CADTH COVID-19 PANDEMIC

COVID-19 CADTH TECHNOLOGY REVIEW

Convalescent Plasma Therapy for the Treatment of COVID-19: A Review of Clinical Effectiveness

This report was originally published on May 28, 2020 and is updated on a monthly basis. The last update was published on August 26, 2020.

To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is chlanging and growing rapidly.

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Abbreviations

COVID-19	coronavirus disease
CP	convalescent plasma
CT	computerized tomography
FDA	Food and Drug Administration
IQR	interquartile range
NRS	non-randomized study
RCT	randomized controlled trial
RNA	ribonucleic acid
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

What's new?

The search update on August 5, 2020 identified one new relevant primary study.[1] Results of all included studies identified as relevant to date have been summarized together, and the conclusions of this report are up to date as of the date of publication. An updated list of ongoing clinical trials is provided in Appendix 6. Key information regarding each version of this living review can be found in Appendix 7.

Context and Policy Issues

Coronavirus disease (COVID-19) is a highly infectious zoonotic disease which emerged towards the end of 2019 and has been rapidly spreading all over the world.[2] COVID-19 is caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS - CoV - 2).[2] With over twenty million confirmed cases and over 730,000 deaths globally as of August 12, 2020,[3] COVID-19 has emerged as one of the biggest global public health concerns in recent history. The World Health Organization (WHO) declared COVID-19 as a pandemic on March 11, 2020.[4] In Canada, the first case of COVID-19 was reported on January 25, 2020, and 120,421 confirmed cases and 8,991 deaths were reported as of August 12, 2020.[5] Several antiviral agents and vaccines are currently being actively researched.[6]

Convalescent plasma (CP) therapy is an intervention in which plasma collected from convalescent or recovered patients is used to treat various infectious diseases, and it has been proposed for emerging viral infections.[7] It is theorized that CP, which contains disease-specific antibodies that could neutralize the viral particles in COVID-19 patients, can be used to treat the disease.[8] CP therapy involves transfusion of a blood product and is therefore associated with a risk of adverse events including anaphylaxis, transfusion related lung injury, transfusion associated circulatory overload, and transmission of infections.[9] The Public Health Agency of Canada reported an overall risk of adverse events related transfusion of blood components as 1 in 2,405 transfusions over the period of 2011 to 2015.[10] Transfusion associated circulatory overload was the most common adverse

transfusion reaction (18.1 per 100,000 units transfused).[10] To mitigate the risk of transfusion related acute lung injury due to donor-derived human leukocyte antigen (predominantly found in females who have been pregnant), male plasma donors may be preferred.[11,12] A risk of antibody dependent enhancement of infection, in which antibodies to one type of coronavirus could amplify infection to another viral strain, has been theorized.[13] A possible molecular mechanism for antibody dependent enhancement has been described in other coronaviruses like the Middle East respiratory syndrome coronavirus.[14]

Regulatory Status

The use of CP as a treatment for COVID-19 was first approved by the US Food and Drug Administration (FDA) on March 25, 2020 as an emergency investigational new drug (eIND).[15] The FDA also issued an Emergency Use Authorization (EUA) for CP therapy for hospitalized COVID-19 patients in the USA on August 23, 2020.[16] In Canada, CP therapy for COVID-19 is currently available only as an investigational drug treatment for participants in the CONCOR-1 clinical trial.[17] To be eligible for the clinical trial participants must be admitted to a participating hospital, diagnosed with confirmed COVID-19 respiratory illness, and be receiving supplemental oxygen without intubation.[18] The CONCOR-1 clinical trial is currently underway and involves more than 50 hospitals across Canada with the intention to recruit 1,500 participants.[15] Preliminary study results are expected to be available at the end of October 2020 with final results available at the end of the year.[15] Additional clinical trials investigating the use of CP therapy for the treatment of COVID-19 are underway around the world (Appendix 6).

Cost and Administration

In 2014, the cost of collecting one unit of plasma through plasmapheresis was reported to be $719.[19] No information was available regarding the current cost of collecting or administering plasma in Canada. Additionally, no information was available regarding any peripheral costs involved in the collection of CP from people who have recovered from COVID-19 and the preparation for administration as a treatment. Such costs might include requirements for additional infrastructure, safety measures, or personnel.

As part of the CONCOR-1 clinical trial participants will receive 500 mL of CP (from one 500 mL unit from one donor or two 250 mL units from one or two donors).[15] The plasma will be collected by apheresis from donors who have recovered from COVID-19.[15] The plasma will be infused over a period of four hours. If two units are used, the second unit will be infused within 12 hours of the first.[15] Different treatment protocols are being used in other ongoing trials (Appendix 6).

Implementation Issues

If found to be effective, a major barrier to implementation of CP as a treatment for COVID-19 is likely to be the availability of both donors and plasma.[18] For this reason, its use as a treatment will be prioritized to patients with active illness rather than being tested as a preventative treatment for those at high risk of exposure.[18] CP is collected in the same way as a standard plasma donation so existing infrastructure can be used in its production. In Canada, convalescent plasma is being collected from eligible volunteers and prepared for distribution for use in the CONCOR-1 clinical trial by Canadian Blood Services and Héma-Québec.[17] To be eligible, donors have to be free of COVID-19 symptoms for a minimum of 28 days prior to their donation (or 14 days in combination with a negative COVID-19 test) and the donation must take place a maximum of 12 weeks after their COVID-19 symptoms have resolved.[15] Canadian Blood Services and Héma-Québec are

working with provincial health authorities to identify and contact people who have recovered from COVID-19 and might be eligible for plasma donation.[18] Potential donors are also able to self-identify through a questionnaire that is accessible via social media.[15]

A report published by CADTH in May 2020 identified evidence regarding the clinical effectiveness of CP therapy in COVID-19 along with detailed information on ongoing clinical trials.[20] The purpose of the current report is to update and summarize the evidence regarding the clinical effectiveness of CP therapy for the treatment of COVID-19. This report will be conducted as a living review with intended updates on a monthly basis.

Research Question

What is the clinical effectiveness of convalescent plasma therapy for the treatment of coronavirus disease (COVID-19)?

Key Findings

One randomized controlled trial and four non-randomized studies were identified in this report that compared the clinical effectiveness of convalescent plasma (CP) therapy with standard care for the treatment of coronavirus disease (COVID-19). Evidence from the included studies was of low to moderate quality with several methodological limitations and risk of bias.

Two studies found no differences in mortality between patients who received CP therapy and those who received standard care alone; however, two other studies found that there were more deaths in the group that received standard care alone. There was low- to moderate-quality evidence from two non-randomized studies that duration of illness (defined as time between onset of symptoms and hospital discharge or death) was longer in patients who received CP transfusion compared to those who received standard care alone. Among these two studies, one found no difference in mortality between the groups and one found lower mortality in patients that received CP therapy. Taken together, the evidence suggested that patients may have survived longer with CP therapy.

In one non-randomized study, among COVID-19 patients who did not require intubation or mechanical ventilation at baseline, significantly fewer patients who received CP therapy required subsequent intubation compared to those who received standard care. This suggested better clinical improvement. Results from the randomized study that included both severe and critically ill patients did not show any difference in clinical improvement between CP and standard care treatment groups, but the study was underpowered to detect any significant effect.

Two of the included studies measured the rate of viral clearance and found a higher rate of viral clearance in patients who received CP therapy compared to those who received standard care. Methodological limitations such as ambiguity in outcome assessment, baseline differences between the groups, and co-administered medications led to uncertainty in the results.

Across studies, there were six non-severe adverse events in patients who received CP (out of a total of 329 patients), which either self-resolved or improved with treatment. This suggests that CP therapy may be a safe treatment option.

No evidence was found regarding the effectiveness of CP therapy in pediatric populations. No evidence was found comparing the effectiveness of CP therapy to placebo, or other active treatments (e.g., hydroxychloroquine, remdesivir) or regarding the effectiveness of CP therapy with respect to reducing the viral load.

This report includes a list of ongoing clinical trials, which could provide additional evidence regarding the clinical effectiveness CP therapy for COVID-19.

Methods

Study Design

This report will be conducted as a living review, following the Cochrane guidance for living systematic reviews.[21] This model will allow for ongoing assessment of the clinical effectiveness and safety of CP therapy, incorporating the results from several ongoing clinical trials with expected completion dates ranging from the year 2020 through 2023,[20] and any other relevant studies that may be published.

CADTH will review the appropriateness of continuing to maintain the review in living mode on an ongoing basis. The review will be regularly updated as described until: 1) the research question is no longer a priority for decision-making, 2) a reasonable level of certainty has been reached in the existing evidence, or 3) research that might impact the conclusions of the review is no longer emerging (e.g., the research area is no longer active). CADTH will consider the research question no longer a priority for decision-making in situations where the intervention has been superseded or withdrawn. Additionally, CADTH will seek input from decision-makers in Canadian jurisdictions to determine whether there is continued interest in this topic. This may be assessed by asking the jurisdictional representatives whether there have already been decisions made about CP therapy and whether additional information from a review would change their current practices. This report may also transition out of living mode based on lack of available resources.

Literature Search Methods

Baseline Review

A limited literature search was conducted on May 6, 2020 by an information specialist on key resources including Medline via OVID, PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, Cochrane Central Register of Controlled Trials (CENTRAL), the US National Institutes of Health's clinicaltrials.gov, Health Canada's clinical trials database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were convalescent plasma and COVID-19. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2019 and May 6, 2020. Reference lists of identified systematic reviews on convalescent plasma therapy for the treatment of COVID-19 were also hand-searched for potentially relevant primary studies.

Living Updates

After the initial literature search is completed, database literature and trial registry searches (in Medline via OVID, PubMed, the Cochrane Library, CRD, CENTRAL, the US National Institutes of Health's clinicaltrials.gov, and Health Canada's clinical trials database) will be updated on a monthly basis. Websites of Canadian and international health technology agencies and a focused internet search will be updated every six months. Relevant publications may also be identified between regular alerts (e.g., via hand-searching). The frequency of updating the search will be revisited quarterly. Details regarding the most recent search will be provided in the "What's New" and "Quantity of Research Available" sections.

Selection Criteria and Methods

Baseline Review

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles based on the inclusion criteria presented in Table 1.

Living Updates

Relevant publications identified in each subsequent search will be incorporated into the corresponding version updates. In addition, relevant publications that are identified via other means (e.g., hand-searching) will be incorporated. The selection criteria and methods will be identical to the criteria of the baseline review.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to January 2019.

Critical Appraisal of Individual Studies

Baseline Review

The included publications were critically appraised by one reviewer using the Downs and Black checklist[22] for randomized and non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Living Updates

Critical appraisal will involve the same processes as the baseline review and will be conducted when updating the review.

Table 1: Selection Criteria

Population	Individuals (of all ages) with confirmed or presumptive coronavirus disease (COVID-19)
Intervention	Convalescent plasma therapy
Comparator	No treatment; placebo; standard care; other active treatments (e.g. hydroxychloroquine, remdesivir)
Outcomes	Clinical effectiveness (e.g., mortality, length of hospital stay, severity of clinical symptoms, viral load, safety [e.g., rate of adverse events])
Study Designs	Randomized controlled trials and non-randomized studies

COVID-19 = coronavirus disease.

Summary of Evidence

Quantity of Research Available

The updated search of the databases and trial registry was last conducted on August 5, 2020; the focused internet search was last conducted on May 6, 2020.

In total, 1,327 citations were identified in the literature searches. Following screening of titles and abstracts, 1,245 citations were excluded and 82 potentially relevant reports from the electronic searches were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 78 publications were excluded for various reasons, and 5 publications met the inclusion criteria and were included in this report. These comprised one randomized controlled trial (RCT)[23] and four non-randomized studies (NRSs).[1,24-26] Appendix 1 presents the PRISMA[27] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5. A list of ongoing clinical trials is provided in Appendix 6, Table 5.

Summary of Study Characteristics

One RCT[23] and four NRSs[1,24-26] were identified and included in this report. Detailed study characteristics are available in Appendix 2, Table 2

Study Design

One of the included studies was an open label multicenter RCT.[23]

Four NRSs were included in this report.[1,24-26] One study[25] was a pilot observational study in which the CP therapy group was observed prospectively and the control group was a retrospective historic control. Two NRSs were retrospective observational studies,[24,26] and the fourth NRS was a prospective observational study.[1]

Country of Origin

The RCT and three of the NRSs were conducted in China.[23-26] One NRS was conducted in Iran.[1]

Patient Population

The RCT by Li et al.[23] enrolled hospitalized adult COVID-19 patients who were diagnosed based on a positive polymerase chain reaction (PCR) test. Inclusion criteria were: clinical symptoms meeting severe or life-threatening COVID-19, positive PCR within 72 hours prior

to randomization, and pneumonia confirmed with imaging. The study excluded patients who: were pregnant or lactating; had a known IgA deficiency, immunoglobulin allergy or risk of thrombosis; a life expectancy of < 24 hours; disseminated intravascular coagulation; severe septic shock; PaO2 < 100 mm Hg; severe congestive heart failure; or a high titer of S-RBD-specific (receptor binding domain) IgG antibody. Based on these criteria, 103 patients were enrolled (CP group, n = 52, control group, n = 51) with a median age of 70 years (interquartile range [IQR]: 62 to 80 years) in the CP group and 69 years (IQR: 63 to 76 years) in the control group. There were no significant differences in demographics, baseline laboratory results and severity of disease or coexisting conditions between the groups.

Two of the NRSs[24,25] included in this report were conducted in adult patients with COVID-19 diagnosed based on the WHO interim guidance.[28] The pilot study by Duan and colleagues[25] enrolled adult COVID-19 patients who had respiratory distress (respiratory rate ≥30/min), oxygen saturation level < 93% in resting state, and a PaO2 ≤ 300 mm Hg. Patients with previous allergic history to plasma or its ingredients and those with serious general conditions with organ dysfunction were excluded from receiving CP therapy. Ten patients admitted to three participating hospitals with severe COVID-19 with a mean age of 52.5 years (IQR: 45.0 years to 59.5 years) received CP transfusion. Three patients had underlying hypertension and one had cardiovascular and cerebrovascular diseases. All patients received concomitant antiviral drugs (most commonly Arbidol) and six received corticosteroids. Three patients received mechanical ventilation before CP therapy. A sex- and age-matched historic control group of 10 patients was selected from the same hospitals with a median age of 53 years (IQR: 46.5 years to 60.5 years). Baseline laboratory parameters were similar in both groups. It was not reported whether the CP treatment group and the control group were similar in other characteristics like severity of disease, specific co-morbidities, respiratory support and other treatments given (antivirals, steroids, immunoglobulins).

The study by Zeng and colleagues[24] enrolled 21 contemporaneous patients with COVID-19 from two referral hospitals. Among them, six patients with a median age of 61.5 years (IQR: 31.5 years to 77.8 years) received CP therapy. In that group, one patient had hypertension, one had diabetes and one had cardiovascular disease. There were fifteen patients in the control group and the median age was 73 years (IQR: 60 years to 79 years). All patients in the study had severe disease with respiratory failure and were admitted to the Intensive Care Unit. The CP treatment group and the control group were similar in other characteristics like clinical symptoms, specific co-morbidities, need for mechanical ventilation, laboratory parameters and concomitant treatments given (antivirals, steroids, intravenous immunoglobulins).

As for the third NRS,[26] 1,568 severe or critical COVID-19 patients who were admitted to a Wuhan hospital from February 4 to March 30, 2020 were included in the study (CP group, n = 138; control group, n = 1,430). Additional eligibility criteria for CP therapy were laboratory confirmation of COVID-19, abnormalities in computerized tomography (CT) imaging of chest, critical illness and absence of improvement on standard care alone (whether all or just one of these criteria needed to be met for inclusion was unclear). Patients allergic to plasma products were excluded. Participants in the control group were slightly but significantly younger than those in the CP therapy group (median age of 63, IQR: 53 to 71 years, and 65, IQR: 57 to 73 years, respectively). On average, the CP group had more severe disease; critically ill patients constituted 15% of the patients in the CP group compared to 8.8% in the control group (P < 0.05). The CP treatment group and the control

group were similar with respect to prevalence of comorbidities (e.g., hypertension, chronic obstructive pulmonary disease), with the exception that diabetes was significantly more prevalent in the CP group compared to the control group. Patients in the CP group also reported higher rates of shortness of breath symptoms compared to those in the control group prior to treatment, while other symptoms were similar between groups.

In the NRS by Abolghasemi and colleagues,[1] adult patients with COVID-19 disease confirmed through qRT-PCR or CT imaging of the chest who were ≤ 7 days since onset of illness, and had respiratory symptoms (RR ≥20/min), PaO2 ≤ 93% on room air, fever and cough were included. Patients who were intubated or on mechanical ventilation, had severe liver or kidney disease, septic shock, known plasma hypersensitivity, or were showing improved clinical condition to warrant discharge from the hospital were excluded. Based on these criteria, 189 patients were enrolled (CP group, n = 115, control group, n = 74) with a mean age of 54.4 years (standard deviation [SD] = 13.71) in the CP group and 56.8 years (SD = 14.5) in the control group. There were no significant differences in demographics, baseline laboratory results, or comorbidities and clinical conditions between the group.

Interventions and Comparators

The intervention in all studies included in this report was administration of CP collected from recovered COVID-19 patients who donated their plasma.[1,23-26] All patients received plasma compatible with their blood group (ABO compatible). No CP therapy was administered to patients in the control group.

In the RCT by Li et al.,[23] CP with S-RBD-specific IgG titer ≥ 1:1280 was transfused (4 to 13 mL/kg of body weight). The median plasma volume given was 200 mL (IQR: 200 to 300 mL). The median time from onset of symptoms to randomization and CP treatment was 30 days (IQR: 20 to 39 days). Participants in both CP group and control groups received standard care which included symptomatic control and supportive care including antivirals, steroids, immunoglobulin and Chinese herbal medicines.

In the pilot study by Duan and colleagues,[25] one dose of 200 mL inactivated CP with a neutralization activity of > 1:640 was transfused to the patients over 4 hours. The median time from onset of symptoms to CP transfusion was 16.6 days (IQR: 11 days to 19.3 days). Zeng and colleagues[24] administered CP to the patients in volumes ranging from 200 to 600 mL (median dose 300 mL). Three patients in the CP treatment group received CP therapy once and other three patients received CP transfusion twice. The volume per transfusion for each patient was unclear and not standardized. The rationale of administering CP therapy more than once to three patients was unclear. The median time from onset of symptoms to CP transfusion was unclear

In the RCT by Xia et al.,[26] CP with antibody titers ≥ 1: 160 were transfused in a dose of 4 to 5 mL/kg of the recipient body weight. Most patients received 1 to2 units (200 mL to 400 mL) of plasma, with 58.6% patients receiving a transfusion only once. In patients with severe disease, multiple transfusions were given as needed (up to a maximum of five). The median duration from onset of symptoms to CP transfusion was 45 days (IQR: 39 to 54 days). All patients in the study received standard care such as antivirals, traditional Chinese medicine and respiratory support.

In the NRS by Abolghasemi et al.,[1] one unit (500 mL) of CP was transfused over 4 hours, within the first 3 days of hospitalization. If there was no improvement in 24 hours, one more unit was transfused based on the judgment of the treating physician. Patients in both

groups received antiviral therapy (Lopinavir or Ritonaivir), Hydroxychloroquine, and an anti-inflammatory agent.

Outcomes

The primary end point in the RCT by Li et al.[23] was the time to clinical improvement within 28 days. Clinical improvement was defined as either hospital discharge or two-point reduction in a six-point disease severity scale used in other COVID-19 trials (scores ranged from 1 [hospital discharge] to 6 [death]).[29] Secondary outcomes considered in the study were 28-day mortality, duration of hospital stay and viral clearance using PCR test in nasopharyngeal swabs assessed at 24, 48 and 72 hours.

The pilot study by Duan and colleagues[25] considered safety as the primary outcome in the CP treatment group. Secondary outcomes included improvement in clinical, laboratory, and radiological parameters within three days of CP transfusion. Relevant to this report, the comparative outcomes assessed between the CP treatment group and the control group were death, and proportion of patients who were stable, improved, or discharged. The definitions of the outcomes "stable" and "improved" were unclear.

In the Zeng et al. study,[24] the safety and efficacy of CP therapy were measured as the incidence of adverse events, clinical outcomes (discharge, fatality, and remained in hospital), and SARS-CoV-2 clearance. The SARS-CoV-2 clearance was tested using a qualitative ribonucleic acid (RNA) detection kit developed for the detection of presence of SARS-CoV-2 infection in the COVID-19 epidemic.

In the third NRS by Xia et al.,[26] the primary outcome was mortality rate. Relevant to the current report, additional outcomes were clinical improvement based on the six-point disease severity scale[29] and safety outcomes such as transfusion-associated reactions and laboratory results. Outcomes were assessed at a single time point on April 20, 2020.

The primary outcomes in the NRS by Abolghasemi et al.[1] were all-cause mortality and length of hospital stay. Relevant to the current report, secondary outcomes were the need for intubation, improvement in clinical symptoms (measured using the rate of hospital discharge), and adverse events.

Summary of Critical Appraisal

The strengths and limitations of the four studies[23-26] included in this report are summarized below. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 3.

Randomized Controlled Trial

The included RCT[23] described their objectives clearly, and reported the population, intervention, comparators and outcomes of the study in detail. The participants were enrolled from eight hospitals in China over the same period and were representative of the population and treatment. Baseline characteristics including age, demographics, severity of disease, co-morbid conditions and concomitant treatments (antivirals, steroids, immunoglobulins) were similar across groups. There was random allocation of participants to each group using computer generated random numbers, stratified for severity of disease. Details on the volume, dosage, timing and administration of CP was provided along with a description of medications and support given as standard care in both groups. CP collection from the donors was controlled, and only CP with high antibody titer (≥ 1:1280) was used in the trial. The study outcomes considered for the study were appropriate. Outcome

assessors were blinded to participant group. Main study findings were reported clearly with simple outcome data. Random variability in data was considered in reporting using IQRs and 95% confidence intervals. One patient in each group (1.9%) dropped out of the study after randomization, and reasons were reported (one patient in CP group withdrew and one patient in control group was given CP). The authors conducted primary intent to treat analysis as well as per protocol analysis (excluding the dropped-out patients).

The main limitation of the study was that it was terminated early due to a decline in the number of patients. The study enrolled 103 patients, which was half of the intended number of participants (200), leading to inadequate power for statistical analysis. Low powered analyses contribute to less likelihood of detecting true effects and larger estimates of effect sizes when an effect is found. Neither participants nor the treating clinicians were blinded to the intervention groups. Standard concomitant treatment including steroids and antivirals were given to patients in both groups as needed, which could affect the outcomes. Additionally, the median time between onset of symptoms to CP therapy was 30 days. It has been suggested that early administration of CP early in the disease could be more beneficial in diseases with viral etiology.[30] As there are many features of COVID-19, including time to recovery and long-term effects, are still unknown, the short follow up period of 28 days may have led to detection of improvement or deterioration of patients after that time. Furthermore, the trial was conducted in China making the generalizability to Canadian settings unclear.

Non-randomized Studies

The following strengths were common to all four NRSs:[1,24-26] they reported simple outcome data for the study findings; no patients were lost to follow-up and compliance with the interventions was reliable; adverse events were described; estimates of random variability were reported in the form of IQRs and SDs; and appropriate statistical tests were used to compare intervention and treatment groups.[1,23-26] Three of the included NRSs[1,24,25] described their objectives clearly. Three studies [1,25,26] reported the methods of plasma collection and the dosage and timing of the CP transfusion. Baseline characteristics of patients in each group were described and compared in three studies,[1,24,26] and no significant differences in potential confounders like comorbidities, concomitant medications, baseline clinical symptoms between the two groups were found.

The included NRSs[1,24-26] had several limitations that affected their internal and external validity. None of the studies were randomized, and neither patients nor outcome assessors were blinded to treatment groups.[1,24-26] There was also a risk of sampling bias, without clear random selection of patients. The authors of all four studies[1,24-26] did not perform power calculations prior to recruiting participants. As a result, studies may have been underpowered to detect statistically significant differences for some outcomes of interest, although the Xia et al.[26] study had a sample size of 1,568.[1] As for the studies by Zeng et al.[24] and Duan et al.,[25] both studies had small sample sizes, with a combined total of 16 patients receiving CP therapy. In two studies,[1,26] it was unclear how long the participants were followed, including for the outcome all-cause mortality. In all of the included NRSs, all patients were administered concomitant medications, and it is possible these co-administered medications could have affected the outcomes.[1,24-26]

Additionally, in the NRS by Xia et al.,[26] the clinical status of all patients was assessed on a single day and the duration of standard care for patients in both groups and the duration between CP therapy and date of assessment in the CP group were unclear; these factors could affect clinical status. The main limitation of this study[26] was that the participants in CP

group and control groups were significantly different in several baseline characteristics such as age, diabetes rates, shortness of breath, median duration from symptom onset to hospitalization, and severity of disease. Patients who did not respond to standard care alone were eligible for CP therapy. All these factors could mean patients in the CP group were different from control group lowering the internal validity of the study.

The pilot feasibility study by Duan et al.[25] had some additional major limitations. Firstly, the control group was selected from a pool of historic patients matched for age and sex, which increased the risk of selection bias. Characteristics of the control group were not described and potential confounders like specific co-morbidities, severity of the disease, need for mechanical ventilation, complications, and concomitant treatments (antiviral drugs, steroids) were not considered and adjusted. The end point of the study was safety of CP therapy; however, the definition was unclear, and a list of possible adverse events was not reported. Comparative outcomes between the two groups were also not clearly defined and it was unclear whether the comparisons were planned a priori. It was unclear when the outcome measures were assessed in the control group. For example, the number of days since onset of illness when "death" or "stability" were measured in the historic control group were not reported. Days since onset of illness were not matched between treatment group and control group. Along with the short follow-up time (three days) in the CP therapy group, these could limit the validity of the comparative findings.

In the observational study by Zeng et al.,[24] the main limitation was that there was no standardized dosing of CP therapy. The volume and number of doses of CP transfusion differed between the six patients in the treatment group. The frequency and timing of the CP administration were unclear. SARS-CoV-2 clearance was not quantified, but rather only the presence or absence of the SARS-CoV-2 RNA was detected; this was a technical limitation of the test.

Overall, the evidence from three NRSs[24-26] was considered low-quality and the evidence from the fourth NRS[1] was considered moderate-quality. Factors like concomitant management with antiviral drugs and other medications, along with the other limitations outlined above, contributed to the limited quality of the evidence. Furthermore, the included studies were conducted in China[24-26] and Iran[1] making the generalizability to Canadian settings unclear.

Summary of Findings

Clinical Effectiveness of Convalescent Plasma Therapy

The five included studies in this report provided evidence regarding the clinical effectiveness of CP therapy in COVID-19 patients.[1,23-26] Study findings relevant to this report are summarized below. Appendix 4 presents the main study findings and authors' conclusions.

Mortality

In the included RCT, for all patients irrespective of disease severity, there was no significant difference in mortality between patients who received CP therapy (8/51, 15.7%) and those who received standard care only (12/50, 24%) at 28-day follow-up.[23] There were also no significant differences between CP and standard care groups among those with severe disease (CP group: 0/23; control group: 2/22, 9.1%) and those with life-threatening disease (CP group: 8/28, 28.6%; control group: 10/28, 35.7%).[23]

Similarly, two of the NRSs[1,24] showed no significant differences in mortality between patients who received CP therapy and patients who received standard care alone.

In the NRS by Duan and colleagues[25] no patients died in the CP treatment group, compared to three in the control group. Though described as statistically significant, evidence was of limited quality due to the ambiguity in defining and measuring outcomes and small sample size (10 patients each in CP therapy group and control).

In the NRS[26] of 1,568 patients, as of the day of assessment, there were three deaths (2.2%) in the CP group compared to 59 (4.1%) in the control group. The CP group and control group were statistically different when all clinical status factors were considered (i.e., death, discharged from hospital, or still hospitalized) ($P < 0.001$).

Severity of clinical symptoms

Findings from the RCT showed that there was no significant difference in clinical improvement rate between the CP and control groups.[23] Among patients with severe disease, median time to clinical improvement was less in patients who received CP therapy (13 days) compared to those who received standard care alone (19 days) (HR: 2.15; 95% CI, 1.07 to 4.32, P = 0.03). No significant differences were found in clinical improvement between the groups among patients with life-threatening disease.

In one NRS,[1] among patients who did not require intubation or mechanical ventilation at baseline, significantly more patients in the control group (20.3%) needed subsequent intubation compared to those in the CP group (7.0%) during their hospital stay. This suggested that CP group had less severe disease outcomes compared to the standard care group.

One NRS reported that seven patients (70%) in the CP treatment group improved compared to one in the historic control group.[25] Though reported as statistically significant, the definition of "improved" and the time of outcome measurement was unclear in the control group.

Length of hospital stay

In the RCT,[23] there were no significant differences in the rates of hospital discharge at 28 days between patients who received CP therapy (51%) and those who received standard care alone (36%). No significant differences were found between the groups among patients with severe disease (91% in CP group versus 68.2% in control group) and among those with life-threatening disease (17.9% in CP group versus 10.7% in control group).[23] Length of hospital stay measured as time from hospitalization to discharge and from randomization to discharge were also similar between both groups for all patients.[23]

However, results from an NRS[1] showed that patients in CP therapy group had a significantly shorter hospital stay on average (mean length of stay 9.5 days) compared to those in the control group (mean length of stay 12.88 days). Significantly more patients in the CP group were discharged within 5 days of hospitalization than those in the control group. While the NRS[1] only enrolled patients whose disease was not severe enough to warrant intubation or mechanical ventilation, the sample size in the RCT[23] was inadequate to ensure adequate power, which might account for the inconsistent results.

Viral clearance

Evidence from the RCT[23] showed that the rates of negative PCR tests at 24, 48 and 72 hours were significantly higher in the CP group compared to control group. The negative test rates were 44.7%, 68.1% and 87.2% in the CP group, and 15.0%, 32.5% and 37.5% in the control group at 24, 48 and 72 hours respectively. Among patients with severe disease, significantly more patients obtained a negative test at 72 hours, but no differences were seen between the groups at 24 and 48 hours. Among patients with life-threatening disease, viral clearance rates were significantly higher in those who received CP therapy at all three times.[23]

According to the findings from one NRS,[24] all patients in the CP therapy group obtained viral clearance by the study end point, compared to 23.7% of patients in the control group. Among the deceased patients, 100% (5/5) and 21.4% (3/14) of patients had achieved SARS-CoV-2 clearance before death in treatment and control groups, respectively ($P < 0.005$). The duration of viral shedding was numerically shorter in the control group with a median 20 days (IQR: 19 days to 24 days) compared to 23.5 days (IQR: 19.5 days to 24.5 days) in the CP therapy group, but this finding was not statistically significant.

Duration of illness

The NRS by Zeng et al.[24] reported that in the CP therapy group, the median duration of illness (calculated as the number of days from the onset of illness to discharge/death) was 45.5 days (IQR: 37.8 days to 59 days), which was longer than that in the control group (31 days; IQR: 30 days to 36 days; $P < 0.05$). Similarly, results from the study by Xia and colleagues[26] showed that the median time from onset of symptoms to discharge from the hospital was significantly longer in patients who received CP (22 days) compared to those who received only standard care (14 days).

In the study by Zeng et al.,[24] there was no significant difference in mortality between CP therapy and control groups, while in the NRS by Xia et al.,[26] mortality was lower in the CP group compared with control group, as described earlier. Taken together, these findings suggest that patients may have survived longer with CP therapy.

Adverse events

No life-threatening transfusion associated adverse events were reported by the included studies. Two adverse events were reported in the RCT:[23] one incidence of a non-severe allergic transfusion reaction (and probable febrile hemolytic transfusion reaction) and another incidence of severe transfusion associated dyspnea that improved with treatment. One NRS[26] reported three minor allergic reactions (pruritus or erythema) and no severe transfusion reactions among 138 patients who received CP therapy, and another[1] reported one instance of transient fever with chills among 115 patients who received CP transfusion.

No adverse reactions or safety events were reported in the other two NRSs,[24,25] except for a temporary facial red spot in one patient in the CP group.[25]

Limitations

The main limitation was the lack of sufficient quantity and quality of evidence regarding the clinical effectiveness of CP therapy in COVID-19. The included RCT[23] was terminated early and enrolled fewer participants (103 out of 200 expected) than needed to ensure adequate power. Underpowered analysis could fail to detect an important difference or exaggerate

the effect size when one is detected. In all the included studies,[1,23-26] patient outcomes could also have been affected by the provision of standard care, which was given to both groups based on the decisions of the treating physicians (not standardized) who were not blinded to treatment groups. Two of the included NRSs had small sample sizes (with a total of 16 patients receiving CP therapy in these two studies).[24,25] The studies also had moderate to high risk of bias and provided limited quality evidence.

No evidence was found comparing the effectiveness of CP therapy to placebo, or to other active treatments (e.g. hydroxychloroquine, remdesivir). No evidence was found for the effectiveness of CP therapy in pediatric populations. No evidence was found regarding the effectiveness of CP therapy in lowering the viral load. All included studies were conducted in China, so the generalizability to Canadian settings is unclear. As COVID-19 is a novel emerging disease, there is a huge knowledge gap in the understanding and management of the disease.

Conclusions and Implications for Decision- or Policy-Making

The purpose of the current report is to summarize the evidence regarding the clinical effectiveness of CP therapy for the treatment of COVID-19. Overall, the quantity and quality of evidence was limited. No evidence was found regarding the effectiveness of CP therapy in pediatric populations, the effectiveness of CP therapy compared to placebo or other active treatments (e.g. hydroxychloroquine, remdesivir), or the effectiveness of CP therapy in lowering the SARS-CoV-2 viral load. In total, one RCT[23] and four NRSs[1,24-26] were included in this report that provided limited-quality evidence regarding the clinical effectiveness of CP therapy in adults with COVID-19.

While the RCT[23] and one NRS[1] found no significant differences in mortality between the patients who received CP and those who received standard care alone, one NRS[26] of limited quality found that there were fewer deaths in the CP group (when three clinical status factors - death, discharged from hospital, or still hospitalized – were considered together). However, there were key methodological limitations in this study[26] (e.g., differences between the groups and ambiguity in follow up time). A pilot study[25] that compared 10 COVID-19 patients who received CP therapy with a historic control group of 10 patients (who received standard care) found that there were significantly more deaths in the control group, and that more patients improved in the CP therapy group. However, these findings were limited due to the small number of included patients (total of 20), and the high risk of selection bias and confounding bias.

Evidence regarding clinical improvement rate, as obtained from two studies, was also conflicting as the RCT[23] found no difference and one NRS[1] found more patients in the control group needed intubation, suggesting a worse outcome compared to CP therapy. Similarly, the RCT[23] found no significant differences in the length of hospital stay between the two groups, but moderate-to-high-quality evidence from the NRS[1] showed that patients in the CP group had significantly shorter mean hospital stay compared to those in the control group. The inconsistency in findings could be due in part to differences in the patients between the two studies (only enrolled patients whose disease was not severe enough to warrant intubation or mechanical ventilation were enrolled in the NRS[1]), and/or inadequate statistical power in the RCT.[23]

With respect to viral clearance, limited-quality evidence from one RCT[23] showed that patients who received CP therapy had higher rates of negative viral PCR tests at 24, 48 and 72 hours compared to those who received standard care. Findings from a small NRS[24] (n = 21) showed that significantly more patients in the CP group had obtained viral clearance by the end of the study compared to those in the standard care group. Low- to moderate-quality evidence from two NRSs[24,26] showed that duration of illness (defined as time between onset of symptoms to discharge or death) as longer in patients who received CP compared to those who received standard care alone.

The safety findings from the included studies[1,23-26] suggested that CP therapy was safe, with six instances of mild or non-severe reactions observed after CP therapy (out of 329 patients who received CP). No severe transfusion-associated reactions were reported.

Overall, limited low-quality evidence exists regarding the clinical effectiveness of CP therapy in patients with COVID-19. A small number of case series and case reports have been published on this topic; although not eligible for inclusion in the current report, these publications provide some support for the potential utility and safety of CP therapy.[31-35] Systematic reviews have also been conducted to evaluate the effectiveness of CP therapy in COVID-19 patients; a list of these publications is included in Appendix 5. These reviews, in conjunction with the current report, have highlighted the lack of sufficient-quality evidence and the need for well-designed large trials.[36-39] A rapid Cochrane systematic review, which is being conducted as a living review, is also currently underway. The latest version of this rapid Cochrane systematic review included 20 studies (RCT, NRSs and single-arm studies), and concluded that the evidence regarding the effectiveness of CP was uncertain due the high risk of bias in the included studies and low reporting quality.[40] This is consistent with the conclusions of this report. Future well-designed randomized studies are warranted that can examine the clinical effectiveness and feasibility of CP therapy for the treatment of COVID-19. As the COVID-19 pandemic continues, a number of clinical trials on CP therapy are currently in progress (Appendix 6).

The availability of CP, which should be collected from recovered patients that are willing to donate plasma, is a major barrier to the widespread use of CP in COVID-19 patients. Ensuring the safety of CP by adequate regulations in the collection, inactivation and compatibility matching of the donated plasma, along with regulations in its appropriate and safe use in active patients, is also of high importance. Budgetary (cost of collecting, processing and administering CP) and ethical implications[41] of CP therapy (donor related issues like autonomy, consent, medical and psychosocial condition of the convalescent patients) should also be considered.

COIVID-19 is a highly infectious disease which has emerged as major global public health concern. With no established cure or vaccination for the disease, immediate well-designed research on the management of COVID-19 is of paramount importance.

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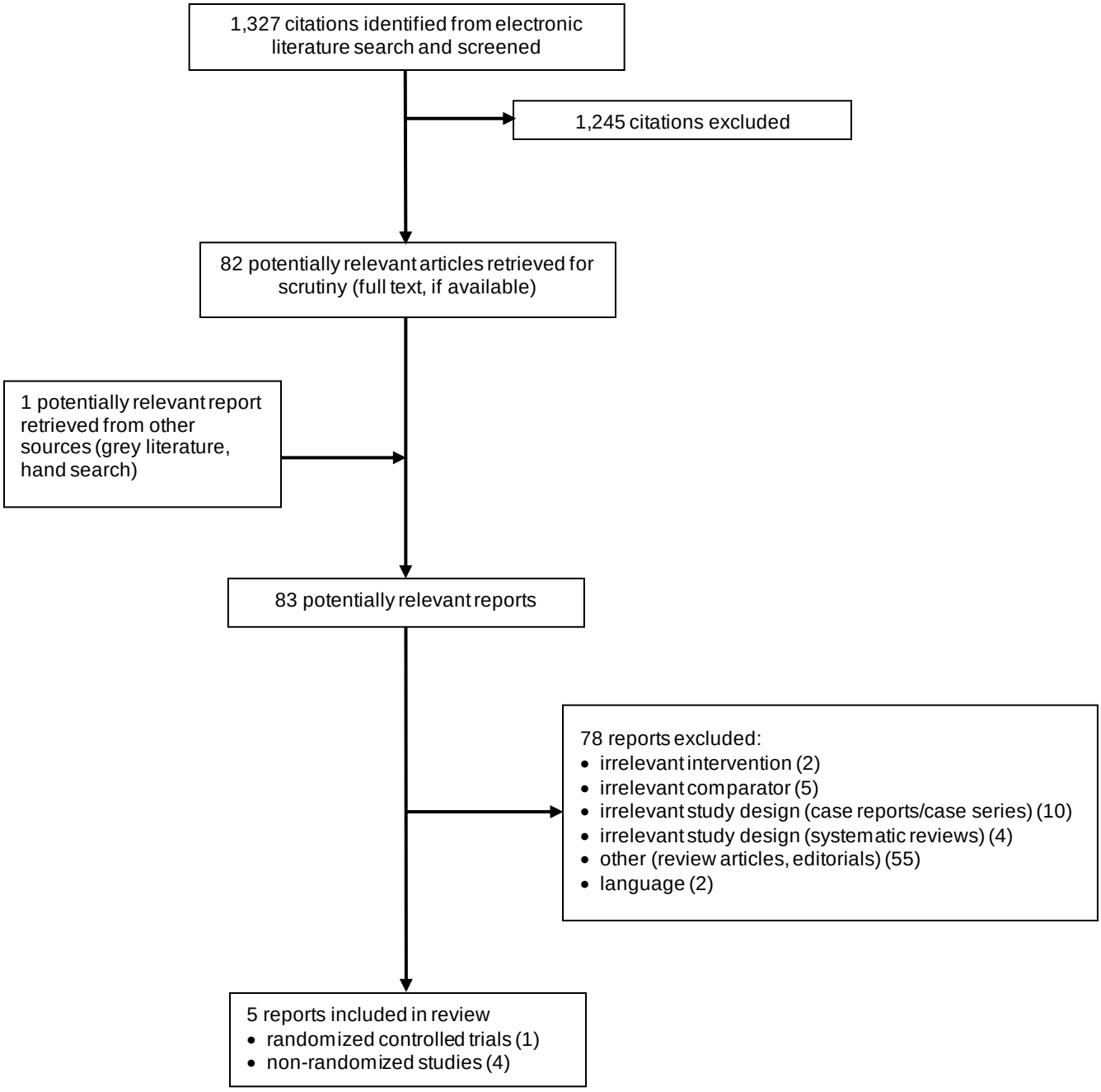
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Randomized controlled studies				
Li et al., 2020[23] **Country:** China **Funding source:** Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) grants 2020-I2M-CoV19-006, 2016-I2M-3-024 and 2017-I2M-1-009; Nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences grant 2018PT32016	**Study design:** Open label randomized clinical trial **Objective**: To evaluate the efficacy and safety of CP therapy using a standardized approach in donor selection and CP quality control	**Inclusion criteria:** Adult patients hospitalized with COVID-19 diagnosed based on PCR testing and had, (1) positive PCR within 72 hours prior to randomization, (2) pneumonia confirmed with imaging, and (3) symptoms meeting severe or life-threatening COVID-19 **Exclusion criteria**: Pregnancy/lactation, IgA deficiency, immunoglobulin allergy, risk of thrombosis due to pre-existing comorbidity, life expectancy less than 24 hours, DIC, severe septic shock, PaO2<100, severe CHF, High titer of S RBD-specific IgG antibody ≥ 1:640, participation in antiviral clinical trials within 30 days, physician determined contraindications *Severe COVID-19* was defined as respiratory distress, Rate ≥ 30/min; resting state oxygen saturation level less than 93% in room air and PaO2 ≤ 300 mmHg *Life-threatening COVID-19* was defined as respiratory failure requiring mechanical ventilation, shock, other organ failure requiring ICU monitoring **Number of participants**: Total number of participants, N=103 CP group, n=52 Control group, n=51 *Severe disease:* CP group, n= 23, control group, n=22 *Life-threatening disease:* CP group, n=29; control group, n= 29	**Intervention:** ABO compatible CP with S-RBD-specific IgG tire ≥1:1280. *Dose*: 4 mL/kg to 3 mL/kg of recipient body weight. *Administration*: 10 mL for the first 15 min, then increased to 100 mL/hr with monitoring. *Volume:* Median 200 mL (IQR,200 to 300mL), 96% of patients received single dose *Timing:* Median time from onset of symptoms to randomization = 30 days (IQR: 20 to 39 days) **Comparator**: Standard care All patients received symptomatic control and supportive care including antivirals, steroids, immunoglobulin, antibiotics and Chinese herbal medicines.	**Primary end point:** Time to clinical improvement. *Clinical improvement definition:* Decrease of two points on the disease severity scale. *Disease severity scale:* Hospital discharge: 1 point; Hospitalization with no supplemental oxygen: 2 points; Hospitalization plus supplemental oxygen (not high-flow or noninvasive ventilation: 3 points; Hospitalization plus noninvasive ventilation or high-flow supplemental oxygen: 4 points; Hospitalization plus ECMO or invasive mechanical ventilation: 5 points; Death: 6 points **Secondary outcomes:** 28 day mortality, duration of hospitalization, viral clearance from nasopharyngeal swab **Time to follow-up:** 28 days from randomization

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Median age (IQR): CP group: 70 years (62 to 80) Control group:69 years (63 to76) **Sex:** CP group: 48.1% females Control group:35.3% females		
Non-randomized controlled studies				
Abolghasemi et al., 2020[1] **Country:** Iran **Funding source:** Baqiyatallah Medical Science University, Tehran, Iran Blood Transfusion Organization, Tehran, Iran and Darman Ara Company, Tehran, Iran.	**Study design:** Prospective observational study	Adult patients with confirmed COVID-19 through laboratory (qRT-PCR) or CT imaging. **Inclusion Criteria:** Presence of some or all of disease clinical symptoms such as dyspnea, respiratory rate ≥20/ min, fever and cough; SpO2 ≤ 93% on room air; ≤ 7 days since onset of illness; willingness to participate in study. **Exclusion criteria**: Intubated patients or patients on mechanical ventilation; severe liver or kidney disease; septic shock; improving clinical condition to meet discharge criteria; known plasma hypersensitivity; physician decision. **Number of participants**: Total number of participants, N = 189 CP group, n = 115 Control group, n = 74 **Mean age (SD):** CP group: 54.41 (13.71) Control group: 56.83 (14.98) **Sex:** CP group: 41.7% females Control group: 50.0 % females	**Intervention:** ABO compatible CP, 500 mL (one unit) transfused over 4 hours, during the first three days of hospitalization. If no improvement, one more unit was transfused based on physician decision. **Comparator**: Standard care Patients in both groups received antiviral therapy including Lopinavir or Ritonavir, hydroxychloroquine, and an anti-inflammatory agent.	**Primary outcomes:** Patient survival and length of hospital stay **Secondary outcomes**: need for intubation, clinical symptom improvement such as tachypnea, "para clinical measured of the patients" and adverse events. **Length of follow up:** Till discharge from hospital or death.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Xia et al., 2020[26] **Country:** China **Funding source:** National Natural Science Foundation of China (Grant Nos. 81572893, 81972358, 81959113), Key Foundation of Wuhan Huoshenshan Hospital (Grant No. 2020[18]), Key Research& Development Program of Jiangsu Province (Grant Nos. BE2017733, BE2018713), Medical Innovation Project of Logistics Service (Grant No. 18JS005) and Basic Research Program of Jiangsu Province (Grant No. BK20180036).	**Study design:** Retrospective observational study	Severe or critical COVID-19 patients. **Inclusion Criteria for CP group:** Laboratory confirmed case, abnormal CT chest findings, no improvement after standard care, critical illness. **Exclusion criteria for CP group:** Allergy to plasma contents. *Severe COVID-19* was defined as respiratory distress, Rate ≥ 30/min; resting state oxygen saturation level less than 93% in room air and PaO2 ≤ 300 mmHg. Chest imaging with obvious lesion progression over 24 to 48 hours >50% was also considered as severe. *Critical COVID-19* was defined as respiratory failure requiring mechanical ventilation, shock, other organ failure requiring ICU monitoring **Number of participants**: Total number of participants, N = 1,568 CP group, n = 138 Control group, n = 1,430 **Median age (IQR):** CP group: 65 years (57 to 73) Control group: 63 years (53 to 71) **Sex:** CP group: 44.2% females Control group: 49.7% females	**Intervention:** ABO compatible CP with titers ≥ 1: 160 *Dose*: 4 to 5 mL/kg of recipient body weight. *Administration*: Slow transfusion for the first 15 min, and then with monitoring. *Volume:* 117 (84.7%) patients received 1 to 2 units (200 to 400 mL); 81 patients (58.6%) received CP once. *Timing:* Median time from onset of symptoms to CP transfusion 45 days (IQR: 39 to 54) **Comparator**: Standard care All patients received antivirals, traditional Chinese medicine and respiratory support.	**Clinical outcomes:** Mortality rate, clinical improvement based on six category scale. **Safety outcomes:** Transfusion-related reactions, laboratory parameters assessed after CP transfusion **Time of outcome measurement:** April 20, 2020 (for the outcome mortality) **Length of follow up:** Not reported

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Duan et al., 2020[25] **Country:** China **Funding source:** 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); Shanghai Guangci Translational Medicine Development Foundation	**Study design:** Pilot prospective cohort with a historical control group. **Objective**: To assess the feasibility of CP treatment in severe COVID-19 patients.	**Inclusion criteria:** Adult patients with severe COVID-19 according to WHO interim Guidance[28] and the guideline of diagnosis and treatment of COVID-19 of National Health Commission of China with confirmation by real-time PCR assay, and having at least two of: 1) respiratory distress, Rate ≥ 30/min; 2) oxygen saturation level less than 93% in resting state, 3) PaO2 ≤ 300 mmHg. **Exclusion criteria**: 1) previous allergic history to plasma or ingredients, 2) serious general condition (organ dysfunction) who were not suitable for CP transfusion. **Number of participants**: 20 (10 in the CP group; 10 in the placebo group). **Median age:** 52.5 years in the CP group; 53.0 years in the control group. **Sex**: 40% female in the CP group; 40% female in the control group.	**Intervention:** One dose of 200 mL of inactivated CP with neutralization activity of 1:640 transfused over 4 hours. **Comparator**: Standard care All patients received antiviral therapy, steroids and supportive care as appropriate.	**Primary end point:** Safety of CP treatment **Secondary end points**: Improvement of clinical symptoms, laboratory and radiographical parameters **Time to follow-up:** within 3 days of CP transfusion
Zeng et al. 2020[24] **Country:** China **Funding source:** The National Natural Science Foundation of China (No. 81970517), Zhongyuan (Henan) Thousands Outstanding Talents Plan (No. ZYQR201912179), Foundation for Distinguished Young Talents of Zhengzhou University Medical School (No.2020ZQLMS), and The Key Scientific Research Project of Henan	**Study design:** Retrospective observational study **Objective:** To analyze the efficacy of CP treatment in COVID-19 patients	**Inclusion criteria:** Patients with COVID-19 (based on WHO interim guidance[28]) **Exclusion criteria**: Not reported **Number of participants**: 21 (6 in the CP group; 15 in the placebo group). **Median age:** 61.5 years in the CP group; 73.0 years in the control group. **Sex**: 16.6% female in the CP group; 26.6% female in the control group.	**Intervention**: CP therapy. Mean volume 300 mL (range 200 to 600 mL). **Comparator**: Standard care All patients received supportive care, antivirals, steroid and immunoglobulins as appropriate.	**Outcomes measured:** Clinical outcomes, SARS-CoV-2 clearance, adverse events **Primary endpoint:** fatality or recovery **Follow up**: Patients were followed up until they reached any of the end points.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Higher Education Institutions of China (No. 20B320028)				

COVID-19 = coronavirus disease; CHF: congestive heart failure; CP = convalescent plasma; CT: computerized tomography; DIC: disseminated intravascular coagulation; ECMO: extracorporeal membrane oxygenation; IQR = interquartile range; PaO2 = partial pressure of oxygen; PCR = polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; S-RBD-specific IgG: S-receptor binding domain- specific immunoglobulin G; WHO: World Health Organization.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[22]

Strengths	Limitations
Li et al., 2020[23]	
• The objectives of the study were clearly described. • Well-described inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of the patients were compared and reported in detail. • There was random allocation of participants to each group. • The interventions of interest including dosage, timings and the standard care given to both groups were well described • The outcomes of interest were reported in detail with definitions. They were appropriate to the study. Patients were followed up to the same time in both groups • Potential confounders like age, severity of disease, comorbid conditions and other medications were addressed. • Main study findings were reported with simple outcome data (medians and IQRs for the continuous outcomes, effect estimates and 95% confidence intervals, actual probability values when P value was < 0.001, and appropriate statistical tests were used) • Incidence of adverse events was described. • Characteristics of patients lost to follow up were described (one in each group) • Patients were recruited from seven centers, over the same period and were representative of the population. • Outcome assessment was blinded. • There was intent to treat analysis, and the per protocol analysis • Conflict of interest of the authors were reported (and there were no concerns).	• This was an open-label study where the patients and treating clinicians were not blinded to the intervention • The study was terminated early due to a decision by the study sponsor and investigator as the case numbers in the population were low. • The investigators recruited half of the expected number of participants in each group, resulting in inadequate power. • Participants in both groups received standard treatments including antivirals, steroids and immunoglobulins leading to potential confounding.
Abolghasemi et al., 2020[1]	
• The objectives of the study were clearly described. • Well-described inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of the patients were compared between groups and reported in detail. • Study outcomes were clearly described and defined. • The study intervention and the standard care given to both groups were described. • Main study findings were reported with simple outcome data (means and SD for the continuous outcomes, effect estimates and 95% confidence intervals, actual probability values and appropriate statistical tests were used) • Adverse events were measured and reported, and no patients were lost to follow up. • Study participants were recruited from four hospitals in Iran over the same period of time. They were representative of the source population.	• The study was observational in design with no randomized allocation or blinding. • The length of follow up in the CP group and control group were unclear. • It was unclear whether a sample size calculation was done to determine the number of participants required for adequate statistical power.

Strengths	Limitations
• Potential confounders like age, comorbid conditions, baseline laboratory parameters, severity of disease and other medications were similar between the groups.	
Xia et al., 2020[26]	
• The outcomes of interest were reported in detail with definitions. They were appropriate to the study. • Characteristics of the study participants were reported including demographics, comorbidities, severity of disease and symptoms. • The intervention was reported clearly including dose, administration, timing of administration and collection of CP from donors. • Main study findings were reported with simple outcomes data (medians and IQRs for the continuous outcomes, effect estimates and 95% confidence intervals, actual probability values when P value was < 0.001). • Important adverse events were recorded and reported. • Because of the nature of the study (inpatient treatment, observational study), no patients were lost to follow up.	• The study was observational in design with no randomized allocation or blinding. • Only the eligibility criteria for CP therapy was reported. Other study inclusion and exclusion criteria (for the control group) were not reported. It is possible that all patients hospitalized during the study period were included in the study, and among them eligible patients were given CP. • Patients who did not improve with standard care alone were administered CP. This means patients in CP arm were different from those in the control arm, lowering internal validity, and patients in both arms were followed up for different durations. • Participants in CP groups were significantly different from those in the control group in several characteristics such as age, rate of diabetes, symptoms (shortness of breath), median duration since symptom onset to hospitalization, and severity of disease. This could potentially affect the study outcomes. • All patients received standard care including antivirals and traditional Chinese medicine, which increased the risk of confounding bias. Potential confounders were not adjusted for in the analysis. • Study participants were not followed for a given duration, but rather the clinical outcomes were assessed on a particular day for all patients. Median duration from hospitalization to outcomes assessment was not reported. • It was unclear whether the staff and facilities were representative of the treatment majority of the patients receive. Generalizability to a Canadian setting was unclear.
Duan et al.,2020[25]	
• The objective of the study was clearly described. • The characteristics of the patients in the CP treatment group were reported. • The intervention was reported clearly including dose, administration and timing of administration. • Simple outcome data were reported. • Median and IQR for the continuous outcome were reported. Actual probability values were reported for baseline comparison between CP treatment and the control group. • No participants were lost to follow-up and the compliance to the intervention was good. • Appropriate statistical test (Fischer's exact test) was used to compare intervention and treatment groups.	• The study was a pilot study with small sample size (n = 20). • The control group was selected from historic patients who were matched for age and sex. This indicates a non-random sampling with a risk of sampling bias. Control group participants were not recruited over the same time period as the treatment group. Unclear if the comparison to historic control group was planned upfront. • The characteristics of patients in the historic control group were unclear. Thy types of comorbidities in the control group were unclear. • The representativeness of the participants to the entire population of interest was unclear. • The primary end point of the study was described as safety, but the definition was unclear. The definitions for the outcome measures used to compare CP group and the control group were unclear. • Multiple potential confounders were not described and adjusted for in the comparison. These confounders included comorbidities (cardiovascular and respiratory conditions),

Strengths	Limitations
	severity of the disease, need for mechanical ventilation, complications, and co-administered treatments (antiviral drugs, steroids). • Lists of possible adverse events were not provided even though safety of the CP transfusion was the primary end point. • The study was non-randomized and unblinded compared with a historic cohort. The internal validity of the study was low. • Follow-up time very short in the treatment group (3 days). • It was unclear when the outcome measures were assessed in the control group. For example, the number of days since onset of illness when "death" or "stability" were measured in the historic control group was not reported. Days since onset of illness were not matched between treatment group and control group. • Sample size calculation was not done to determine the number of participants required for adequate power. • It was unclear whether the staff and facilities were representative of the treatment majority of the patients receive. Generalizability to a Canadian setting was unclear.
Zeng et al. 2020[24]	
• The objective of the study was clearly described. • The main outcomes and end points of the study were described and were appropriate. • The characteristics of the patients in the study were clearly described including demographics, clinical symptoms, comorbidities and other interventions administered. • Potential confounders like comorbidities and other treatments in both groups were reported and compared. There were no differences between the two groups. • Simple outcome data for all measured outcomes were reported clearly. • Median and IQR were reported for continuous variables. Actual probability values were reported for P > 0.001. • Adverse events of the intervention were reported. • No patients were lost to follow-up. • Participants of both groups were recruited from two referral hospitals for COVID-19 over the same period. • There was no evidence of data-dredging by way of unplanned sub-group analysis. • Study end points was clearly described and were the same for both study arms. • Appropriate statistical tests (Fischer's exact test) were used to compare intervention and treatment groups. • No participants were lost to follow-up and the compliance to the intervention was good.	• A retrospective observational study with a small sample size (n = 21). • There was no standardized dosing of the CP therapy. The volume and number of doses differed between patients in the treatment group. The frequency and timing of the CP administration were unclear. • The inclusion exclusion criteria were not clearly described. • The selection of eligible participants and sampling was unclear, increasing the risk of selection bias. • The study was non-randomized and unblinded increasing risk of bias and lowering internal validity. The outcome measurements were not blinded. • Sample size calculation was not done to determine the number of participants required for adequate power. • It was unclear whether the staff and facilities were representative of the treatment majority of the patients receive. Generalizability to a Canadian setting was unclear.

COVID-19 = coronavirus disease; CP = convalescent plasma; IQR = interquartile range; n = number of participants; SD: standard deviation.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Li et al., 2020[23]	
An open-label RCT to evaluate the efficacy and safety of CP therapy compared to standard care. Total number of participants, N=103 CP group, n=52; Control group, n=51 There were no significant differences in demographics, baseline laboratory results and severity of disease, coexisting conditions, between the groups. **Rate of clinical improvement at 28 days, n/N (%)** • **All patients**: ○ CP group: 27/52 (51.9%) ○ Control group: 22/51 (43.10%) ○ Absolute difference = 8.8% (-10.4 to 28.0%) ○ Median time to improvement, days ▪ CP group: 28.00 (IQR 13.00 to indeterminate) ▪ Control group: indeterminate ▪ HR = 1.40 (0.79 to 2.49) • **Patients with severe disease** ○ CP group: 21/23 (91.3%) ○ Control group:15/22 (68.2%) ○ Absolute difference = 23.1% (-3.9 to 50.2%) ○ Median time to improvement, days ▪ CP group: 13.00 (9 to 21) ▪ Control group: 19.0 (IQR 15 to indeterminate) ▪ HR = 2.15 (1.07 to 4.32) • **Patients with life-threatening disease** ○ CP group: 6/29 (20.7%) ○ Control group:7/29 (24.1%) ○ Absolute difference = -3.4% (-24.9 to 18.0%) ○ Median time to improvement, days ▪ Indeterminate in both groups ▪ HR = 0.88 (0.30 to 2.63) **Discharge rate, n/N (%)** • **All patients:** ○ CP group: 26/51 (51%) ○ Control group:18/50 (36%) ○ OR (95%CI) = 1.42 (0.90 to 2.24) ○ P value = 0.13 ○ Median time from hospitalization to discharge, days ▪ CP group: 41.00 (IQR 31 to indeterminate) ▪ Control group: 53.00 (IQR 35.00 to indeterminate) ▪ HR = 1.68 (0.92 to 3.08) • **Patients with severe disease** ○ CP group: 21/23 (91.3%) ○ Control group:15/22 (68.2%) ○ OR (95%CI) = 1.34(00.98 to 1.83) ○ P value = 0.07 ○ Median time from hospitalization to discharge, days ▪ CP group: 32.00 (IQR 26 to 40) ▪ Control group: 41.00 (IQR 30 to 53) ▪ HR = 1.74 (0.89 to 3.41)	"Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not significantly improve the time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference."[23] (p. E10)

Main study findings	Authors' conclusion
• **Patients with life-threatening disease** ○ CP group: 5/28 (17.9%) ○ Control group:3/28 (10.7%) ○ OR (95%CI) = 1.67 (0.44 to 6.32) ○ P value = 0.71 ○ Median time from hospitalization to discharge, days ▪ Indeterminate in both groups ▪ HR = 1.90 (0.45 to 8.04) **Mortality at 28 days, n/N (%)** • **All patients:** ○ CP group: 8/51 (15.7%) ○ Control group:12/50 (24.0%) ○ OR (95%CI) = 0.65 (0.29 to 1.46) ○ P value = 0.30 • **Patients with severe disease** ○ CP group: 0/23 ○ Control group: 2/22 (9.1%) • **Patients with life-threatening disease** ○ CP group: 8/28 (28.6%) ○ Control group:10/28 (35.7%) ○ OR (95%CI) = 0.80 (0.37 to 1.72) ○ P value = 0.57 **Viral nucleic acid negative rate, n/N (%)** • **All patients:** ○ At 24h ▪ CP group:21/47 (44.7%) ▪ Control group:6/40 (15 %) ▪ OR (95%CI) = 4.58 (1.62 to 12.96); P value = 0.003 ○ At 48 hours ▪ CP group:32/47 (68.1%) ▪ Control group:13/40 (32.5 %) ▪ OR (95%CI) = 4.43 (1.80 to 10.92); P value = 0.001 ○ At 72 hours ▪ CP group:41/47 (87.2%) ▪ Control group:15/40 (37.5 %) ▪ OR (95%CI) = 11.39 (3.91 to 33.18); P value < 0.001 • **Patients with severe disease** ○ At 24h ▪ CP group: 7/21 (33.3%) ▪ Control group:2/17 (11.8 %) ▪ OR (95%CI) = 3.75 (0.66 to 21.2); P value = 0.15 ○ At 48 hours ▪ CP group:13/21 (61.9%) ▪ Control group:6/17 (35.3%) ▪ OR (95%CI) = 2.98 (0.79 to 11.25); P value = 0.10 ○ At 72 hours ▪ CP group: 19/21 (90.5%) ▪ Control group: 7/17(41.2%) ▪ OR (95%CI) = 13.57 (2.36 to77.95); P value < 0.001 • **Patients with life-threatening disease** ○ At 24h ▪ CP group: 14/26 (53.8%)	

Main study findings	Authors' conclusion
▪ Control group: 4/23 (17.4%) ▪ OR (95%CI) = 5.54 (1.47 – 20.86); P value = 0.01 ○ At 48 hours ▪ CP group:19/26 (73.1%) ▪ Control group:7/26 (30.4%) ▪ OR (95%CI) = 6.20 (1.79 to 24.46); P value = 0.003 ○ At 72 hours ▪ CP group:22/26 (84.6%) ▪ Control group:8/23(34.8%) ▪ OR (95%CI) = 10.31 (2.63 to 40.50); P value < 0.001 **Adverse events in the CP group:** ○ Chills and rashes, n = 1 ○ Severe transfusion associated dyspnea, n = 1	
Abolghasemi et al., 2020[1]	
A case control study comparing CP therapy and standard care in COVID-19 patients. CP group, n = 115 Control group, n = 74 **Baseline characteristics:** There were no significant differences in demographics, baseline laboratory results and vital signs, and comorbidities between the groups. • **Hypertension, n (%)** ○ CP group = 22 (27.5) ○ Control group = 19 (38.0) ○ P = 0.210 • **Diabetes, n (%)** ○ CP group = 27 (33.8) ○ Control group = 16 (32.0) ○ P = 0.837 • **On admission chest CT scan score, mean (SD)** ○ CP group = 13.81 (4.87); Range = 4 to 23 ○ Control group = 13.36 (5.67); Range = 2 to 23 ○ P = 0.719 **Study findings** • **All-cause mortality, n (%)** ○ CP group = 17 (14.8) ○ Control group = 18 (24.3) ○ P = 0.09 • **Length of hospital stay (Since date of admission), mean (SD)** ○ CP group = 9.54 days (5.07); Range = 2 to 24 ○ Control group = 12.88 days (7.19); Range = 2 to 32 ○ P = 0.002 • **Length of hospital stay (Since date of CP therapy in CP group), mean (SD)** ○ CP group = 6.25 days (4.33); Range = 0 to 20 ○ Control group (since admission) = 12.88 days (7.19); Range = 2 to 32 ○ P = 0.000 • **Patients discharged from hospital ≤ 5 days post-admission, n (%)** ○ CP group = 27 (28.1) ○ Control group = 5 (8.9) ○ P = 0.010	"The nonrandomized clinical trial presented here demonstrates the clinical efficacy of convalescent plasma in COVID-19 infected patients and indicates that convalescent plasma treatment should be considered as a safe and effective therapy for COVID-19 patients. Convalescent plasma therapy substantially improved patients' survival, significantly reduced hospitalization period and needs for intubation in COVID-19 patients in comparison with control group. Despite some limitations, this clinical study provides strong evidence to support the efficacy of convalescent plasma therapy in COVID-19 patients and therefore this therapy is recommended for better management of these patients." (p. 4)[1]

Main study findings	Authors' conclusion
• **Intubated patients, n (%)** ○ CP group = 8 (7.0) ○ Control group = 15 (20.3) ○ P = 0.006 **Adverse events in the CP group:** • Transient mild fever and chill, n = 1 **Adverse events in the Control group: Not reported**	
Xia et al., 2020[26]	
A non-randomized study comparing CP therapy and standard care in COVID-19 patients. CP group, n=138 Control group, n=1,430 **Baseline characteristics:** **Degree of severity, n (%)** • **Severe disease, n (%)** ○ CP treatment group = 116 (84.1); Control group = 1,304 (91.2) • **Critical disease, n (%)** ○ CP treatment group = 22 (15.9); Control group = 126 (8.8) ○ P = 0.009 **Comorbidities:** • **Diabetes, n (%)** ○ CP treatment group = 31 (22.5); Control group = 218 (15.2) ○ P = 0.04 • **Hypertension, n (%)** ○ CP treatment group = 53 (38.4); Control group = 508 (35.5) ○ P = 0.5 • **Cardiovascular disease, n (%)** ○ CP treatment group = 27 (19.6); Control group = 210 (14.7) ○ P = 0.1 • **Cerebrovascular disease, n (%)** ○ CP treatment group = 12 (8.7); Control group = 75 (5.2) ○ P = 0.1 • **Malignancy, n (%)** ○ CP treatment group = 4 (2.9); Control group = 53 (3.7) ○ P = 0.8 • **Chronic obstructive pulmonary disease, n (%)** ○ CP treatment group = 12 (8.7); Control group = 91 (6.4) ○ P = 0.3 • **Chronic renal disease, n (%)** ○ CP treatment group = 4 (2.8); Control group = 33 (2.3) ○ P = 0.6 • **Chronic liver disease, n (%)** ○ CP treatment group = 4 (2.9); Control group = 39 (2.7) ○ P = 0.8 • **Immunodeficiency, n (%)** ○ CP treatment group = 2 (1.4); Control group = 4 (0.28) ○ P = 0.09 • **Days from symptoms onset to admission, median (IQR)** ○ CP treatment group = 35 (18 to 40); Control group = 25 (14 to 35) ○ P < 0.001	"Our results suggest that CCP, transfused even after two weeks (median of 45 days in our cohort) of symptom onset, could improve the symptoms and mortality in severe or critical COVID-19 patients. We anticipate that this study could shed new light in clinical practice and monoclonal antibody development for COVID-19."[26] (p. 6-7)

Main study findings	Authors' conclusion
• **Days from symptoms onset to discharge, median (IQR)** ○ CP treatment group = 22 (16 to 30); Control group = 14 (8 to 21) ○ P < 0.001 **Symptoms at baseline** • **Fatigue, n (%)** ○ CP treatment group = 57 (41.3); Control group = 564 (39.4) ○ P = 0.7 • **Fever, n (%)** ○ CP treatment group = 93 (67.4); Control group = 984 (68.8) ○ P = 0.8 • **Highest temperature (°C), median (IQR)** ○ CP treatment group = 37.2 (37.0 to 37.4); Control group = 37.1 (36.9 to 37.3) ○ P = 0.008 • **Cough, n (%)** ○ CP treatment group = 83 (60.1); Control group = 863 (60.3) ○ P = 1 • **Shortness of breath, n (%)** ○ CP treatment group = 28 (20.3); Control group = 150 (10.5) ○ P = 0.001 • **Chest congestion, n (%)** ○ CP treatment group = 24 (17.4); Control group = 175 (12.2) ○ P = 0.1 • **Nausea or vomiting, n (%)** ○ CP treatment group = 2 (1.4); Control group = 13 (0.9) ○ P = 0.4 • **Diarrhea, n (%)** ○ CP treatment group = 4 (2.9); Control group = 39 (2.7) ○ P = 0.8 **ICU admission, n (%)** ○ CP treatment group (among 126 patients who were not admitted to ICU prior to CP therapy) = 3 (2.4) ○ Control group = 72 (5.1) ○ P = 0.2 **Highest six category scale during hospitalization** • **2: Hospitalized, but not requiring oxygen, n (%)** ○ CP treatment group = 55 (39.9); Control group = 675 (50.4) • **3: Low flow oxygen therapy, n (%)** ○ CP treatment group = 50 (36.2); Control group = 469 (35.0) • **4: High-flow oxygen therapy or noninvasive mechanical ventilation, n (%)** ○ CP treatment group = 28 (20.3); Control group = 224 (16.7) • **5: ECMO or invasive mechanical ventilation, n (%)** ○ CP treatment group = 2 (1.4); Control group = 3 (0.2) • P = 0.04 **Clinical outcomes, n (%) – As of April 20, 2020** • **Death** ○ CP treatment group = 3 (2.2); Control group = 59 (4.1) • **Discharge from hospital** ○ CP treatment group = 121 (87.7); Control group = 1366 (95.5) • **Hospitalization** ○ CP treatment group = 14 (10.1); Control group = 5 (0.3) • **P < 0.001**	

Main study findings	Authors' conclusion
Adverse events in the CP group: ○ Minor allergic reaction (pruritus or erythema), n= 3 ○ Severe transfusion reaction, n = 0 The study reported that "none of [laboratory] indexes showed significant differences before and after [CP] therapy, except for the decrease in total bilirubin. In addition, levels of cytokines such as TNF-α, IL-10, and IL-6 were compared before and after CCP therapy. The results showed that all of these cytokines remained at the original level"[26] (p. 4)	
Duan et al.,2020 [25]	
A non-randomized pilot study to assess the effectiveness of CP therapy. 10 COVID-19 patients received one dose of 200 mL CP infusion, compared with age- and sex-matched historic control. CP treatment group, n=10 Historic Control group, n=10 **Baseline characteristics** • Age, median (IQR) ○ CP treatment group = 52.5 (45 to 59.5) ○ Historic control group = 53 (46.5 to 60.5) • Sex, n (%) ○ CP treatment group = 4 (40%) female ○ Historic control group = 4 (40%) female • Co-morbidity, n (%) ○ CP treatment group = 4 (40%) had co-morbidities ○ Historic control group = 6 (60%) had co-morbidities **Study findings** • **Death, n (%)** ○ CP treatment group = 0 ○ Historic control group = 3 (30) • **Stable, n (%)** ○ CP treatment group = 0 ○ Historic control group = 6 (60) • **Improved, n (%)** ○ CP treatment group = 7 (70) ○ Historic control group = 1 (10) • **Discharged, n (%)** ○ CP treatment group = 3 (30) ○ Historic control group = 0	"In conclusion, this pilot study on CP therapy shows a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients. One dose of CP with a high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes. The optimal dose and treatment time point, as well as the definite clinical benefits of CP therapy, need to be further investigated in randomized clinical studies."[25] (p. 9496)
Zeng et al. 2020[24]	
A retrospective observational study to assess the clinical effectiveness of CP therapy in COVID-19 patients. Six patients received CP therapy compared with 15 patients in the control group. **Baseline characteristics:** *Demographics:* • Age, median (IQR) ○ CP treatment group = 61.5 (31.5 to 77.8) ○ Control group = 73 (60 to 79)	"In conclusion, the current study firstly suggests that convalescent plasma therapy can discontinue the viral shedding and contribute longer survival duration in COVID-19 patients with respiratory failure, although it cannot reduce the mortality in critically end-stage patients. Additionally, we suggest that convalescent plasma treatment should be infused for potentially critical COVD-19 patients at their early

Main study findings	Authors' conclusion

• Sex, females n/N (%)
  ○ CP treatment group = 1/6 (16.6)
  ○ Control group = 5/15 (26.6)
 	
Chronic comorbidities:
• **Diabetes, n (%)**
  ○ CP treatment group = 1 (16.7); Control group = 5 (33.3)
  ○ P = 0.623
• **Hypertension, n (%)**
  ○ CP treatment group = 1 (16.7); Control group = 3 (20)
  ○ P = 1.0
• **Chronic liver disease, n (%)**
  ○ CP treatment group = 0; Control group = 2 (13.3)
  ○ P = 1.0
• **Cardiovascular disease, n (%)**
  ○ CP treatment group = 1 (16.7); Control group = 0
  ○ P = 0.286
• **Respiratory diseases, n (%)**
  ○ CP treatment group = 0; Control group =1 (16.7)
  ○ P = 1.0
• **Chronic kidney disease, n (%)**
  ○ CP treatment group = 0; Control group = 1 (16.7)
  ○ P = 1.0
 	
Baseline symptoms and interventions administered:
• **Fever, n (%)**
  ○ CP treatment group = 5 (83.3); Control group = 13 (86.7)
  ○ P = 1.0
• **Cough, n (%)**
  ○ CP treatment group = 5 (83.3); Control group = 14 (93.3)
  ○ P = 0.5
• **Shortness of breath, n (%)**
  ○ CP treatment group = 4 (66.7); Control group = 12 (80)
  ○ P = 0.598
• **Dyspnoea, n (%)**
  ○ CP treatment group = 3 (50); Control group = 8 (53.3)
  ○ P = 1.0
• **ICU admission, n (%)**
  ○ CP treatment group = 6 (100); Control group = 15 (100)
  ○ P = 1.0
• **Antiviral therapy, n (%)**
  ○ CP treatment group = 4 (66.7); Control group = 12 (80)
  ○ P = 0.598
• **Glucocorticoid therapy, n (%)**
  ○ CP treatment group = 4 (66.7); Control group = 12 (80)
  ○ P = 0.598
• **High flow nasal cannula oxygen, n (%)**
  ○ CP treatment group = 6 (100); Control group = 15 (100)
  ○ P = 1.0
• **Mechanical ventilators, n (%)**
  ○ CP treatment group = 5 (83.3); Control group = 13 (86.6)
  ○ P = 1.0
 	
Study findings:
• **SARS-CoV-2 clearance before death in deceased patients, n (%)**
	phase based on the current study. Future large-scale studies are needed to investigate whether early phase infusion of convalescent plasma in proper receiving populations can prevent clinical deterioration and improve survival rate."[24] (p. 10)

Main study findings	Authors' conclusion
○ CP treatment group = 5 (100) ○ Control group = 3/14 (21.4) ○ P = 0.005 • **Duration of illness, days (IQR)** ○ CP treatment group = 45.5 (37.8 to 59.0) ○ Control group = 31 (30 to 36) ○ P = 0.029 • **Duration of viral shedding, days (IQR)** ○ CP treatment group = 23.5 (19.5 to 24.5) ○ Control group = 20 (19 to 24) ○ P = 0.381 • **Fatality, n (%)** ○ CP treatment group = 5 (83.3) ○ Control group = 14 (93.3) ○ P = 0.500 • **Discharge, n (%)** ○ CP treatment group = 1 (16.7) ○ Control group = 1 (16.7) • **SARS-CoV-2 clearance before death in deceased patients, n (%)** ○ CP treatment group = 5 (100) ○ Control group = 3/14 (21.4) ○ P = 0.005 • **SARS-CoV-2 clearance in all patients (living and deceased), n (%)** ○ CP treatment group = 6 (100) ○ Control group = 4 (26.7) ○ P = 0.004 • **Adverse events in CP treatment group, n (%)** ○ Anaphylaxis = 0; Fever = 0	

COVID-19 = coronavirus disease; CP = convalescent plasma; HR = Hazard ratio; ICU = Intensive Care Unit; IQR = interquartile range; n = number of participants; OR = Odd's ratio; RCT: randomized controlled trial; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Appendix 5: Further Information

Systematic Reviews and Meta-Analyses

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Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systematic review. *J Med Virol*. 2020 05;92(5):479-490.
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PubMed: PM32313660

Mehta N, Mazer-Amirshahi M, Alkindi N, Pourmand A. Pharmacotherapy in COVID-19; a narrative review for emergency providers. *Am J Emerg Med*. 2020; S0735-6757(20)30263-1. [online ahead of print]
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Single-arm Study

Perotti C, Baldanti F, Bruno R, et al. Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma. A proof of concept single arm multicenter trial. *Haematologica*. 2020 Jul 23;haematol.2020.261784.
PubMed: PM32703797

Case Reports and Case Series

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Appendix 6: Ongoing Clinical Trials

Table 5: Registered Clinical Trials of Convalescent Plasma for People with COVID-19

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Ongoing Canadian Trials						
CONCOR-1 CONvalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness (NCT04348656) https://clinicaltrials.gov/ct2/show/NCT04348656	Canada Hamilton Health Sciences Corporation	Open label RCT	Phase III	1,200 participants	16 years and older	December 31, 2020
CONCOR-KIDS Efficacy of Human Coronavirus-immune Convalescent Plasma for the Treatment of COVID-19 Disease in Hospitalized Children (NCT0437758) https://clinicaltrials.gov/ct2/show/NCT04377568	Canada The Hospital for Sick Children	Multicentered, open label, RCT	Phase II	100 participants	up to 18 years	May 1, 2022
Ongoing International Trials						
Study for using the healed novel coronavirus pneumonia (COVID-19) patients plasma in the treatment of severe critical cases http://www.chictr.org.cn/hvshowproject.aspx?id=23284	China The First Affiliated Hospital of Zhengzhou University	RCT	NR	30 participants	NR	May 30, 2020
COV19-PLASMA Hyperimmune Plasma for Critical Patients With COVID-19 (NCT04321421) https://clinicaltrials.gov/ct2/show/NCT04321421	Italy Foundation IRCCS San Matteo Hospital	Single group, open label	NA	49 participants	18 years and older	May 31, 2020
Exchange Transfusion Versus Plasma From Convalescent Patients With Methylene Blue in Patients With COVID-19 (COVID-19) (NCT04376788) https://clinicaltrials.gov/ct2/show/NCT04376788	Egypt Ain Shams University	Open label RCT	Phase II	15 participants	18 to 65 years	June 1, 2020
CORIPLASM Efficacy of Convalescent Plasma to Treat COVID-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort (NCT04345991) https://clinicaltrials.gov/ct2/show/NCT04345991	France Assistance Publique - Hôpitaux de Paris	Open label RCT	Phase II	120 participants	18 years and older	June 1, 2020

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Convalescent Plasma Trial in COVID -19 Patients (NCT04356534) https://clinicaltrials.gov/ct2/show/NCT04356534	Bahrain Royal College of Surgeons in Ireland - Medical University of Bahrain	Open label RCT	NA	40 participants	21 years and older	June 20, 2020
Convalescent Plasma for COVID-19 (NCT04365439) https://clinicaltrials.gov/ct2/show/NCT04365439	Italy Enos Bernasconi	Single group, open label	NA	10 participants	18 to 75 years	June 30, 2020
Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients (NCT04346446) https://clinicaltrials.gov/ct2/show/NCT04346446	India Institute of Liver and Biliary Sciences, India	Open label RCT	Phase II	40 participants	18 years and older	June 30, 2020
Convalescent Antibodies Infusion in Critically Ill COVID 19 Patients (NCT04346589) https://clinicaltrials.gov/ct2/show/NCT04346589	Italy A.O. Ospedale Papa Giovanni XXIII	Single group, open label	NA	10 participants	18 years and older	July 2020
ConPlas-19 Convalescent Plasma Therapy vs. SOC for the Treatment of COVID19 in Hospitalized Patients (NCT04345523) https://clinicaltrials.gov/ct2/show/NCT04345523	Spain Cristina Avendaño Solá	Open label RCT	Phase II	278 participants	18 years and older	July 2020
CONCOVID Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease (NCT04342182) https://clinicaltrials.gov/ct2/show/NCT04342182	Netherlands Erasmus Medical Center	Open label RCT	Phase II and III	426 participants	18 years and older	July 1, 2020
COPLA Treatment of Severe Forms of COronavirus Infection With Convalescent PLAsma (NCT04357106) https://clinicaltrials.gov/ct2/show/NCT04357106	Mexico Centro de Hematología y Medicina Interna	Single group, open label	Phase II	10 participants	18 years and older	August 2020

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
CoVID-19 Plasma in Treatment of COVID-19 Patients (NCT04355897) https://clinicaltrials.gov/ct2/show/NCT04355897	USA The Christ Hospital	Single group, open label	Early Phase I	100 participants	18 to 80 years	August 2020
Plasma of the convalescent in the treatment of novel coronavirus pneumonia (COVID-19) common patient: a prospective clinical trial http://www.chictr.org.cn/hvshowproject.aspx?id=23426	China China-Japan friendship hospital	Open label RCT	NR	50 participants	18 years and older	August 15, 2020
Investigating Effect of Convalescent Plasma on COVID-19 Patients Outcome: A Clinical Trial (NCT04327349) https://clinicaltrials.gov/ct2/show/NCT04327349	Iran Mazandaran University of Medical Sciences	Single group, open label	NA	30 participants	30 to 70 years	September 30, 2020
COPLASCOV19 Convalescent Plasma for Ill Patients by Covid-19 (NCT04356482) https://clinicaltrials.gov/ct2/show/NCT04356482	Mexico Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado	Single group, open label	Phase I and II	90 participants	16 years and older	December 2020
CP-COVID-19 Convalescent Plasma for Patients With COVID-19: A Randomized, Open Label, Parallel, Controlled Clinical Study (NCT04332835) https://clinicaltrials.gov/ct2/show/NCT04332835	Columbia Universidad del Rosario	Open label RCT	Phase II and III	80 participants	18 to 60 years	December 31, 2020
Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19 (NCT04292340) https://clinicaltrials.gov/ct2/show/NCT04292340	China Shanghai Public Health Clinical Center	Prospective observational	NR	15 participants	NR	December 31, 2020
Convalescent plasma for the treatment of severe novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial http://www.chictr.org.cn/hvshowproject.aspx?id=23000	China China-Japan friendship hospital	Open label non-randomized	NR	200 participants	18 to 55 years	February 5, 2021

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Convalescent Plasma Collection and Treatment in Pediatrics and Adults (NCT04376034) https://clinicaltrials.gov/ct2/show/NCT04376034	USA West Virginia University	Prospective, non-randomized comparative	Phase III	240 participants	1 month and older	March 30, 2021
PassItOnII Passive Immunity Trial of Nashville II for COVID-19 (NCT04362176) https://clinicaltrials.gov/ct2/show/NCT04362176	USA Vanderbilt University Medical Center Dolly Parton	Triple blind, placebo-controlled RCT	Phase III	500 participants	18 years and older	April 2021
Plasma Therapy of COVID-19 in Critically Ill Patients (NCT04359810) https://clinicaltrials.gov/ct2/show/NCT04359810	USA Columbia University	Double blind RCT	Phase II	105 participants	18 years and older	April 2021
Experimental Use of Convalescent Plasma for Passive Immunization in Current COVID-19 Pandemic in Pakistan in 2020 (NCT04352751) https://clinicaltrials.gov/ct2/show/NCT04352751	Pakistan Hilton Pharma	Single group, open label	NA	2,000 participants	18 to 55 years	April 2021
Anti COVID-19 Convalescent Plasma Therapy (NCT04345679) https://clinicaltrials.gov/ct2/show/NCT04345679	Hungary Orthosera Kft.	Single group, open label	Early Phase I	20 participants	18 years and older	April 1, 2021
Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection (NCT04343755) https://clinicaltrials.gov/ct2/show/NCT04343755	USA Hackensack Meridian Health	Single group, open label	Phase IIa	55 participants	18 years and older	April 2021
Convalescent Plasma in the Treatment of COVID 19 (NCT04343261) https://clinicaltrials.gov/ct2/show/NCT04343261	USA Saint Francis Care	Single group, open label	Phase II	15 participants	18 years and older	April 1, 2021
Convalescent Plasma for Treatment of COVID-19 Patients With Pneumonia (NCT04374565) https://clinicaltrials.gov/ct2/show/NCT04374565	USA University of Virginia	Single group, open label	Phase II	29 participants	18 years and older	April 5, 2021
Potential Efficacy of Convalescent Plasma to Treat Severe COVID-19 and Patients at High Risk of Developing Severe COVID-19 (NCT04347681) https://clinicaltrials.gov/ct2/show/NCT04347681	Saudi Arabia King Fahad Specialist Hospital Dammam	Open label non-randomized	Phase II	40 participants	18 to 85 years	April 11, 2021

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Therapeutic Plasma Exchange Alone or in Combination With Ruxolitinib in COVID-19 Associated CRS (NCT04374149) https://clinicaltrials.gov/ct2/show/NCT04374149	USA Prisma Health-Upstate	Open label non-randomized	Phase II	20 participants	12 to 80 years	April 30, 2021
Safety in Convalescent Plasma Transfusion to COVID-19 (NCT04333355) https://clinicaltrials.gov/ct2/show/NCT04333355	Mexico Hospital San Jose Tec de Monterrey	Single group, open label	Phase I	20 participants	18 years and older	April 30, 2021
PLASCOSSA Efficacy of Convalescent Plasma Therapy in the Early Care of COVID-19 Patients (NCT04372979) https://clinicaltrials.gov/ct2/show/NCT04372979	France Direction Centrale du Service de Santé des Armées	Triple blind RCT	Phase III	80 participants	18 to 80 years	May 2021
Convalescent Plasma in ICU Patients With COVID-19-induced Respiratory Failure (NCT04353206) https://clinicaltrials.gov/ct2/show/NCT04353206	USA	Single group, open label	Early Phase I	90 participants	18 years and older	May 2021
A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications (NCT04374487) https://clinicaltrials.gov/ct2/show/NCT04374487	India Max Healthcare Institute Limited	Open label RCT	Phase II	100 participants	18 to 85 years	May 9, 2021
COP-COVID-19 Convalescent Plasma Compared to the Best Available Therapy for the Treatment of SARS-CoV-2 Pneumonia (NCT04358783) https://clinicaltrials.gov/ct2/show/NCT04358783	Mexico Hospital Universitario	Quadruple blind RCT	Phase II	30 participants	18 years and older	May 30, 2021
CCAP Efficacy and Safety of Novel Treatment Options for Adults With COVID-19 Pneumonia (NCT04345289) https://clinicaltrials.gov/ct2/show/NCT04345289	Denmark Hvidovre University Hospital	Quadruple blind RCT	Phase III	1,500 participants	18 years and older	June 15, 2021

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
LIFESAVER Early transfusion of Convalescent Plasma in Elderly COVID-19 Patients. to Prevent Disease Progression. (NCT04374526) https://clinicaltrials.gov/ct2/show/NCT04374526	Italy Fondazione Policlinico Universitario Agostino Gemelli IRCCS	Multicentered, open label, RCT	Phase II and III	182 participants	65 years and older	June 30, 2021
REP-COVID Plasma Exchange in Patients With COVID-19 Disease and Invasive Mechanical Ventilation: a Randomized Controlled Trial (NCT04374539) https://clinicaltrials.gov/ct2/show/NCT04374539	Spain Fundacion Clinic per a la Recerca Biomédica	Multicentered, open label, RCT	Phase II	116 participants	18 years and older	August 29, 2021
Convalescent Plasma vs. Standard Plasma for COVID-19 (NCT04344535) https://clinicaltrials.gov/ct2/show/NCT04344535	USA Stony Brook University	Quadruple blind RCT	Phase I and II	500 participants	18 years and older	August 31, 2021
Efficacy and Safety of Early COVID-19 Convalescent Plasma in Patients Admitted for COVID-19 Infection (NCT04375098) https://clinicaltrials.gov/ct2/show/NCT04375098	Chile Pontificia Universidad Catolica de Chile	Open label RCT	Phase II	30 participants	18 years and older	December 2021
Clinical Trial to Evaluate the Efficacy of Treatment With Hyperimmune Plasma Obtained From Convalescent Antibodies of COVID-19 Infection (NCT04366245) https://clinicaltrials.gov/ct2/show/NCT04366245	Spain Andalusian Network for Design and Translation of Advanced Therapies	Open label RCT	Phase I and II	72 participants	18 to 80 years	December 2021
ESCAPE Evaluation of SARS-CoV-2 (COVID-19) Antibody-containing Plasma thErapy (NCT04361253) https://clinicaltrials.gov/ct2/show/NCT04361253	USA Brigham and Women's Hospital	Double blind RCT	Phase III	220 participants	12 months and older	December 2021
COVID-19 Convalescent Plasma (NCT04340050) https://clinicaltrials.gov/ct2/show/NCT04340050	USA University of Chicago	Single group, open label	Early Phase I	10 participants	18 years and older	December 31, 2021

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Study on convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19) http://www.chictr.org.cn/hvshowproject.aspx?id=22455	China The First Affiliated Hospital of Zhejiang University School of Medicine	Open label non-randomized	NR	20 participants	18 to 99 years	February 15, 2022
Human Convalescent Plasma for High Risk Children Exposed or Infected With SARS-CoV-2 (NCT04377672) https://clinicaltrials.gov/ct2/show/NCT04377672	USA Johns Hopkins University	Single group, open label	Phase I	30 participants	1 Month to 18 Years	May 18, 2022
Convalescent Plasma vs. Placebo in Emergency Room Patients With COVID-19 (NCT04355767) https://clinicaltrials.gov/ct2/show/NCT04355767	USA Stanford University	Double blind RCT	Phase II	206 participants	18 years and older	December 2022
Study Testing Convalescent Plasma vs Best Supportive Care (NCT04333251) https://clinicaltrials.gov/ct2/show/NCT04333251	USA Baylor Research Institute	Open label RCT	Phase I	115 participants	18 years and older	December 31, 2022
Convalescent Plasma to Stem Coronavirus (CSSC-001) (CSSC-001) (NCT04323800) https://clinicaltrials.gov/ct2/show/NCT04323800	USA Johns Hopkins University	Triple blind RCT	Phase II	150 participants	18 years and older	January 2023
Convalescent Plasma to Limit SARS-CoV-2 Associated Complications (CSSC-004) (NCT04373460) https://clinicaltrials.gov/ct2/show/NCT04373460	USA Johns Hopkins University	Triple blind RCT	Phase II	1,344 participants	18 years and older	Jan 31, 2023
Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients (NCT04364737) https://clinicaltrials.gov/ct2/show/NCT04364737	USA NYU Langone Health	Double blind RCT	Phase II	300 participants	18 to 80 years	April 30, 2023
A Study Evaluating the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma in Hospitalized Patients With COVID-19 Infection (NCT04354831) https://clinicaltrials.gov/ct2/show/NCT04354831	USA Medical College of Wisconsin	Open label non-randomized	Phase II	131 participants	18 years and older	May 1, 2023

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
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) http://www.chictr.org.cn/showprojen.aspx?proj=50696	China Renmin Hospital of Wuhan University	Double-blind RCT	NR	NR	NR	NR
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) http://www.chictr.org.cn/showprojen.aspx?proj=49777	China Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)	Double-blind RCT	NR	NR	NR	NR
Clinical study for infusing convalescent plasma to treat patients with new coronavirus pneumonia (COVID-19) http://www.chictr.org.cn/hvshowproject.aspx?id=22631	China Affiliated Hospital of Xuzhou Medical University	Open label non-randomized	NR	90 participants	18 to 60 years	NR
Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19) http://www.chictr.org.cn/hvshowproject.aspx?id=22719	China The First Affiliated Hospital of Nanchang University	RCT	NR	100 participants	18 to 65 years	NR
A Trial of CONvalescent Plasma for Hospitalized Adults With Acute COVID-19 Respiratory Illness (CONCOR-1) (NCT04418518) https://clinicaltrials.gov/ct2/show/NCT04418518	USA Weill Medical College of Cornell University	RCT	Phase III	1,200 participants	18 to 70 years	December 2021
Convalescent Antibodies Infusion in COVID 19 Patients (NCT04418531) https://clinicaltrials.gov/ct2/show/NCT04418531	Italy Piero Luigi Ruggenenti	Open Label RCT	NR	10 participants	18 years and older	September, 2020
Treatment of Patients With COVID-19 With Convalescent Plasma (COOPCOVID-19) (NCT04415086) https://clinicaltrials.gov/ct2/show/NCT04415086	Brazil University of Sao Paulo General Hospital	RCT	Phase II	120 participants	18 years and older	May 22, 2022

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Convalescent Plasma of Covid-19 to Treat SARS-COV-2 a Randomized Doble Blind 2 Center Trial (CPC-SARS) (NCT04405310) https://clinicaltrials.gov/ct2/show/NCT04405310	Bangladesh Bangabandhu Sheikh Mujib Medical University	RCT	Phase II	20 participants	16 Years and older	October 30, 2020
Convalescent Plasma for the Treatment of Patients With Severe COVID-19 Infection (NCT04408209) https://clinicaltrials.gov/ct2/show/NCT04408209	Greece National and Kapodistrian University of Athens	Single group, open label	NR	60 participants	18 years and older	September 15, 2021
Use of Convalescent Plasma for COVID-19 (NCT04408040) https://clinicaltrials.gov/ct2/show/NCT04408040	USA Northside Hospital, Inc.	Open Label RCT	Phase II	700 participants	18 years and older	June 2022
Feasibility Study of Anti-SARS-CoV-2 Plasma Transfusions in COVID-19 Patients With SRD (NCT04411602) https://clinicaltrials.gov/ct2/show/NCT04411602	USA Ascension South East Michigan	Single group, open label	Phase I	90 participants	18 years and older	December 31, 2020
COVID-19 Convalescent Plasma (CCP) Transfusion (NCT04412486) https://clinicaltrials.gov/ct2/show/NCT04412486	USA Gailen D. Marshall Jr., MD PhD	Single group, open label	Early Phase I	100 participants	18 years and older	May 31, 2022
Convalescent Plasma Compared to Anti-COVID-19 Human Immunoglobulin and Standard Treatment (TE) in Hospitalized Patients (NCT04395170) https://clinicaltrials.gov/ct2/show/NCT04395170	Colombia Lifefactors Zona Franca, SAS	Open Label RCT	Phase II	75 participants	18 years and older	June 2021
Transfusion of Convalescent Plasma for the Early Treatment of Patients With COVID-19 (TSUNAMI) (NCT04393727) https://clinicaltrials.gov/ct2/show/NCT04393727	Italy Azienda Ospedaliero, Universitaria Pisana	Open Label RCT	Phase II	126 participants	18 years and older	October 30, 2020

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
COVID-19 Convalescent Plasma for the Treatment of Hospitalized Patients With Pneumonia Caused by SARS-CoV-2. (NCT04397757) https://clinicaltrials.gov/ct2/show/NCT04397757	USA University of Pennsylvania	Open Label RCT	Phase I	80 participants	18 years and older	November 13, 2020
Efficacy and Safety of COVID-19 Convalescent Plasma (NCT04397523) https://clinicaltrials.gov/ct2/show/NCT04397523	North Macedonia Institute for Transfusion Medicine of RNM	Single group, open label	NR	20 participants	18 years and older	April 29, 2021
Hyperimmune Convalescent Plasma in Moderate and Severe COVID-19 Disease (NCT04392414) https://clinicaltrials.gov/ct2/show/NCT04392414	Russia Federal Research Clinical Center of Federal Medical & Biological Agency,	Open Label RCT	Phase II	60 participants	18 to 75 years	September 15, 2020
Convalescent Plasma for the Treatment of Severe SARS-CoV-2 (COVID-19) (NCT04391101) https://clinicaltrials.gov/ct2/show/NCT04391101	Colombia Hospital San Vicente Fundación	Open Label RCT	Phase III	231 participants	18 years and older	December 2021
A Study of COVID 19 Convalescent Plasma in High Risk Patients With COVID 19 Infection (NCT04392232) https://clinicaltrials.gov/ct2/show/NCT04392232	USA TriHealth Inc.	Single group, open label	Phase II	100 participants	16 years and older	December 31, 2020
Convalescent Plasma as Treatment for Acute Coronavirus Disease (COVID-19) (NCT04390178) https://clinicaltrials.gov/ct2/show/NCT04390178	Sweden Joakim Dillner	Single group, open label	Phase I Phase II	10 participants	18 to 80 years	December 2020
Amotosalen-Ultraviolet A Pathogen-Inactivated Convalescent Plasma in Addition to Best Supportive Care and Antiviral Therapy on Clinical Deterioration in Adults Presenting With Moderate to Severe COVID-19 (NCT04389944) https://clinicaltrials.gov/ct2/show/NCT04389944	Switzerland University Hospital, Basel	Single group, open label	NR	15 participants	18 years and older	June 30, 2020

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Convalescent Plasma for the Treatment of COVID-19 (NCT04389710) https://clinicaltrials.gov/ct2/show/NCT04389710	USA Thomas Jefferson University	Single group, open label	Phase II	100 participants	18 years and older	April 14, 2021
Convalescent Plasma for COVID-19 Close Contacts (NCT04390503) https://clinicaltrials.gov/ct2/show/NCT04390503	USA Columbia University	RCT	Phase II	200 participants	18 years and older	April 2021
Safety and Efficacy of Convalescent Plasma Transfusion for Patients With COVID-19 (EPCOvid-1) (NCT04388410) https://clinicaltrials.gov/ct2/show/NCT04388410	Mexico Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran	RCT	Phase II	250 participants	18 years and older	December 31, 2020
COVID-19 Convalescent Plasma for Mechanically Ventilated Population (NCT04388527) https://clinicaltrials.gov/ct2/show/NCT04388527	USA University of Pennsylvania	Single group, open label	Phase I	50 participants	18 years and older	September 30, 2020
Inactivated Convalescent Plasma as a Therapeutic Alternative in Patients CoViD-19 (NCT04385186) https://clinicaltrials.gov/ct2/show/NCT04385186	National Blood Center Foundation, Hemolife	Multicentered RCT	Phase II	60 participants	18 years and older	December 30, 2020
Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia (PLASM-AR) (NCT04383535) https://clinicaltrials.gov/ct2/show/NCT04383535	Argentina Hospital Italiano de Buenos Aires	Multicentered RCT	NR	333 participants	18 years and older	August 20, 2020
Convalescent Plasma for Patients With COVID-19 (NCT04385199) https://clinicaltrials.gov/ct2/show/NCT04385199	USA Henry Ford Health System	Open Label RCT	Phase II	30 participants	18 years and older	August 1, 2020
COVID19-Convalescent Plasma for Treating Patients With Active Symptomatic COVID 19 Infection (FALP-COVID) (FALP-COVID) (NCT04384588) https://clinicaltrials.gov/ct2/show/NCT04384588	Chile Fundacion Arturo Lopez Perez	Multicenter non-randomized, 4 arms	Phase II	100 participants	15 years and older	April 6, 2021

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Convalescent Plasma for Treatment of COVID-19: An Exploratory Dose Identifying Study (NCT04384497) https://clinicaltrials.gov/ct2/show/NCT04384497	Sweden Joakim Dillner	Single group, open label	Phase I	50 participants	18 years and older	December 2020
Hyperimmune Plasma in Patients With COVID-19 Severe Infection (COV2-CP) (NCT04385043) https://clinicaltrials.gov/ct2/show/NCT04385043	Italy University of Catanzaro	Open Label RCT	Phase II	400 participants	18 to 60 years	May 15, 2021
Convalescent Plasma vs Human Immunoglobulin to Treat COVID-19 Pneumonia (NCT04381858) https://clinicaltrials.gov/ct2/show/NCT04381858	Mexico Centenario Hospital Miguel Hidalgo	Double blinded RCT	Phase III	500 participants	16 to 90 years	September 30, 2020
Effectiveness and Safety of Convalescent Plasma Therapy on COVID-19 Patients With Acute Respiratory Distress Syndrome (NCT04380935) https://clinicaltrials.gov/ct2/show/NCT04380935	Indonesia Indonesia University	Open Label RCT	Phase II	60 participants	18 years and older	August 31, 2020
Convalescent Plasma as Treatment for Subjects With Early COVID-19 Infection (NCT04456413) https://clinicaltrials.gov/ct2/show/NCT04456413	USA Hackensack Meridian Health	Open Label RCT	Phase II	306 participants	18 years and older	July 2021
Statistical and Epidemiological Study Based on the Use of Convalescent Plasma for the Management of Patients With COVID-19 (PROMETEO) (NCT04452812) https://clinicaltrials.gov/ct2/show/NCT04452812	Mexico Universidad Autonoma de Coahuila	Double blinded RCT	Phase I Phase II	15 participants	18 years and older	April 1, 2021
PERUCONPLASMA: Evaluating the Use of Convalescent Plasma as Management of COVID-19 https://clinicaltrials.gov/ct2/show/NCT04497324?term=plasma	Peru Universidad Peruana Cayetano Heredia	Open Label RCT	Phase II	100 participants	18 years and older	December 31, 2020
Analysis of Coronavirus Disease 19 (COVID-19) Convalescent Plasma (NCT04497779) https://clinicaltrials.gov/ct2/show/NCT04497779?term=plasma	USA City of Hope Medical Center	Prospective cohort	Not reported	800 participants	18 years and older	August 21, 2022

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Australasian COVID-19 Trial (ASCOT) (ASCOT) (NCT04483960) https://clinicaltrials.gov/ct2/show/NCT04483960?term=plasma	Australia University of Melbourne	Open Label RCT	Phase III	2,400 participants	18 years and older	June 12, 2022
Prevention of Severe Covid-19 in Infected Elderly by Early Administration of Convalescent Plasma With High-titers of Antibody Against SARS-CoV2 (NCT04479163) https://clinicaltrials.gov/ct2/show/NCT04479163?term=plasma	Argentina Fundacion Infant	Quadruple blinded RCT	N/A	210 participants	65 years and older	July 30, 2020
Convalescent Plasma Treatment in COVID-19 (COLLATE) (NCT04476888) https://clinicaltrials.gov/ct2/show/NCT04476888?term=plasma	Pakistan Aga Khan University	Open Label RCT	NR	100 participants	18 years and older	September 2020
COVID-19 Convalescent Plasma Treatment in SARS-CoV-2 Infected Patients (NCT04474340) https://clinicaltrials.gov/ct2/show/NCT04474340?term=plasma	Kuwait Ministry of Health, Kuwait	Open label non-randomized	Phase I	300 participants	15 Years to 85 Years	December 30, 2020
An Observational Cohort Trial of Outcomes and Antibody Responses Following Treatment With COVID19 Convalescent Plasma in Hospitalized COVID-19 Patients (NCT04471051) https://clinicaltrials.gov/ct2/show/NCT04471051?term=plasma	USA University of Colorado, Denver	Prospective cohort	NR	150 participants	18 years and older	April 2021
Treatment of Critically Ill Patients With Covid-19 With Convalescent Plasma (NCT04468009) https://clinicaltrials.gov/ct2/show/NCT04468009?term=plasma	Argentina Hospital de Infecciosas Francisco Javier Muniz	Open Label RCT	Phase II	36 participants	18 Years to 100 Years	June 2021
Administration of Anti-SARS-CoV-2 Convalescent Plasma in Hospitalized, Non-ICU Patients With COVID-19 (NCT04467151) https://clinicaltrials.gov/ct2/show/NCT04467151?term=plasma	USA Kashif Khan	Triple blinded RCT	Phase II	96 participants	18 years and older	December 2021

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
"NORPLASMA" Covid-19 Convalescent Plasma Treatment Monitoring Study (MONITOR) (NCT04463823) https://clinicaltrials.gov/ct2/show/NCT04463823?term=plasma	Norway Oslo University Hospital	Single arm prospective observational	NA	500 participants	18 years and older	May 31, 2025
Covid-19 Convalescent Plasma as Prevention and Treatment for Children With Underlying Medical Conditions (NCT04462848) https://clinicaltrials.gov/ct2/show/NCT04462848?term=plasma	USA University of California, Los Angeles	Single group, open label	Phase I	30 participants	1 Month to 17 Years	December 2024
Convalescent Plasma in Pediatric COVID-19 (/NCT04458363) https://clinicaltrials.gov/ct2/show/NCT04458363?term=plasma	USA Emory University	Single group, open label	Early Phase I	50 participants	up to 22 Years	June 2022
Expanded Access to Convalescent Plasma for Treatment of COVID-19 (NCT04472572) https://clinicaltrials.gov/ct2/show/NCT04472572?term=plasma	USA Hackensack Meridian Health	Expanded access	NA		18 Years and older	

COVID-19 = coronavirus disease; NA = not applicable; NR = not reported; RCT = randomized controlled trial.

Appendix 7: Report Version Details

Table 6: Key Information Regarding Each Version of this Living Review

Version Number	Date of Publication	Report Version Details
Version 1.0	May 28, 2020	**Date of database literature and trial registry search:** May 6, 2020 **Date of focused internet search:** May 6, 2020 **Number of included studies:** Two[24,25]
Version 2.0	June 19, 2020	**Date of literature search update:** June 8, 2020 **Date of focused internet search:** May 6, 2020 **Number of new relevant studies included in this update:** One[23] **Total number of included studies:** Three[23-25] **What is new:** New evidence was found, and the overall conclusions have not changed. Findings from a randomized controlled trial were similar to those from the previously included studies. An updated list of ongoing COVID-19 clinical trials is given in Appendix 6. The conclusions of this report are up to date as of the date of publication.
Version 3.0	July 22, 2020	**Date of literature search update:** July 7, 2020 **Date of focused internet search:** May 6, 2020 **Number of new relevant studies included in this update:** One[26] **Total number of included studies:** Four[23-26] **What is new:** New evidence was found and the overall conclusions have not changed. Findings from a non-randomized study were similar to those from the previously included studies. An updated list of ongoing COVID-19 clinical trials is given in Appendix 6. The conclusions of this report are up to date as of the date of publication.
Version 4.0	August 26, 2020	**Date of literature search update:** August 5, 2020 **Date of focused internet search:** May 6, 2020 **Number of new relevant studies included in this update:** One[1] **Total number of included studies:** Five[1,23-26] **What is new:** New evidence was found and the overall conclusions have not changed. Findings from a non-randomized study were similar to those from the previously included studies. An updated list of ongoing COVID-19 clinical trials is given in Appendix 6. The conclusions of this report are up to date as of the date of publication.