04345991; NCT04346446; NCT04346589; NCT04347681; NCT04348656; NCT04348877; NCT04352751; NCT04353206; NCT04354831; NCT04355767; NCT04355897; NCT04356482; NCT04356534; NCT04357106). See PRISMA flow diagram (Figure 1; Moher 2009).

Figure 1. Study flow diagram

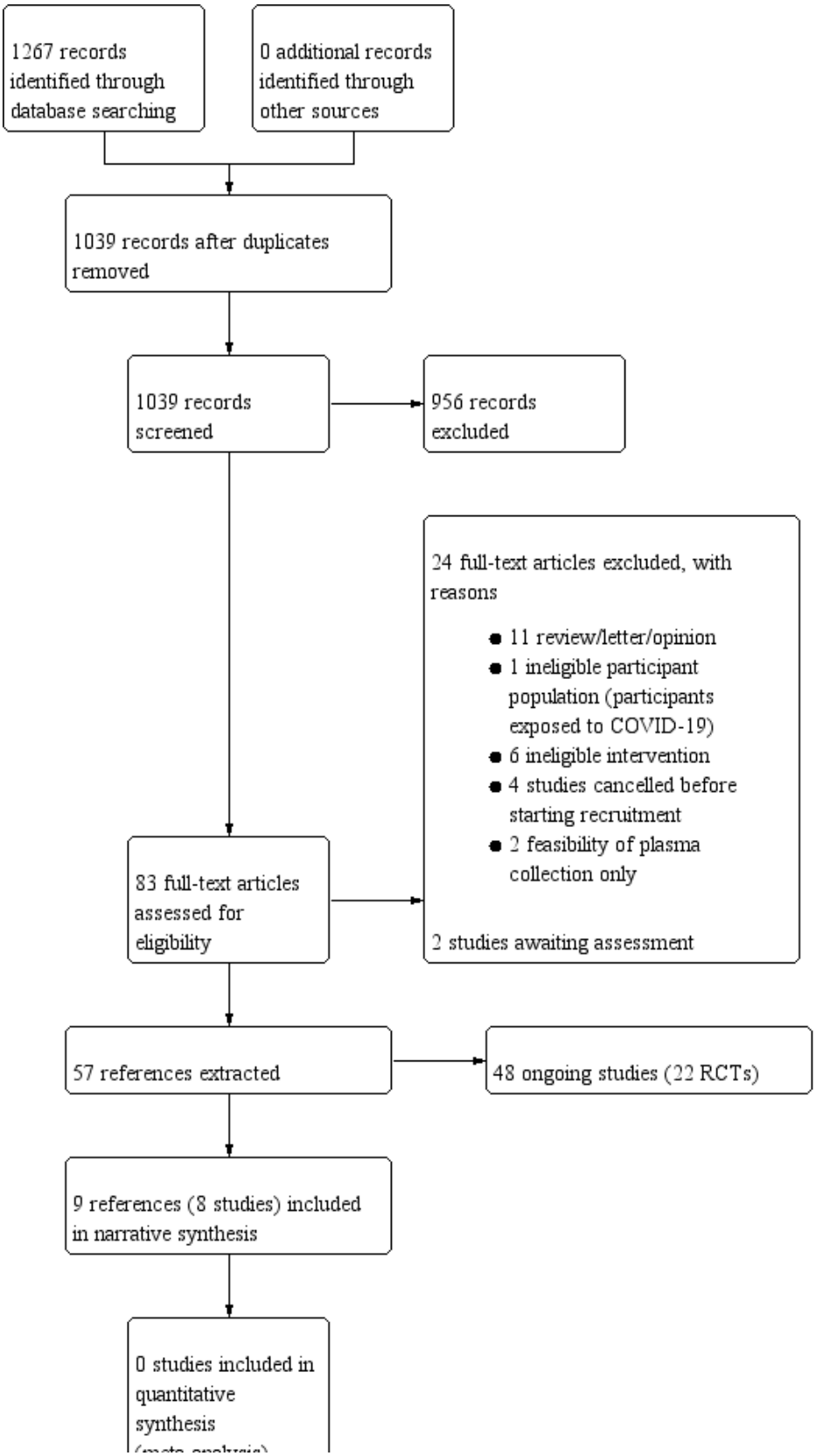
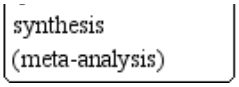


Figure 1. (Continued)



Included studies

We included eight studies describing 32 participants in this review (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b). The eight included studies were all uncontrolled studies, seven studies were case series (Ahn 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), and one was a prospectively registered single-arm intervention study (Duan 2020). Of the eight included studies, seven originated from China (Duan 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), and one from South Korea (Ahn 2020). In seven of the eight studies, convalescent plasma was transfused in critically ill individuals (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Ye 2020; Zhang 2020a; Zhang 2020b). One study described a person with moderate disease severity (Pei 2020), and one study described a hospitalised participant with moderate disease severity (Tan 2020).

The dose, volume and timing of convalescent plasma varied greatly between studies. The total volume of convalescent plasma transfused varied between 200 mL and 2400 mL, with participants receiving between one to eight doses of plasma. Antibody titres were reported in four studies (Duan 2020; Pei 2020; Shen 2020; Zhang 2020b). Characteristics of the donors of convalescent plasma also varied between studies, although reporting was not complete. Out of the eight studies, only six reported information on plasma donors (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Ye 2020; Zhang 2020b). Most donors were male, but Pei 2020 included a female donor with a previous history of pregnancy. The age of the donors varied: Ahn 2020 included donors in their twenties; Shen 2020 included donors aged between 18 and 60 years; Duan 2020 included donors with a median age of 42 years; and Zhang 2020b included donors aged between 30 and 50. Some studies provided information on previously reported symptoms and disease severity of convalescent plasma donors (Ahn 2020; Duan 2020; Zhang 2020b). Ahn 2020 reported that the two included donors had been admitted to hospital with fever, cough and pneumonia. Duan 2020 reported that donors had been admitted to hospital, but no other information on severity of illness was available. Zhang 2020b reported that all six donors had fever and cough during the course of disease and were admitted to the hospital. In the five studies that reported assessment of donor recovery, all donors were symptom-free and completely recovered from coronavirus disease 2019 (COVID-19) prior to donating plasma (Ahn 2020; Duan 2020; Shen 2020; Ye 2020; Zhang 2020b). Four studies required a negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription polymerase chain reaction (RT-PCR) test prior to convalescent plasma donation (Duan 2020; Shen 2020; Ye 2020; Zhang 2020b), with three studies requiring two consecutive negative results as a requirement for donation (Duan 2020; Ye 2020; Zhang 2020b). Four studies used an enzyme-linked immunosorbent assay (ELISA) to quantify neutralising antibodies (Duan 2020; Pei 2020; Shen 2020; Zhang 2020b), with limited information available on the type of ELISA that was used. One study additionally used a plaque reduction neutralisation assay to assess the neutralising activity of the plasma (Duan 2020).

We had also planned to include studies on hyperimmune immunoglobulin therapy in this rapid review. However we did not identify any eligible studies.

Please refer to the Characteristics of included studies for more detailed information.

Ongoing studies

Of the 48 ongoing studies, 22 are RCTs (ChiCTR2000029757; ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030929; EUCTR2020-001310-38; IRCT20200310046736N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; NCT04332835; NCT04333251; NCT04342182; NCT04344535; NCT04345289; NCT04345991; NCT04345523; NCT04355767; NCT04346446; NCT04348656; NCT04356534).

Of these, 16 are expected to be completed in 2020 (ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030929; IRCT20200310046736N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; NCT04332835; NCT04342182; NCT04345523; NCT04345991; NCT04346446; NCT04348656; NCT04356534), and plan to evaluate between 15 and 1200 participants.

Two further large RCTs are planned to be completed in 2021: NCT04344535, randomising 500 participants and NCT04345289, evaluating 1500 participants.

Please refer to Characteristics of ongoing studies for more detailed information.

Excluded studies

We excluded 24 studies that did not match our inclusion criteria:

- 11 were a review of the literature, a letter or an opinion (Bloch 2020; Casadevall 2020; Chen 2020; Jawhara 2020; Roback 2020; Syal 2020; Tanne 2020; Tiberghien 2020; Wong 2020; Yoo 2020; Zhao 2020b);
- six studies were performed with an intervention other than convalescent plasma or hyperimmune immunoglobulin (Cao 2020; Díez 2020; Hu 2020; NCT04261426; Shi 2020; Xie 2020);
- four studies were cancelled by the investigator before recruiting participants into the study (ChiCTR2000030312; ChiCTR2000030381; ChiCTR2000030442; NCT04325672);
- two studies pertained to feasibility of collection of convalescent plasma only (NCT04344015; NCT04344977);
- one study included the wrong participant population (participants exposed to COVID-19; NCT04323800).

Risk of bias in included studies

Overall, we rated the risk of bias within and across studies to be serious. In addition to the high risk of bias due to the non-randomised study design, we assessed the internal and external

validity as outlined in the 'Risk of bias' assessment criteria for observational studies tool provided by the Cochrane Childhood Cancer Group (see Table 1; Mulder 2019). The full judgement per trial and category is presented in Figure 2 and the support for judgement in the Characteristics of included studies.

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study

Allocation

All studies were at high risk of selection bias. We considered study groups not to be representative, as all studies included low numbers of participants (1 to 10 participants) with no control groups.

Blinding

All studies were unblinded and therefore at high risk of performance and detection bias for subjective outcomes. All outcomes apart from all-cause mortality are subjective to a greater or lesser extent and therefore at risk of bias.

Incomplete outcome data

We assessed attrition bias in terms of whether studies (equally) assessed outcomes for all participants. We evaluated attrition bias for three outcome categories.

Mortality

All studies assessed this outcome until discharge from hospital or the latest point of follow-up. We judged the risk for attrition bias to be unclear for seven studies (Ahn 2020; Duan 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), because some participants were either still hospitalised or it was unclear whether participants had been discharged. Therefore the outcome for these participants is unknown.

We judged the risk for attrition bias to be low for one study (Pei 2020), as all participants had been free of disease and were discharged from the hospital.

Adverse events

We judged the risk of attrition bias to be low for four studies (Ahn 2020; Duan 2020; Ye 2020; Zhang 2020b), because they assessed and reported adverse events for all participants.

We judged the risk of attrition bias to be unclear for the other four studies (Pei 2020; Shen 2020; Tan 2020; Zhang 2020a), because it was unclear whether they had assessed adverse events for all participants or whether they had selectively reported outcomes. Pei 2020 reported one serious adverse event occurring in one participant, however did not report whether they had assessed or observed other adverse events. Shen 2020 did not provide any information regarding the safety of plasma transfusion. Tan 2020 reported that their participant experienced moderate fever after the transfusion, however did not report whether other adverse events occurred. Zhang 2020a described that they had observed no adverse events for one of their participants after plasma transfusion, but did not provide any information regarding the occurrence of adverse events for the other participants. They stated in the conclusions that they had not observed any serious adverse events.

Clinical improvements

We judged the risk of bias to be low for six studies (Ahn 2020; Duan 2020; Shen 2020; Ye 2020; Zhang 2020a; Zhang 2020b), because they assessed and reported clinical improvements for all participants.

We judged the risk of attrition bias to be high for one study (Tan 2020), because it was unclear why the participant was still hospitalised and they did not report clinical improvements.

Pei 2020 did not report the course of disease after convalescent plasma transfusion so we judged it at unclear risk of bias for this domain.

Selective reporting

We assessed reporting bias in terms of whether the study group and intervention were well-defined and whether the outcomes were equally reported for all participants and the length of follow-up was mentioned.

Well-defined study group and intervention

We judged the risk of reporting bias to be low for four studies (Ahn 2020; Duan 2020; Shen 2020; Ye 2020), because both the study population and intervention were well described.

Zhang 2020a described the study population, but reported only limited information on the intervention. Zhang 2020b provided clear information on the intervention, but scarcely described the participant. We therefore judged the risk of reporting bias to be unclear for these two studies.

We judged the risk of bias to be high for two studies (Pei 2020; Tan 2020), which only reported limited information on the study population and the intervention. However, Pei 2020 was a preprint only, and claimed that the patient characteristics would be provided in the supplementary material once published.

Well-defined outcomes

We evaluated reporting bias for three outcome categories.

Mortality

We judged the risk for reporting bias to be low for seven studies (Ahn 2020; Pei 2020; Shen 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), because all reported information for this outcome per participant until discharge from hospital or the latest point of follow-up.

We judged the risk for reporting bias to be high for Duan 2020 because the follow-up was unclear and it was unclear whether all participants were free of disease and discharged.

Adverse events

We judged the risk of reporting bias to be low for two studies (Ye 2020; Zhang 2020b), because observation period and results were reported for all participants.

We judged the risk of reporting bias to be high for the other six studies (Ahn 2020; Duan 2020; Pei 2020; Shen 2020; Tan 2020; Zhang 2020a), because it was unclear whether adverse events had not been (equally) assessed for all participants or whether outcomes were selectively reported. Pei 2020 reported one serious adverse event occurring in one participant, however did not report whether they had assessed or observed other adverse events. Shen 2020 did not provide any information regarding the safety of plasma transfusion. Tan 2020 reported that their participant experienced moderate fever after the transfusion, however did not report whether other adverse events occurred. Zhang 2020a described they had not observed any adverse events for one of their participants after plasma transfusion, but did not provide any information regarding the occurrence of adverse events for the other participants. They stated in the conclusions that they had not observed any serious adverse events.

Clinical improvements

Reporting of clinical improvements was very heterogeneous across studies.

We judged the risk of reporting bias to be low for three studies (Duan 2020; Ye 2020; Zhang 2020a), which clearly described clinical improvements and periods of follow-up per participant.

We judged the risk of reporting bias to be unclear for three studies (Ahn 2020; Shen 2020; Zhang 2020b), because of the following reasons. Reporting and follow-up was unclear for one participant of Ahn 2020, two participants of Shen 2020 probably were still on the intensive care unit (ICU) but it was unclear, and Zhang 2020b did not provide details but the participant was transferred to another ward.

We judged the risk of reporting bias to be high for Tan 2020 because neither clinical symptoms nor clinical improvement were reported in detail, but the participant was still in hospital.

Pei 2020 did not report the course of disease after convalescent plasma transfusion so we judged it at unclear risk of bias for this domain.

Other potential sources of bias

We further considered confounding and poorly-defined risk estimates as potential sources of bias.

Confounding

All studies were at high risk of confounding because none of the studies adjusted for confounding factors, including concomitant treatments.

Poorly-defined risk estimates

None of the studies performed any analyses.

Effects of interventions

In the 'Evidence profile' (Table 2), we present certainty of the evidence for the outcomes that were prioritised in the protocol (Piechotta 2020).

Effectiveness of convalescent plasma for people with COVID-19

As no RCTs or well conducted non-randomised studies evaluating benefits and harms of convalescent plasma have yet been completed, we are not sure if the following results are related to convalescent plasma therapy; they could also be related to the underlying natural history of the disease or other concomitant treatments.

All-cause mortality at hospital discharge

All-cause mortality at hospital discharge cannot be fully evaluated, as not all of the participants had been discharged at the end of follow-up. None of the studies reported any deaths during their study periods, meaning that all 32 participants were alive at the end of follow-up. Participants were followed until discharge from hospital or from three (Duan 2020), to 37 days (Shen 2020), after transfusion. Two participants of Shen 2020 and one participant each of Ahn 2020, Ye 2020, Zhang 2020a, and Zhang 2020b were still hospitalised. The participant in Zhang 2020a still remained on the ICU. Further, it was unclear, whether all 11 participants of Duan 2020 and Tan 2020 had been discharged from hospital.

Time to death

All participants were alive at the end of follow-up (3 to 37 days).

Improvement of clinical symptoms (assessed by need for respiratory support)

The effect of convalescent plasma on improvement of clinical symptoms was reported in six included studies (Ahn 2020; Duan 2020; Shen 2020; Ye 2020; Zhang 2020a; Zhang 2020b), including 24 participants on respiratory support at baseline, and four participants who did not require respiratory support. The results of these studies can be found in Table 3. We grouped them according to the prespecified time points; day 7, day 15, and day 30 after the plasma transfusion, and summarised baseline information and clinical status at the longest time of follow-up for each study.

Six studies reported on improvement of clinical symptoms, but we could not extract all information about timing of improvement and types of respiratory support from all the studies.

Ahn 2020 described two critically ill people with COVID-19 requiring intubation and mechanical ventilation. The two participants received a tracheotomy and one participant was reportedly successfully weaned from the ventilator by day 18 after convalescent plasma therapy. For the other participant, the date of cessation of respiratory support was not evident from the publication, but tracheotomy and weaning from mechanical ventilation were reported during the study period.

Duan 2020 reported decreased need for respiratory support in four out of 10 participants within three days of convalescent plasma transfusion. One other participant was reported to require only intermittent oxygenation after previously receiving continuous low-flow oxygenation via nasal cannula. The study also reported on two individuals who required no respiratory support preceding convalescent plasma therapy. No information on improvement of clinical symptoms for other time points was available.

Shen 2020 reported a case series that included five participants who were described as critically ill at baseline, with four participants in need of mechanical ventilation and intubation and one participant receiving extracorporeal membrane oxygenation (ECMO). Of these five participants, three were discharged from hospital at the end of the study period, and two were in a stable condition, intubated and receiving mechanical ventilation.

Ye 2020 included six participants, four of whom required oxygen at baseline (one via nasal cannula, with the other modes not specified in the publication). Two individuals did not require respiratory support before convalescent plasma was administered. All four participants previously requiring respiratory support experienced alleviation of symptoms after convalescent plasma therapy, with none of them requiring respiratory support at the end of the study follow-up. The study reports information on respiratory support but lacks information on the type of support received by the participants, and the timing of this outcome is not part of the presented data for all participants.

Zhang 2020a reported in detail the clinical characteristics and timing of convalescent plasma therapy for four people with COVID-19. One participant was on non-invasive ventilation (NIV) and high-flow oxygenation, one participant was mechanically ventilated and intubated at baseline, and two participants received ECMO. Three out of the four participants were discharged at the end of the study period, and all participants were reported to have recovered from the infection eventually. For one participant it was unclear whether oxygen support was still required by the end of the study period.

Zhang 2020b described one participant who was mechanically ventilated and intubated before receiving convalescent plasma therapy. At day 11 after convalescent plasma therapy, the participant was removed from mechanical ventilation. Whether the participant required other types of respiratory support was not reported.

30-day and 90-day mortality

All participants were alive at the end of follow-up. Participants were followed until discharge from hospital or three (Duan 2020), to 37 days (Shen 2020), after transfusion.

Time to discharge from hospital

The time to discharge was reported for at least some of the participants in six studies (Ahn 2020; Pei 2020; Shen 2020; Ye 2020; Zhang 2020a; Zhang 2020b). The day of discharge after convalescent plasma therapy ranged from 4 days to 35 days. Only one study (3 participants) reported time to discharge from hospital for all participants (Pei 2020). Please refer to Table 4 for further information regarding each trial and participant.

It was unclear, whether all participants of Duan 2020 and Tan 2020 had been discharged from the hospital.

Admission on the ICU

This outcome was not reported in a consistent way in the included studies. Ye 2020, Zhang 2020a and Zhang 2020b reported the number of participants on the ICU at baseline (Table 5). These were none of six (Ye 2020), four of four (Zhang 2020a), and one of one (Zhang 2020b), respectively. The other studies did not report the number of participants on the ICU at baseline, however Ahn 2020, Duan 2020, Pei 2020, and Shen 2020 reported the number of participants that were mechanically ventilated, and so presumably on the ICU (please see Table 5). The participant reported in Tan 2020 presented with moderate symptoms only, and so presumably was not on the ICU.

Length of stay on the ICU

We could not evaluate the length of stay on the ICU as none of the included studies reported this outcome in a consistent way. Zhang 2020a reported that one participant was still on the ICU at the end of follow-up, the other three participants had been discharged from the ICU. Zhang 2020b reported that their participant could be released from the ICU 11 days after plasma transfusion to a general ward; 18 days after admission on the ICU. Based on the reported clinical course of disease presumably one participant of Ahn 2020 and two participants of Shen 2020 were also still on the ICU at the end of follow-up (please see Table 5). However, this was not clearly reported.

Safety of convalescent plasma for people with COVID-19

Number of participants with adverse events of possibly grade 3 or grade 4 severity

Seven studies reported assessment of adverse events (Ahn 2020; Duan 2020; Pei 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), however, Zhang 2020a only reported for one of their participants that no adverse event had been observed. It was unclear whether the other three participants did or did not experience any adverse events.

Six studies therefore reported the presence or absence of adverse events for all participants. Two studies reported adverse events that were possibly grade 3 or 4 severity but they did not report the degree of severity (see Table 6). Tan 2020, a case study, reported that their participant experienced moderate fever (38.9 °C) after convalescent plasma transfusion. One of the three participants in Pei 2020 had severe anaphylactic shock after receiving 30 mL of plasma from a female donor with a history of pregnancy. Four other studies reported no adverse events that were possibly of grade 3 or grade 4 severity (19 participants; Ahn 2020; Duan 2020; Ye 2020; Zhang 2020b).

Number of participants with serious adverse events

Seven studies assessed and reported serious adverse events (Ahn 2020; Duan 2020; Pei 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b). One participant in Pei 2020 (3 participants) experienced a serious adverse event (see Table 7). As described above, this individual had severe anaphylactic shock after receiving convalescent plasma from a female donor with a history of pregnancy. No serious adverse events occurred in six studies (24 participants).

DISCUSSION

Summary of main results

The aim of this review was to assess the effectiveness and safety of convalescent plasma and hyperimmune immunoglobulin in the treatment of coronavirus disease 2019 (COVID-19) illness.

We included eight studies in this review - seven case-series and one prospectively planned, single-arm intervention study, all evaluating convalescent plasma (32 participants in total). There were no completed studies evaluating hyperimmune immunoglobulin. We identified 47 ongoing studies evaluating convalescent plasma and one ongoing study evaluating hyperimmune immunoglobulin. Twenty-two of the ongoing studies on convalescent plasma are randomised.

Effectiveness of convalescent plasma for people with COVID-19

As no RCTs or high-quality, non-randomised studies evaluating benefits and harms of convalescent plasma are completed yet, we do not know whether the following results are related to the underlying natural history of the disease, other concomitant treatment, or convalescent plasma.

All-cause mortality at hospital discharge

All studies reported mortality, and all participants were alive at the end of reporting, but not all of the participants had been discharged from hospital at the end of follow-up. We do not know whether

convalescent plasma has any effect on all-cause mortality (very low-certainty evidence).

Improvement of clinical symptoms (as assessed by respiratory support)

Six studies reported on the level of respiratory support required in participants; most participants required respiratory support at baseline. All studies reported improvement in clinical symptoms in at least some of their participants. We do not know whether convalescent plasma improves clinical symptoms or whether this improvement was due to other interventions, or the natural history of the disease (very low-certainty evidence).

Time to discharge from the hospital

Six studies reported time to discharge from hospital for at least some of their participants. The day of discharge after convalescent plasma therapy ranged from 4 to 35 days.

Admission on the intensive care unit (ICU)

Six studies included participants who were critically ill. The majority of these participants were no longer on the ICU or no longer required mechanical ventilation at final follow-up.

Length of stay on the ICU

None of the studies clearly reported this outcome.

Safety of convalescent plasma for people with COVID-19

Adverse events

Two studies reported participants who had experienced adverse events, presumably of grade 3 or 4 (they did not report degree of severity). One case study reported a participant who had moderate fever (38.9 °C) after the transfusion of convalescent plasma. The other study (3 participants) reported a case of severe anaphylactic shock after convalescent plasma transfusion. Four studies reported that no participants experienced moderate or severe adverse events (19 participants). We are very uncertain whether convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence).

Serious adverse events

One study with three participants reported one serious adverse event. This participant had severe anaphylactic shock after receiving convalescent plasma. Six studies reported that no serious adverse events occurred. We are very uncertain whether convalescent plasma therapy affects the risk of serious adverse events (very low-certainty evidence).

Overall completeness and applicability of evidence

We found eight published non-randomised, uncontrolled studies (seven case-series, one prospectively planned study) evaluating convalescent plasma in adults, most with severe COVID-19. These studies included 32 participants (ranging from 1 to 10 participants). Most of these participants had already received different treatment options either solely or in combination. These included antivirals, antifungals or antibiotics, corticosteroids, hydroxychloroquine and respiratory support (extracorporeal membrane oxygenation (ECMO), mechanical ventilation or oxygen). Therefore, the participant population might have been too small and heterogeneous to generalise results.

We identified 48 ongoing studies, of which 22 are designed as RCTs. Of these ongoing studies, 47 evaluate convalescent plasma and one evaluates hyperimmune immunoglobulin. Sixteen RCTs are planned to be completed in 2020. The publication of the results of these studies will necessitate an update of this review. The conclusions of the updated review could differ from those of the present review, and may allow for a better judgement regarding the effectiveness and safety of convalescent plasma therapy.

Certainty of the evidence

It is important to note that the outcome measures are heterogeneous with wide variation in reporting across the included studies. Only one study was prospectively planned (Duan 2020), a non-randomised and uncontrolled study, evaluating 10 participants. However, this study reported a very short follow-up only (three days after convalescent plasma was given). The other seven small case-series studies were not registered. These study designs lead to high risk of bias, both in terms of selection and detection bias. Studies were not adjusted for potential confounders (e.g. severity of disease, comorbidities, previous or concomitant COVID-19 treatment). Currently, there is no standard instrument available to assess risk of bias for this type of study. We used the form developed by the Cochrane Childhood Cancer Group (Table 1; Mulder 2019).

As we included eight small observational studies only (32 participants altogether), the results are very imprecise and very inconsistent, with very high risk of bias. Therefore, the certainty of the evidence is very low for all prioritised outcomes.

Potential biases in the review process

To avoid potential bias in the review, we had planned to include the best available evidence. However, as COVID-19 is a novel disease, results from RCTs and non-RCTs are not yet available. In fact, we could only identify uncontrolled studies, reporting on a small number of participants. To increase the informative value of our review, we are tracking all registered trials and will update this review on a monthly basis as more evidence becomes available.

Two experienced Information Specialists developed a sensitive search strategy, to identify all ongoing and completed studies. We searched all relevant databases and trials registries, and in contrast to the recommendations of the Cochrane Rapid Reviews Methods Group, we decided to conduct all review steps regarding the study selection in duplicate by two independent review authors. We are confident that we identified all relevant published and ongoing studies and will monitor them closely in the future.

Unlike standard Cochrane methodology, only one review author performed data extraction and 'Risk of bias' and GRADE assessments for this rapid review. To minimise bias in these steps, at least one other review author verified the accuracy and (where applicable) the plausibility of extractions and assessment.

Although we have very limited confidence in the available evidence, we are not aware of any deficiencies in our review process. However, we are certain that the results are likely to be substantially different and conclusions may change as soon as high-certainty evidence becomes available.

Agreements and disagreements with other studies or reviews

This systematic review identified very low-certainty evidence on the safety and effectiveness of convalescent plasma for people with COVID-19.

A recent systematic review and meta-analysis found low-certainty evidence for the use of convalescent plasma for treating people with infections with different aetiologies (Mair-Jenkins 2015). The authors reported a systematic review and meta-analysis of the literature on the use of convalescent plasma and hyperimmune immunoglobulin in treating severe acute respiratory infections of viral aetiology, and found that this treatment is likely to be both safe and effective in preventing mortality. The study identified a 75% reduction in the odds of mortality in their exploratory post hoc meta-analysis across all viral aetiologies. The studies included in this review were performed with people treated with convalescent plasma for severe acute respiratory syndrome (SARS) and influenza. The limited number of identified studies and the low quality of included, mainly uncontrolled studies restricted the authors' ability to analyse extensively the risks and benefits of convalescent plasma therapy. Recommendations from the authors were to investigate the use of convalescent plasma and hyperimmune immunoglobulin in large, well-designed clinical trials or other formal evaluations to obtain better-certainty evidence, and to evaluate the optimal treatment regimen.

Results from several large RCTs on the use of convalescent plasma and hyperimmune immunoglobulin in treating severe influenza have recently been made public (Beigel 2017; Beigel 2019; Davey 2019; Hung 2013). However, the results from these studies are inconsistent, with some studies showing a beneficial effect of convalescent plasma for treating people with severe influenza, whereas other studies show no benefit. The studies were well designed and reported in detail the timing of the intervention and relevant outcomes. One trial reported effectiveness of hyperimmune immunoglobulin, but only in a post hoc analysis of a subgroup of participants treated within five days of symptom onset (Hung 2013). In a different trial, for the subgroup analysis of people with influenza B, the effect of hyperimmune immunoglobulin also resulted in a demonstrable clinical and virological benefit (Davey 2019). Different mechanisms in the human immune system and their role in responding to different circulating influenza strains might further explain why the results of clinical trials of convalescent plasma and hyperimmune immunoglobulin for influenza varied (Davey 2019). Influenza A immunity is reported to carry over to the next years, known as heterosubtypic immunity (Kreijtz 2011), and the current outbreak of COVID-19 can, in that sense, not be compared with seasonal influenza. Notwithstanding these dissimilarities which might explain why the aforementioned influenza studies were not successful in clearly demonstrating benefit, the possibility of a null effect of convalescent plasma over a suitable comparator cannot be ruled out with the currently available evidence on COVID-19.

The adverse events associated with plasma transfusions are well characterised. Critically ill patients receiving plasma transfusions have an especially high risk of transfusion-associated circulatory overload (TACO), which is the leading cause of transfusion-related mortality (Pandey 2012). Many countries have now introduced risk mitigation strategies to decrease the risk of transfusion-related acute lung injury (TRALI). In the UK in 2018 there was only one confirmed case of TRALI.

In this systematic review of the literature, which mainly identified studies that included people with COVID-19 with critical illness, we identified one potentially grade 3 adverse event and one potentially grade 4 adverse event (which also qualified as a serious adverse event). With the information available at this moment from published trials registry entries, it is apparent that the majority of clinical trials are enrolling people with COVID-19 who have progressed to moderate or severe disease. Despite there being some evidence from other infectious diseases that early therapy might be more effective (Mair-Jenkins 2015), targeting this population is justifiable given the evident lack of effective interventions for COVID-19. The population that is eligible for treatment in these trials with convalescent plasma is potentially at high risk of transfusion reactions, and when treating critically ill people with COVID-19, their status should be carefully monitored.

AUTHORS' CONCLUSIONS

Implications for practice

The currently available evidence on the safety and effectiveness of convalescent plasma and hyperimmune immunoglobulin for treatment of people with COVID-19 is of very low certainty. Thus, any conclusions that are drawn based on these data are of limited value and these conclusions are subject to change as more reliable results become available. For the primary outcomes, the included studies reported that all participants were alive at the end of follow-up. Clinical improvement assessed through the need for respiratory support was reported by most studies, but details on timing and type of respiratory support were not clear for all studies. Other outcomes that were reported in a subset of the included studies were length of stay on the intensive care unit (ICU) and time to discharge from hospital, but reporting of these outcomes was not complete. Two studies reported adverse events that were potentially grade 3 and grade 4, of which one was a serious adverse event. More thorough investigations, preferably well-designed clinical trials, are needed in order to assess the benefits and risks of convalescent plasma therapy for people with COVID-19.

Implications for research

In this systematic review of the literature, we identified seven case-series studies and one prospectively planned, single-arm intervention study. We encountered difficulties while extracting data from these studies because there were major differences in the way these studies reported participant characteristics, details on the intervention, and outcomes. Future publications could benefit from more standardised reporting, especially of timing of intervention and clinically relevant outcomes, like days until discharge from hospital and improvement of clinical symptoms. We support the adoption of a reporting guideline in this rapidly evolving field of research.

Randomised controlled trials (RCTs) or at least non-randomised trials with a control group are needed to confirm the findings of this review. As there are 47 ongoing studies evaluating convalescent plasma and one ongoing study evaluating hyperimmune immunoglobulin, of which 22 are randomised, we will screen search results monthly and publish updates as a living systematic review in

the near future. It might well be that this update will show different results than those published in this rapid review.

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REFERENCES

References to studies included in this review

Ahn 2020 *{published data only}*

Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. *Journal of Korean Medical Science* 2020; **35**(14):e149.

Duan 2020 *{published data only}*

* Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. In: National Academy of Sciences of the United States of America. Vol. 202004168. 2020. [DOI: 10.1073/pnas.2004168117]

Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. medRxiv 2020. [DOI: 101/2020.03.16.20036145]

Pei 2020 *{published data only}*

Pei S, Yuan X, Zhimin ZZ, Run YR, Xie Y, Minxue SM, et al. Convalescent plasma to treat COVID-19: Chinese strategy and experiences. medRxiv 2020. [DOI: 10.1101/2020.04.07.20056440]

Shen 2020 *{published data only}*

Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020. [DOI: 10.1001/jama.2020.4783]

Tan 2020 *{published data only}*

Tan L, Kang X, Zhang B, Zheng S, Liu B, Yu T, et al. A special case of COVID-19 with long duration of viral shedding for 49 days. medRxiv 2020. [DOI: 10.1101/2020.03.22.20040071]

Ye 2020 *{published data only}*

Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. Journal of Medical Virology 2020. [DOI: 10.1002/jmv.25882]

Zhang 2020a *{published data only}*

Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. Chest 2020 Mar 31 [Epub ahead of print]. [DOI: 10.1016/j.chest.2020.03.039]

Zhang 2020b *{published data only}*

Zhang L, Pang R, Xue X, Bao J, Ye S, Dai Y, et al. Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. Aging 2020 Apr 22 [Epub ahead of print];**12**. [DOI: 10.18632/aging.103102]

References to studies excluded from this review

Bloch 2020 *{published data only}*

Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. Journal of Clinical Investigation 2020. [DOI: 10.1172/JCI138745]

Cao 2020 *{published data only}*

Cao W, Liu X, Bai T, Fan H, Hong K, Song H, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infectious Diseases* 2020; **7**(3):ofaa102.

Casadevall 2020 *{published data only}*

Casadevall A, Pirofski L A. The convalescent sera option for containing COVID-19. *Journal of Clinical Investigation* 2020; **130**(4):1545-8.

Chen 2020 *{published data only}*

Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infectious Diseases* 2020; **27**:27.

ChiCTR2000030312 *{published data only}*

. Cancelled, due to modify the protocol A single-center, open-label and single arm trial to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment& [A single-center, open-label and single arm trial to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia (COVID-19) patient]. www.chictr.org.cn/showproj.aspx?proj=50258 (first received 23 April 2020).

ChiCTR2000030381 *{published data only}*

. Cancelled by investigator A randomized, open-label, controlled and single-center trial to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia (COVID-19) patient [A randomized, open-label, controlled and single-center trial to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia (COVID-19) patient]. www.chictr.org.cn/showproj.aspx?proj=50290 (first received 23 April 2020).

ChiCTR2000030442 *{published data only}*

. Combination of tocilizumab, IVIG and CRRT in severe patients with novel coronavirus pneumonia (COVID-19). www.chictr.org.cn/showproj.aspx?proj=50380 (first received 23 April 2020).

Díez 2020 *{published data only}*

Díez JM, Romero C, Gajardo R. Currently available intravenous immunoglobulin (Gamunex-C and Flebogamma© DIF) contains antibodies reacting against SARS-CoV-2 antigens. bioRxiv 2020. [DOI: 10.1101/2020.04.07.029017]

Hu 2020 *{published data only}*

Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *European Heart Journal* 2020; **16**:16.

Jawhara 2020 *{published data only}*

Jawhara S. Could intravenous immunoglobulin collected from recovered coronavirus patients protect against COVID-19 and strengthen the immune system of new patients? *International Journal of Molecular Sciences* 2020; **21**(7):2272. [DOI: 10.3390/ijms21072272]

NCT04261426 *{published data only}*

. The efficacy of intravenous immunoglobulin therapy for severe 2019-nCoV infected pneumonia. clinicaltrials.gov/ct2/show/NCT04261426 (first received 23 April 2020).

NCT04323800 *{published data only}*

. Convalescent plasma to stem coronavirus: a randomized, blinded phase 2 study comparing the efficacy and safety human coronavirus immune plasma (HCIP) vs. control (SARS-CoV-2 non-immune plasma) among adults exposed to COVID-19. clinicaltrials.gov/show/NCT04323800 (first received 23 April 2020).

NCT04325672 *{published data only}*

. Convalescent plasma to limit coronavirus associated complications: an open label, phase 2A study of high-titer anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19. clinicaltrials.gov/show/NCT04325672 (first received 23 April 2020).

NCT04344015 *{published data only}*

. COVID-19 plasma collection. ClinicalTrials.gov/show/NCT04344015 (first received 23 April 2020).

NCT04344977 *{published data only}*

. COVID-19 plasma collection. clinicaltrials.gov/ct2/show/NCT04344977 (first received 23 April 2020).

Roback 2020 *{published data only}*

Roback JD, Guarner J. Convalescent plasma to treat COVID-19: possibilities and challenges. JAMA 2020. [DOI: 10.1001/jama.2020.4940]

Shi 2020 *{published data only}*

Shi H, Zhou C, He P, Huang S, Duan Y, Wang X, et al. Successful treatment of plasma exchange followed by intravenous immunoglobulin in a critically ill patient with 2019 novel coronavirus infection. International Journal of Antimicrobial Agents 2020:105974.

Syal 2020 *{published data only}*

Syal K. COVID-19: herd immunity and convalescent plasma transfer therapy. *Journal of Medical Virology* 2020; **13**:13.

Tanne 2020 *{published data only}*

Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. *BMJ* 2020; **368**:m1256.

Tiberghien 2020 *{published data only}*

Tiberghien P, de Lambalerie X, Morel P, Gallian P, Lacombe K, Yazdanpanah Y. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how. Vox Sanguinis 2020. [DOI: 10.1111/vox.12926]

Wong 2020 *{published data only}*

Wong HK, Lee CK. Pivotal role of convalescent plasma in managing emerging infectious diseases. Vox Sanguinis 2020. [DOI: 10.1111/vox.12927]

Xie 2020 *{published data only}*

Xie Y, Cao S, Li Q, Chen E, Dong H, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. Journal of Infection 2020:S0163-4453(20)30172-9.

Yoo 2020 *{published data only}*

Yoo JH. Convalescent plasma therapy for corona virus disease 2019: a long way to go but worth trying. *Journal of Korean Medical Science* 2020; **35**(14):e150.

Zhao 2020b *{published data only}*

Zhao Q, He Y. Challenges of convalescent plasma therapy on COVID-19. *Journal of Clinical Virology* 2020; **127**:104358.

References to studies awaiting assessment

Qiu 2020 *{published data only}*

Qiu T, Wang J, Zhou J, Zou J, Chen Z, Ma X, et al. The report of two cases infection with novel coronavirus (2019-ncov) after kidney transplantation and the association literature analyzation. *Chinese Journal of Organ Transplantation* 2020; **41**(0):E004.

Tu 2020 *{published data only}*

Tu Y, Wu X, Liu F, Wang J, Luo Y, Cai Z, et al. Two clinical cases of novel coronavirus pneumonia (NCP) in renal transplant recipients. *Chinese Journal of Organ Transplantation* 2020; **41**(0):E005.

References to ongoing studies

ChiCTR2000029757 *{published data only}*

. Convalescent plasma for the treatment of severe and critical novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial. www.chictr.org.cn/showproj.aspx?proj=49081 (first received 12 February 2020).

ChiCTR2000029850 *{published data only}*

. Effecacy and safety of convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19): a prospective cohort study. www.chictr.org.cn/showproj.aspx?proj=49533 (first received 15 February 2020).

ChiCTR2000030010 *{published data only}*

. A randomized, double-blind, parallel-controlled, trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19). www.chictr.org.cn/showproj.aspx?proj=49777 (first received 19 February 2020).

ChiCTR2000030039 *{published data only}*

. Clinical study for infusing convalescent plasma to treat patients with new coronavirus pneumonia (COVID-19). www.chictr.org.cn/showproj.aspx?proj=49544 (first received 21 February 2020).

ChiCTR2000030179 *{published data only}*

. Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus

pneumonia (COVID-19). www.chictr.org.cn/showproj.aspx?proj=50059 (first received 24 February 2020).

ChiCTR2000030627 *{published data only}*

. Study on the application of convalescent plasma therapy in severe COVID-19. www.chictr.org.cn/showproj.aspx?proj=50727 (first received 8 March 2020).

ChiCTR2000030702 *{published data only}*

. Convalescent plasma for the treatment of common COVID-19: a prospective randomized controlled trial. www.chictr.org.cn/showproj.aspx?proj=50537 (first received 10 March 2020).

ChiCTR2000030841 *{published data only}*

. Treatment of acute severe COVID-19 with immunoglobulin from cured COVID-19 patients. www.chictr.org.cn/showproj.aspx?proj=51072 (first received 15 March 2020).

ChiCTR2000030929 *{published data only}*

. A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia (COVID-19). www.chictr.org.cn/showproj.aspx?proj=50696 (first received 17 March 2020).

ChiCTR2000031501 *{published data only}*

. The efficacy of convalescent plasma in patients with critical novel coronavirus pneumonia (COVID-19): a pragmatic, prospective cohort study. www.chictr.org.cn/showproj.aspx?proj=50254 (first received 2 April 2020).

EUCTR2020-001310-38 *{published data only}*

. A randomized, prospective, open label clinical trial on the use of convalescent plasma compared to best supportive care in patients with severe COVID-19. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001310-38 (first received 23 April 2020).

IRCT20151228025732N53 *{published data only}*

. Therapeutic effects of plasma of recovered people from COVID-19 on hospitalized patients with this disease. en.irct.ir/trial/46931 (first received 10 April 2020).

IRCT20200310046736N1 *{published data only}*

. Comparison of the therapeutic effect of convalescent plasma and plasma-derived immunoglobulin-enriched solution on COVID-19 patients. en.irct.ir/trial/46424 (first received 1 April 2020).

IRCT20200325046860N1 *{published data only}*

. Convalescent plasma therapy for COVID-19 patients. en.irct.ir/trial/46759 (first received 30 March 2020).

IRCT20200404046948N1 *{published data only}*

. Efficacy and safety of convalescent plasma in the treatment of COVID-19. en.irct.ir/trial/46973 (first received 15 April 2020).

IRCT20200409047007N1 *{published data only}*

. Effect of COVID 19 survivors plasma in COVID 19 patients with ARDS. en.irct.ir/trial/47058 (first received 12 April 2020).

IRCT20200413047056N1 *{published data only}*

. Comparison between the efficacy of intravenous immunoglobulin and convalescent plasma in COVID-19. en.irct.ir/trial/47212 (first received 17 April 2020).

NCT04264858 *{published data only}*

. An exploratory clinical study on the treatment of acute severe 2019-nCoV pneumonia with immunoglobulin from cured 2019-nCoV pneumonia patients. clinicaltrials.gov/show/NCT04264858 (first received 11 February 2020).

NCT04292340 *{published data only}*

. The efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia patient (COVID-19): an observational study. clinicaltrials.gov/show/NCT04292340 (first received 3 March 2020).

NCT04321421 *{published data only}*

. Plasma from donors recovered from new coronavirus 2019 as therapy for critical patients with COVID-19. clinicaltrials.gov/show/NCT04321421 (first received 25 March 2020).

NCT04327349 *{published data only}*

. Investigating effect of convalescent plasma on COVID-19 patients outcome: a clinical trial. clinicaltrials.gov/show/NCT04327349 (first received 31 March 2020).

NCT04332380 *{published data only}*

. Convalescent plasma for patients with COVID-19: a pilot study. clinicaltrials.gov/show/NCT04332380 (first received 2 April 2020).

NCT04332835 *{published data only}*

. Convalescent plasma for patients with COVID-19: a randomized, open label, parallel, controlled clinical study. clinicaltrials.gov/show/NCT04332835 (first received 3 April 2020).

NCT04333251 *{published data only}*

. Evaluating convalescent plasma to decrease coronavirus associated complications. A phase I study comparing the efficacy and safety of high-titer anti-Sars-CoV-2 plasma vs best supportive care in hospitalized patients with interstitial pneumonia due to COVID-19. clinicaltrials.gov/show/NCT04333251 (first received 3 April 2020).

NCT04333355 *{published data only}*

. Phase 1 study to evaluate the safety of convalescent plasma as an adjuvant therapy in patients with SARS-CoV-2 infection. clinicaltrials.gov/show/NCT04333355 (first received 3 April 2020).

NCT04338360 *{published data only}*

. Expanded access to convalescent plasma for the treatment of patients with COVID-19. ClinicalTrials.gov/show/NCT04338360 (first received 8 April 2020).

NCT04340050 *{published data only}*

. COVID-19 convalescent plasma. ClinicalTrials.gov/show/NCT04340050 (first received 9 April 2020).

NCT04342182 *{published data only}*

. Convalescent plasma as therapy for Covid-19 severe SARS-CoV-2 disease (CONCOVID Study) (ConCoVid-19). ClinicalTrials.gov/show/NCT04342182 (first received 10 April 2020).

NCT04343261 *{published data only}*

. Convalescent plasma in the treatment of COVID 19. ClinicalTrials.gov/show/NCT04343261 (first received 13 April 2020).

NCT04343755 *{published data only}*

. Convalescent plasma as treatment for hospitalized subjects with COVID-19 infection. ClinicalTrials.gov/show/NCT04343755 (first received 13 April 2020).

NCT04344535 *{published data only}*

. Convalescent plasma vs. standard plasma for COVID-19. ClinicalTrials.gov/show/NCT04344535 (first received 14 April 2020).

NCT04345289 *{published data only}*

. Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia. apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2020-001367-88-DK (first received 14 April 2020).

. Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia (CCAP). ClinicalTrials.gov/show/NCT04345289 (first received 14 April 2020).

NCT04345523 *{published data only}*

. Convalescent plasma therapy vs. SOC for the treatment of COVID19 in hospitalized patients (ConPlas-19). ClinicalTrials.gov/show/NCT04345523 (first received 14 April 2020).

NCT04345679 *{published data only}*

. Anti COVID-19 convalescent plasma therapy. ClinicalTrials.gov/show/NCT04345679 (first received 14 April 2020).

NCT04345991 *{published data only}*

. Efficacy of convalescent plasma to treat COVID-19 patients, a nested trial in the CORIMUNO-19 cohort. ClinicalTrials.gov/show/NCT04345991 (first received 15 April 2020).

NCT04346446 *{published data only}*

. Efficacy of convalescent plasma therapy in severely sick COVID-19 patients. ClinicalTrials.gov/show/NCT04346446 (first received 15 April 2020).

NCT04346589 *{published data only}*

. Convalescent antibodies infusion in critically ill COVID 19 patients. clinicaltrials.gov/ct2/show/NCT04346589 (first received 15 April 2020).

NCT04347681 *{published data only}*

. Potential efficacy of convalescent plasma to treat severe COVID-19 and patients at high risk of developing severe COVID-19. ClinicalTrials.gov/show/NCT04347681 (first received 15 April 2020).

NCT04348656 *{published data only}*

. Convalescent plasma for hospitalized adults with COVID-19 respiratory illness (CONCOR-1). ClinicalTrials.gov/show/NCT04348656 (first received 16 April 2020).

NCT04348877 *{published data only}*

. Plasma rich antibodies from recovered patients from COVID19. ClinicalTrials.gov/show/NCT04348877 (first received 16 April 2020).

NCT04352751 *{published data only}*

. Experimental use of convalescent plasma for passive immunization in current COVID-19 pandemic in Pakistan in 2020. ClinicalTrials.gov/show/NCT04352751 (first received 20 April 2020).

NCT04353206 *{published data only}*

. Convalescent plasma in ICU patients with COVID-19-induced respiratory failure. ClinicalTrials.gov/show/NCT04353206 (first received 20 April 2020).

NCT04354831 *{published data only}*

. A study evaluating the efficacy and safety of high-titer anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 infection. clinicaltrials.gov/ct2/show/NCT04354831 (first received 21 April 2020).

NCT04355767 *{published data only}*

. Convalescent plasma vs. placebo in emergency room patients with COVID-19. clinicaltrials.gov/ct2/show/NCT04355767 (first received 21 April 2020).

NCT04355897 *{published data only}*

. CoVID-19 plasma in treatment of COVID-19 patients. clinicaltrials.gov/ct2/show/NCT04355897 (first received 21 April 2020).

NCT04356482 *{published data only}*

. Convalescent plasma for ill patients by COVID-19. ClinicalTrials.gov/show/NCT04356482 (first received 22 April 2020).

NCT04356534 *{published data only}*

. Convalescent plasma trial in COVID -19 patients. ClinicalTrials.gov/show/NCT04356534 (first received 22 April 2020).

NCT04357106 *{published data only}*

. COPLA study: treatment of severe forms of coronavirus infection with convalescent plasma. ClinicalTrials.gov/show/NCT04357106 (first received 22 April 2020).

Additional references

Bao 2020

Bao L, Deng W, Gao H, Xiao C, Liu J, Xue J, et al. Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. bioRxiv (accessed 13 April 2020). [DOI: 10.1101/2020.03.13.990226]

Baudel 2020

Baudel JL, Vigneron C, Pras-Landre V, Joffre J, Marjot F, Ait-Oufella H, et al. Transfusion-related acute lung injury (TRALI) after intravenous immunoglobulins: French multicentre study and literature review. *Clinical Rheumatology* 2020; **39**(2):541-6.

Beigel 2017

Beigel JH, Tebas P, Elie-Turenne MC, Bajwa E, Bell TE, Cairns B, et al. Immune plasma for the treatment of severe influenza: an open-label, multicentre, phase 2 randomised study. *Lancet Respiratory Medicine* 2017; **5**(6):500-11. [DOI: 10.1016/S2213-2600(17)30174-1]

Beigel 2019

Beigel JH, Aga E, , Cho J, Tebas P, Clark CL, et al. Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial. *Lancet Respiratory Medicine* 2019; **7**(11):941-50. [DOI: 10.1016/S2213-2600(19)30199-7]

Brennan 2003

Brennan VM, Salomé-Bentley NJ, Chapel HM, Immunology Nurses Study. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. *Clinical and Experimental Immunology* 2003; **133**(2):247-51.

CDC 2020a

Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19). www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html (accessed 13 April 2020).

CDC 2020b

Centers for Disease Control and Prevention (CDC). Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html (last accessed 26 April 2020).

Chun 2016

Chun S, Chung CR, Ha YE, Han TH, Ki CS, Kang ES, . Possible transfusion-related acute lung injury following convalescent plasma transfusion in a patient with Middle East respiratory syndrome. *Annals of Laboratory Medicine* 2016; **36**(4):393-5. [DOI: 10.3343/alm.2016.36.4.393]

COMET 2020

Core outcome set developers' response to COVID-19 (2nd April 2020). www.comet-initiative.org/Studies/Details/1538 (accessed 9 April 2020).

Covidence [Computer program]

Veritas Health Innovation Covidence. Version accessed 20 April 2020. Melbourne, Australia: Veritas Health Innovation.Available at covidence.org.

Davey 2019

, Fernández-Cruz E, Markowitz N, Pett S, Babiker AG, Wentworth D, et al. Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial. *Lancet Respiratory Medicine* 2019; **7**(11):951-63. [DOI: 10.1016/S2213-2600(19)30253-X]

Deeks 2019

Deeks JJ, Higgins JP, Altman DG, . Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Driggin 2020

Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *Journal of the American College of Cardiology* 2020; **75**(18):2352-71.

Eibl 2008

Eibl MM. History of immunoglobulin replacement. *Immunology and Allergy Clinics of North America* 2008; **28**(4):737-64. [DOI: 10.1016/j.iac.2008.06.004]

EPOC 2017

. What study designs can be considered for inclusion in an EPOC review and what should they be called? EPOC Resources for review authors. Available from epoc.cochrane.org/resources/epoc-resources-review-authors (accessed 23 April 2019).

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 20 April 2020. Hamilton (ON): McMaster University (developed by Evidence Prime).Available at gradepro.org.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**:557-60.

Higgins 2019a

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, . Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Higgins 2019b

Higgins JP, Deeks JJ, . Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Ho 2005

Ho MS, Chen WJ, Chen HY, Lin SF, Wang MC, Di J, et al. Neutralizing antibody response and SARS severity. *Emerging Infectious Diseases* 2005; **11**(11):1730-7.

Huang 2020

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan,

China. *Lancet* 2020; **395**(10223):497-506. [DOI: 10.1016/S0140-6736(20)30183-5]

Hung 2013

Hung IF, To KK, Lee CK, Lee KL, Yan WW, Chan K, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest* 2013; **144**(2):464-73. [DOI: 10.1378/chest.12-2907]

Kim 2020

, Choe YJ, . Understanding and interpretation of case fatality rate of coronavirus disease 2019. *Journal of Korean Medical Science* 2020; **35**(12):e137. [DOI: 10.3346/jkms.2020.35.e137]

Kreijtz 2011

Kreijtz JH, Fouchier RA, Rimmelzwaan GF. Immune responses to influenza virus infection. *Virus Research* 2011; **162**(1-2):19-30. [DOI: 10.1016/j.virusres.2011.09.022]

Lauer 2020

Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Annals of Internal Medicine 2020. [DOI: 10.7326/M20-0504]

Lefebvre 2019

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Li 2019

Li T, Higgins JP, Deeks JJ, . Chapter 5: Collecting data. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Liang 2020

Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncology* 2020; **21**(3):335-7. [DOI: 10.1016/S1470-2045(20)30096-6]

Luke 2006

Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Annals of Internal Medicine* 2006; **145**(8):599-609.

Mair-Jenkins 2015

Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *Journal of Infectious Diseases* 2015; **211**(1):80-90. [DOI: 10.1093/infdis/jiu396]

Microsoft Corporation 2018 [Computer program]

Microsoft Corporation, available at: office.microsoft.com/excel Mircosoft Excel. . Microsoft Corporation, available at: office.microsoft.com/excel, 2018.

Mo 2006

Mo H, Zeng G, Ren X, Li H, Ke C, Tan Y, et al. Longitudinal profile of antibodies against SARS-coronavirus in SARS patients and their clinical significance. *Respirology* 2006; **11**(1):49-53. [DOI: 10.1111/j.1440-1843.2006.00783.x]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009; **62**(10):1006-12.

Morens 1994

Morens DM. Antibody-dependent enhancement of infection and the pathogenesis of viral disease. *Clinical Infectious Diseases* 1994; **19**(3):500-12.

Mulder 2019

Mulder RL, Bresters D, Van den Hof M, Koot BG, Castellino SM, Loke YK, et al. Hepatic late adverse effects after antineoplastic treatment for childhood cancer. *Cochrane Database of Systematic Reviews* 2019, Issue 4. [DOI: 10.1002/14651858.CD008205.pub3]

Otrock 2017

Otrock ZK, Liu C, Grossman BJ. Transfusion-related acute lung injury risk mitigation: an update. *Vox Sanguinis* 2017; **112**(8):694-703.

Pandey 2012

Pandey S, Vyas GN. Adverse effects of plasma transfusion. *Transfusion* 2012; **52 Suppl 1**:65S-79S.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998; **17**(24):2815-34.

Payne 2016

Payne DC, Iblan I, Rha B, Algasrawi S, Hin A, Al Nsour M, et al. Persistence of antibodies against Middle East respiratory syndrome coronavirus. *Emerging Infectious Disease Journal* 2016; **22**(10):1824-6. [DOI: 10.3201/eid2210.160706]

Reeves 2019

Reeves BC, Deeks JJ, Higgins JP, Shea B, Tugwell P, Wells GA. Chapter 24: Including non-randomized studies on intervention effects. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions *V*ersion 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Review Manager Web [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). The Cochrane Collaboration, 2019.Available from revman.cochrane.org.

Ricke 2020

Ricke D, Malone R. Medical countermeasures analysis of 2019-nCoV and vaccine risks for antibody-dependent enhancement (ADE). www.preprints.org/manuscript/202003.0138/v1 2020; **2020030138**. [DOI: 10.20944/preprints202003.0138.v1]

Robbins 1995

Robbins JB, Schneerson R, Szu SC. Perspective: hypothesis: serum IgG antibody is sufficient to confer protection against infectious diseases by inactivating the inoculum. *Journal of Infectious Diseases* 1995; **171**(6):1387-98.

Rock 2011

Rock G. A comparison of methods of pathogen inactivation of FFP. *Vox Sanguinis* 2011; **100**(2):169-78.

Schünemann 2019

Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s) Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Sekul 1994

Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Annals of Internal Medicine* 1994; **121**(4):259-62.

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**:i4919.

Sterne 2019

Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**:l4898.

Stiehm 2013

Stiehm ER. Adverse effects of human immunoglobulin therapy. *Transfusion Medicine Reviews* 2013; **27**(3):171-8.

Team 2020

Team NCPERE . Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China. China CDC Weekly 2020; **2**(8):113-22. [DOI: 10.3760/cma.j.issn.0254-6450.2020.02.003]

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; **8**:16.

Tolouian 2020

Tolouian R, Vahed SZ, Ghiyasvand S, Tolouian A, Ardalan M. COVID-19 interactions with angiotensin-converting enzyme 2 (ACE2) and the kinin system; looking at a potential treatment. *Journal of Renal Injury Prevention* 2020; **9**(2):e19. [DOI: 10.34172/jrip.2020.19]

Van de Veerdonk 2020

Van de Veerdonk F, Netea MG, Van Deuren M, Van der Meer JW, De Mast Q, Bruggemann RJ, et al. Kinins and cytokines in COVID-19: a comprehensive pathophysiological approach. *Preprints 2020* (accessed 13 April 2020);**2020040023**. [DOI: 10.20944/preprints202004.0023.v1]

Wan 2020

Wan Y, Shang J, Sun S, Tai W, Chen J, Geng Q, et al. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *Journal of Virology* 2020; **94**(5):e02015-19.

Wang 2014

, , , , , , et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. *Biochemical and Biophysical Research Communications* 2014; **451**(2):208-14.

WHO 2007

World Health Organization (WHO). Cumulative number of reported probable cases of SARS. www.who.int/csr/sars/country/2003_07_11/en/ (accessed 13 April 2020).

WHO 2019

World Health Organization (WHO). Middle East respiratory syndrome coronavirus (MERS-CoV). www.who.int/emergencies/mers-cov/en/ (accessed 13 April 2020).

WHO 2020a

World Health Organization (WHO). Report of the WHO-China Joint Mission on coronavirus disease 2019 (COVID-19); February 2020. Available at www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.

WHO 2020b

World Health Organization (WHO). Rolling updates on coronavirus diseases (COVID-19). www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen (accessed 13 April 2020).

WHO 2020c

World Health Organization (WHO). Coronavirus disease (COVID-2019) situation report-105; 4 May 2020. Available at www.who.int/docs/default-source/coronaviruse/situation-reports/20200504-covid-19-sitrep-105.pdf.

WHO 2020d

World Health Organization (WHO). Clinical management of severe acute respiratory infection (SARI) when COVID19 disease is suspected: interim guidance. World Health Organization 2020; **WHO/2019-nCoV/clinical/2020.4**.

Wu 2020a

Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and

death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Internal Medicine 2020. [DOI: 10.1001/jamainternmed.2020.0994]

Wu 2020b

Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv (accessed 13 April 2020). [DOI: 110.1101/2020.03.30.2004736]

Xu 2020

Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respiratory Medicine* 2020; **8**(4):420-2. [DOI: 10.1016/S2213-2600(20)30076-X]

Zhao 2020

Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. medRxiv 2020. [DOI: 10.1101/2020.03.02.20030189]

References to other published versions of this review

Piechotta 2020

Piechotta V, Valk SJ, Chai KL, Wood EM, Lamikanra A, Kimber C, et al. Safety and effectiveness of convalescent plasma or hyperimmune globulin for people with COVID-19: a rapid review. available at: doi.org/10.17605/OSF.IO/DWF53.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahn 2020

Study characteristics	
Methods	• Trial design: case series • Type of publication: journal publication • Setting and dates: ICU, 22 February 2020-29 March 2020 • Country: South Korea • Language: English • Number of centres: 1 • Inclusion/exclusion criteria: NR • Trial registration number: NR
Participants	• Age: 67 and 71 • Gender: 1 male, 1 female • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 2 • Severity of disease: critical • Additional diagnoses: case 2: medical history of hypertension • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): 400 mg of hydroxychloroquine once daily and lopinavir/ritonavir 400 mg/100 mg twice daily, empirical antibiotics, 4 L/min oxygen flow via nasal cannula, high-flow oxygen therapy

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: apheresis plasma, apheresis performed with Spectra Optia apheresis system (CM-NC software; Spectra Optia IDL Tubing set; Terumo BCT, Lakewood, CO, USA)
	  * volume: 500 mL total
	  * number of doses: 2
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): administered 7 (case 2) and 22 (case 1) days after admission
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: 400 mg of hydroxychloroquine once daily and lopinavir/ritonavir 400 mg/100 mg twice daily, empirical antibiotics, intubation and mechanical ventilator care, IV methylpred-

Ahn 2020 *(Continued)*

	nisolone (0.5/1 mg/kg/day daily). Unclear whether these treatments were stopped before plasma transfusion or continuously given • Duration of follow-up: up to 26 days • Treatment cross-overs: not applicable • Compliance with assigned treatment: good (all compliant)
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge: reported * Time to death: not applicable • Secondary outcomes * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): reported * Number of participants with SAEs: reported * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported * 30-day and 90-day mortality: not applicable * Admission on the ICU: reported * Length of stay on the ICU: reported * Time to discharge from hospital: reported • Additional outcomes: SARS-CoV-2 RNA by rRT-PCR, IL-6 and CRP, white blood cell count, lymphocyte count, arterial blood gas analysis (PaO2/FiO2), chest X-ray, improvement of clinical symptoms
Notes	• Sponsor/funding: funding for this research was provided by: Ministry of Health and Welfare (HI14C1324), Korea HIV/AIDS Cohort Study (2019-ER5101-00) • COIs: the authors have no potential conflicts of interest to disclose • Other: "this study was approved by the IRB of Severance Hospital (IRB No. 4-2020-0076) and with participants' written informed consent. The images are published under agreement of the patients."

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	2 participants only
Outcome detectors blinded to intervention (detection bias) Objective outcomes (e.g. mortality)	Low risk	Not blinded, but awareness of intervention cannot bias assessment of objective outcomes
Outcome detectors blinded to intervention (detection bias) Subjective outcomes	High risk	Not blinded, awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow up (attrition bias) Mortality	Unclear risk	Both cases of SARS-CoV-2 negative at the time of publication, case 1 still hospitalised
Complete outcome assessment/follow up (attrition bias) Adverse events	Low risk	Assessed and reported for both cases

Ahn 2020 *(Continued)*

Complete outcome assessment/follow up (attrition bias) Clinical improvement	Low risk	Assessed and reported for both cases
Well-defined study group (reporting bias)	Low risk	Population and intervention are well described
Well-defined outcome (reporting bias) Mortality	Low risk	Both cases of SARS-CoV-2 negative at the time of publication, case 1 still hospitalised
Well-defined outcome (reporting bias) Adverse events	High risk	No adverse reaction occurred after the administration of CP in both cases. Observation period NR
Well-defined outcome (reporting bias) Clinical improvement	Unclear risk	Improvement of symptoms described until the time of publication, case 1 still hospitalised
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Not adjusted for confounding factors

Duan 2020

Study characteristics	
Methods	• Trial design: prospective single-arm pilot study • Type of publication: journal publication • Setting and dates: inpatient, 23 January 2020-19 February 2020 • Country: China • Language: English • Number of centres: 3 • Inclusion/exclusion criteria: inclusion criteria: one of the conditions 2-4 plus condition 1: 1) age ≥ 18 years; 2) respiratory distress, respiratory rate ≥ 30 breaths/min; 3) oxygen saturation level < 93% in resting state; and 4) partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤ 300 mmHg (1 mmHg = 0.133 kPa). Exclusion criteria: 1) previous allergic history to plasma or ingredients (sodium citrate); 2) cases with serious general conditions, such as severe organ dysfunction, who were not suitable for CP transfusion • Trial registration number: ChiCTR2000030046

Participants	• Age: median age 52.5 years (IQR 45.0-59.5 years)
	• Gender: 6 male, 4 female
	• Ethnicity: NR
	• Number of participants (recruited/allocated/evaluated): 10
	• Severity of disease: critical
	• Additional diagnoses: cardiovascular and/or cerebrovascular diseases and essential hypertension
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation):
	  * oxygen support (9/10 before CP therapy, 8/10 after CP therapy): mechanical ventilation, high-flow nasal cannula oxygenation, conventional low-flow nasal cannula oxygenation
	  * antiviral treatments (10/10): arbidol 0.2 g every 8 h) by mouth, monotherapy or combination therapy with remdesivir 0.2 g per day IV or ribavirin 0.5 g per day IV or peramivir 0.3 g per day IV, or

Duan 2020 *(Continued)*

	ribavirin 0.5 g per day IV monotherapy, IFN-α 500 MIU per day inhalation, oseltamivir 75 mg every 12 h by mouth, peramivir 0.3 g per day IV * antibacterial or antifungal treatment (8/10): when participants had coinfection, * corticosteroids 6/10): IV methylprednisolone (20 mg every 24 h)
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP: * Type of plasma: apheresis plasma. Apheresis was performed using a Baxter CS 300 cell separator (Baxter). Convalescent plasma for treatment was collected from 40 donors. The median age was 42.0 years (IQR, 32.5-49 years). A 200- to 400-mL ABO-compatible plasma sample was harvested from each donor depending on age and body weight, and each sample was divided and stored as 200-mL aliquots at 4 °C without any detergent or heat treatment. The CP was then treated with methylene blue and light treatment for 30 min in the medical plasma virus inactivation cabinet (Shandong Zhongbaokang Medical Appliance Co, Ltd) * Volume: 200 mL * number of doses: 1 * Antibody-titre: > 1:640 * Pathogen inactivated or not: methylene blue photochemistry • Treatment details, including time of plasma therapy (e.g. early stage of disease): administered between 10 and 20 days after admission (median: 16.5 days) • For studies including a control group: comparator (type): historic control, matched by age, gender and severity of disease • Concomitant therapy: mechanical ventilation, high-flow nasal cannula oxygenation, conventional low-flow nasal cannula oxygenation, arbidol 0.2 g every 8 h by mouth, monotherapy or combination therapy with remdesivir 0.2 g per day IV or ribavirin 0.5 g per day IV or peramivir 0.3 g per day IV, or ribavirin 0.5 g per day IV monotherapy, IFN-α 500 MIU per day inhalation, oseltamivir 75 mg every 12 h by mouth, peramivir 0.3 g per day IV, antibacterial or antifungal treatment when participants had coinfection, IV methylprednisolone (20 mg every 24 h) • Duration of follow-up: NR • Treatment cross-overs: not applicable • Compliance with assigned treatment: good (all compliant)
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge: NR * Time to death: NR • Secondary outcomes * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): only CP transfusion-related AEs reported (evanescent facial red spot) * Number of participants with SAEs: reported, none occurred * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported; up to day 4 * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR • Additional outcomes: lymphocyte count, CRP, alanine aminotransferase, aspartate aminotransferase, total bilirubin, SaO_2, clinical symptoms improvement, clinical outcome, defined as: death, stable, improved, discharged, neutralising antibody titres, SARS-CoV-2 RNA by RT-PCR, reduction of pulmonary lesions on chest CT
Notes	• Sponsor/funding: This study was funded by Key projects of the Ministry of Science and Technology China 'Preparation of specific plasma and specific globulin from patients with a recovery period of COVID-19 infection' (Project 2020YFC0841800). This work was also supported by Shanghai Guangci Translational Medicine Development Foundation. We thank all patients and donors involved in this study.

Duan 2020 *(Continued)*

- COIs: study authors declare no competing interests
- Other: "written informed consent according to the Declaration of Helsinki was obtained from each patient or legal relatives. This study was approved by the Ethics Committee of the China National Biotec Group Co., Ltd. (Approval number 2020-0001)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	10 participants only
Outcome detectors blinded to intervention (detection bias) Objective outcomes (e.g. mortality)	Low risk	Not blinded, but awareness of intervention cannot bias assessment of objective outcomes
Outcome detectors blinded to intervention (detection bias) Subjective outcomes	High risk	Not blinded, awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow up (attrition bias) Mortality	Unclear risk	Unclear whether all participants free of disease and discharged
Complete outcome assessment/follow up (attrition bias) Adverse events	Low risk	Assessed for all participants over study period
Complete outcome assessment/follow up (attrition bias) Clinical improvement	Low risk	Assessed for all participants over study period
Well-defined study group (reporting bias)	Low risk	Study population and intervention is well described
Well-defined outcome (reporting bias) Mortality	High risk	Follow-up not described
Well-defined outcome (reporting bias) Adverse events	High risk	Follow-up not described
Well-defined outcome (reporting bias) Clinical improvement	Low risk	Clinical improvement described for all participants until day 4 post-transfusion
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Not adjusted for confounding factors

Pei 2020

Study characteristics	

Methods	• Trial design: case series
	• Type of publication: preprint, supplementary material missing
	• Setting and dates: NR
	• Country: China
	• Language: English
	• Number of centres: 1
	• Inclusion/exclusion criteria:
	  * Inclusion criteria: severely and critically ill COVID-19 patients, and patients suffering advanced stages of the disease. Duration of the disease is within 3 weeks, novel coronavirus virus nucleic acid test is positive with viraemia. Severely and critically ill COVID-19 patients assessed by clinicians. Patients with long-term (> 4 weeks) positive novel coronavirus nucleic acid test
	  * Exclusion criteria: congenital IgA deficiency. A history of allergy including plasma infusion, human plasma protein products, sodium citrate. Plasma inactivated by methylene blue virus is strictly prohibited in patients with methylene blue allergy. Other history of severe allergies and contraindications. At the end of critical illness with irreversible multiple organ failure. Other conditions that are not suitable for infusion assessed by clinicians.
	• Trial registration number: NR

Participants	(Preprint only, participant characteristics will be described in the supplementary material; not accessible yet) • Age: NR • Gender: NR • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 3 • Severity of disease: moderate to critical • Additional diagnoses: NR • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: apheresis plasma. Fully automatic apheresis machine or a fully automatic blood cell separator (refer to technical operation procedures of blood station). Volume: 200-400 mL (the exact volume should be assessed by clinicians). The interval between plasma collection should be > 2 weeks. Storage: it is made available under a CC-BY-NC 4.0 International license. Follow the principle of sterility, repackaging the plasma 100-200 mL each. Store at 2-6 °C for 48 h. For long-term storage, it should be rapidly frozen to − 20 °C. Packaging: labelling requirements - refer to technical operation procedures of blood station.
	  * volume: according to the clinical status and the participant's weight. Usually the infusion dose is 200-500 mL (4-5 mL/kg).
	  * number of doses: according to the clinical status and the participant's weight. Usually the infusion dose is 200-500 mL (4-5 mL/kg).
	  * Antibody-titre: > 1:160
	  * Pathogen inactivated or not: NR
	  * Donor characteristics: > 3 weeks after the onset of symptoms of COVID-19 and complete resolution of symptoms at least 14 days prior to donation; age: 18-55 years old; weight: male ≥ 50 kg, female ≥ 45 kg; no history of blood-transmitted diseases; assessed by clinicians
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): administered between 12 and 27 days after admission
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: NR

Pei 2020 *(Continued)*

- Duration of follow-up: up to 36 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: moderate (2/3 compliant, 1 participant received 30 mL of CP and experienced an AE)

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: reported
	  * Time to death: not applicable
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: reported
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  * 30-day and 90-day mortality: not applicable
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: reported
	• Additional outcomes: SARS-CoV-2 nucleic acid test

Notes	• Sponsor/funding: no funding received • COIs: all study authors declare no competing interests • Other: "the participants gave their written informed consent and approved by the hospital ethics committee. All relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript. Yes. All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived. Yes. I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance). Yes. I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable. Yes"

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	3 participants only
Outcome detectors blinded to intervention (detection bias) Objective outcomes (e.g. mortality)	Low risk	Not blinded, but awareness of intervention cannot bias assessment of objective outcomes
Outcome detectors blinded to intervention (detection bias) Subjective outcomes	High risk	Not blinded, awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow up (attrition bias) Mortality	Low risk	Assessed for all participants until hospital discharge

Pei 2020 *(Continued)*

Complete outcome assessment/follow up (attrition bias) Adverse events	Unclear risk	SAE reported for 1 participant, not reported whether other participants experienced any AEs
Complete outcome assessment/follow up (attrition bias) Clinical improvement	Unclear risk	Course of disease after convalescent plasma transfusion not reported
Well-defined study group (reporting bias)	High risk	Study population and intervention insufficiently described
Well-defined outcome (reporting bias) Mortality	Low risk	Followed until hospital discharge
Well-defined outcome (reporting bias) Adverse events	High risk	Observation period not described
Well-defined outcome (reporting bias) Clinical improvement	Unclear risk	Course of disease after convalescent plasma transfusion not reported
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Comorbidities and disease presentation and course not clearly reported; not adjusted for confounding factors

Shen 2020

Study characteristics	
Methods	• Trial design: case series • Type of publication: preliminary communication in JAMA • Setting and dates: 20 January 2020-25 March 2020 • Country: China • Language: English • Number of centres: 1 • Inclusion/exclusion criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; PAO2/FIO2 < 300; and mechanical ventilation • Trial registration number: NR
Participants	• Age: 36-65 years • Gender: 3 male, 2 female • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 5 • Severity of disease: critical • Comorbidities: hypertension, mitral insufficiency (1 participant), none in 4 participants • Additional diagnoses: bacterial pneumonia; fungal pneumonia; severe ARDS; myocardial damage, MODS

Shen 2020 *(Continued)*

- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antiviral therapy (including lopinavir/ritonavir; interferon alfa-1b; favipiravir, arbidol; darunavir), corticosteroids (methylprednisolone), mechanical ventilation

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: CP prepared from 5 donors aged 18-60 years by apheresis. All donors had been previously diagnosed with laboratory-confirmed COVID-19 and subsequently tested negative for SARS-CoV-2 and other respiratory viruses, as well as for hepatitis B virus, hepatitis C virus, HIV, and syphilis at the time of blood donation. The donors had been well (asymptomatic) for at least 10 days.
	  * Volume: 400 mL total of ABO-compatible CP on the same day it was obtained from the donor
	  * number of doses: 2 (each dose 200-250 mL) on the same day
	  * Antibody-titre: SARS-CoV-2–specific antibody (IgG) binding titre > 1:1000 (end point dilution titre, by ELISA) and a neutralisation titre > 40 (end point dilution titre)
	  * Pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): administered between 10 and 22 days after admission
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: antiviral therapy (including lopinavir/ritonavir; interferon alfa-1b; favipiravir, arbidol; darunavir), corticosteroids (methylprednisolone)
	• Duration of follow-up: up to 63 days from hospital admission
	• Treatment cross-overs: none
	• Compliance with assigned treatment: good (all compliant)

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: reported
	  * Time to death: not applicable
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: 3 discharged from hospital, 2 remained in hospital (stable)
	  * 30-day and 90-day mortality: NR (all alive)
	  * Admission on the ICU: all were admitted to ICU
	  * Length of stay on the ICU: 11, 14, 18 days for 3 participants, remained in ICU for 2 participants
	  * Time to discharge from hospital: 51-55 days (3 participants), 2 remained in hospital (stable)
	• Additional outcomes: changes of body temperature, Sequential Organ Failure Assessment (SOFA) score (range 0-24, with higher scores indicating more severe illness), PAO2/FIO2, viral load (qRT-PCR), serum antibody titre (ELISA), routine blood biochemical index (CRP, procalcitonin, IL6), ARDS, and ventilatory and ECMO supports before and after CP transfusion, CT chest findings

Notes	• Sponsor/funding: "this work was supported by the National Science and Technology Major Project (2018ZX10711001, 2017ZX10103011, 2017ZX10204401), Sanming Project of Medicine in Shenzhen (SZSM201412003, SZSM201512005), China Postdoctoral Science Foundation (2019T120147, 2018M641508), Shenzhen Science and Technology Research and Development Project (202002073000001), National Natural Science Foundation of China (81902058), Shenzhen Science and Technology Research and Development Project (202002073000002), and The Key Technology R&D Program of Tianjin (17YFZCSY01090)." • COIs: no conflicts to disclose • Other:" the study was approved by the ethics committees from Shenzhen Third People's Hospital, and each participant gave written informed consent."

Risk of bias

Shen 2020 *(Continued)*

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	5 participants only
Outcome detectors blinded to intervention (detection bias) Objective outcomes (e.g. mortality)	Low risk	Not blinded, but awareness of intervention cannot bias assessment of objective outcomes
Outcome detectors blinded to intervention (detection bias) Subjective outcomes	High risk	Not blinded, but awareness of intervention cannot bias assessment of objective outcomes. Data on clinical improvement taken from hospital computer medical system
Complete outcome assessment/follow up (attrition bias) Mortality	Unclear risk	Not all participants discharged
Complete outcome assessment/follow up (attrition bias) Adverse events	Unclear risk	Unclear whether AEs occurred; outcome NR
Complete outcome assessment/follow up (attrition bias) Clinical improvement	Low risk	Reported for all 5 participants
Well-defined study group (reporting bias)	Low risk	Study population well described, clear inclusion criteria
Well-defined outcome (reporting bias) Mortality	Low risk	All participants alive, 2 still hospitalised
Well-defined outcome (reporting bias) Adverse events	High risk	Outcome NR, unclear whether AEs occurred
Well-defined outcome (reporting bias) Clinical improvement	Unclear risk	Probably still 2 participants on ICU, but unclear
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Not adjusted for confounding factors

Tan 2020

Study characteristics	
Methods	• Trial design: case report

Tan 2020 *(Continued)*

- Type of publication: preprinted article from medRxiv and bioRxiv (not peer-reviewed)
- Setting and dates: a designated hospital in Wuhan, China. 25 January-19 March 2020
- Country: China
- Language: English
- Number of centres: 1
- Inclusion/exclusion criteria: NR
- Trial registration number: NR (not applicable)

Participants	• Age: 40-50 • Gender: male • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1 (note: 1 other patient case described, but did not receive CP and general characteristics of 130 patients admitted with COVID-19 were described and compared to participant) • Severity of disease: moderate • Comorbidities: none reported • Additional diagnoses: none • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antiviral therapy, Chinese traditional medicine, supportive care, antipyrexials

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: plasma was collected from recovered patients with COVID-19
	  * volume: 400 mL
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): day 48 of hospital admission
	• For studies including a control group: comparator (type): other patients admitted to the same hospital, 1 specific patient used as comparator (middle-aged woman with moderate-severity illness)
	• Concomitant therapy: antiviral therapy (type: NR), Chinese traditional medicine (type: NR)
	• Duration of follow-up: 55 days
	• Treatment cross-overs: none
	• Compliance with assigned treatment: good (all compliant)

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: reported
	  * Time to death: not applicable
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): none
	  * Number of participants with SAEs: patient developed fever 4 h into transfusion
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days:
	  * 30-day and 90-day mortality: NR (alive)
	  * Admission on the ICU: not admitted to ICU
	  * Length of stay on the ICU: not admitted to ICU
	  * Time to discharge from hospital: discharge date NR
	• Additional outcomes: viral load, fever, cough, lung infection, biochemical markers (IL6 levels, procalcitonin levels), full blood examination, lymphocyte subsets, coagulation profile

Tan 2020 *(Continued)*

Notes

- Sponsor/funding: "this work was supported in part by award numbers 81872028 and 81672693 (H.M.) from the National Natural Science Foundation of China, cstc2017jcyjBX0071 (H.M.) from the Foundation and Frontier Research Project of Chongqing and T04010019 (H.M.) from the Chongqing Youth Top Talent Project"
- COIs: none to disclose
- Other: "all relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript. Yes, all necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived. Yes I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).YesI have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable. Yes"

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	1 participant only
Outcome detectors blinded to intervention (detection bias) Objective outcomes (e.g. mortality)	Low risk	Not blinded, but awareness of intervention cannot bias assessment of objective outcomes
Outcome detectors blinded to intervention (detection bias) Subjective outcomes	High risk	Not blinded, but awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow up (attrition bias) Mortality	Unclear risk	Participant alive at last follow-up, in hospital
Complete outcome assessment/follow up (attrition bias) Adverse events	Unclear risk	Only fever reported, not reported whether other AEs occurred
Complete outcome assessment/follow up (attrition bias) Clinical improvement	High risk	Unclear why participant is still in hospital, clinical improvement not reported
Well-defined study group (reporting bias)	High risk	1 participant only, not much information (e.g. age, comorbidities, clinical symptoms), intervention not described in detail
Well-defined outcome (reporting bias) Mortality	Low risk	1 participant is still in hospital
Well-defined outcome (reporting bias)	High risk	Only fever reported, not reported whether other AEs occurred

Tan 2020 *(Continued)*

Adverse events

Well-defined outcome (reporting bias) Clinical improvement	High risk	Neither clinical symptoms nor clinical improvement reported in detail, but participant still in hospital
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Not adjusted for confounding factors

Ye 2020

Study characteristics

Methods	• Trial design: case series
	• Type of publication: preprint
	• Setting and dates: inpatient, 31 January 2020-22 March 2020
	• Country: China
	• Language: English
	• Number of centres: 1
	• Inclusion/exclusion criteria
	  * Inclusion criteria: (1) laboratory confirmed cases; (2) patients with abnormalities in chest CT (participant 5 was an exception); (3) patients with deteriorated symptoms after standard treatment; (4) patients with persistent positive result of throat swab; (5) critically ill patients.
	  * Exclusion criteria: (1) patients allergic to plasma contents; (2) patients positive for HBV, HCV and HIV; (3) patients with uncontrolled bacterial mixed infection; (4) patients with malignant tumours; (5) patients who developed multiple organ dysfunction syndrome.
	• Trial registration number: none

Participants	• Age: 28-75 years (participants 1-6: 69, 75, 56, 63, 28, 57) • Gender: 3 male, 3 female (participants 1-6: M, F, M, F, F, M) • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 6 • Severity of disease: critical (note: participant 5 was not critically ill), late course of disease, laboratory values mostly normal • Comorbidities: bronchitis and Sjogren's in participants 3 and 4, none in other participants • Additional diagnoses: none • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): oxygen therapy (nasal) in 4 participants, antiviral therapy (arbidol in all participants), antibiotics (levofloxacin in 1 participant)

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * Type of plasma: ABO-compatible CP; CP was collected from patients who had recovered from COVID-19. Recovery was defined as an afebrile status for at least 3 days, alleviation of respiratory symptoms, negative for SARS-CoV-2 nucleic acid for consecutive 2 RT-PCR tests, and at least 3 weeks following disease onset. The donors needed to be seronegative for anti-HBV, HCV and HIV, and seropositive for anti-SARS-CoV-2. As a routine check with plasma donation, the CP was also confirmed free of residual SARS-CoV-2 by real-time PCR.
	  * Volume: 200 mL
	  * number of doses: ≥ 1 (ranges 1-3; participants 1-6: 3, 2, 3, 1, 1, 1)
	  * Antibody-titre: anti-SARS-CoV-2 IgM and IgG
	  * Pathogen inactivated or not: NR

Ye 2020 *(Continued)*

- Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill participants in later stages of infection
  - admission to study centre on 7 February, first transfusion on 10 March, repeated transfusions on 13 and 16 March
  - admission to study centre on 12 February, first transfusion on 5 March, repeated transfusion on 9 March
  - admission to study centre on 12 February, first transfusion on 5 March, repeated transfusion on 6 and 9 March
  - admission to study centre on 11 February, first transfusion on 10 March
  - admission to study centre on 5 March, first transfusion on 13 March
  - admission to study centre on 12 March, first transfusion on 18 March
- For studies including a control group: comparator (type): none
- Concomitant therapy: oxygen therapy, antiviral therapy (arbidol in all participants), antibiotics (levofloxacin in 1 participant)
- Duration of follow-up: up to discharge (5 participants; 1 further monitored after negative swab tests (follow-up unclear))
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary outcomes
  - All-cause mortality at hospital discharge: reported
  - Time to death: not applicable
- Secondary outcomes
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported, none occurred (3-day follow-up)
  - Number of participants with SAEs: reported, none occurred (3-day follow-up)
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: specific time of recovery NR
  - 30-day and 90-day mortality: reported (all alive and time point not reached)
  - Admission on the ICU: none admitted to ICU
  - Length of stay on the ICU: reported, none admitted to ICU
  - Time to discharge from hospital: reported in 5 participants, range 10-34 days, 1 further monitored after negative swab tests (follow-up unclear)
- Additional outcomes: the primary outcome was the improvement in symptoms and chest CT in the following days after indicated intervention. Blood and swab samples were obtained to measure serum anti-SARS-CoV-2 IgM and IgG titres and throat SARS-CoV-2 nucleic acid, respectively

Notes

- Sponsor/funding: "this study was partially sponsored by grants National Natural Science Foundation of China (#81802301 to Mingxiang Ye, #81772500 to Tangfeng Lv), and Jiangsu Provincial Key Research and Development Program (BE2018713 to Xinyi Xia)."
- COIs: study authors declare no competing interests
- Other: "this study was reviewed and approved by the Medical Ethical Committee of Wuhan Huoshenshan Hospital. Written informed consent was obtained from each participant. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	6 participants only

Ye 2020 *(Continued)*

Outcome detectors blinded to intervention (detection bias) Objective outcomes (e.g. mortality)	Low risk	Not blinded, but awareness of intervention cannot bias assessment of objective outcomes
Outcome detectors blinded to intervention (detection bias) Subjective outcomes	High risk	Not blinded, but awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow up (attrition bias) Mortality	Unclear risk	All participants alive (1 participant further monitored)
Complete outcome assessment/follow up (attrition bias) Adverse events	Low risk	None occurred (3-day follow-up)
Complete outcome assessment/follow up (attrition bias) Clinical improvement	Low risk	Reported for all participants
Well-defined study group (reporting bias)	Low risk	Study population and intervention well described
Well-defined outcome (reporting bias) Mortality	Low risk	All alive (1 participant further monitored)
Well-defined outcome (reporting bias) Adverse events	Low risk	3-day follow-up
Well-defined outcome (reporting bias) Clinical improvement	Low risk	Reported until considered cured or discharged
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Not adjusted for confounding factors

Zhang 2020a

Study characteristics	
Methods	• Trial design: case series • Type of publication: novel report in Chest journal • Setting and dates: hospitals in China, 30 January-17 March 2020 • Country: China • Language: English

Zhang 2020a *(Continued)*

- Number of centres: 4
- Inclusion/exclusion criteria: NR
- Trial registration number: NR (case series)

Participants	• Age: 31-73 years
	  * participant 1: 69, participant 2: 55, participant 3: 73, participant 4: 31
	• Gender: 2 male, 2 female
	  * participant 1: F, participant 2: M, participant 3: M, participant 4: F
	• Ethnicity: not stated
	• Number of participants (recruited/allocated/evaluated): 4
	• Severity of disease: critical
	• Comorbidities: hypertension (participants 1 and 3), COPD (participant 2), chronic kidney impairment (participant 3), pregnancy (participant 4)
	• Additional diagnoses:
	  * participant 1: bacterial pneumonia, fungal pneumonia, pneumorrhagia, ARDS, septic shock
	  * participant 2: ARDS
	  * participant 3: ARDS, renal failure, fungal pneumonia, multiple organ failure, septic shock, pneumorrhagia, cystorrhagia, GI bleeding, pneumothorax
	  * participant 4: ARDS, septic shock, multiple organ failure, cardiac failure, newborn death due to asphyxia, bacterial infection
	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
	  * participant 1: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha), antibacterial therapy, antifungal therapy, supportive care, IVIG, albumin, zadaxin, mechanical ventilation
	  * participant 2: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2a), noninvasive mechanical ventilation/high-flow nasal cannula, corticosteroids (methylprednisolone)
	  * participant 3: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2b, oseltamivir, ribavirin), mechanical ventilation, renal replacement therapy, antifungal therapy (caspofungin, voriconazole), venovenous ECMO
	  * participant 4: antiviral therapy (lopinavir-ritonavir, ribavirin), mechanical ventilation, renal replacement therapy, antibacterial therapy (imipenem, vancomycin), caesarean section, venovenous ECMO

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: prepared from recovered patients, no other information provided
	  * volume: 200-2400 mL
	  ☐ participant 1: 900 mL
	  ☐ participant 2: 200 mL
	  ☐ participant 3: 2400 mL
	  ☐ participant 4: 300 mL
	  * number of doses: 1-8 doses
	  ☐ participant 1: 3 doses (200 mL, 400 mL, 300 mL each)
	  ☐ participant 2: 1 dose
	  ☐ participant 3: 8 doses (each dose not stated)
	  ☐ participant 4: 1 dose
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): days 11-41 admission
	  * participant 1: days 19, 29, 30 admission
	  * participant 2: day 11 admission
	  * participant 3: day 15, 23, 27, 30, 32, 34, 38, 41 admission
	  * participant 4: day 19 admission
	• For studies including a control group: comparator (type): none (not applicable)

Zhang 2020a *(Continued)*

- Concomitant therapy:
  - participant 1: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha), antibacterial therapy, antifungal therapy, supportive care, IVIG, albumin, zadaxin, mechanical ventilation
  - participant 2: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2a), noninvasive mechanical ventilation/high-flow nasal cannula, corticosteroids (methylprednisolone)
  - participant 3: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2b, oseltamivir, ribavirin), mechanical ventilation, renal replacement therapy, antifungal therapy (caspofungin, voriconazole), venovenous ECMO
  - participant 4: antiviral therapy (lopinavir-ritonavir, ribavirin), mechanical ventilation, renal replacement therapy, antibacterial therapy (imipenem, vancomycin), caesarean section, venovenous ECMO
- Duration of follow-up: up to 51 days
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary outcomes
  - All-cause mortality at hospital discharge: reported
  - Time to death: not applicable
- Secondary outcomes
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): none
  - Number of participants with SAEs: none
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (extubation date reported), 15 days post-first plasma infusion (participant 1) and 22 days post-first plasma infusion (participant 4), participant 2 already off respiratory support prior to plasma infusion, participant 3 remains in ICU
  - 30-day and 90-day mortality: NR (all alive)
  - Admission on the ICU: all in ICU at baseline
  - Length of stay on the ICU: NR
  - Time to discharge from hospital: 3 participants, 1 remains in ICU
- Additional outcomes: viral load, antibody (ELISA), chest imaging results

Notes

- Sponsor/funding: NR
- COIs: none disclosed
- Other: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	4 participants only
Outcome detectors blinded to intervention (detection bias) Objective outcomes (e.g. mortality)	Low risk	Not blinded, but awareness of intervention cannot bias assessment of objective outcomes
Outcome detectors blinded to intervention (detection bias) Subjective outcomes	High risk	Not blinded, but awareness of intervention can bias assessment of subjective outcomes

Zhang 2020a *(Continued)*

Complete outcome assessment/follow up (attrition bias) Mortality	Unclear risk	All participants alive, 1 still on ICU
Complete outcome assessment/follow up (attrition bias) Adverse events	Unclear risk	Clinical course reported, but not whether AEs occurred
Complete outcome assessment/follow up (attrition bias) Clinical improvement	Low risk	Reported for all 4 participants
Well-defined study group (reporting bias)	Unclear risk	Study group well described but not intervention
Well-defined outcome (reporting bias) Mortality	Low risk	All participants alive, 1 still hospitalised
Well-defined outcome (reporting bias) Adverse events	High risk	Not described in detail, unclear whether AEs occurred
Well-defined outcome (reporting bias) Clinical improvement	Low risk	Well defined
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Not adjusted for confounding factors

Zhang 2020b

Study characteristics	
Methods	• Trial design: case report • Type of publication: open-access article • Setting and dates: inpatient/ICU • Country: China • Language: English • Number of centres: 1 • Inclusion/exclusion criteria: NR • Trial registration number: NR (case report)
Participants	• Age: 64 years • Gender: female • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1 • Severity of disease: severe • Comorbidities: hypertension, diabetes

Zhang 2020b *(Continued)*

- Additional diagnoses: NR
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): mechanical ventilation

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: IgM reactive plasma; free of hepatitis B and C virus, HIV, syphilis, and residual SARS-CoV-2
	  * volume: 200 mL
	  * number of doses: unclear
	  * antibody-titre: IgG titrated by semiquantitative ELISA: 1:1: 6.59; 1:10: 5.33; 1:20: 4.87; 1:40: 3.87; 1:80: 3.24; 1:160: 2.20; 1:320: 2.17/> 1:160
	  * Pathogen inactivated or not: NR
	  * Donor characteristics: 6 donors, 4 male, 2 female, aged from 30-50 years old, with laboratory-confirmed SARS-CoV-2 infection during the COVID-19 outbreak and the subsequent recovery certificated by 2 consecutively negative SARS-CoV-2 PCR assays and resolution of clinical symptoms
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): 1 week after admission to ICU
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: NR
	• Duration of follow-up: 11 days after transfusion; then transferred to general ward
	• Treatment cross-overs: none
	• Compliance with assigned treatment: good (compliant), transferred to general ward

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: reported
	  * Time to death: not applicable
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): none
	  * Number of participants with SAEs: none
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported for day 11
	  * 30-day and 90-day mortality: NR (all alive)
	  * Admission on the ICU: reported
	  * Length of stay on the ICU: reported
	  * Time to discharge from hospital: remains on general ward
	• Additional outcomes: lymphocyte count, renal and liver function, prothrombin time, CPK, LDH and myocardial enzymes

Notes	• Sponsor/funding: "this study was supported by Medical Science and Technology Development Foundation, Nanjing Department of Health (ZKX18050). Dr. Xiang Xue is supported by the National Institutes of Health (K01DK114390) and a Research Scholar Grant from the American Cancer Society (RSG-18-050-01-NEC)." • COIs: declared to have no conflicts of interest • Other: case series focusing on CP donors

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	1 participant only

Zhang 2020b *(Continued)*

Outcome detectors blinded to intervention (detection bias) Objective outcomes (e.g. mortality)	Low risk	Not blinded, but awareness of intervention cannot bias assessment of objective outcomes
Outcome detectors blinded to intervention (detection bias) Subjective outcomes	High risk	Not blinded, awareness of intervention cannot bias assessment of subjective outcomes
Complete outcome assessment/follow up (attrition bias) Mortality	Unclear risk	Alive but transferred to another ward
Complete outcome assessment/follow up (attrition bias) Adverse events	Low risk	Reported that no TRALIs were observed
Complete outcome assessment/follow up (attrition bias) Clinical improvement	Low risk	Clinical course assessed and briefly reported
Well-defined study group (reporting bias)	Unclear risk	Participant not described in detail
Well-defined outcome (reporting bias) Mortality	Low risk	Participant alive and transferred to general ward
Well-defined outcome (reporting bias) Adverse events	Low risk	No AEs occurred
Well-defined outcome (reporting bias) Clinical improvement	Unclear risk	Not described in detail; transferred to another ward
Important prognostic factors or follow-up taken adequately into account (confounding)	High risk	Not adjusted for confounding factors

AE: adverse event; **ARDS:** acute respiratory distress syndrome; **COI:** conflict of interest; **COPD:** chronic obstructive pulmonary disease; **CP:** convalescent plasma; **CPK:** creatine phosphokinase; **CRP:** C-reactive protein; **CT:** computed tomography; **ECMO:** extracorporeal membrane oxygenation; **ELISA:** enzyme-linked immunosorbent assay; **FiO2:** fractional inspired oxygen; **GI:** gastrointestinal; **HBV/HCV:** hepatitis B/C; **ICU:** intensive care unit; **IgA (B/G/M):** immunoglobulin A (B/G/M); **IL-6:** interleukin-6; **IQR:** interquartile range; **IRB:** Institutional Review Board; **IV:** intravenous; **IVIG:** intravenous immunoglobulin; **LDH:** lactate dehydrogenase; **MODS:** multiple organ dysfunction syndrome; **NR:** not reported; **PaO2:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **RNA:** ribonucleic acid; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SARS:** severe acute respiratory syndrome; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TRALI:** transfusion-related acute lung injury

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bloch 2020	Review
Cao 2020	Ineligible intervention
Casadevall 2020	Review
Chen 2020	Review
ChiCTR2000030312	Study cancelled before starting recruitment
ChiCTR2000030381	Study cancelled before starting recruitment
ChiCTR2000030442	Study cancelled before starting recruitment
Díez 2020	Ineligible intervention
Hu 2020	Ineligible intervention
Jawhara 2020	Review
NCT04261426	Ineligible intervention
NCT04323800	Ineligible participant population (participants exposed to COVID-19)
NCT04325672	Study cancelled before starting recruitment
NCT04344015	Feasibility of plasma collection only
NCT04344977	Feasibility of plasma collection only
Roback 2020	Review
Shi 2020	Ineligible intervention
Syal 2020	Review
Tanne 2020	Review
Tiberghien 2020	Review
Wong 2020	Review
Xie 2020	Ineligible intervention
Yoo 2020	Review
Zhao 2020b	Review

Characteristics of studies awaiting classification *[ordered by study ID]*

Qiu 2020

Methods	• Trial design: case series • Type of publication: journal publication

Qiu 2020 *(Continued)*

	• Setting and dates: unclear, awaiting translation • Country: China • Language: only abstract in English, full text in Chinese • Number of centres: 1, Renmin Jospital of Wuhan University • Inclusion/exclusion criteria: unclear, awaiting translation • Trial registration number: NR
Participants	• Age: 48 years and 59 years • Gender: both male • Ethnicity: unclear, awaiting translation • Number of participants (recruited/allocated/evaluated): 2 • Severity of disease: unclear, awaiting translation • Additional diagnoses: unclear, awaiting translation, both received kidney transplants • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): cefoperazone sulbactam sodium + linezolid to resist infection, gamma globulin to enhance immunity function, methylprednisolone to control inflammatory response, antiviral regimens including arbidol tablets + lopina-velitonavir tablet

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: unclear, awaiting translation
	• Details of CP:
	  * type of plasma: not applicable
	  * volume: not applicable
	  * number of doses: not applicable
	  * antibody-titre: not applicable
	  * pathogen inactivated or not: not applicable
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): unclear, awaiting translation
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: cefoperazone sulbactam sodium + linezolid to resist infection, gamma globulin to enhance immunity function, methylprednisolone to control inflammatory response, antiviral regimens including arbidol tablets + lopina-velitonavir tablet
	• Duration of follow-up: 3 weeks
	• Treatment cross-overs: unclear, awaiting translation
	• Compliance with assigned treatment: unclear, awaiting translation

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: both alive
	  * Time to death: not applicable
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): unclear, awaiting translation
	  * Number of participants with SAEs: unclear, awaiting translation
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
	  * 30-day and 90-day mortality: not applicable
	  * Admission on the ICU: unclear, awaiting translation
	  * Length of stay on the ICU: unclear, awaiting translation
	  * Time to discharge from hospital: unclear, awaiting translation
	• Additional outcomes: unclear, awaiting translation

Notes	• Sponsor/funding: unclear, awaiting translation • COIs: unclear, awaiting translation

Qiu 2020 *(Continued)*

	• Other: unclear, awaiting translation

Tu 2020

Methods	• Trial design: case series • Type of publication: journal publication • Setting and dates: unclear, awaiting translation • Country: China • Language: only abstract in English, full text in Chinese • Number of centres: unclear, awaiting translation • Inclusion/exclusion criteria: unclear, awaiting translation • Trial registration number: NR
Participants	• Age: unclear, awaiting translation • Gender: unclear, awaiting translation • Ethnicity: unclear, awaiting translation • Number of participants (recruited/allocated/evaluated): 2 • Severity of disease: unclear, awaiting translation • Additional diagnoses: unclear, awaiting translation, both received kidney transplants • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): unclear, awaiting translation

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: unclear, awaiting translation
	• Details of CP:
	  * type of plasma: not applicable
	  * volume: not applicable
	  * number of doses: not applicable
	  * antibody-titre: not applicable
	  * pathogen inactivated or not: not applicable
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): unclear, awaiting translation
	• For studies including a control group: comparator (type): unclear, awaiting translation
	• Concomitant therapy: symptomatic supportive treatment by antiviral agents, stop uses of immunosuppression agents, small amount of hormone maintenance, IV drip of gamma globulin and respiratory support to avoid secondary infections
	• Duration of follow-up: unclear, awaiting translation
	• Treatment cross-overs: unclear, awaiting translation
	• Compliance with assigned treatment: unclear, awaiting translation

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: both alive
	  * Time to death: not applicable

Tu 2020 *(Continued)*

	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): unclear, awaiting translation
	  * Number of participants with SAEs: unclear, awaiting translation
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
	  * 30-day and 90-day mortality: not applicable
	  * Admission on the ICU: unclear, awaiting translation
	  * Length of stay on the ICU: unclear, awaiting translation
	  * Time to discharge from hospital: reported for 1 participant
	• Additional outcomes: unclear, awaiting translation

Notes	• Sponsor/funding: unclear, awaiting translation • COIs: unclear, awaiting translation • Other: unclear, awaiting translation

AE: adverse event; **COI:** conflict of interest; **CP:** convalescent plasma; **ICU:** intensive care unit; **IV:** intravenous; **NR:** not reported; **SAE:** serious adverse event; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TRALI:** transfusion-related acute lung injury

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR2000029757

Study name	Convalescent plasma for the treatment of severe and critical novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial
Methods	• Trial design: multicentre, randomised, open, parallel, controlled trial • Sample size: 100 in each arm (200) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  * Signed an informed consent form to participate in the study
	  * Aged ≥ 18 years
	  * COVID-19 patients diagnosed by PCR
	  * Nucleic acid positive within 72 h before blood transfusion
	  * Pneumonia confirmed by imaging
	  * Clinical symptoms reach the standard of severe or critical. Severe patients meet any of the following: a) respiratory distress, respiratory rate ≥ 30 breaths/min; b) in resting state, oxygen saturation ≤ 93%; c) partial pressure of oxygen in arterial blood (PaO2)/oxygen concentration (FiO2) ≤ 300 mmHg (1 mmHg = 0.133 kPa). Critically ill patients meet any of the following: a) respiratory failure and need mechanical ventilation; b) shock; c) patients with other organ failure need ICU monitoring treatment
	  * Accept random grouping into any group
	  * Hospitalised before the end of the clinical study
	  * Willing to participate in all necessary research directions and be able to participate in follow-up
	  * During the period of participating in this study, they will no longer participate in clinical trials such as other antiviral drugs.

ChiCTR2000029757 *(Continued)*

	• Exclusion criteria * Doctor believes that the patient is not suitable to participate in this trial, including those who may not co-operate, do not comply with the requirements of the procedure, or participate in this trial may put the patient in an unsafe situation * Pregnant or lactating women * Immunoglobulin allergy * IgA deficiency * There are diseases that may increase the risk of thrombosis, such as cold globulinaemia, severe refractory hypertriglyceridaemia, clinically defined monoclonal gamma globulinaemia, etc. * High titre of anti-novel coronavirus antibody RBDIgG (> 1) could be detected * Received any experimental treatment for novel coronavirus infection within 30 days before screening * Study authors judged that the patients had the following life-threatening conditions, including, but not limited to, Phammer F < 100 mmHg, near-death state or expected survival time < 24 h, severe septic shock or disseminated intravascular coagulation ((DIC)), etc * Severe congestive heart failure, or other relative contraindications for plasma transfusion determined by study authors
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: conventional treatment and CP therapy • Details of CP: * type of plasma: NR * volume: NR * number of doses NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): conventional treatment • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge * Time to death • Secondary outcomes * Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (cumulative incidence of AEs (AE), grades 3 and 4 AE), Incidence of adverse plasma transfusion reactions * Number of participants with SAEs: yes (cumulative incidence of severe AEs (SAE)) * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days * 30-day and 90-day mortality: yes (28-day mortality) * Admission on the ICU: yes * Length of stay on the ICU: yes (ICU hospitalisation) * Time to discharge from hospital: yes (hospitalisation time) • Additional outcomes * Invasive mechanical ventilation during infection * ECMO duration during infection * Proportion of viral nucleic acid negative (3 days after transfusion) * Results of laboratory tests and vital signs
Starting date	14 February 2020
Contact information	Liu Zhong

ChiCTR2000029757 *(Continued)*

	Institute of Blood Transfusion, Chinese Academy of Medical Sciences, 26 Huacai Road, Chenghua District, Chengdu, Sichuan, 610000, Liuz@ibt.pumc.edu.cn Cao Bin Cherry Blossom Garden East Street, Chaoyang District, Beijing, 100029, caobin_ben@163.com
Notes	• Recruitment status: recruiting • Prospective completion date: 5 February 2021 • Sponsor/funding: China-Japan friendship hospital, Institute of Blood Transfusion, Chinese Academy of Medical Sciences, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Government

ChiCTR2000029850

Study name	Study on convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19)
Methods	• Trial design: prospective cohort study • Sample size: 10 in each arm (20) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  * Laboratory-confirmed diagnosis of COVID19 infection by RT-PCR
	  * Aged > 18 years
	  * Written informed consent given by the patient or next-of-kin
	  * Clinical deterioration despite conventional treatment that required intensive care
	• Exclusion criteria
	  * Hypersensitive to immunoglobulin
	  * IgA deficiency

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: standardised comprehensive treatment combined with CP treatment
	• Details of CP: NR
	  * type of plasma: NR
	  * volume: NR
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): standardised comprehensive treatment
	• Concomitant therapy: NR
	• Treatment cross-overs: no

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (fatality rate)
	  * Time to death

ChiCTR2000029850 *(Continued)*

	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
	  * Number of participants with SAEs
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: incubation period
	  * 30-day and 90-day mortality
	  * Admission on the ICU: ICU stay duration
	  * Length of stay on the ICU
	  * Time to discharge from hospital: hospital stay duration
	• Additional outcomes
	  * Viral titres in respiratory samples
	  * PaO2/FiO2
	  * Cytokines/chemokines

Starting date	15 February 2020
Contact information	Liang Yu The First Affiliated Hospital of Zhejiang University, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Disease, 79 Qingchun Road, Shangcheng District, Hangzhou, Zhejiang, 310003, yu-liang@zju.edu.cn Xiaowei Xu 79 Qingchun Road, Shangcheng District, Hangzhou, Zhejiang, China, 310003, xxw69@126.com
Notes	• Recruitment status: recruiting • Prospective completion date: 15 February 2022 • Sponsor/funding: The First Affiliated Hospital of Zhejiang University School of Medicine, Key Research and Development Project of Zhejiang Province

ChiCTR2000030010

Study name	A randomized, double-blind, parallel-controlled, trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)
Methods	• Trial design: randomised, double-blind, parallel-controlled trial • Sample size: 50 in each arm (100) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  * Aged 18-70 years old, inpatients, male or female
	  * Patients with severe novel coronavirus infection: according to the "Pneumonitis Diagnosis and Treatment Guideline for the Novel Coronavirus Infection (Trial Version 5)", clinically diagnosed cases (suspected cases with pneumonia imaging features) or suspected cases. Severe patients must also meet any of the following: 1) respiratory distress, respiratory rate ≥ 30 times/min;

ChiCTR2000030010 *(Continued)*

	2) In the resting state, the oxygen saturation is ≤ 93%; 3) PaO2/FiO2 ≤ 300 mmHg (1 mm Hg = 0.133 kPa) * Participants and/or legal guardians of the participants volunteered to participate in the study and voluntarily signed informed consent • Exclusion criteria * The clinical classification of patients with severe novel coronavirus infection is to meet any of the following: 1) respiratory failure occurs and requires mechanical ventilation; 2) shock occurs; 3) combined failure of other organs requires ICU monitoring and treatment * Those who are allergic to blood products or plasma components and auxiliary materials (sodium citrate) * There is multiple organ failure, and the estimated survival time is < 3 days * Those who tested positive for HIV antibodies before enrolment * Women who are pregnant or breastfeeding or have a birth plan within the past year * Participants in other clinical trials within 3 months before screening * Poor adherence or other conditions that the study author believes are not suitable for inclusion (such as poor physical condition)
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: Anti-SARS-CoV-2 virus inactivated plasma • Details of CP: * type of plasma: NR * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: probably inactivated • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): ordinary plasma • Concomitant therapy: no • Treatment cross-overs: no
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge: 14- and 28-day all-cause mortality * Time to death • Secondary outcomes * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions) * Number of participants with SAEs * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: main clinical manifestations subsided or significantly improved (fever, dry cough, fatigue, etc.) * 30-day and 90-day mortality * Admission on the ICU * Length of stay on the ICU: ICU hospitalisation days * Time to discharge from hospital • Additional outcomes * Improvement of clinical symptoms (clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital)
Starting date	19 February 2020
Contact information	Liu Ying Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital) , 1 Yintan Road, Dongxihu District, Wuhan, Hubei, China , 430023, whsjytyy_gcp@163.com Zhang Dingyu

ChiCTR2000030010 *(Continued)*

	1 Yintan Road, Dongxihu District, Wuhan, Hubei, China, 430023, 1813886398@qq.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31 May 2020 • Sponsor/funding: Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital), Sinopharm Wuhan Blood Products Co., Ltd., Sinopharm Wuhan Blood Products Co., Ltd

ChiCTR2000030039

Study name	Clinical study for infusing convalescent plasma to treat patients with new coronavirus pneumonia (COVID-19)
Methods	• Trial design: non-randomised controlled • Sample size: 30 experimental, 60 control group • Setting: inpatient • Country: China • Language: translated into English • Number of centres: 8

Participants	• Inclusion criteria
	  * Diagnosis conforms to the diagnostic criteria of "pneumonia diagnosis and treatment program for new coronavirus infection (trial version 5)"
	  * Clinical classification is normal, severe or critical
	  * Patient aged ≥ 18 years old
	  * Patient or his/her legal guardian will participate voluntarily and sign the informed consent
	• Exclusion criteria
	  * Highly allergic constitution or history of severe allergy, especially plasma allergy
	  * Doctor believes that there are other reasons not to include the patient

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: conventional therapy with Infusion of CP
	• Details of CP
	  * type of plasma: CP
	  * volume: 200-500 mL
	  * number of doses: 2 infusions are recommended
	  * antibody-titre: NR
	  * pathogen inactivated or not: reported
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): conventional therapy
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge
	  * Time to death

ChiCTR2000030039 *(Continued)*

- Secondary outcomes
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
  - Number of participants with SAEs
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days
  - 30-day and 90-day mortality
  - Admission on the ICU
  - Length of stay on the ICU
  - Time to discharge from hospital
- Additional outcomes
  - SARS-CoV-2 DNA: infusion day 1 and recheck according to the participant's condition
  - SARS-CoV-2 antibody levels: infusion day 1 and recheck according to the participant's condition
  - SARS-CoV-2 antibody levels: infusion day 1 and recheck according to the participant's condition
  - CRP: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge
  - IL-6: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge
  - LDH: hospitalised day 1, day 3, day 7, day 14, infusion day1, day 2, 14 days after discharge
  - CPK: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge
  - Liver function: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge
  - Renal function: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge
  - Respiratory rate: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge
  - SiO2: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge
  - Thoracic spiral CT: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge

Starting date	1 February 2020
Contact information	Liping Wang Affiliated Hospital of Xuzhou Medical University, 9 Kunpeng Road, Gulou District, Xuzhou, Jiangsu, 163wangliping@163.com China Xuebing Yan 9 Kunpeng Road, Gulou District, Xuzhou, Jiangsu, China, yxbxuzhou@126.com
Notes	• Recruitment status: recruiting • Prospective completion date: 1 February 2020 • Sponsor/funding: Affiliated Hospital of Xuzhou Medical University, Affiliated Hospital of Xuzhou Medical University, the working unit

ChiCTR2000030179

Study name	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)
Methods	• Trial design: randomised • Sample size: 50 in each arm (100)

ChiCTR2000030179 *(Continued)*

- Setting: inpatient
- Country: China
- Language: translated to English
- Number of centres: 1

Participants	• Inclusion criteria
	  * Confirmed participant (or legal guardian) agrees to participate in the study and signs the informed consent form
	  * Aged 18-65 years
	  * Real-time fluorescent RT-PCR of respiratory specimens or blood specimens to detect patients positive for novel coronavirus
	  * Patients diagnosed as severe and critically ill and with rapid disease progression according to the "Diagnosis and Treatment Program for Pneumonia of New Coronavirus Infection (Trial Version 6)".
	• Exclusion criteria
	  * Any situation where the solution cannot be carried out safely
	  * Allergic constitution, allergic to plasma or drugs
	  * Being too old, with severe underlying diseases that affect survival, including uncontrolled clinically significant heart, lung, kidney, digestive, haematological, neuropsychiatric, immune, metabolic, or malignant tumours, severe malnutrition, etc
	  * Patients with severe respiratory failure, heart failure, and multiple organ failure
	  * Participants in other clinical trials

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: routine treatment + plasma treatment
	• Details of CP
	  * type of plasma: NR
	  * volume: NR
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): routine treatment
	• Concomitant therapy: no
	• Treatment cross-overs: no

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: mortality
	  * Time to death
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
	  * Number of participants with SAEs
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days
	  * 30-day and 90-day mortality
	  * Admission on the ICU
	  * Length of stay on the ICU
	  * Time to discharge from hospital: length of stay
	• Additional outcomes
	• Cure rate

Starting date	24 February 2020
Contact information	Liu Wei

ChiCTR2000030179 *(Continued)*

	The First Affiliated Hospital of Nanchang University, 17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, cdyfyliuwei@163.com Le Aiping 17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, leaiping@126.com
Notes	• Recruitment status: recruiting • Prospective completion date: 24 April 2020 • Sponsor/funding: The First Affiliated Hospital of Nanchang University, raise independently

ChiCTR2000030627

Study name	Study for using the healed novel coronavirus pneumonia (COVID-19) patients plasma in the treatment of severe critical cases
Methods	• Trial design: randomised • Sample size: 15 in each arm (30) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  * Patients who were diagnosed as COVID-19 by nucleic acid test and were in accordance with the clinical classification of severe or critically illness. (Refer to the clinical classification criteria in the pneumonia diagnosis and treatment program of novel coronavirus infection, General Office of the National Health Commission (trial version 4))
	• Exclusion criteria
	  * Patients with hypersensitivity to plasma products; patients with severe transfusion reactions in the past; patients with acute pulmonary oedema, congestive heart failure, pulmonary embolism, malignant hypertension, polycythaemia vera, extreme renal failure and other diseases

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy + routine treatment
	• Details of CP: NR
	  * type of plasma: NR
	  * volume: NR
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): routine treatment
	• Concomitant therapy: no
	• Treatment cross-overs: no

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: mortality rate
	  * Time to death

ChiCTR2000030627 *(Continued)*

- Secondary outcomes
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): incidence of AEs in blood transfusion
  - Number of participants with SAEs
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days
  - 30-day and 90-day mortality
  - Admission on the ICU
  - Length of stay on the ICU
  - Time to discharge from hospital
- Additional outcomes
  - Laboratory examination
  - Virus nucleic acid detection
  - Temperature
  - Length of admission

Starting date	1 February 2020
Contact information	Guojun Zhang The First Affiliated Hospital of Zhengzhou University, 1 Jianshe Road East, Zhengzhou, He'nan, China, zlgj-001@126.com Guojun Zhang 1 Jianshe Road East, Zhengzhou, He'nan, China, zlgj-001@126.com
Notes	• Recruitment status: recruiting • Prospective completion date: 30 May 2020 • Sponsor/funding: The First Affiliated Hospital of Zhengzhou University, Science and Technology Department of He'nan Province

ChiCTR2000030702

Study name	Plasma of the convalescent in the treatment of novel coronavirus pneumonia (COVID-19) common patient: a prospective clinical trial
Methods	• Trial design: parallel • Sample size: 25 in each arm (50) • Setting: inpatient • Country: China • Language: translated to English • Number of Centres: multicentre

ChiCTR2000030702 *(Continued)*

Participants	• Inclusion criteria * Patient signed an informed consent form to participate in the study of CP therapy * Patient age ≥ 18 years old * COVID-19 patients diagnosed by PCR * Nucleic acid positive within 72 h before blood transfusion * Pneumonia confirmed by imaging * Hospitalisation for fever (axillary temperature ≥ 36.7 °C, or oral temperature ≥ 38.0 °C, or anal or ear temperature ≥ 38.6 °C) and respiratory rate > 24 breaths/min or cough (at least 1 of the 2) * Severe clinical warning indicators: such as a progressive decrease in peripheral blood lymphocytes, a progressive increase in peripheral blood inflammatory factors, a progressive increase in lactic acid, and rapid progress of lung lesions in the short term, et al. * Accept random grouping into any group * Hospitalised before the end of the clinical study * Willing to participate in all necessary research directions and be able to participate in follow-up * During the period of participating in this study, they will no longer participate in clinical trials such as other antiviral drugs • Exclusion criteria * Doctor believes that the patient is not suitable to participate in this trial, including those who may not co-operate, do not comply with the requirements of the procedure, or participating in this trial may put the patient in an unsafe situation * Pregnant or lactation periods women * Immunoglobulin allergy * IgA deficiency * Clinical symptoms are mild (no pneumonia on imaging) * Clinical symptoms are severe or critical where severe patients meet any of the following: 1) respiratory distress, respiratory rate ≥ 30 breaths/min; 2) in resting state, oxygen saturation ≤ 93%; 3) partial PaO2/FiO2 ≤ 300 mmHg (1 mmHg = 0.133 kPa); and critically ill patients meet any of the following: 1) respiratory failure and need mechanical ventilation; 2) shock; 3) patients with other organ failure need ICU monitoring treatment * Diseases that may increase the risk of thrombosis, such as cold globulinaemia, severe refractory hypertriglyceridaemia, clinically defined monoclonal gamma globulinaemia, etc * Detection of high titre of anti-novel coronavirus antibody RBDIgG (> 1) * Received any experimental treatment for novel coronavirus infection within 30 days before screening * Researchers judged that the patients had the following life-threatening conditions, including, but not limited to, Phammer F < 100 mmHg, near-death state or expected survival time < 24 h, severe septic shock or disseminated intravascular coagulation ((DIC)), etc * Severe congestive heart failure, or other relative contraindications for plasma transfusion determined by study authors
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: conventional treatment and CP therapy • Details of CP: * type of plasma: NR * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: conventional treatment • Concomitant therapy: symptomatic treatment, antiviral treatment, and antibacterial treatment • Treatment cross-overs: NR
Outcomes	• Primary outcomes * Time to clinical recovery after randomisation

ChiCTR2000030702 *(Continued)*

	• Secondary outcomes
	  * 28-day mortality
	  * Hospitalisation time
	  * Cumulative incidence of severe AEs (SAE)
	  * Cumulative incidence of AEs (AE), grades 3 and 4 AE
	  * 28-day assisted oxygen therapy or non-invasive mechanical ventilation rate
	  * Incidence of ICU surveillance required during infection
	  * Incidence of clinical support measures increased during infection
	  * Incidence of adverse plasma transfusion reactions
	• Additional outcomes
	  * Incidence of breathing exacerbations
	  * Proportion of viral nucleic acid negative

Starting date	15 February 2020
Contact information	Liu Zhong Institute of Blood Transfusion, Chinese Academy of Medical Sciences, 26 Huacai Road, Chenghua District, Chengdu, Sichuan, China, 610000, Liuz@ibt.pumc.edu.cn Cao Bin 2 Yinghua Street East, Chaoyang District, Beijing, China, 100029, caobin_ben@163.com
Notes	• Recruitment status: recruiting • Prospective completion date: 15 August 2020 • Sponsor/funding: China-Japan friendship hospital, Beijing, Institute of Blood Transfusion, Chinese Academy of Medical Sciences, Beijing, Government

ChiCTR2000030841

Study name	Exploratory study for immunoglobulin from cured COVID-19 patients in the treatment of acute severe novel coronavirus pneuvirus (COVID-19)
Methods	• Trial design: non-randomised study • Sample size: 5 in each arm (10) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  * Volunteers who have understood and signed the informed consent
	  * Aged ≥ 18 years
	  * Patients diagnosed with acute severe COVID-19 pneumonia
	  * Laboratory (RT-PCR) confirmed infection with COVID-19
	  * Lung involvement confirmed with pulmonary CT scan
	  * At least 1 of the following conditions should be met: respiratory distress, respiratory rate ≥ 30 times/min; oxygen saturation ≤ 93% in resting state; PaO2/FiO2 ≤ 300 mmHg; respiratory failure and mechanical ventilation are required; shock occurs; ICU monitoring and treatment is required in combination with other organ failure.

ChiCTR2000030841 *(Continued)*

	• Exclusion criteria
	  * Viral pneumonia with other viruses besides COVID-19
	  * Patients are not suitable for immunoglobulin therapy
	  * Participation in other studies
	  * Other circumstances in which the study author determined that the patient is not suitable for the clinical trial

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: NR
	  * volume: NR
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): gamma globulin
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): no
	  * Number of participants with SAEs: NR
	• Additional outcomes:
	  * Time to clinical improvement
	  * Clinical status as assessed by ordinal scale
	  * Differences in oxygen intake methods
	  * Duration of supplemental oxygen
	  * Duration of mechanical ventilation
	  * Mean PaO2/FiO2
	  * The lesions of the pulmonary segment numbers involved in pulmonary CT
	  * Time to COVID-19 RT-PCR negativity in respiratory tract specimens
	  * Dynamic changes of COVID-19 antibody titre in blood
	  * Length of hospital stay (days)

Starting date	17 February 2020
Contact information	Xiang Cheng nathancx@hust.edu.cn Union hospital of Tongji Medical College, Huazhong University of Science and Technology 1277 Jiefang Avenue, Jianghan District, Wuhan, Hubei, China
Notes	• Recruitment status: recruiting • Prospective completion date: 31 May 2020 • Sponsor/funding: 1277 Jiefang Avenue, Jianghan District, Wuhan, Hubei, China

ChiCTR2000030929

Study name	A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia (COVID-19)
Methods	• Trial design: randomised, double-blind, parallel-controlled trial • Sample size: 15 in each arm (30) • Setting: inpatient • Country: China • Language: translated to English • Number of centres
Participants	• Inclusion criteria * Aged 18-70 years old, inpatients, male or female * Patients with severe COVID-19: confirmed cases shall be in compliance with guideline of "Diagnosis and Treatment Plan for COVID-19 (Version 7)" or updated versions. * Confirmed cases can be defined if suspected cases have characteristic of following pathogeny or serology ☐ detect nucleic acid of novel coronavirus positive by real-time fluorescent RT-PCR ☐ have highly homologous to known novel coronavirus by sequencing ☐ detect sero-specific lgM and lgG positive; IgG-specific against new coronavirus positive conversion or the titre of IgG is 4 times higher in convalescent period than in acute period * Adult patients with severe COVID-19 shall meet any of the following: ☐ respiratory distress, respiratory rate ≥ 30 times/minute ☐ in the resting state, oxygen saturation is ≤ 93% ☐ for lung radiology, the lesion has obtained > 50% obvious improvement within 24-48 h ☐ PaO2)/FiO2 ≤ 300 mmHg (1 mmHg = 0.133 kPa) * Patients and/or their legal guardians volunteered to participate in the study and voluntarily signed informed consent. • Exclusion criteria * Clinical classification of patients with severe novel coronavirus infection is to meet any of the following: ☐ respiratory failure occurs and requires mechanical ventilation; ☐ shock occurs; ☐ combined failure of other organs requires ICU monitoring and treatment * Those who are allergic to blood products or plasma components and auxiliary materials (sodium citrate) * Multiple organ failure, and the estimated survival time is < 3 days * Those who tested positive for HIV antibodies before enrolment * Women who are pregnant or breastfeeding or have a birth plan within the past year * Participants in other clinical trials within 1 month before screening * Poor adherence or other conditions that the study author believes are not suitable for inclusion (such as poor physical condition)
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * type of plasma: anti-SARS CoV virus inactivated plasma * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: probably inactivated • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type) - ordinary plasma • Concomitant therapy: NR

ChiCTR2000030929 *(Continued)*

	• Treatment cross-overs: NR

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (at 14- and 28-day)
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	• Additional outcomes
	  * Improvement of clinical symptoms (clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital)
	  * Improving time of main clinical symptoms (wheezing, cough, sputum, etc)
	  * ICU hospitalisation days

Starting date	17 March 2020
Contact information	Lianghao Zhang 11443556@qq.com Sinopharm Wuhan Blood Products Co., Ltd. 1 Golden Industrial Park Road, Zhengdian, Jiangxia District, Wuhan, Hubei, China
Notes	• Recruitment status: recruiting • Prospective completion date: 16 June 2020 • Sponsor/funding: Renmin Hospital of Wuhan University, 99 Zhang-Zhi-Dong Road, Wuchang District, Wuhan, Hubei, China

ChiCTR2000031501

Study name	The efficacy of convalescent plasma in patients with critical novel coronavirus pneumonia (COVID-19): a pragmatic, prospective cohort study
Methods	• Trial design: prospective cohort study • Sample size: 10 in each arm (20) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  * Severe or critical patients with COVID-19 pneumonia confirmed by novel coronavirus diagnosis and treatment plan (7th Edition)
	  * 18-85 years old
	  * Obtaining informed consent

ChiCTR2000031501 *(Continued)*

- Exclusion criteria
  - Participating in clinical trials of other drugs
  - Pregnant or lactating women
  - ALT/AST > 5-fold ULN, neutrophil < 0.5 x 10^9/L, platelet < 50 x 10^9/L
  - Diagnosis of rheumatic immune-related diseases was clear
  - Long-term oral anti-rejection drugs or immunomodulatory drugs
  - Hypersensitive reaction to mAb or any adjuvant
  - Active TB patients with definite bacterial and fungal infection
  - Patients with organ transplantation history within 3 months
  - History of percutaneous coronary intervention in the past 60 days;
  - COPD with end-stage chronic diseases, including heart failure above NYHA grade III, chronic kidney disease with CCR < 40 mL/min or requiring family oxygen therapy

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
  - type of plasma: NR
  - volume: NR
  - number of doses: NR
  - antibody-titre: NR
  - pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): routine treatment
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary outcomes
  - All-cause mortality at hospital discharge: yes
  - Time to death: yes
- Secondary outcomes
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
  - Number of participants with SAEs: NR
- Additional outcomes
  - Time to COVID-19 RT-PCR negative in surviving patients
  - Time of medical imaging improvement
  - New receipt of high-flow oxygen absorption
  - New receipt of non-invasive mechanical ventilation
  - New receipt of continuous renal replacement therapy
  - New receipt of ECMO
  - Lymphocyte count
  - CRP
  - IL-6
  - New onset organ failure
  - New ICU admission rate
  - Length of hospital stay
  - Length of ICU stay
  - Incidence of secondary bacterial infection
  - Incidence of secondary fungal infection
  - Incidence of critical illness in severe patients
  - Day 90 mortality
  - Day 90 readmission for COVID-19 pneumonia

ChiCTR2000031501 *(Continued)*

Starting date	17 March 2020
Contact information	Weiqin LI liweiqindr@vip.163.com Eastern Theater General Hospital 305 Zhongshandong road, Xuanwu district, Nanjing, Jiangsu, China
Notes	• Recruitment status: recruiting • Prospective completion date: 17 July 2020 • Sponsor/funding: Eastern Theater General Hospital, 305 Zhongshan Road East, Xuanwu District, Nanjing, Jiangsu, China

EUCTR2020-001310-38

Study name	A randomized, prospective, open label clinical trial on the use of convalescent plasma compared to best supportive care in patients with severe COVID-19
Methods	• Trial design: randomised, clinical trial • Sample size: 106 • Setting: hospitalised patients • Country: Germany • Language: English • Number of centres: NR
Participants	• Inclusion criteria * Patients with SARS-CoV-2 infection * Age ≥ 18 years and ≤ 75 years * SARS-CoV-2 infection confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swab) * Severe disease defined by at least 1 of the following: ☐ respiratory rate ≥ 30 breaths/minute under ambient air ☐ requirement of any type of ventilation support ☐ needs ICU treatment * Written informed consent by patient or legally authorised representative

EUCTR2020-001310-38 *(Continued)*

- Exclusion criteria
  * Accompanying diseases other than COVID-19 with an expected survival time of < 12 months
  * In the opinion of the clinical team, progression to death is imminent and inevitable within the next 48 h, irrespective of the provision of treatment
  * Interval > 72 h since start of ventilation support
  * Not considered eligible for extracorporeal oxygenation support (even in case of severe ARDS according to Berlin classification with Horovitz-Index < 100 mg Hg)
  * Chronic obstructive lung disease (COPD), stage 4
  * Lung fibrosis with UIP pattern in CT and severe emphysema
  * Chronic heart failure NYHA ≥ 3 and/or pre-existing reduction of left ventricular ejection fraction to ≤ 30%
  * Cardiovascular failure requiring ≥ 0.5 µg/kg/min noradrenaline (or equivalent) or requiring > 2 types of vasopressor medication
  * Liver cirrhosis Child C
  * Liver failure: bilirubin > 5 x ULN and elevation of ALT or AST (> 10 x ULN)
  * Any history of adverse reactions to plasma proteins
  * Known deficiency of IgA
  * Pregnancy
  * Breastfeeding women
  * Volume overload until sufficiently treated
  * Pulmonary oedema
  * Participation in another clinical trial for treatment of COVID-19

Interventions	Interventions • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * type of plasma: NR * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): randomised 1:1 to CP and best supportive care • Concomitant therapy: NR • Treatment cross-overs: cross-over allowed for patients with progressive COVID-19
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge: yes ☐ Survival * Time to death: yes • Secondary outcomes * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: case fatality rate at 21, 35, 60 days * Admission on the ICU: NR * Length of stay on the ICU: yes * Time to discharge from hospital: yes

EUCTR2020-001310-38 *(Continued)*

- Additional outcomes
  * Time until negative SARS-CoV-2 PCR
  * Predictive value of comorbidities and inflammation markers
  * Feasibility of collection of plasma units
  * Kinetics of anti-SARS-CoV-2 antibodies in plasma of participants = plasma donors who recovered from a SARS-CoV-2 infection
  * Titre of anti-SARS-CoV-2 in transfused plasma units
  * Impact of donor characteristics on anti-SARS-CoV-2 humoral response
  * Course of anti-SARS-CoV-2 titre in participants
  * Effect of timing of plasma transfusions on outcome

Starting date	6 April 2020
Contact information	Sixten Körper, IKT Ulm, 89081 Ulm, Germany; s.koerper@blutspende.de
Notes	• Recruitment status: ongoing • Prospective completion date: NR • Sponsor/funding: DRK-Bluspendedienst Baden-Württemberg - Hessen gGmbH, Germany

IRCT20151228025732N53

Study name	Evaluation of the therapeutic effects of convalescent plasma (CP) of recovered people from COVID-19 in improving clinical and laboratory symptoms of hospitalised patients
Methods	• Trial design: non-randomised, parallel group • Sample size: 12 (6 control 6 intervention) • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Patients admitted to the ICU who receive mechanical invasive or non-invasive ventilation, Pa02/FiO2 ratio < 300 mmHg (93%). Currently receiving IV vasoactive medications to maintain mean arterial pressure > 65 mmHg; respiratory frequency ≥ 30/min; laboratory-confirmed COVID-19 infection (by real-time PCR).
	• Exclusion criteria
	  * Negative real-time PCR from respiratory secretions or blood within 48 h prior to CP transfusion
	  * History of allergic reaction to blood or plasma products
	  * Known IgA deficiency

Interventions	• CP therapy or hyperimmune globulin therapy: CP
	• Details of CP:
	  * type of plasma: CP, prepared from recovered patients
	  * volume: 2 units
	  * number of doses: 2
	  * antibody-titre: > 1:320
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised participants
	• For studies including a control group: comparator (type): conventional treatment
	• Concomitant therapy: conventional treatment

IRCT20151228025732N53 *(Continued)*

	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: NR
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: Yes (30 min after intervention and daily)
	  * 30-day and 90-day mortality: NR
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	• Additional outcomes: white blood cell count, CRP, percentage of CD8+ T cells in peripheral blood, percentage of CD4+ T cells in peripheral blood

Starting date	20 April 2020
Contact information	Alireza Emadi Semnan University of Medical Sciences, Semnan, Iran +98 23 3345 1336 are20935@semums.ac.ir
Notes	• Recruitment status: recruiting • Prospective completion date: 20 June 2020 (recruitment end date) • Sponsor/funding: Semnan University of Medical Sciences

IRCT20200310046736N1

Study name	Comparison of the therapeutic effect of convalescent plasma and plasma-derived immunoglobulin-enriched solution on COVID-19 patients
Methods	• Trial design: a hospital-based, parallel-group, single-blind, and randomised controlled trial • Sample size: 45 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * COVID-19 patients who have the clinical signs of COVID-19 infection such as fever, cough, sputum production, sore throat, and so on
	  * Positive CT scan
	  * Declare informed consent for this study
	  * Age: 20-45 years

IRCT20200310046736N1 *(Continued)*

	• Exclusion criteria
	  * Pregnant women (based on WHO protocol)
	  * Lactating women (based on WHO protocol)
	  * Individuals who exhibit specific allergic reactions to IV administration
	  * History of dangerous underlying diseases such as IgA deficiency
	  * History of dangerous diseases such as cardiovascular and or haematological disorders (haemophilia, thalassaemia, leukaemia)
	  * History of underlying diseases such as liver and kidney disease
	  * Smokers

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: obtained from fully recovered patients according to inclusion criteria
	  * volume: 200 cc/day IV administration for 1-4 h
	  * number of doses: for 1-4 days
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): randomised (3 arms): CP, plasma-derived immunoglobulin-enriched solution and best supportive care or routine care without any new therapeutic interventions
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: NR
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: NR
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	• Additional outcomes:
	  * Negative result for COVID-19 RT-PCR test
	  * Normal CT scan
	  * Recovery and normal levels of biomarkers associated with COVID-19

Starting date	24 March 2020
Contact information	Parastoo Moradi Choghakabodi, Iran (Islamic Republic of); parastoomoradi40@yahoo.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 24 July 2020 • Sponsor/funding: Ahvaz University of Medical Sciences, 61357-15794 Ahvaz, Iran

IRCT20200325046860N1

Study name	Evaluation of convalescent plasma therapy in the treatment of patients with COVID-19 disease
Methods	• Trial design: non-randomised, parallel group • Sample size: 200 • Setting: moderate to severe disease • Country: Iran • Language: English • Number of centres: 4

Participants	• Inclusion criteria
	  * Blood oxygen saturation < 90%
	  * Abnormal lung CT scan
	  * Significant shortness of breath
	  * Fever
	  * Not improving in the next 48 h
	  * No possibility of discharge in the next 48 h
	  * Consent
	• Exclusion criteria
	  * Patient should not be connected to a ventilator
	  * Patient has not given consent

Interventions	• CP therapy or hyperimmune globulin therapy: CP
	• Details of CP:
	  * type of plasma: CP, preparation details not described (guideline of Iran blood transfusion organization criteria), max 650 mL collected
	  * volume: 400 mL
	  * number of doses: 1
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): conventional treatment
	• Concomitant therapy: conventional treatment
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes
	  * Time to death: yes
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: yes (no follow-up period stated)
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: yes

Starting date	15 March 2020
Contact information	Hassan Abolghasemi +98 21 8126 3166

IRCT20200325046860N1 *(Continued)*

	h.abolghasemi.ha@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 20 August 2020 (expected recruitment end date) • Sponsor/funding: Darmanara Co, Iran Blood Transfusion Organization

IRCT20200404046948N1

Study name	Randomized, parallel-controlled and multi-center clinical study evaluating the efficacy and safety of convalescent plasma, in the treatment of patients with severe SARS-CoV-2 infection (COVID-19)
Methods	• Trial design: randomised, clinical trial • Sample size: 60 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 4

Participants	Participants
	• Inclusion criteria
	  * Laboratory confirmed COVID-19 by PCR
	  * Aged 18-70 years old
	  * Inpatients
	  * Clinical severe or immediately life-threatening COVID-19 (severe patients meet any of the following: dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93% (in resting state), PaO2/FiO2 < 300, and/or lung infiltrates > 50% within 24-48 h
	  * Life-threatening disease is defined as: respiratory failure and need mechanical ventilation, septic shock, and/or multiple organ dysfunction or failure
	  * Patient or his/her legal guardian will sign the informed consent and participate voluntarily
	  * Accepting randomised allocation (allocating into any group)
	  * Being hospitalised before the end of the clinical trial and available for any follow-up
	• Exclusion criteria
	  * History of allergy to blood products or plasma components and auxiliary materials (sodium citrate)
	  * Critical conditions like multiple organ failure, and the estimated survival time is < 3 days
	  * Severe congestive heart failure, or any other conditions in which plasma transfusion is contraindicated decided by study authors
	  * Any risk factor that may increase the risk of thrombosis
	  * Pregnant or breastfeeding women
	  * Participation in another clinical trial
	  * Taking any other medicine for COVID 19 treatment out of the protocol
	  * Doctor believes that the patient is not suitable to participate in this trial

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: NR
	  * volume: 200-500 mL
	  * number of doses: 2 IV infusions during 2 consecutive days
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

IRCT20200404046948N1 *(Continued)*

	• For studies including a control group: comparator (type): conventional therapy and CP or conventional therapy only • Concomitant therapy: conventional therapy • Treatment cross-overs: NR
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge: yes ☐ Mortality in 2 groups during 14 days * Time to death: NR, 14 days only • Secondary outcomes * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: yes * Time to discharge from hospital: yes • Additional outcomes * Proportion of PCR negative (3 and 7 days after transfusion) * Clinical characteristics including fever, respiratory frequency and PaO2/FiO2
Starting date	13 April 2020
Contact information	Ramin Hamidi Farahani, Artesh University of Medical Sciences, Tehran, Iran; Amir.salarian@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 20 June 2020 • Sponsor/funding: Artesh University of Medical Sciences, 1411718541 Tehran, Iran

IRCT20200409047007N1

Study name	The effect of plasma administration of COVID-19 survivors in patients with acute respiratory distress syndrome due to COVID-19
Methods	• Trial design: randomised, clinical trial • Sample size: 32 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 1
Participants	• Inclusion criteria * PaO2/FIO2 ratio < 300 despite receiving standard treatment * Patient should be 50-75 years old * Normal IgA level * < 1 week has passed since the patient entered the ICU

IRCT20200409047007N1 *(Continued)*

	• Exclusion criteria * Uncontrolled hypertension * Advanced heart failure * Systolic blood pressure < 90 mm Hg * COPD * Patient is intubated * Chronic renal failure with GFR < 30
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * type of plasma: survivors' plasma. For the preparation of fresh plasma products, survivors aged 18-60 years were contacted and tested for CRP, complete blood count, HBV, HCV, HIV, human T-lymphtropic virus 1 and COVID-19 PCR if they were without symptoms for at least 10 days. If all tests were normal, 500 cc plasma taken from them and are prescribed to patients in the ICU in < 12 h. Survivors should have a positive initial PCR test for coronavirus, be male, or have no history of pregnancy if they are female. The donor and the patient must be the same in blood group and Rh * volume: 500 cc each time * number of doses: up to 3 times a day * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): this treatment is started as soon as possible after the patient enters the ICU and within a week • For studies including a control group: comparator (type): in the control group, patients benefit from all available supportive and specific therapies based on existing standards • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge: yes ☐ mortality rate in first month from the time of entry into the study * Time to death: NR, first month only • Secondary outcomes * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR * 30-day and 90-day mortality: yes * Admission on the ICU: NR * Length of stay on the ICU: yes * Time to discharge from hospital: NR
Starting date	13 April 2020
Contact information	Dr Mohsen Seddigh Shamsi, Mashhad University of Medical Sciences, Department of Internal Medicine, Taqi Abad Square, Mashhad, Iran
Notes	• Recruitment status: recruiting • Prospective completion date: 15 August 2020 • Sponsor/funding: Mashhad University of Medical Sciences, Mashhad, Iran

IRCT20200413047056N1

Study name	Comparison between the efficacy of intravenous immunoglobulin and convalescent plasma in improving the condition of patients with COVID-19: a randomized clinical trial
Methods	• Trial design: randomised, clinical trial • Sample size: 15 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 1
Participants	• Inclusion criteria * 18-50 years old * RT-PCR * Confirm the infection in the throat swab or sputum or lower respiratory tract samples * Signed informed consent form on a voluntary basis * Meet any of the following criteria for severe or critical ill conditions: ☐ respiratory rate ≥ 30/min; or ☐ rest SpO2 ≤ 90%; or ☐ PaO2/FiO2 ≤ 300 mmHg; or ☐ respiratory failure and needs mechanical ventilation; or ☐ multiple organ failure and needs ICU monitoring • Exclusion criteria * NR
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * type of plasma: NR * volume: 200 cc each time * number of doses: twice * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): 3 arms: CP; IV immunoglobulin (400 mg/kg/d); this group will receive common national protocol • Concomitant therapy: common national protocol • Treatment cross-overs: NR
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge: NR * Time to death: NR • Secondary outcomes * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: yes

IRCT20200413047056N1 *(Continued)*

	• Additional outcomes * Lung involvement in X-ray and CT-scan * SpO2 * LDH enzyme * Viral load * Acute phase protein * White blood cell count * Erythrocyte sedimentation rate
Starting date	18 April 2020
Contact information	Malihe Zangoue, Birjand University of Medical Sciences, Birjadn, Iran; mzangoue@yahoo.com
Notes	• Recruitment status: recruiting • Prospective completion date: 15 August 2020 • Sponsor/funding: Birjand University of Medical Sciences, Birjand, Iran

NCT04264858

Study name	Treatment of acute severe 2019-nCoV pneumonia with immunoglobulin from cured patients
Methods	• Trial design: non-randomised, parallel-assigned, open trial • Sample size: 10 • Setting: inpatients • Country: China • Language: English • Number of centres: 1
Participants	• Inclusion criteria * Volunteers who have understood and signed the informed consent * Age ≥ 18 years, gender unlimited * Patients diagnosed with acute severe COVID-19 pneumonia ☐ laboratory (RT-PCR) confirmed infection with COVID-19 ☐ lung involvement confirmed with pulmonary CT scan ☐ at least 1 of the following conditions should be met: respiratory distress, respiratory rate ≥ 30 times/min; oxygen saturation ≤ 93% in resting state; PaO2/FiO2 ≤ 300 mmHg; respiratory failure and mechanical ventilation are required; shock occurs; ICU monitoring and treatment is required in combination with other organ failure • Exclusion criteria * Viral pneumonia with other viruses besides COVID-19 * Patients are not suitable for immunoglobulin therapy * Participation in other studies * Other circumstances in which the investigator determined that the patient is not suitable for the clinical trial
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: immunoglobulin of cured patients • Details of CP: * type of plasma: immunoglobulin * volume: 0.2 g/kg * number of doses: daily for 3 doses * antibody-titre: NA * pathogen inactivated or not: NR

NCT04264858 *(Continued)*

	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): gamma globulin 0.2 g/kg • Concomitant therapy: NR • Treatment cross-overs: NR

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (up to day 28)
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	• Additional outcomes
	  * Time to clinical improvement up to day 28 - using 6 category ordinal scale on days 7, 14, 21, and 28
	  ☐ no need for supplemental oxygenation
	  ☐ nasal cathete oxygen inhalation
	  ☐ mask oxygen inhalation
	  ☐ noninvasive ventilator oxygen supply
	  ☐ invasive ventilator oxygen supply
	  ☐ the detection frequency could be increased according to clinician's decision
	  ☐ the antibody titre is detected on days 3 and 28
	  * Clinical status assessed by the ordinal scale (time frame: up to 28 days)
	  * The differences in oxygen intake methods (time frame: up to 28 days)
	  * Duration (days) of supplemental oxygenation (time frame: up to 28 days)
	  * Duration (days) of mechanical ventilation (time frame: up to 28 days)
	  * Mean PaO2/FiO2 (time frame: up to 28 days)
	  * Lesions of the pulmonary segment numbers involved in pulmonary CT (every 7 days) (time frame: up to 28 days)
	  * Time to COVID-19 RT-PCR negativity in respiratory tract specimens (every 3 days) (time frame: up to 28 days)
	  * Dynamic changes of COVID-19 antibody titre in blood (time frame: up to 28 days)
	  * Length of hospital stay (days) (time frame: up to 28 days)

Starting date	17 March 2020
Contact information	Xiang Cheng Department of Cardiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan, Hubei, China, 430022
Notes	• Recruitment status: recruiting • Prospective completion date: 31 May 2020 • Sponsor/funding: Wuhan Union Hospital, China

NCT04292340

Study name	The efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia patient (COVID-19): an observational study
Methods	• Trial design: observational, prospective

NCT04292340 *(Continued)*

	• Sample size: 15 • Setting: inpatient • Country: China • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Participants were diagnosed as COVID-19
	  * Participants received anti-SARS-CoV-2 inactivated CP
	  * Written informed consent
	• Exclusion criteria
	  * Participants lacked detailed medical history

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: NR
	  * volume: NR
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): NR
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: yes
	• Additional outcomes
	  * SARS-CoV-2 nucleic acid was quantified using RT-PCR
	  * Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 1, day 3 and day 7 (time frame: 1 day/3 days/7 days after receiving plasma transmission)
	  * Numbers of participants with different clinical outcomes(time frame: from receiving plasma transmission to 4 weeks)
	  ☐ clinical outcomes include death, critical illness, recovery

Starting date	1 February 2020
Contact information	Hongzhou Lu, Ph.D+86-021-37990333 ext 3222luhongzhou@fudan.edu.cn Shanghai Public Health Clinical Center Shanghai, Shanghai, China, 201508
Notes	• Recruitment status: recruiting • Prospective completion date: 31 July 2020 • Sponsor/funding: Shanghai Public Health Clinical Center

NCT04321421

Study name	Plasma from donors recovered from new coronavirus 2019 as therapy for critical patients with Covid-19
Methods	• Trial design: single-arm, open-label, interventional trial • Sample size: 49 • Setting: inpatient • Country: Italy • Language: English • Number of centres

Participants	• Inclusion criteria
	  * Age ≥ 18 years
	  * Positive for RT-PCR SARS-CoV-2
	  * ARDS, moderate to severe, according to Berlin definition, lasting < 10 days
	  * PCR increased by 3.5 with respect to baseline or > 18 mg/dL
	  * Need for mechanical ventilation or CPAP
	  * Signed informed consent unless unfeasible for the critical condition
	• Exclusion criteria
	  * Moderate to severe ARDS lasting > 10 days
	  * Proven hypersensitivity or allergic reaction to hemoderivatives or immunoglobulins
	  * Consent denied

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: clinical plasma
	  * volume: 250-300 mL
	  * number of doses: up to 3 over 5 days
	  * antibody-titre: NR
	  * pathogen inactivated or not: not pathogen inactivated
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: NR
	• Treatment cross-overs: not applicable

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes, up to 7 days
	  * Time to death: no
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): no
	  * Number of participants with SAEs: no
	• Additional outcomes
	  * Time to extubation (time frame: within 7 days) - days since intubation
	  * Length of ICU stay (time frame: within 7 days) - days from entry to exit from ICU
	  * Time to CPAP weaning (time frame: within 7 days) - days since CPAP initiation
	  * Viral load (time frame: at days 1, 3 and 7) - naso-pharyngeal swab, sputum and BAL
	  * Immune response (time frame: at days 1, 3 and 7) - neutralising title

Starting date	17 March 2020
Contact information	Catherine KlersyPavia, PV, Italy, 27100

NCT04321421 *(Continued)*

	Principal Investigator: Cesare Perotti, MDFoundation IRCCS San Matteo Hospital
Notes	• Recruitment status: active, not recruiting • Prospective completion date: 31 May 2020 • Sponsor/funding: Foundation IRCCS San Matteo Hospital, Italy

NCT04327349

Study name	Investigating effect of convalescent plasma on COVID-19 patients outcome: a clinical trial
Methods	• Trial design: single-arm intervention study • Sample size: 30 • Setting: hospital • Country: Iran • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * COVID-19 patients
	  * Consent to attend the study
	  * Age 30-70 years
	  * Not intubated
	  * PaO2/FiO2 is > 200 or SpO2 is > 85%
	• Exclusion criteria
	  * History of hypersensitivity to blood transfusions or its products
	  * History of IgA deficiency
	  * Heart failure or any other factor that prevents the transmission of 500 mL plasma
	  * Entering the intubation stage

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: NR
	  * volume: NR
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: NR
	
	Treatment cross-overs: not applicable

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge
	  * Time to death

NCT04327349 *(Continued)*

- Secondary outcomes
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
  - Number of participants with SAEs
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days
  - 30-day and 90-day mortality
  - Admission on the ICU
  - Length of stay on the ICU
  - Time to discharge from hospital
- Additional outcomes
  - Changes of CRP
  - Changes of IL
  - Changes of tumour necrosis factor-α
  - Changes of PaO2/FiO2
  - Changes of CD4, CD8,C CD4/CD8 ratio
  - Changes of lymphocyte count
  - Changes of leukocyte count
  - Changes of ALT/AST
  - Changes of alkaline phosphatase (ALP)
  - Changes of LDH
  - Changes of CPK
  - Changes of CPK-MB
  - Changes of specific IgG
  - Radiological findings by CT scan and chest X-Ray

Starting date	28 March 2020
Contact information	NR
Notes	• Recruitment status: enrolling by invitation • Prospective completion date: 30 September 2020 • Sponsor/funding: NR

NCT04332380

Study name	Convalescent plasma for patients with COVID-19: a pilot study (CP-COVID-19)
Methods	• Trial design: single-arm intervention study • Sample size: 10 • Setting: hospital • Country: Colombia • Language: English • Number of centres: 1

NCT04332380 *(Continued)*

Participants	• Inclusion criteria
	  * Aged 18-60 years, male or female
	  * Hospitalised participants with diagnosis for COVID 19 by RT-PCR
	  * Without treatment
	  * Moderate cases according to the official guideline 'Pneumonia Diagnosis and Treatment Scheme for Novel Coronavirus Infection (Trial Version 6)'
	  * Confusion, Urea, Respiratory rate, blood pressure-65 score (CURB-65 score) ≥ 2
	  * SOFA < 6
	  * Ability to understand and willing to sign a written informed consent document
	• Exclusion criteria
	  * Pregnant or breastfeeding
	  * Prior allergic reactions to transfusions
	  * Critically ill patients in ICUs
	  * Patients with surgical procedures in the last 30 days
	  * Patients with active treatment for cancer (radiotherapy or chemotherapy)
	  * HIV diagnosed patients with viral failure (detectable viral load > 1000 copies/mL persistent, 2 consecutive viral load measurements within a 3-month interval, with medication adherence between measurements after at least 6 months of starting a new regimen antiretrovirals)
	  * Patients who have suspicion or evidence of co-infections
	  * End-stage chronic kidney disease (GFR < 15 mL/min/1.73 m2)
	  * Child Pugh C stage liver cirrhosis
	  * High cardiac output diseases
	  * Autoimmune diseases or IgA nephropathy
	  * Patients have any condition that in the judgement of the Investigators would make the person inappropriate for entry into this study

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: NR
	  * volume: 500 mL total
	  * number of doses: 2
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: NR
	• Treatment cross-overs: not applicable

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge
	  * Time to death
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
	  * Number of participants with SAEs
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days
	  * 30-day and 90-day mortality
	  * Admission on the ICU
	  * Length of stay on the ICU
	  * Time to discharge from hospital

NCT04332380 *(Continued)*

	• Additional outcomes
	  * Change in viral load
	  * Change in Immunoglobulin M COVID-19 antibodies titres
	  * Change in Immunoglobulin G COVID-19 antibodies titres
	  * Clinical status assessed according to the WHO guideline

Starting date	1 April 2020
Contact information	Juan M Anaya Cabrera, MD, PhD ; +57 321 233 9828; anayajm@gmail.com Manuel E Rojas Quintana, MD, MSc; +57 315 459 9951; manuel_9316@hotmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31 December 2020 • Sponsor/funding: NR

NCT04332835

Study name	Convalescent plasma for patients with COVID-19: a randomized, open label, parallel, controlled clinical study (CP-COVID-19)
Methods	• Trial design: randomised, open-label, parallel-controlled trial • Sample size: 40 in each arm (80) • Setting: hospital • Country: Colombia • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Aged 18-60 years, male or female
	  * Hospitalised participants with diagnosis of COVID 19 by RT-PCR
	  * Moderate cases according to the official guideline 'Pneumonia Diagnosis and Treatment Scheme for Novel Coronavirus Infection (Trial Version 6)'
	  * Confusion, urea, respiratory rate, blood pressure-65 score (CURB-65 score) ≥ 2
	  * SOFA < 6
	  * Ability to understand and the willingness to sign a written informed consent document
	• Exclusion criteria
	  * Pregnant or breastfeeding
	  * Prior allergic reactions to transfusions
	  * Critically ill patients in ICUs
	  * Patients with surgical procedures in the last 30 days
	  * Patients with active treatment for cancer (radiotherapy or chemotherapy)
	  * HIV-diagnosed patients with viral failure (detectable viral load > 1000 copies/mL persistent, 2 consecutive viral load measurements within a 3-month interval, with medication adherence between measurements after at least 6 months of starting a new regimen antiretrovirals)
	  * Suspicion or evidence of co-infections
	  * End-stage chronic kidney disease (GFR < 15 mL/min /1.73 m2)
	  * Child Pugh C stage liver cirrhosis
	  * High cardiac output diseases
	  * Autoimmune diseases or IgA nephropathy
	  * Any condition that in the judgement of the Investigators would make the patient inappropriate for entry into this study

NCT04332835 *(Continued)*

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: NR
	  * volume: 500 mL total
	  * number of doses: 2
	  * antibody-titre
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): azithromycin (500 mg daily) and hydroxychloroquine (400 mg every 12 h) for 10 days
	• Concomitant therapy: azithromycin (500 mg daily) and hydroxychloroquine (400 mg every 12 h) for 10 days
	• Treatment cross-overs: not applicable

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge
	  * Time to death
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
	  * Number of participants with SAEs
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days
	  * 30-day and 90-day mortality
	  * Admission on the ICU
	  * Length of stay on the ICU
	  * Time to discharge from hospital
	• Additional outcomes
	  * Change in viral load
	  * Change in immunoglobulin M COVID-19 antibodies titres
	  * Change in immunoglobulin G COVID-19 antibodies titres
	  * Clinical status assessed according to the WHO guideline

Starting date	1 April 2020
Contact information	Juan M Anaya Cabrera, MD, PhD; +57 321 233 9828; anayajm@gmail.com Manuel E Rojas Quintana, MD, MSc; +57 315 459 9951; manuel_9316@hotmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31 December 2020 • Sponsor/funding

NCT04333251

Study name	Study testing convalescent plasma vs best supportive care
Methods	• Trial design: randomised, open-label, phase I, parallel-controlled trial • Sample size: 115 • Setting: hospital • Country: USA

NCT04333251 *(Continued)*

	• Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * ≥ 18 years
	  * Must have been hospitalised with COVID-19 respiratory symptoms within 3-7 days from the beginning of illness
	  * Patient and/or LAR willing to provide informed consent
	  * Patient agrees to storage of specimens for future testing
	• Exclusion criteria
	  * ≤ 18 years
	  * Receipt of pooled immunoglobulin in past 30 days
	  * Contraindication to transfusion or history or prior reactions to transfusion blood products
	  * Women who are identified as donors must not be pregnant

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: NR
	  * volume: NR
	  * number of doses: 1-2 units
	  * antibody-titre > 1:64
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease):
	• For studies including a control group: comparator (type): best supportive care
	• Concomitant therapy: oxygen therapy
	• Treatment cross-overs

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge
	  * Time to death
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
	  * Number of participants with SAEs
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days
	  * 30-day and 90-day mortality
	  * Admission on the ICU
	  * Length of stay on the ICU
	  * Time to discharge from hospital

Starting date	1 April 2020
Contact information	NR
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31 December 2022 • Sponsor/funding: NR

NCT04333355

Study name	Safety in convalescent plasma transfusion to COVID-19
Methods	• Trial design: single-arm, phase I, intervention study • Sample size: 20 • Setting: hospital • Country: Mexico • Language: English • Number of centres: 1
Participants	• Inclusion criteria * Patients ≥ 18 years * Confirmed SARS-CoV-2 infection by RT-PCR * Serious or life-threatening infection defined as: ☐ serious: dyspnoea; respiratory rate ≥ 30 cycles/min; blood oxygen saturation ≤ 93% with an oxygen supply > 60%; PaO2/FiO2 < 300; 50% increase in pulmonary infiltrates defined by CT scans in 24-48 h ☐ life-threatening infection: respiratory failure; septic shock; dysfunction or multiple organ failure * Refractory to treatment with azithromycin/hydroxychloroquine or chloroquine/ritonavir/lopinavir defined as: 48 h with no improvement in the modified parameters such as serious or clinically imminent infection * Signed informed consent by the patient or by the person responsible for the patient in the case of critically ill patients (spouse or parents) • Exclusion criteria * Patients with a history of allergic reaction to any type of previous transfusion * Heart failure patients at risk of volume overload * Patients with a history of chronic kidney failure in the dialysis phase * Patients with previous haematological diseases (anaemia < 10 g of haemoglobin, platelets > 100,000/µL) * Any case where the study author decides that the patient is not suitable for the protocol
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP: * type of plasma: apheresis plasma * volume: 500 mL total * number of doses: 2 * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): not applicable • Concomitant therapy: supportive standard care • Treatment cross-overs: not applicable
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge * Time to death

NCT04333355 *(Continued)*

	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
	  * Number of participants with SAEs
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days
	  * 30-day and 90-day mortality
	  * Admission on the ICU
	  * Length of stay on the ICU
	  * Time to discharge from hospital
	• Additional outcomes
	  * Heart failure
	  * Pulmonary oedema
	  * Lung infiltrates by thorax CT
	  * Viral load of SARS-CoV-2 by RT-PCR

Starting date	15 April 2020
Contact information	Servando Cardona-Huerta, MD., Ph.D; +5218112121946; servandocardona@tec.mx Sylvia De la Rosa, MD; +5218111832730; sylvia.delarosa@tec.mx
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 30 April 2021 • Sponsor/funding: NR

NCT04338360

Study name	Expanded access to convalescent plasma for the treatment of patients with COVID-19
Methods	• Trial design: expanded access • Sample size: NR • Setting: hospital • Country: USA • Language: English • Number of centres: 12

Participants	• Inclusion criteria
	  * Age ≥ 18 years
	  * Laboratory-confirmed diagnosis of infection with SARS-CoV-2
	  * Admitted to an acute care facility for the treatment of COVID-19 complications
	  * Severe or life-threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease. (Severe COVID-19 is defined by one or more of the following: dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, PaO2/FiO2 < 300, lung infiltrates > 50% within 24-48 h. Life-threatening COVID-19 is defined as one or more of the following: multiple organ dysfunction or failure, septic shock, respiratory failure.)
	  * Informed consent provided by the patient or healthcare proxy
	• Exclusion criteria: none

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy

NCT04338360 *(Continued)*

	• Details of CP:
	  * type of plasma:
	  * volume: NR
	  * number of doses: 1
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: NR
	• Treatment cross-overs: not applicable

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge
	  * Time to death
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
	  * Number of participants with SAEs
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days
	  * 30-day and 90-day mortality
	  * Admission on the ICU
	  * Length of stay on the ICU
	  * Time to discharge from hospital

Starting date	NR
Contact information	Michael Joyner, MD; 507-255-4288; USCOVIDplasma@mayo.edu
Notes	• Recruitment status: expanded access available • Prospective completion date: NR • Sponsor/funding: NR

NCT04340050

Study name	COVID-19 convalescent plasma
Methods	• Trial design: single-arm, phase I, intervention study • Sample size: 10 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * ≥ 18 years
	  * Laboratory-confirmed COVID-19
	  * Severe or immediately life-threatening COVID-19. (Severe defined as dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, PaO2/FiO2 < 300, and/or lung infiltrates > 50% within 24- 48 hours. Life-threatening defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Lower priority should be given to patients with septic

NCT04340050 *(Continued)*

	shock or multiple organ dysfunction or failure since their disease may have progressed to a point where they are not able to benefit from CP therapy.) * Must be < 21 days from the start of illness * Written informed consent, willingness to comply with all protocol requirements, agreement to storage of specimens for future testing from patient or power of attorney or a healthcare proxy • Exclusion criteria * Positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period * Receipt of pooled immunoglobulin in past 30 days * Contraindication to transfusion or history of prior reactions to transfusion blood products * Patients currently enrolled in other drug trials that preclude investigational treatment with anti-SARS-CoV-2 CP
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP: * type of plasma * volume: 300 mL * number of doses: 1 * antibody-titre * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): must be < 21 days from the start of illness • For studies including a control group: comparator (type): not applicable • Concomitant therapy: NR • Treatment cross-overs: not applicable
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge * Time to death • Secondary outcomes * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions) * Number of participants with SAEs * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days * 30-day and 90-day mortality * Admission on the ICU * Length of stay on the ICU * Time to discharge from hospital • Additional outcomes * Feasibility of performing study pathway consisting of consenting convalescent donors, harvesting CP, application for FDA emergency investigational new drug use for administering CP to the patients * Type of respiratory support defined as room air, high-flow oxygen, intubation * Cardiac arrest * Time to transfer to ICU * ICU mortality
Starting date	10 April 2020
Contact information	Maria Lucia Madariaga, MD; 773-270-2004; mlmadariaga@bsd.uchicago.edu
Notes	• Recruitment status: recruiting • Prospective completion date: 31 December 2021

NCT04340050 *(Continued)*

- Sponsor/funding: NR

NCT04342182

Study name	Convalescent plasma therapy from recovered COVID-19 patients as therapy for hospitalized patients with COVID-19 (CONCOVID Study) (ConCoVid-19)
Methods	• Trial design: randomised comparative trial. Patients will be randomised between the infusion of 300 mL of CP with standard care • Sample size: 426 • Setting: hospitalised patients • Country: Netherlands • Language: English • Number of centres: 2

Participants	• Inclusion criteria
	  * Patients with PCR-confirmed COVID disease
	  * Written informed consent by patient or legal patient representative
	  * Age > 18
	• Exclusion criteria
	  * Patient in which a 'no ICU admission' or 'no invasive ventilation' restriction was implemented at the time of screening for the study
	• Donor eligibility criteria
	  * Donors with a history of COVID infection that was documented by PCR
	  * Known ABO-Resus(D) blood group
	  * Negative screening for irregular antibodies
	  * Asymptomatic for at least 24 h
	  * Written informed consent regarding the plasmapheresis procedure
	• Donor exclusion criteria
	  * Donors excluded if age < 18 years and > 66 years
	  * Weight < 45 kg
	  * Medical history of heart failure
	  * History of transfusion with red blood cells, platelets or plasma

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: Infusion of plasma retrieved from donors with a history of PCR-proven symptomatic COVID
	  * volume: 300 mL
	  * number of doses: 1
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): standard of care (supportive care, oxygen, antibiotics)
	• Concomitant therapy: standard of care
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (overall mortality until discharge from the hospital or a maximum of 60 days after admission whichever comes first)
	  * Time to death: yes

NCT04342182 *(Continued)*

	• Secondary outcomes:
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: yes (up to 30 days post-discharge)
	  * Admission on the ICU: yes
	  * Length of stay on the ICU: yes
	  * Time to discharge from hospital: yes
	• Additional outcomes
	  * Impact of plasma therapy on the decrease in SARS-CoV-2 shedding from airways (time frame: until hospital discharge, estimated average 2 weeks)

Starting date	8 April 2020
Contact information	Bart Rijnders, MD, PhD+31107033510; b.rijnders@erasmusmc.nl
Notes	• Recruitment status: recruiting (1 site only, 2nd site not yet recruiting) • Prospective completion date: 1 July 2020 • Sponsor/funding: Erasmus Medical Center

NCT04343261

Study name	Convalescent plasma in the treatment of COVID 19
Methods	• Trial design: single-arm intervention study • Sample size: 15 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * All genders
	  * Age > 18 years and < 90 years
	  * Must have laboratory-confirmed COVID-19
	  * Must provide informed consent
	  * Must have severe or immediately life-threatening COVID-19
	• Exclusion criteria
	  * No gender exclusion
	  * Age < 18 years and > 90 years
	  * COVID-19 negative

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: CP, details NR
	  * volume: 2 units (mL NR)
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR

NCT04343261 *(Continued)*

	• Treatment details, including time of plasma therapy (e.g. early stage of disease): severe or life-threatening • For studies including a control group: comparator (type): none (single-arm) • Concomitant therapy: NR • Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (within 28 days)
	  * Time to death: yes (within 28 days)
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  * 30-day and 90-day mortality: NR (within 28 days only)
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	• Additional outcomes:
	  * Reduction of viral load
	  * Change in serum antibody titres

Starting date	10 April 2020
Contact information	Contact: Latha Dulipsingh, MD860-714-4402; Latha.Dulipsingh@trinityhealthofne.org
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 1 April 2021 • Sponsor/funding: Saint Francis Care

NCT04343755

Study name	Convalescent plasma as treatment for hospitalized subjects with COVID-19 infection
Methods	• Trial design: single-arm, phase IIa study. Up to 36 patients in track 2, and 19 patients in track 3 as described in the statistical section 8 • Sample size: 55 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Recipients age > 18 years old, are assigned to 1 of 2 clinical tracks, track 2 or 3, based on COVID-19 disease severity
	  * Track 2:
	  ☐ hospitalised, moderate symptoms requiring medical care for COVID-19 infection
	  ☐ symptoms may include fever, dyspnoea, dehydration among others
	  ☐ hypoxaemia may be present but is not a requirement
	  * Track 3:
	  ☐ requiring mechanical ventilation for the care of COVID-19 infection

NCT04343755 *(Continued)*

- Exclusion criteria
  - History of severe transfusion reaction to plasma products
  - Infusion of immune globulin within the previous 30 days
  - AST or ALT > 10 x ULN
  - Requirement for vasopressors
  - COVID-19-associated acute kidney injury requiring dialysis
- Donor eligibility criteria:
  - Age 18-60
  - History of a positive nasopharyngeal swab for COVID-19
  - At least 14 days from resolution of COVID-19-associated symptoms
  - 2 negative nasopharyngeal swabs done at least 24 h apart for COVID-19 RNA
  - COVID-19 neutralising antibody > 1:64
  - Adequate venous access for apheresis
  - Meets donor eligibility criteria in accordance to Hackensack University Medical Center (HUMC) Collection Facility at the John Theurer Cancer Center (JTCC) and all regulatory agencies as describes in SOP 800 01
  - Required testing of the donor and product must be performed in accordance to FDA regulations (21 CFR 610.40), and the donation must be found suitable (21 CFR 630.30)

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: NR
	  * volume: NR
	  * number of doses: 1
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): none (single-arm)
	• Concomitant therapy: NR
	• Treatment cross-overs: none (single-arm)

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (up to 60 days)
	  * Time to death: yes (up to 60 days)
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (need and duration of mechanical ventilation)
	  * 30-day and 90-day mortality: yes (up to 60 days)
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: yes (up to 60 days)

Starting date	9 April 2020
Contact information	• Mariefel Vendivil; 551-996-5828; Mariefel.Vendivil@HackensackMeridian.org • Marlo Kemp; 551-996-4464; Marlo.Kemp@HackensackMeridian.org
Notes	• Recruitment status: recruiting • Prospective completion date: April 2021 • Sponsor/funding: Hackensack Meridian Health

NCT04344535

Study name	Convalescent plasma to reduce complications associated with COVID-19 infection: a randomized trial comparing the efficacy and safety of high-titre anti-SARS-CoV-2 plasma vs. standard plasma in hospitalized patients with COVID-19 infection
Methods	• Trial design: randomised phase 1/2 • Sample size: 500 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Adults ≥ 18 years
	  * Hospitalised with PCR+ COVID-19 infection
	  * If female must not be pregnant and/or breastfeeding
	• Exclusion criteria
	  * Unable to randomise patient within 14 days of admission to Stony Brook Hospital (or any other hospital if a transfer to Stony Brook Hospital)
	  * In the treating physician's opinion, the patient cannot tolerate a 450-550 mL infusion of plasma over up to 8 h (4 h max per unit), even if prophylaxed with IV diuretic
	  * Contraindication to transfusion or history of prior reactions to blood transfusions
	• Inclusion criteria for plasma recipients
	  * Adults ≥ 18 years
	  * Hospitalised with PCR+ COVID-19 infection
	  * If female must not be pregnant and/or breastfeeding

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: CP, specific preparation NR
	  * volume: 450-550 mL
	  * number of doses: 2
	  * antibody-titre: ideally > 1:320, but meeting minimum titre per FDA Guidelines for CP
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): within 14 days of hospitalisation
	• For studies including a control group: comparator (type): 450-550 mL of plasma with low titre to anti-SARS-CoV-2 antibodies (standard plasma)
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (90-day all-cause mortality)
	  * Time to death: yes

NCT04344535 *(Continued)*

	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: yes
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	• Additional outcomes: number of days patient remains ventilator-free (up to 28 days)

Starting date	8 April 2020
Contact information	Contact information not shared Responsible party: Elliott Bennett-Guerrero, Professor of Anesthesiology, Stony Brook University
Notes	• Recruitment status: enrolling by invitation • Prospective completion date: 31 August 2021 • Sponsor/funding: Stony Brook University

NCT04345289

Study name	Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia. A double-blinded, randomized, multi-stage, 6-armed placebo-controlled trial in the framework of an adaptive trial platform
Methods	• Trial design: investigator-initiated, multicentre, randomised, double-blinded, placebo-controlled, multi-stage trial (Phase 3) • Sample size: 1500 • Setting: multicentre sites • Country: Denmark • Language: English • Number of centres: 12

Participants	• Inclusion criteria
	  * ≥ 18 years of age
	  * Confirmed COVID-19 infection by presence of SARS-CoV-2 nucleic acid by PCR
	  * Evidence of pneumonia given by at least 1 of the following: SpO2 ≤ 93% on ambient air or PaO2/FiO2 < 300 mmHg/40 kPa or radiographic findings compatible with COVID-19 pneumonia
	  * Onset of first experienced symptom, defined as 1 respiratory symptom or fever, not > 10 days before admission
	  * For women of childbearing potential: negative pregnancy test and willingness to use contraceptive (consistent with local regulations) during study period
	  * Signed informed consent form by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorised representatives

NCT04345289 *(Continued)*

- Exclusion criteria
  - In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 h, irrespective of the provision of treatment
  - History of allergic reaction to study drug (as judged by the site investigator)
  - Participating in other drug clinical trials (participation in COVID-19 antiviral trials may be permitted if approved by sponsor)
  - Pregnant or breastfeeding, positive pregnancy test in a pre-dose examination or patients family planning within 3 months after receiving study agent
  - Estimated GFR < 30 mL/min
  - Severe liver dysfunction (Child Pugh score C)
  - Known history of the following medical conditions: active or latent TB or history of incompletely treated TB; chronic hepatitis B or C infection; retinopathy or maculopathy; neurogenic hearing impairment
  - Presence of any of the following abnormal laboratory values at screening: absolute neutrophil count (ANC) < 1000 mm3 (= 1.0 x 10^9 /L); ALT > 5 x ULN; platelet count < 50,000 per mm3 (= 50 x 10^9 /L)
  - Immunosuppression, defined as following: treatment with immunosuppressive agents, chemotherapy or immunomodulatory drugs within 30 days prior to inclusion; use of chronic oral corticosteroids for a non-COVID-19-related condition in a dose higher than prednisolone 20 mg or equivalent per day for 4 weeks; ongoing chemotherapy
  - Any serious medical condition or abnormality of clinical laboratory tests that, in the study author's judgment, precludes the patient's safe participation in and completion of the study

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: randomised 1:1:1:1:1:1 to parallel treatment arms: CP, sarilumab, hydroxychloroquine, baricitinib, IV and SC placebo, or oral placebo
	• Details of CP:
	  * type of plasma: preparation method NR
	  * volume: 600 mL
	  * number of doses: 2 x 300 mL given in single infusion
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): sarilumab, hydroxychloroquine, baricitinib, IV and SC placebo, or oral placebo
	• Concomitant therapy: placebo treatment with saline 0.9% (1.14 mL) as a single SC injection, in addition to standard care
	• Treatment cross-overs

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (up to 90 days)
	  * Time to death: yes
	• Secondary outcomes:
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
	  * Number of participants with SAEs: yes
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: yes
	  * Admission on the ICU
	  * Length of stay on the ICU
	  * Time to discharge from hospital: yes

NCT04345289 *(Continued)*

- Additional outcomes
  - * composite endpoint of all-cause mortality or need of invasive mechanical ventilation (up to 28 days)
  - * Ventilator-free days (time frame: 28 days)
  - * Organ failure-free days (time frame: 28 days)
  - * Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status (time frame: 90 days)
    - ☐ number of days to improvement of at least 2 categories relative to baseline on the ordinal scale. Categories are as follows: death; hospitalised, in ICU requiring ECMO or mechanical ventilation; hospitalised, on non-invasive ventilation or high-flow oxygen device; hospitalised, requiring supplemental oxygen; hospitalised, not requiring supplemental oxygen; not hospitalised, limitation on activities and/or requiring home oxygen; not hospitalised, no limitations on activities

Starting date	20 April 2020
Contact information	Contact: Thomas Benfield, MD, DMSc+45 38622302 thomas.lars.benfield@regionh.dk
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 15 June 2021 • Sponsor/funding: Thomas Benfield

NCT04345523

Study name	Multi-center, randomized clinical trial of convalescent plasma therapy versus standard of care for the treatment of COVID-19 in hospitalized patients
Methods	• Trial design: multicentre, randomised, clinical trial • Sample size: 278 • Setting: hospital • Country: Spain • Language: English • Number of centres: 9
Participants	• Inclusion criteria * Written informed consent prior to performing study procedures. Witnessed oral consent will be accepted in order to avoid paper handling. Written consent by patient or representatives will be obtained as soon as possible. * Male or female adult patient ≥ 18 years of age at time of enrolment * Laboratory-confirmed SARS-CoV-2 infection as determined by PCR in naso/oropharyngeal swabs or any other relevant specimen * Patients requiring hospitalisation for COVID-19 without mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices and at least 1 of the following: ☐ radiographic evidence of pulmonary infiltrates by imaging (chest X-ray, CT scan, etc.), or ☐ clinical assessment (evidence of rales/crackles on exam) and SpO2 ≤ 94% on room air that requires supplemental oxygen * Not > 12 days between the onset of symptoms (fever or cough) and treatment administration day

NCT04345523 *(Continued)*

- Exclusion criteria
  - Requiring mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices
  - > 12 days since symptoms (fever or cough)
  - Participation in any other clinical trial of an experimental treatment for COVID-19
  - In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 h, irrespective of the provision of treatments
  - Any incompatibility or allergy to the administration of human plasma
  - Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated GFR < 30)

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: prepared approximately 140-200 CP donors
	  * volume: NR
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage within 12 days
	• For studies including a control group: comparator (type): randomised 1:1 to CP and standard of care vs standard of care including any drugs that are being used in clinical practice (e.g. lopinavir/ritonavir; darunavir/cobicistat; hydroxy/chloroquine, tocilizumab, etc.), other than those used as part of another clinical trial
	• Concomitant therapy: standard of care as specified above
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes
	  ☐ mortality of any cause at 15 days (time frame: 15 days)
	  ☐ mortality of any cause at 29 days (time frame: 29 days)
	  * Time to death: yes (up to 29 days)
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
	  * Number of participants with SAEs: yes
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: NR (up to 29 days)
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR

NCT04345523 *(Continued)*

- Additional outcomes
  * Category changes in ordinal scale (time frame: 15 days)
    ☐ proportion of patients in categories 5, 6 or 7 of the 7-point ordinal scale at day 15 ordinal scale:
      ○ not hospitalised, no limitations on activities
      ○ not hospitalised, limitation on activities
      ○ hospitalised, not requiring supplemental oxygen
      ○ hospitalised, requiring supplemental oxygen
      ○ hospitalised, on non-invasive ventilation or high-flow oxygen devices
      ○ hospitalised, on invasive mechanical ventilation or ECMO
      ○ death
  * Time to category 5, 6 or 7 of the ordinal scale (time frame: 29 days)
    ☐ time to change from baseline category to worsening into 5, 6 or 7 categories of the ordinal scale
  * Oxygenation-free days (time frame: 29 days)
  * Ventilator-free days
  * Change in biological parameters (time frame: days 1, 3, 5, 8, 11 and 29) - serum levels of CRP, lymphocyte count, LDH, D Dimer, IL-6, coagulation tests at baseline and days 3, 5, 8, 11, 15 and 29
  * Antibodies levels in CP donors recovered from COVID-19 (time frame: 3 months)
    ☐ quantitative total antibodies and neutralising antibody activity against SARSCoV-2 in the sera from donors and patients using viral pseudotypes
  * Viral load (time frame: days 1, 3, 5, 8, 11 and 29)
    ☐ change in PCR for SARS-CoV-2 in naso/oropharyngeal swabs and blood at baseline and on days 3, 5, 8, 11 (while hospitalised); and days 15 and 29 (if able to return to clinic or still hospitalised)

Starting date	3 April 2020
Contact information	Cristina Avendaño Solá, MD, PhD +34 91 191 64 79 cavendano@salud.madrid.org
Notes	• Recruitment status: recruiting (1 site, the rest not yet recruiting) • Prospective completion date: July 2020 • Sponsor/funding: Cristina Avendaño Solá

NCT04345679

Study name	Anti COVID-19 convalescent plasma therapy
Methods	• Trial design: phase 1, single-arm study • Sample size: 20 • Setting: hospital • Country: Hungary • Language: English • Number of centres
Participants	• Inclusion criteria * Age: > 18 years * Admitted to hospital due to SARS CoV-2 infection * Written informed consent

NCT04345679 *(Continued)*

	• Exclusion criteria
	  * Age: < 18 years
	  * Female patients who are pregnant or breastfeeding
	  * Patients with prior allergic reaction to transfusion
	  * Patients who received in the past 30 days immunoglobulin therapy
	• Inclusion criteria for blood donors
	  * Age: > 18 and < 60 years
	  * Body weight: > 50 kg
	  * Confirmed previous SARS CoV-2 infection
	  * 2 negative SARS CoV-2 test results
	  * Written informed consent
	  * Neutralising antibody titre min 1:120
	• Exclusion criteria for blood donors
	  * Age: < 18 or > 60 years
	  * Female patients who are pregnant
	  * HIV1/2 hepatitis B/C or syphilis infection

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: plasmapheresis donation of 400 mL will be performed in participants who recovered from COVID-19 and who are otherwise eligible for plasma donation, blood-type matched
	  * volume: 200 mL
	  * number of doses: 1
	  * antibody-titre: NR
	  * pathogen inactivated or not: > level of 1:320
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): none (single-arm)
	• Concomitant therapy: NR
	• Treatment cross-overs: none (single-arm)

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes
	  ☐ mortality (time frame: day 7, 12, 28)
	  * Time to death: yes (up to 28 days)
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (duration of mechanical ventilation up to 28 days)
	  * 30-day and 90-day mortality: NR (up to 28 days)
	  * Admission on the ICU: yes
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: yes
	• Additional outcomes
	  * Changing of viral load of SARS-CoV2 (time frame: day 1,3, 7, 12)
	  * Clinical status (time frame: day 7, 12, 28)
	  ☐ clinical status assessed according to the WHO guideline
	  * Changes in immunoglobulin G COVID-19 antibody titre (time frame: 12 days)
	  * Changes at the cytokine pattern (time frame: 12 days)

Starting date	14 April 2020

NCT04345679 *(Continued)*

Contact information	• Eszter Fodor, medical doctor; +36306640494; eszter.fodor@orthosera.com • Zsombor Lacza, MD, PhD; +36305249554; zsombor.lacza@orthosera.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 1 April 2021 • Sponsor/funding: Orthosera Kft

NCT04345991

Study name	Cohort multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in covid-19 patients - CORIMUNO-CORIPLASM: efficacy of convalescent plasma to treat SARS-CoV2 infected patients
Methods	• Trial design: randomised, parallel-assignment • Sample size: 120 (60 in each arm) • Setting: early-stage disease • Country: France • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Patients included in the CORIMUNO-19 cohort
	  * Onset of COVID-19 functional signs < 8 days (plasma transfusion may occur up to day 10 of onset)
	  * Mild severity as described in the WHO scale
	• Exclusion criteria
	  * Pregnancy
	  * Current documented and uncontrolled bacterial infection
	  * Prior severe (grade 3) allergic reactions to plasma transfusion

Interventions	• CP therapy or hyperimmune globulin therapy: CP
	• Details of CP:
	  * type of plasma: details of preparation not described
	  * volume: 200-220 mL
	  * number of doses: 2-4
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage (within 10 days of symptom onset)
	• For studies including a control group: comparator (type): standard of care
	• Concomitant therapy: standard of care
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes
	  * Time to death: yes

NCT04345991 *(Continued)*

	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
	  * Number of participants with SAEs: yes
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: no (up to 28 days)
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: yes
	• Additional outcomes
	  * WHO progression scale (time frame: at 4, 7 and 14 days after randomisation)
	  * Survival without needs of ventilator utilisation (time frame: at 4, 7 and 14 days after randomisation)
	  * Survival without use of immunomodulatory drugs (time frame: at day 14 after randomisation)

Starting date	14 April 2020
Contact information	Karine LACOMBE, PU-PH +33 149283196 karine.lacombe2@aphp.fr
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 1 June 2020 • Sponsor/funding: Assistance Publique - Hôpitaux de Paris

NCT04346446

Study name	Efficacy of convalescent plasma therapy in severely sick COVID-19 patients
Methods	• Trial design: randomised, clinical trial • Sample size: 20 • Setting: hospital • Country: India • Language: English • Number of centres: 2

Participants	• Inclusion criteria
	  * Severe COVID-19 infections defined as WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (version 5.0) with confirmation by RT-PCR assay with severe disease i.e. meeting any 2 of the following criteria:
	  ☐ respiratory distress, respiratory rate ≥ 30 breaths/min
	  ☐ oxygen saturation level < 93% in resting state
	  ☐ PaO2)/FiO2 ≤ 300 mmHg
	  ☐ lung infiltrates > 50% within 24-48 h

NCT04346446 *(Continued)*

	• Exclusion criteria * Donors who gave negative consent to participate in the study * Aged < 18 years or > 65 years * Known comorbid diseases (cardiopulmonary disease-structural or valvular heart disease, coronary artery disease, COPD, chronic liver disease, chronic kidney disease) * Multi-organ failure or requiring mechanical ventilation * Pregnancy * HIV or hepatitis * BMI > 35 kg/m2 * Extremely moribund patients with an expected life expectancy of < 24 h * Failure to give informed consent from the patient or family members * Haemodynamic instability requiring vasopressors * Previous allergic history to plasma * PaO2/FiO2 < 150 * Donors who were recovered with use of steroids during treatment
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * type of plasma: NR, up to 500 mL collected * volume: 200-600 mL * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): randomised 1:1 to CP or random plasma and best supportive care • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge: yes ☐ mortality in both groups (time frame: day 28) * Time to death: NR • Secondary outcomes * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: yes * Time to discharge from hospital: yes • Additional outcomes * Improvement in Pa02/Fi02 ratio in both groups (time frame: day 2) * Improvement in Pa02/Fi02 ratio in both groups (time frame: day 7) * Improvement in SOFA score in both groups (time frame: day 2) * Improvement in SOFA score in both groups (time frame: day 7) * Requirements of vasopressor in both groups (time frame: day 28) * Days free of dialysis in both groups (time frame: day 28)
Starting date	14 April 2020

NCT04346446 *(Continued)*

Contact information	Dr Meenu Bajpai, MD, Institute of Liver and Biliary Sciences, India mailto:meenubajpai%40hotmail.com?subject=NCT04346446, ILBS-COVID-02, Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients
Notes	• Recruitment status: recruiting • Prospective completion date: 20 June 2020 • Sponsor/funding: Institute of Liver and Biliary Sciences, India

NCT04346589

Study name	A pilot study to explore the efficacy and safety of rescue therapy with antibodies from convalescent patients obtained with double -filtration plasmapheresis (DFPP) and infused in critically ill ventilated patients with coronavirus disease 2019 (COVID-19)
Methods	• Trial design: interventional (single-arm) • Sample size: 10 • Setting: critically ill patients • Country: Italy • Language: English • Number of centres: 5
Participants	• Inclusion criteria * > 18-years, men and women * COVID-19 pneumonia diagnosed by standard criteria * Need of ventilator support * Informed consent for participation in the study (critically ill patients will be unable to provide consent. Consent will be oral if a written consent will be impossible. If the patient is incapable of giving an informed consent and an authorised representative is not available without a delay that would, in the opinion of the Investigator, compromise the potential life-saving effect of the treatment this can be administered without consent. Consent to remain in the research should be sought as soon as the conditions of the patient will allow it). * < 48 h of mechanical ventilation • Exclusion criteria * Patient being treated with other anti-COVID-19 experimental treatments
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * type of plasma: anti-coronavirus antibodies obtained with double-filtration plasmapheresis (DFPP) from convalescent patients * volume: convalescent antibodies will be obtained with one DFPP procedure from consenting donors * number of doses: 1 * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill mechanically ventilated patients (< 48 h mechanical ventilation) • For studies including a control group: comparator (type): none (single-arm) • Concomitant therapy: NR • Treatment cross-overs: none (single-arm)
Outcomes	• Primary outcomes * All-cause mortality at hospital discharge: yes (up to 6 months) * Time to death: yes

NCT04346589 *(Continued)*

	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: reported
	  * Admission on the ICU: reported
	  * Length of stay on the ICU: reported
	  * Time to discharge from hospital
	• Additional outcomes
	  * Number of mechanical ventilation days
	  * Shift to CPAP ventilation

Starting date	April 2020
Contact information	Piero Luigi Ruggenenti, MD; 0039 035 267 ext 3814; pruggenenti@asst-pg23.it
Notes	• Recruitment status: not yet recruiting • Prospective completion date: July 2020 • Sponsor/funding: A.O. Ospedale Papa Giovanni XXIII, Aferetica - Italy (BO)

NCT04347681

Study name	A national collaborative multicenter phase II study for potential efficacy of convalescent plasma to treat severe COVID-19 and patients at high risk of developing severe COVID-19
Methods	• Trial design: non-randomised, parallel assignment • Sample size: 40 (all receiving intervention) • Setting: hospital • Country: Saudi Arabia • Language: English • Number of centres: 10

Participants	• Inclusion criteria
	  * ≥ 18 years
	  * COVID 19 confirmed as per case definition of CDC or Ministry of Health/Waqayah
	  * Must have been requiring ICU care or severe or immediately life-threatening care: 1. patient requiring ICU admission; 2. severe disease, defined as:
	  ☐ dyspnoea
	  ☐ respiratory frequency ≥ 30/min
	  ☐ blood oxygen saturation ≤ 93%
	  ☐ PaO2/FiO2 < 300, and/or lung infiltrates > 50% within 24-48 h
	  * 3. Life-threatening disease is defined as:
	  ☐ respiratory failure
	  ☐ septic shock, and/or
	  ☐ multiple organ dysfunction or failure
	• Exclusion criteria
	  * Negative or non-conclusive test COVID-19 rRT-PCR test for SARS-CoV-2
	  * Mild symptoms
	  * Hospitalisation not requiring ICU admission

NCT04347681 *(Continued)*

Interventions	• CP therapy or hyperimmune globulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: NR
	  * volume: 10-15 mL/kg body weight of recipient
	  * number of doses: 1-5 (up to 5 times daily)
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): none
	• Concomitant therapy: NR
	• Treatment cross-overs: none (single-arm)

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (up to 12 weeks)
	  * Time to death: yes (up to 12 weeks)
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
	  * Number of participants with SAEs: yes
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: yes
	  * Admission on the ICU: yes
	  * Length of stay on the ICU: yes
	  * Time to discharge from hospital: NR
	• Additional outcomes
	  * Days to clinical recovery, defined as number of days to symptoms resolution and COVID 19 negative PCR (by NP swap) (time frame: time from signing consent to recovery, up to 12 weeks)

Starting date	12 April 2020
Contact information	Hani AL-Hashmi, MD; 00966564773377; hanih.hashmi@kfsh.med.sa Mahammad Awadallah, MSc; 00966545032312; mahammad.awadalla@kfsh.med.sa
Notes	• Recruitment status: recruiting in 1 site • Prospective completion date: 11 April 2021 • Sponsor/funding: King Fahad Specialist Hospital Dammam

NCT04348656

Study name	A randomized open-label trial of CONvalenscent plasma for hospitalized adults with acute COVID-19 respiratory illness (CONCOR-1)
Methods	• Trial design: randomised, clinical trial • Sample size: 1200 • Setting: hospital • Country: Canada • Language: English • Number of centres: 27

NCT04348656 *(Continued)*

Participants	• Inclusion criteria
	  * ≥ 16 years old
	  * Admitted to hospital with confirmed COVID-19 respiratory illness
	  * Receiving supplemental oxygen
	  * 500 mL of ABO-compatible CP is available
	• Exclusion criteria
	  * Onset of symptoms > 12 days prior to randomisation
	  * Intubated or plan in place for intubation
	  * Plasma is contraindicated (e.g. history of anaphylaxis from transfusion)
	  * Decision in place for no active treatment

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * volume: 500 mL of CP (from 1 single-donor unit of 500 mL or 2 units of 250 mL from 1-2 donations) collected by apheresis from donors who have recovered from COVID-19 and frozen (1 year expiration date from date of collection)
	  * number of doses: when administering 2 units of 250 mL, the 2nd unit will be administered after the first, and no longer than 12 h later
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): randomised 1:1 to CP and standard care
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes
	  ☐ intubation or death in hospital (time frame: day 30)
	  * Time to death: yes
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
	  * Number of participants with SAEs: yes
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: yes
	  * Admission on the ICU: yes
	  * Length of stay on the ICU: yes
	  * Time to discharge from hospital: yes
	• Additional outcomes
	  * Need for renal replacement therapy (time frame: day 30)
	  * Development of myocarditis (time frame: day 30)

Starting date	27 April 2020
Contact information	Donald M Arnold, MD, McMaster University, Hamilton, Canada arnold@mcmaster.ca
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31 December 2020 • Sponsor/funding: Hamilton Health Sciences Corporation, Canada

NCT04348877

Study name	Plasma rich antibodies from recovered patients from COVID19 (PRA-001)
Methods	• Trial design: single-arm, interventional • Sample size: 20 • Setting: critically ill patients • Country: Egypt • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * 18-80 years old
	  * Laboratory-confirmed COVID-19
	  * Severe or immediately life-threatening COVID-19 (severe disease is defined as: dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, PaO2/FiO2 < 300, and/or lung infiltrates > 50% within 24-48 h. Life-threatening disease is defined as: respiratory failure, septic shock, and/or multiple organ dysfunction or failure)
	  * Must provide informed consent by patient or his/her legal guardian or professional legal representative
	• Exclusion criteria
	  * Mild or moderate COVID-19
	  * Participation in any investigational clinical study, other than observational, within the past 30 days; or plans to participate in such a study at any time from the day of enrolment until 30 days post-treatment in the current study

Interventions	• CP therapy or hyperimmune globulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: other details not specified
	  * volume: 400 mL
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): none
	• Concomitant therapy: standard of care (antiviral, hydroxychloroquine and antibiotics)
	  * (oseltamivir (75 mg/12 h for 5-10 days) and hydroxychloroquine (400 mg twice in first day, 200 twice for 4-9 days) ± azithromycin 500 mg daily for 5 days
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: NR
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  * 30-day and 90-day mortality: NR
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR

NCT04348877 *(Continued)*

	• Additional outcomes • Viral COVID-19 clearance (time frame: 14 days) • Radiological improvement (time frame: 14 days) • Clinical improvement in form of normal body temperature for 48 h (time frame: 14 days)
Starting date	20 April 2020
Contact information	Hossam Fahmy, Professor of Faculty of Medicine, Ain Shams University
Notes	• Recruitment status: not yet recruiting • Prospective completion date: December 2020 • Sponsor/funding: Ain Shams University

NCT04352751

Study name	Experimental use of convalescent plasma for passive immunization in current COVID-19 pandemic in Pakistan in 2020
Methods	• Trial design: single-arm, interventional • Sample size: 2000 • Setting: moderate-severe cases • Country: Pakistan • Language: English • Number of centres: 1 reported
Participants	• Inclusion criteria * Informed consent must have been obtained * Confirmed COVID-19 cases confirmed by RT-PCR laboratory tests * Moderately severe or severe life-threatening COVID-19 related features: ☐ moderately severe disease as defined by the following features: shortness of breath; respiratory rate ≥ 30/min; arterial blood oxygen saturation ≤ 92%,; and/or lung infiltrates > 25% within 24-48 h ☐ severe life-threatening disease as defined by the presence of any of the following features: respiratory failure; shock; multiple organ dysfunction • Exclusion criteria * Allergy history of plasma, sodium citrate and methylene blue * For patients with history of autoimmune system diseases or selective IgA deficiency, the application of CP should be evaluated cautiously by clinicians * Patients having evidence of uncontrolled cytokine release syndrome leading to end-stage multiorgan failure
Interventions	• CP therapy or hyperimmune globulin therapy: CP • Details of CP: * type of plasma: standard apheresis plasma collection protocol using Haemonetics MCS+ intermittent blood flow system or Terumo Optia, Cobe-Spectra, Trima or Fresenius continuous flow system to be used. 900-1000 mL collected each time * volume ☐ children: 15 mL/kg over 4-6 h once in patients under 35 kg body weight ☐ adults: maximum 450-500 mL over 4-6 h once in all adult patients * number of doses: 1 * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

NCT04352751 *(Continued)*

	• For studies including a control group: comparator (type): none • Concomitant therapy: NR • Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: NR
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (information will be recorded)
	  * Number of participants with SAEs: yes (information will be recorded)
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (up to 4 weeks post-treatment)
	  * 30-day and 90-day mortality: NR
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	• Additional outcomes
	  * Change in COVID-19 severity status (time frame: up to 9 days). Improvement in disease severity will be regarded as a shift from critical to severe or from severe to mild disease category. The various disease categories are defined as following:
	  ☐ mild COVID-19, defined by the absence of features given in criteria for moderate and severe disease
	  ☐ severe COVID-19, defined by the presence of any of the following features: shortness of breath; respiratory rate ≥ 30/min; arterial blood oxygen saturation ≤ 93%; lung infiltrates > 50% within 24-48 h
	  ☐ critical COVID-19, defined by the presence of any of the following features: respiratory failure; shock; multiple organ dysfunction

Starting date	April 2020
Contact information	Contact: Dr. Arshi Naz, PhD,Diplab; 00923232234376; labarshi@yahoo.com Contact: Dr. Neeta Maheshwary, MBBS M.Phil; 00923208247773; drneeta@hiltonpharma.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: April 2021 • Sponsor/funding: Hilton Pharma

NCT04353206

Study name	A feasibility study assessing the safety of multiple doses of anti-SARS-CoV-2 plasma in mechanically ventilated intubated patients with respiratory failure due to COVID-19
Methods	• Trial design: single-arm, interventional • Sample size: 90 • Setting: ICU • Country: USA • Language: English • Number of centres: 3

NCT04353206 *(Continued)*

Participants	• Inclusion criteria
	  * ≥ 18 years
	  * Respiratory failure requiring mechanical ventilation due to COVID-19-induced pneumonia with confirmation via SARS-CoV-2 RT-PCR testing
	  * PaO2/FiO2 ratio < 300 (or SpO2/FiO2 < 315)
	  * Bilateral pulmonary infiltrates
	• Exclusion criteria
	  * Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products)
	  * In the opinion of the site investigator or primary clinical care team, anticipated to die within 48 h
	  * Acute or chronic disease/illness that, in the opinion of the site investigator, has an expected life expectancy of < 28 days unrelated to COVID-19-induced pneumonia (e.g. stage IV malignancy, neurodegenerative disease, anoxic brain injury, etc.)
	  * Use of home oxygen at baseline
	  * Use of home mechanical ventilation at baseline (CPAP or bi-level positive airway pressure without need for oxygen is NOT an exclusion)
	  * Respiratory failure caused by illness other than SARS-CoV-2
	  * Other documented uncontrolled infection
	  * > 72 h have elapsed since first meeting inclusion criteria
	  * Severe disseminated intravascular coagulation, TTP, or antithrombin III deficiency needing factor replacement, fresh-frozen plasma, cryoprecipitate
	  * On warfarin and deemed necessary to maintain therapeutic international normalised ratio (because the CP will reverse the warfarin effect)
	  * On dialysis at the time enrolment is considered
	  * Active intracranial bleeding
	  * Clinically significant myocardial ischaemia
	  * Prisoner or incarceration
	  * Pregnancy or active breast feeding
	  * Has already received CP for COVID-19 infection during current admission
	  * Current participation in another interventional research study
	  * Inability or unwillingness of subject or legal surrogate/representative to give written informed consent

Interventions	• CP therapy or hyperimmune globulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: as per FDA guidelines
	  * volume: NR
	  * number of doses: 1-6 (1-2 units day 0, 3, 6)
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): not > 72 h have elapsed since first meeting inclusion criteria
	• For studies including a control group: comparator (type): none
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (up to 60 days)
	  * Time to death: yes (up to 60 days)

NCT04353206 *(Continued)*

	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
	  * 30-day and 90-day mortality: yes (up to 60 days)
	  * Admission on the ICU: yes (all in ICU)
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	• Additional outcomes
	  * Proportion of participants who consent to the study and receive at least one dose of CP. (time frame: 60 days)
	  * Respiratory status and overall clinical status will be reviewed during follow up (on days 14, 28, and 60)

Starting date	May 2020
Contact information	Noah Merin, MD PhD; 310-423-1160; Noah.Merin@cshs.org David Hager, MD PhD; dhager1@jhmi.edu
Notes	• Recruitment status: not yet recruiting • Prospective completion date: May 2021 • Sponsor/funding: Noah Merin, Johns Hopkins University, University of Pittsburgh Medical Center

NCT04354831

Study name	An open label, phase 2 study evaluating the efficacy and safety of high-titre anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 infection
Methods	• Trial design: non-randomised • Sample size: 106 • Setting: hospital • Country: USA • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  * Age ≥ 18 years
	  * Hospitalised as an in-patient with positive COVID-19 test by PCR
	  * Presence of respiratory symptoms with any of severe features as below:
	  ☐ respiratory rate ≥ 24/min
	  ☐ oxygen support > 3 L/min by nasal cannula
	  ☐ new onset or worsening of respiratory symptoms with radiologic confirmation of bilateral ground glass opacities that cannot be attributed to another cause
	  * Patient/HCPOA must agree to storage of blood specimens for future testing
	  * Patient/HCPOA is willing and able to provide electronic informed consent and comply with all protocol requirements. If patient is unable to consent due to incapacity, HCPOA should be defined and able to consent for the patient
	  * Allowed to receive all standard of care. Co-enrolment in other clinical trials is permitted

NCT04354831 *(Continued)*

	• Exclusion criteria
	  * Women of childbearing potential with positive pregnancy test (mandatory)
	  * Breastfeeding
	  * Receipt of pooled immunoglobulin (e.g. IVIG or other hyperimmune globulin products) in past 14 days. This does not apply to monoclonal antibodies
	  * Mechanical ventilation for > 14 days
	  * Days from symptom onset > 21 days
	  * Expected survival < 72 h
	  * Contraindication to transfusion or history of prior reactions to transfusion blood products including any proven history of TRALI
	  * Patients who were previously admitted to ICU cannot be enrolled in the non-ICU cohort. These patients could need ICU-level care subsequently and at that time point could be considered for ICU cohort.

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: SARS-CoV-2 CP
	  * volume: 1-2 units; ~200-400 mL maximum dose as 7 mL/kg adjusted ideal body weight
	  * number of doses: study drug will be administered as a single IV infusion
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): NR
	• Concomitant therapy: NR
	• Treatment cross-overs: not applicable

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: overall mortality within 60 days
	  * Time to death: yes
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs: NR
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  * 30-day and 90-day mortality: NR
	  * Admission on the ICU: yes
	  * Length of stay on the ICU: yes
	  * Time to discharge from hospital: NR

Starting date	1 May 2020
Contact information	Mary Beth Graham, MD, Medical College of Wisconsin, USA mailto:mbgraham%40mcw.edu?subject=NCT04354831, PRO00037712, A Study Evaluating the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma in Hospitalized Patients With COVID-19 Infection
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 1 May 2023 • Sponsor/funding: Medical College of Wisconsin, USA

NCT04355767

Study name	Convalescent plasma to limit coronavirus associated complications: a randomized double-blind, phase 2 study comparing the efficacy and safety of high-titer anti-SARS-CoV-2 plasma vs. placebo in emergency room patients
Methods	• Trial design: RCT • Sample size: 206 • Setting: patients presenting to ED • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Age ≥ 18 years old
	  * Patients requiring clinical evaluation in the ED but who do not require hospital admission
	  * Patients who are within 14 days since the onset of COVID-19 symptoms and are confirmed to have the disease via COVID-19 SARS-CoV-2 RT-PCR testing or rapid RNA assay
	  * Patient agrees to storage of specimens for future testing
	• Exclusion criteria
	  * Women who are pregnant or breastfeeding
	  * Received pooled immunoglobulin in the past 30 days
	  * Contraindication to transfusion or history of prior reactions to transfusion blood products

Interventions	• CP therapy or hyperimmune globulin therapy: CP
	• Details of CP:
	  * type of plasma: CP, other details not provided
	  * volume: 200-600 mL
	  * number of doses:1-2
	  * antibody-titre: > 1:80
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): within 14 days' onset of disease
	• For studies including a control group: comparator (type): normal plasma
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: NR
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
	  * Number of participants with SAEs
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: none
	  * 30-day and 90-day mortality: none
	  * Admission on the ICU: none
	  * Length of stay on the ICU: none
	  * Time to discharge from hospital: none
	• Additional outcomes
	  * Time to disease progression (time frame: 15 days)
	  * Change in symptom severity over time (time frame: 15 days)

NCT04355767 *(Continued)*

Starting date	May 2020
Contact information	Study team; 650-724-7186; jcunning@stanford.edu
Notes	• Recruitment status: not yet recruiting • Prospective completion date: December 2022 • Sponsor/funding: Stanford University

NCT04355897

Study name	CoVID-19 plasma in treatment of COVID-19 patients
Methods	• Trial design: single-arm intervention study • Sample size: 100 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Age 18-80 years
	  * Symptomatic CoVID-19 disease requiring hospitalisation
	  * SARS-CoV-19 PCR positive
	  * Elevated high-sensitivity troponin
	• Exclusion criteria
	  * Multi-organ/system failure
	  * Renal insufficiency (estimated GFR < 30 or renal replacement therapy)
	  * Liver dysfunction (> 3 x ULN serum glutamic oxaloacetic transaminase/serum glutamate pyruvate transaminase)
	  * Chronic immunosuppression therapy
	  * Prior organ transplant
	  * Prior multiple transfusions for myelodysplastic syndrome
	  * Prior treatment with plasma, immunoglobulin transfusion within 30 days
	  * Allergic reaction to blood/ plasma products
	  * Pregnant or breast feeding at the time of study
	  * Inability to provide informed consent

Interventions	• CP therapy or hyperimmune globulin therapy: CP
	• Details of CP:
	  * type of plasma: CP, details of preparation not specified
	  * volume: 500 mL
	  * number of doses: 1
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with elevated high-sensitivity troponin or requiring mechanical ventilation
	• For studies including a control group: comparator (type): none
	• Concomitant therapy: NR
	• Treatment cross-overs: none

NCT04355897 *(Continued)*

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (at day 28)
	  * Time to death: yes
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
	  * Number of participants with SAEs: yes
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (at day 28)
	  * 30-day and 90-day mortality: NR (until day 28)
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	  * Additional outcomes: requirement and duration for mechanical ventilation (at day 28)

Starting date	NR
Contact information	Dean J Kereiakes, MD; 513-585-1777; lindnermd@thechristhospital.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: August 2020 • Sponsor/funding: The Christ Hospital

NCT04356482

Study name	Determination of the dose and effectiveness of convalescent plasma in severely and very severely ill patients by COVID-19
Methods	• Trial design: interventional, single-arm • Sample size: 90 • Setting: critically ill patients • Country: Mexico • Language: English • Number of centres: 4

NCT04356482 *(Continued)*

Participants	• Inclusion criteria
	  * All patients with COVID-19 test positive
	  * Severely ill patient
	  ☐ respiratory difficulty
	  ☐ sat O2 < 93% without O2 but improves with the use of supplemental oxygen
	  ☐ CT scan image: COVID-19-compatible pneumonia
	  ☐ ≥ 1 of at least: SOFA = 0, D-dimer ≥ 500, age ≥ 65 years, comorbidities such as high blood pressure, diabetes mellitus type I and II, chronic kidney failure, controlled or cured cancer, ≥ 1 degree of obesity
	  * Very severely ill
	  ☐ respiratory difficulty that does not improve with supplemental oxygen, requiring intubation and connecting to ventilatory support of no > 72 h or 3 days
	  ☐ CT image: COVID-19 compatible pneumonia
	  ☐ ≥ 1 of at least: SOFA ≥ 1, D-Dimer ≥ 750, age ≥ 65 years, comorbidities such as hypertension, diabetes mellitus type I and II, chronic kidney failure, controlled or cured cancer, ≥ 1 degree of obesity
	  ☐ survival over 5 days
	  * Pregnant women are accepted
	• Exclusion criteria
	  * Patients with asymptomatic/mild disease for COVID-19
	  * Children < 16 years old
	  * Patients with atypical pneumonia without COVID-19 diagnostic for PCR-RT

Interventions	• CP therapy or hyperimmune globulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: CP, details not provided
	  * volume: different amounts to be given to severe vs very severe ill patients, not specified
	  * number of doses: NR
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): none
	• Concomitant therapy: NR
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: NR
	  * Time to death: NR
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
	  * Number of participants with SAEs: yes
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (up to 22 days)
	  * 30-day and 90-day mortality: NR
	  * Admission on the ICU: yes
	  * Length of stay on the ICU: yes
	  * Time to discharge from hospital: NR
	• Additional outcomes
	  * Improvement in tomographic image (time frame: day -1 to day +12)
	  * Test positivity for COVID-19 (time frame: day +6 to day +12)

NCT04356482 *(Continued)*

Starting date	May 2020
Contact information	Luis M Villela, MD; +526624756529; luisvillela@yahoo.com Diego Espinoza, MD; +526623862375; dr.espinoza.peralta@gmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: December 2020 • Sponsor/funding: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado

NCT04356534

Study name	Convalescent plasma trial in COVID -19 patients
Methods	• Trial design: randomised, clinical trial • Sample size: 40 • Setting: hospitalised patients • Country: Bahrain • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * COVID-19 diagnosis
	  * Hypoxia, (oxygen saturation of ≤ 92% or PO2 < 60 mmHg on arterial blood gas analysis) and patient requiring oxygen therapy)
	  * Evidence of infiltrates on chest X-ray or CT scan
	  * Able to give informed consent
	  * Patients age ≥ 21 with no upper age
	• Exclusion criteria
	  * Mild disease not requiring oxygen therapy
	  * Normal chest X-ray and CT scan
	  * Requiring ventilatory support
	  * History of allergy to plasma, sodium citrate or methylene blue
	  * History of autoimmune disease or selective IGA deficiency

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * volume: 400 mL
	  * number of doses: 200 mL x 2 (2 consecutive days)
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): randomised to local standard of care, which include antivirals and supportive care or plasma therapy using CP with antibody against SARS-CoV-2 plus routine local standard of care
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes
	  ☐ mortality rate (time frame: mortality rate at 28 days)
	  * Time to death: yes

NCT04356534 *(Continued)*

- Secondary outcomes
  - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
  - Number of participants with SAEs: NR
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
  - 30-day and 90-day mortality: NR
  - Admission on the ICU: NR
  - Length of stay on the ICU: NR
  - Time to discharge from hospital: NR
- Additional outcomes
  - Time to viral clearance (time frame: 10 days or until discharge)
  - Radiological improvement (time frame: 10 days or until discharge)
  - Reduction in white cell count (time frame: 10 days or until discharge)
  - CRP measurement (time frame: 10 days or until discharge)
  - LDH measurement (time frame: 10 days or until discharge)
  - Procalcitonin measurement (time frame: 10 days or until discharge)
  - D-Dimer measurement (time frame: 10 days or until discharge)
  - Ferritin measurement (time frame: 10 days or until discharge)
  - Troponin T measurement (time frame: 10 days or until discharge)
  - Brain natriuretic peptide measurement (time frame: 10 days or until discharge)

Starting date	19 April 2020
Contact information	Manaf Al Qahtani, Dr. Royal College of Surgeons in Ireland - Bahrain; mailto:mqahtani%40rc-si-mub.com?subject=NCT04356534, BDF/R&REC/2020-423, Convalescent Plasma Trial in COVID -19 Patients
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 30 June 2020 • Sponsor/funding: Royal College of Surgeons in Ireland - Medical University of Bahrain

NCT04357106

Study name	COPLA Study: treatment of severe forms of coronavirus infection with convalescent plasma
Methods	• Trial design: single-arm, interventional • Sample size: 10 • Setting: ICU • Country: Mexico • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * SARS-CoV2 infection with serious evolution and in ICU
	  * With or without ventilatory assistance
	  * Treated or not with hydroxychloroquine 200 mg every 12 h
	  * Either sex
	  * > 18 years
	  * Signed informed consent

NCT04357106 *(Continued)*

	• Exclusion criteria
	  * Treated with the following medications: azithromycin, ritonavir/lopinavir, remdesivir, interferons, ruxolinitib, tocilizumab
	  * Severe kidney failure who require replacement therapy

Interventions	• CP therapy or hyperimmune globulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: apheresis plasma
	  * volume: 200 mL
	  * number of doses: 1
	  * antibody-titre: NR
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
	• For studies including a control group: comparator (type): none
	• Concomitant therapy: with or without ventilation, hydroxychloroquine
	• Treatment cross-overs: none

Outcomes	• Primary outcomes
	  * All-cause mortality at hospital discharge: yes (up to 30 days)
	  * Time to death: yes (up to 30 days)
	• Secondary outcomes
	  * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (up to 7 days)
	  * Number of participants with SAEs: yes (up to 7 days)
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
	  * 30-day and 90-day mortality: yes (up to 30 days)
	  * Admission on the ICU: yes (in ICU)
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	• Additional outcomes
	  * Lung injury defined as PaO2/FiO2 relation (time frame: 7 days)

Starting date	13 April 2020
Contact information	Juan Carlos Olivares-Gazca, MD, MPH; 2222438100; jolivares@hsctmexico.com José Manuel Priesca-Marin, MD; 2222438100; mpriesca@hsctmexico.com
Notes	• Recruitment status: recruiting • Prospective completion date: August 2020 • Sponsor/funding: Centro de Hematología y Medicina Interna

AE: adverse event; **ALT:** alanine transaminase; **ARDS:** acute respiratory distress syndrome; **AST:** aspartate transaminase; **BAL:** bronchoalveolar lavage; **BMI:** body mass index; **CDC:** Centers for Disease Control and Prevention; **COI:** conflict of interest; **COPD:** chronic obstructive pulmonary disease; **CP:** convalescent plasma; **CPAP:** continuous positive airway pressure; **CPK:** creatine phosphokinase; **CRP:** C-reactive protein; **CT:** computed tomography; **ECMO:** extracorporeal membrane oxygenation; **ED:** emergency department; **FDA:** US Food and Drug Administration; **FiO2:** fractional inspired oxygen; **GFR:** glomerular filtration rate; **HBV/HCV:** hepatitis B/C; **HCPOA:** healthcare power of attorney; **ICU:** intensive care unit; **IgA (B/G/M):** immunoglobulin A (B/G/M); **IL-6:** interleukin-6; **IV:** intravenous; **IVIG:** intravenous immunoglobulin; **LAR:** legal authorised representative; **LDH:** lactate dehydrogenase; **NR:** not reported; **NYHA:** New York Heart Association; **PaO2:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **RCT:** randomised controlled trial; **RNA:** ribonucleic acid; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SARS:** severe acute respiratory syndrome; **SC:** subcutaneous; **SOFA:** Sequential Organ Failure Assessment; **SpO2:** peripheral capillary oxygen saturation; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TB:** tuberculosis; **TRALI:** transfusion-related

acute lung injury; **TTP:** thrombotic thrombocytopenic purpura; **UIP:** usual interstitial pneumonia; **ULN:** upper limit of normal; **WHO:** World Health Organization

ADDITIONAL TABLES

Table 1. 'Risk of bias' assessment criteria for observational studies

Heading	Internal validity	External validity
Study group	**Selection bias** (representative: yes/no) • if the described study group consisted of > 80% of individuals with Covid-19 treated with convalescent plasma therapy or hyperimmune globulin in the original cohort **or** • if it was a random sample with respect to the treatment and important prognostic factors	**Reporting bias** (well defined: yes/no) • if the study population is well described (e.g. severity of disease, age, risk factors) **and** • the intervention is well described (e.g. number of doses, volume)
Follow-up	**Attrition bias** (adequate: yes/no) • if the outcome was assessed for > 90% of the study group of interest (++) **or** • if the outcome was assessed for 60% to 90% of the study group of interest (+)	**Reporting bias** (well defined: yes/no) • if the length of follow-up was mentioned
Outcome	**Detection bias** (blind: yes/no) • if the outcome assessors were blinded to the investigated determinant	**Reporting bias** (well defined: yes/no) • if the outcome definition was objective and precise, and the method of detection was provided
Risk estimation	**Confounding** (adjustment for other factors: yes/no) • if important prognostic factors (i.e. age, co-treatment, comorbidities) or follow-up were taken adequately into account	**Analyses** (well defined: yes/no) • if a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi^2 was calculated

Table 2. Certainty of evidence ratings for the effectiveness and safety of convalescent plasma therapy for people with COVID-19

Patients or population: people with COVID-19

Settings: inpatient

Intervention: convalescent plasma transfusion

Comparison: not applicable; observational studies only

Outcome	Risk of bias	Indirectness	Imprecision	Inconsistency	Other considerations	Certainty of the evidence (GRADE)

Table 2. Certainty of evidence ratings for the effectiveness and safety of convalescent plasma therapy for people with COVID-19 *(Continued)*

All-cause mortality at hospital discharge	Very serious[a]	Direct	Very imprecise[b]	Inconsistent[c]	Study design[d]	⊕⊖⊖⊖ **Very low**
Improvement of clinical symptoms Assessed by respiratory support Follow-up: 7 days	Very serious[a]	Direct	Very imprecise[b]	Inconsistent[c]	Study design[d]	⊕⊖⊖⊖ **Very low**
Improvement of clinical symptoms Assessed by respiratory support Follow-up: 15 days	Very serious[a]	Direct	Very imprecise[b]	Inconsistent[c]	Study design[d]	⊕⊖⊖⊖ **Very low**
Improvement of clinical symptoms Assessed by respiratory support Follow-up: 30 days	Very serious[a]	Direct	Very imprecise[b]	Inconsistent[c]	Study design[d]	⊕⊖⊖⊖ **Very low**
Grade 3-4 adverse events [e]	Very serious[a]	Direct	Very imprecise[b]	Inconsistent[c]	Study design[d]	⊕⊖⊖⊖ **Very low**
Serious adverse events	Very serious[a]	Direct	Very imprecise[b]	Inconsistent[c]	Study design[d]	⊕⊖⊖⊖ **Very low**

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Risk of bias within and across studies is serious, so we downgraded two points for risk of bias. We included observational studies only, so we started assessment from 'low' certainty evidence.
[b]We downgraded two points for imprecision because of the very small information size and nonexisting control group; effect estimates cannot be calculated.
[c]We identified clinical heterogeneity among participants (different severity of disease, comorbidities, different number and type of previous treatments), so we downgraded one point for inconsistency.
[d]We included observational studies only, so we started assessment from low-certainty evidence and did not summarise outcome data across studies.
[e]We assume these adverse events are grade 3-4; studies did not report grading of adverse events.

Table 3. Improvement of clinical symptoms (assessed by need for respiratory support)

Study[a]	Number of participants	Convalescent plasma given				
		at baseline	at day 7	at day 15	up to day 30	from baseline to longest follow-up

Table 3. Improvement of clinical symptoms (assessed by need for respiratory support) *(Continued)*

Ahn 2020	2	• 2 mechanical ventilation and intubated	• 0/2 participants with clinical improvement	• 0/2 participants with clinical improvement	• 2/2 participants with clinical improvement	Longest follow-up: 16 and 18 days (2/2 participants with clinical improvement) • 1 'currently' successfully weaned from mechanical ventilation • 1 discharged (no respiratory support)
			• 2 mechanical ventilation and intubated	• 2 mechanical ventilation and intubated	• 1 not ventilated • 1 'currently' weaned from mechanical ventilation (not sure if on oxygen, not reported)	
Duan 2020	10	• 2 mechanical ventilation and high-flow nasal cannula • 1 mechanical ventilation • 3 high-flow nasal cannula • 2 low-flow nasal cannula • 2 no respiratory support	• 3/8 participants with clinical improvement • 1 on mechanical ventilation • 4 on high-flow nasal cannula • 2 on low-flow nasal cannula • 3 no respiratory support	• NR	• NR	Longest follow-up: 3 days after transfusion (3/8 participants with clinical improvement) • 1 on mechanical ventilation • 4 on high-flow nasal cannula • 2 on low-flow nasal cannula • 3 no respiratory support
Shen 2020	5	• 1 ECMO • 4 mechanical ventilation and intubated	• 2/5 participants with clinical improvement	• 5/5 participants with clinical improvement	• 5/5 participants with clinical improvement	Longest follow-up: up to 37 days after first transfusion or until discharge (5/5 participants with clinical improvement) • 2 mechanical ventilation and intubated • 3 discharged (no respiratory support)
			• 0 ECMO • 4 mechanical ventilation and intubated • 1 not ventilated[b]	• 0 ECMO • 2 mechanical ventilation and intubated • 3 not ventilated[b]	• 0 ECMO • 2 mechanical ventilation and intubated • 3 not ventilated[b]	
Ye 2020	6	• 4 on oxygen support (1 via nasal cannula, the other modes not specified)	• 4/4 participants with clinical improvement	• 4/4 participants with clinical improvement	• NR	Longest follow-up: up to 13 days after first transfusion or until discharge (4/4 participants with clinical improvement)
			• 6 no respiratory support (dates not exactly clear, but mostly within 7 days after CP)	• 6 no respiratory support		

Table 3. Improvement of clinical symptoms (assessed by need for respiratory support) *(Continued)*

		• 2 no respiratory support				• 6 no respiratory support
Zhang 2020a	4	• 2 ECMO • 1 mechanical ventilation and intubated • 1 on NIV and high-flow (dates unclear)	• 1/4 participants with clinical improvement	• 2/4 participants with clinical improvement	• 3/4 participants with clinical improvement	Longest follow-up: up to 36 days after first transfusion or until discharge (3/4 participants with clinical improvement, 1 unclear) • 1 ECMO • 2 no respiratory support • 1 respiratory support unclear, discharged on day 7; receiving home oxygen therapy
			• 2 ECMO • 1 mechanical ventilation and intubated • 1 respiratory support unclear; discharged on day 7, receiving home oxygen therapy	• 1 ECMO • 1 mechanical ventilation and intubated • 1 not ventilated[b] • 1 respiratory support unclear; discharged on day 7, receiving home oxygen therapy	• 1 ECMO • 2 not ventilated[b] • 1 respiratory support unclear, discharged on day 7; receiving home oxygen therapy	
Zhang 2020b	1	• 1 mechanical ventilation and intubated	• 0/1 participant with clinical improvement	• 1/1 participant with clinical improvement	• NR	Longest follow-up: 11 days after first transfusion until end of ICU stay (1/1 with clinical improvement) • 1 no respiratory support (remains in general ward
			• 1 mechanical ventilation and intubated	• 1 not ventilated[b]		

CP: convalescent plasma; **ECMO:** extracorporeal membrane oxygenation; **NIV:** non-invasive ventilation; **NR:** not reported

[a]Two studies are not included due to lack of information regarding clinical improvement (Pei 2020; Tan 2020).
[b]Off ventilation and not reported to be on respiratory support.

Table 4. Hospital discharge

Study	Number of participants	Number of participants discharged at end of follow-up	Day of discharge (after convalescent plasma)
Ahn 2020	2	1	Day 18
Duan 2020	10	Not reported	Not reported
Pei 2020	3	3	Day 6 Day 14 Day 23
Shen 2020	5	3	Day 32 Day 33

Table 4. Hospital discharge *(Continued)*

			Day 35
Tan 2020	1	0	Not applicable
Ye 2020	6	5 1 unclear	Day 4 Day 6 Day 6 Day 10 1 unclear
Zhang 2020a	4	3	Day 7 Day 25 Day 27
Zhang 2020b	1	0	Not applicable

Table 5. Intensive care unit (ICU) stay after convalescent plasma

Study	Number of participants	Baseline: number of participants on ICU	End of follow-up: number of participants on ICU
Ahn 2020	2	NR (probably 2)	NR (probably 1; 1 discharged)
Duan 2020	10	NR (probably 3)	NR (probably 1)
Pei 2020	3	NR (probably 2)	0; all discharged
Shen 2020	5	NR (probably 5)	NR (probably 2, 3 discharged)
Tan 2020	1	NR (probably 0)	NR (probably 0)
Ye 2020	6	0	0; 5 discharged
Zhang 2020a	4	4	1; 3 discharged
Zhang 2020b	1	1	0

ICU: intensive care unit; **NR:** not reported

Table 6. Adverse events: grade 3 or 4

Study	Number of participants	Grade 3 or 4 adverse events[a]
Ahn 2020	2	0
Duan 2020 [b]	10	0
Pei 2020	3	1 (anaphylactic shock)
Shen 2020 [c]	5	Not reported
Tan 2020	1	1 (fever)
Ye 2020	6	0
Zhang 2020a [d]	4	0
Zhang 2020b	1	0

[a]We assume that these adverse events were grade 3 or 4, but the studies did not specify the degree of severity.
[b]One participant with evanescent red face (grade unclear).
[c] Shen 2020 did not report whether they assessed or observed adverse events.
[d]Assessment of adverse events only reported for one individual. Unclear information provided for the other three participants.

Table 7. Serious adverse events

Study	Number of participants	Serious adverse events
Ahn 2020	2	0
Duan 2020	10	0
Pei 2020	3	1 (anaphylactic shock)
Shen 2020 [a]	5	Not reported
Tan 2020	1	0
Ye 2020	6	0
Zhang 2020a	4	0
Zhang 2020b	1	0

[a] Shen 2020 did not report whether they assessed or observed serious adverse events.

APPENDICES

Appendix 1. Planned methodology for randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSIs)

Types of studies

To assess the benefits and safety of convalescent plasma for the therapy of COVID-19 we had planned to include randomised controlled trials (RCTs) only, as such studies, if performed appropriately, currently give the best evidence for experimental therapies in highly controlled therapeutic settings. If RCT data had been available, we would have used the methods recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), as specified in the description of the methods.

In case of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs to answer this review's questions we had planned to include prospective controlled non-randomised studies of interventions (NRSIs), including quasi-randomised controlled trials (e.g. assignment to treatment by alternation or by date of birth), controlled before-and-after (CBA) studies, and interrupted time series (ITS) studies. In that case, we would have used the methods proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* for the inclusion of NRSIs in systematic reviews (Reeves 2019).

In case of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs and NRSIs we had planned to include prospective observational studies with a control group and would have adapted the methods for the inclusion of NRSIs in systematic reviews as specified by the *Cochrane Handbook for Systematic Reviews of Interventions* as well (Reeves 2019).

As there was no evidence from RCTs, NRSIs, and only one prospective observational study available, we included prospective non-comparative study designs (e.g. case series) and followed the methodology as specified in the protocol (Piechotta 2020).

Data extraction and management

Assessment of risk of bias in included studies

Randomised controlled trials

We had planned to use the Risk of Bias 2.0 (RoB 2) tool to analyse the risk of bias in the underlying study results (Sterne 2019). Of interest for this review was the effect of the assignment to the intervention (the intention-to-treat (ITT) effect) and we would have performed all assessments with RoB 2 on this effect. The outcomes that we would have addressed are those specified for inclusion in the 'Evidence profile' (Table 2). Accordingly, the outcomes had been prioritised according to the Core Outcome Measures in Effectiveness Trials Initiative for Covid-19 patients (COMET 2020).

One review author would have assessed the risk of bias for each study result. A second review author would have verified the accuracy and the plausibility. In case of discrepancies among their judgements or inability to reach consensus, we had planned to consult a third review author to reach a final decision. We would have assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

To address these types of bias we had planned to use the signalling questions recommended in RoB 2 and make a judgement using the following options:

- 'yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question);
- 'probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'no': if there is firm evidence that the question is unfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question);
- 'probably no': a judgement has been made that the question is unfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'no information' if the study report does not provide sufficient information to allow any judgement.

We had planned to use the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias:

- low risk of bias;
- some concerns;

- high risk of bias.

Subsequently we had planned to derive a 'Risk of bias' rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': the trial is judged to be at low risk of bias for all domains for this result.
- 'Some concerns': the trial is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- 'High risk of bias': the trial is judged to be at high risk of bias in at least one domain for the result or the trial is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the results.

Non-randomised controlled studies

As reported above, we had planned to include non-randomised studies if there were insufficient evidence from RCTs.

One review author would have assessed eligible studies for methodological quality and risk of bias (using the Risk Of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool; Sterne 2016). A second review author would have verified the accuracy and the plausibility. The quality assessment strongly depends upon information on the design, conduct and analysis of the trial. The two review authors would have resolved any disagreements regarding the quality assessments by consulting a third review author until they reached a consensus.

We had planned to assess the following domains of bias.

- Bias due to confounding
- Bias in selection of participants into the study
- Bias in classification of interventions
- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

For every criterion we had planned to make a judgement using one of five response options.

- Yes
- Probably yes
- Probably no
- No
- No information

Measures of treatment effect

Randomised controlled trials

For continuous outcomes, we had planned to record the mean, standard deviation and total number of participants in both the treatment and control groups. For dichotomous outcomes, we had planned to record the number of events and total number of participants in both the treatment and control groups.

For continuous outcomes using the same scale we had planned to perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales we had planned to perform analyses using the standardised mean difference (SMD). For interpreting SMDs, we had planned to re-express it in the original units of a particular scale with the most clinical relevance and impact.

If available, we had planned to extract and report hazard ratios (HRs) for time-to-event outcomes (overall survival, progression-free survival). If HRs had not been available, we had planned to make every effort to estimate as accurately as possible the HR using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007), in an update of this review. If sufficient studies had provided HRs, we had planned to use HRs rather than RRs or MDs in a meta-analysis.

For dichotomous outcomes, we had planned to report the pooled risk ratio (RR) with a 95% CI (Deeks 2019). If the number of observed events had been small (less than 5% of sample per group), and if studies had balanced treatment groups, we had planned to report the Peto odds ratio (OR) with 95% CI (Deeks 2019).

For cluster-randomised trials, we had planned to extract and report direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounts for the clustered design. We had planned to obtain statistical advice to ensure the analysis was appropriate. If appropriate analyses had not been available, we would have made every effort to approximate the analysis following the

recommendations in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b), in an update of this review.

Non-randomised controlled studies

For dichotomous outcomes, if available we had planned to extract and report the RR with a 95% CI from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR post-intervention/RR pre-intervention).

For continuous variables, if available, we had planned to extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models or hierarchical models), or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups/the post-intervention level in the control group; EPOC 2017).

Unit of analysis issues

Studies with multiple treatment groups

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b), for studies with multiple treatment groups we had planned to combine arms as long as they could be regarded as subtypes of the same intervention.

When arms could not be pooled this way, we would have compared each arm with the common comparator separately. For pair-wise meta-analysis, we would have split the 'shared' group into two or more groups with smaller sample size, and included two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, both the number of events and the total number of participants would have been divided up, and for continuous outcomes, the total number of participants would have been divided up with unchanged means and SDs.

Assessment of heterogeneity

We had planned to assess heterogeneity of treatment effects between studies using a Chi^2 test with a significance level at $P < 0.1$. We had planned to use the I^2 statistic (Higgins 2003), to quantify possible heterogeneity (I^2 statistic > 30% to signify moderate heterogeneity, I^2 statistic > 75% to signify considerable heterogeneity; Deeks 2019). If heterogeneity were above 80%, we had planned to explore potential causes through sensitivity and subgroup analyses. If we could not find a reason for heterogeneity, we would not have performed a meta-analysis, but had planned to comment on results from all studies and present these in tables.

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we had planned to pool the data in meta-analysis. We had planned to perform analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019). We would not have conducted meta-analyses that involved both RCTs and non-RCTs. We had planned to conduct separate meta-analyses for each comparison.

We had planned to use the Review Manager Web software for analyses (Review Manager Web). One review author would have entered the data into the software, and a second review author would have checked the data for accuracy.

We had planned to use the random-effects model for all analyses as we anticipate that true effects will be related but will not be the same for included studies. If we could not perform a meta-analysis, we had planned to comment on the results as a narrative with the results from all studies presented in tables.

For RCTs, when meta-analysis had been feasible, we had planned to use the random-effects model for pooling the data. For binary outcomes, we had planned to base the estimation of the between-study variance using the Mantel-Haenszel method. We had planned to use the inverse variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. We planned to explore heterogeneity above 80% with subgroup analyses. If we could not find a cause for the heterogeneity then we had planned not to perform a meta-analysis, but comment on the results as a narrative with the results from all studies presented in tables.

If a meta-analysis had been feasible for non-RCTs, CBA studies, ITS studies, and cohort studies, we had planned to analyse the different types of studies separately. We had planned to only analyse outcomes with adjusted effect estimates if these were adjusted for the same factors using the inverse-variance method as recommended in Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2019).

Appendix 2. Search strategy WHO COVID-19 Database

plasma OR hyperimmune OR hyper-immune OR IVIG OR immunoglobulin OR globulin OR immune-globulin OR gamma-globulin OR γ-Globulin OR hyper-Ig OR immunoglobulins OR globulins OR donor OR donation OR donors OR donating OR donations OR donated

Appendix 3. Search strategy MEDLINE

1. Coronavirus Infections/

2. Coronavirus/

3. "Betacoronavirus"/

4. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kf.

5. (coronavirus* or coronovirus* or coronavirinae* or "2019-nCoV" or 2019nCoV or 2019-CoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or SARSr-cov or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).tw,kf.

6. (((respiratory* adj2 (acute* or symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).tw,kf.

7. ((outbreak* or wildlife* or pandemic* or epidemic*) adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).tw,kf.

8. (anti-flu* or anti-influenza* or antiflu* or antinfluenza*).tw,kf.

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. Plasma/

11. Immunoglobulins/

12. Immunoglobulins, Intravenous/

13. Immune Sera/

14. ((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus neutrali* or virus inactivated or antibod* or high-titre* or high-titer*) adj6 (plasma or blood or serum or sera)).mp.

15. ((plasma adj1 therap*) or gamma-globulin* or "γ-Globulin" or hyper-Ig).tw,kf.

16. ((hyperimmune or hyper-immune or high-dos*) adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kf.

17. (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp.

18. ((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus inactivated or antibody-positive) adj5 (donor* or donat*)).mp.

19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. 9 and 19

21. (Flu-IVIG or ((anti-flu* or anti-influenza* or antiflu* or antinfluenza*) adj5 plasma)).mp.

22. 20 or 21

23. (exp Animals/ or exp Animal Experimentation/ or exp Models, Animal/) not Humans/

24. 22 not 23

25. limit 24 to yr="2019 -Current"

Appendix 4. Search strategy Embase

1. Sars-related Coronavirus/

2. "Coronavirus Infections"/ or "Coronavirus Infection"/

3. Coronavirinae/

4. Coronavirus/

5. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kw.

6. (coronavirus* or coronovirus* or coronavirinae* or "2019-nCoV" or 2019nCoV or 2019-CoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or SARSr-cov or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).tw,kw.

7. (((respiratory* adj2 (acute* or symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).tw,kw.

8. ((outbreak* or wildlife* or pandemic* or epidemic*) adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).tw,kw.

9. (anti-flu* or anti-influenza* or antiflu* or antinfluenza*).tw,kw.

10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11. Plasma Transfusion/

12. exp Immunoglobulin/

13. ((convalesc* or recovered or cured or survivor* or survived or rehabilitat* or virus-positive or virus neutrali* or virus inactivated or antibody-rich or high-titre* or high-titer*) adj6 (plasma or blood or serum or sera)).mp.

14. ((plasma adj1 therap*) or gamma-globulin* or "γ-Globulin" or hyper-Ig).tw,kw.

15. ((hyperimmune or hyper-immune or high-dos*) adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kw.

16. (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp.

17. ((convalesc* or recovered or cured or survivor* or rehabilitat* or survived or virus-positive or virus inactivated or antibody-positive) adj5 (donor* or donat*)).mp.

18. 11 or 12 or 13 or 14 or 15 or 16 or 17

19. 10 and 18

20. (Flu-IVIG or ((anti-flu* or anti-influenza* or antiflu* or antinfluenza*) adj5 plasma)).mp.

21. 19 or 20

22. (exp animal/ or nonhuman/) not exp human/

23. Animal experiment/ not (human experiment/ or human/)

24. 22 or 23

25. 21 not 24

26. limit 25 to yr="2019 -Current"

Appendix 5. Search strategy PubMed

#1 (corona-virus* OR corono-virus* OR coronavirus* OR coronovirus* OR coronavirinae* OR Wuhan* OR Hubei* OR Huanan OR "2019 nCoV" OR 2019nCoV OR 2019 CoV OR nCoV2019 OR "nCoV 2019" OR "COVID 19" OR COVID19 OR "CORVID 19" OR CORVID19 OR "WN CoV" OR WNCoV OR "HCoV 19" OR HCoV19 OR CoV OR "2019 novel*" OR Ncov OR "n cov" OR "SARS CoV 2" OR "SARSCoV 2" OR "SARS-CoV-2" OR "SARSCoV-2" OR "SARSCoV2" OR "SARS CoV2" OR SARSCov19 OR "SARS Cov19" OR "SARSCov 19" OR "SARS Cov 19" OR Ncovor OR Ncorona* OR Ncorono* OR NcovWuhan* OR NcovHubei* OR NcovChina* OR NcovChinese* OR SARSr-cov)

#2 (((respiratory* AND (symptom* OR disease OR diseases OR diseased OR illness* OR condition*)) OR "seafood market*" OR "food market*") AND (Wuhan* OR Hubei* OR China OR "China's" OR Chinese* OR Huanan*))

#3 ((outbreak* OR wildlife* OR pandemic* OR epidemic*) AND (China OR "China's" OR Chinese* OR Huanan* OR Wuhan OR Hubei*))

#4 (anti-flu* OR anti-influenza* OR antiflu* OR antinfluenza*)

#5 #1 OR #2 OR #3 OR #4

#7 ((convalesc*[TIAB] OR recovered[TIAB] OR cured[TIAB] OR survivor*[TIAB] OR survived[TIAB] OR virus-positive[TIAB] OR virus-neutrali*[TIAB] OR "virus inactivated"[TIAB] OR antibod*[TIAB] OR high-titre*[TIAB] OR high-titer*) AND (plasma[TIAB] OR blood[TIAB] OR donor*[TIAB] OR donat*[TIAB]))

#8 ("therapeutic plasma" OR "plasma therapy" OR "immune plasma" OR "plasma exchange" OR gamma-globulin* or "γ-Globulin" or hyper-Ig)

#9 (plasma[TI] AND (immun*[TIAB] OR transfus*[TIAB] OR infus*[TIAB]))

#10 ((hyperimmune OR hyper-immune OR high-dos*) AND (plasma OR immunoglobulin* OR IVIG* OR immune globulin* OR globulin*))

#11 #7 OR #8 OR #9 OR #10

#12 #6 AND #11

#13 (Flu-IVIG OR ((anti-flu* or anti-influenza* or antiflu* or antinfluenza*) AND plasma))

#14 #12 OR #13

#15 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
#16 #13 AND #15: Publication date from 2019/11/01 to present

Appendix 6. Search strategy CDC COVID-19 Database (for searching in Endnote)

Any Field: plasma OR hyperimmune OR hyper-immune OR IVIG OR immunoglobulin OR globulin OR immune-globulin OR gamma-globulin OR γ-Globulin OR hyper-Ig OR immunoglobulins OR globulins

Appendix 7. Search strategy Cochrane COVID-19 Study Register

plasma OR hyperimmune OR hyper-immune OR IVIG OR immunoglobulin OR globulin OR gamma-globulin OR γ-Globulin OR hyper-Ig OR serum OR sera OR donor OR donation

Appendix 8. Search strategy ClinicalTrials.gov

COVID-19 SUBSET

AND

Intervention: "convalescent plasma" OR "hyperimmune IVIG" OR "hyperimmune immunoglobulin" OR "plasma therapy" OR "immune plasma" OR "hyperimmune plasma" OR plasma OR IVIG OR immunoglobulin OR globulin OR immune-globulin OR gamma-globulin OR γ-Globulin OR hyper-Ig OR serum OR sera OR donor OR donation

Appendix 9. Search strategy WHO ICTRP (for searching in EndNote)

COVID-19 SUBSET

AND

Any Field: plasma OR hyperimmune OR hyper-immune OR IVIG OR immunoglobulin OR globulin OR gamma-globulin OR γ-Globulin OR hyper-Ig OR serum OR sera OR donor OR donat

HISTORY

Review first published: Issue 5, 2020

CONTRIBUTIONS OF AUTHORS

SJV: clinical expertise and conception and writing of the review

VP: methodological expertise and conception and writing of the review

KLC: clinical expertise and conception and writing of the review

CD: development of the search strategy

IM: development of the search strategy

EMW: clinical expertise and advice

AL: clinical expertise and advice

CK: clinical expertise and advice

ZM: clinical expertise and advice

CS-O: clinical expertise and advice

LJE: clinical and methodological expertise and conception and writing of the review

NS: methodological expertise and advice and conception and writing of the review

DECLARATIONS OF INTEREST

SJV: none known

VP: none known

KLC: HSANZ Leukaemia Foundation PhD scholarship to support studies at Monash University. This is not related to the work in this review.

CD: none known

IM: none known

EMW: I have sought funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.

AL: none known

CK: none known

ZM: I have sought funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.

CS-O: is a member of the BEST Collaborative Clinical Study Group. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.

LJE: co-lead of the COVID-19 immunoglobulin domain of the REMAP-CAP trial. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.

NS: none known

SOURCES OF SUPPORT

Internal sources

- Sanquin Blood Supply, Netherlands

  Center for Clinical Transfusion Research
- University Hospital of Cologne, Germany

  Cochrane Cancer, Department I of Internal Medicine
- Monash University, Australia

  Transfusion Research Unit, Department of Epidemiology and Preventive Medicine
- NHS Blood and Transplant, UK

  NHS Blood and Transplant

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of outcome measures

We revised the secondary outcome 'Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days' and added to the fourth bullet point: 'plus high-flow oxygen', to differentiate from the third bullet point. It now reads:

Improvement of clinical symptoms, assessed by need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days:

- oxygen by mask or nasal prongs
- oxygen by NIV (non-invasive ventilation) or high flow
- intubation and mechanical ventilation
- mechanical ventilation plus high-flow oxygen
- extracorporeal membrane oxygenation (ECMO)

Electronic searches

As publication bias might influence all subsequent analyses and conclusions, we searched all potential relevant trials registries in detail to detect ongoing as well as completed studies, but not yet published studies. Nowadays, it is mandatory to provide results at least in the trials registry. In case results were not published elsewhere, we had planned to extract and analyse these data. However, no outcome data had yet been added to the trials registries.

Data extraction and management

We had planned to extract data using a standardised data extraction form developed in Covidence. However, we could not adapt the standardised form to our needs. Therefore we generated a customised data extraction form in Microsoft Excel (Microsoft Corporation 2018).

Summary of findings and assessment of the certainty of the evidence

At protocol stage we had planned to assess the certainty of the evidence for our primary outcomes (all-cause mortality at hospital discharge and time to death), only. However, as none of the included studies reported any deaths during their study periods, we decided to assess the certainty of the evidence also for prioritised secondary outcomes (clinical improvement, grade 3 and 4 adverse events, and serious adverse events) to increase the informative value on effectiveness and safety of convalescent plasma therapy.

Some passages in this protocol, especially in the methods section, are from the standard template of Cochrane Haematology.