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 in May 2020,was updated on a monthly basis until November 2020, and is currently published on a regular basis.

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 changing and growing rapidly.

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Authors: Anusree Subramonian, Calvin Young, Hannah Loshak, Suzanne McCormack, Michelle Clark

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Questions or requests for information about this report can be directed to **requests@cadth.ca.**

Abbreviations

BMI	Body Mass Index
COVID-19	coronavirus disease
CP	convalescent plasma
CT	computerized tomography
eIND	emergency investigational new drug
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
IQR	interquartile range
NRS	non-randomized study
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
RBD	receptor binding domain
RCT	randomized controlled trial
RNA	ribonucleic acid
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TACO	transfusion associated circulatory overload
TRALI	transfusion related acute lung injury
WHO	World Health Organization

Key Messages

- Convalescent plasma (CP) therapy is an intervention in which plasma collected from convalescent or recovered patients is used to treat certain infectious diseases. The purpose of this report is to summarize the evidence regarding the clinical effectiveness of CP therapy for the treatment of coronavirus disease (COVID-19).
- In Canada, CP therapy for COVID-19 is currently available only as an investigational drug treatment.
- Four randomized controlled trials and 12 non-randomized studies were included in this report. Evidence from the included studies was of low-to-moderate quality with several methodological limitations, lack of clear reporting, high heterogeneity, and limited generalizability to Canadian settings.
- There were mixed findings regarding a survival benefit associated with CP therapy compared to standard care or placebo (7 studies found no significant effects and 5 studies found favorable effects on mortality with CP). Given the limitations of the evidence as mentioned above, the potential survival benefit is unclear.
- Whether CP was more effective than standard care or placebo for other outcomes (e.g., clinical improvement, requirement for supplemental oxygen or other respiratory support such as mechanical ventilation, or duration of hospital stay) was unclear. In some studies there were no significant differences between CP and standard care alone, in others CP appeared to be comparatively favorable, and in one study CP was comparatively unfavorable (for the outcome duration of hospitalization). However, due to the limited quality of the evidence, the comparative clinical effectiveness remains inconclusive.
- CP therapy may be less effective than remdesivir or other active therapies in terms of mortality, requirement for O_2 supplementation, and duration of hospitalization; however, these findings were from a single nonrandomized study of limited quality.
- Adverse events were reported in 14 studies and were relatively infrequent. Among 1,686 patients who received CP, there were 40 incidences of adverse events with various levels of severity, but most were non-severe. Most of the included studies did not report whether there were adverse in the control groups (e.g., patients who received standard care, remdesivir or other medications).
- This report includes a list of ongoing clinical trials, which could provide additional evidence regarding the clinical effectiveness CP therapy for COVID-19.
- This report is being conducted a living review, allowing incorporation of the latest evidence with regular updates. The February 2021 update of this report incorporated 5 new primary studies and the final version of a study for which “interim data” were previously included. These additions did not result in any material changes to the conclusions of the report.

What’s new?

- The search was updated on January 13, 2020; 6 new relevant primary studies were identified.[1-7] Previous versions of this report included interim results from an ongoing study.[8] The final results of this study are now published and have been incorporated in this report;[6] the interim results have been removed. 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 rapidly spread all over the world.[9] COVID-19 is caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[9] With over 100 million confirmed cases and over 2.2 million deaths globally as of February 3, 2021,[10] 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.[11] In Canada, the first case of COVID-19 was reported on January 25, 2020, and 786,417confirmed cases and 20,213 deaths were reported as of February 3, 2021.[12] Several antiviral agents and vaccines are currently being actively researched.[13] On December 9, 2020, Health Canada authorized the Pfizer-BioNTech COVID-19 mRNA vaccine to be used with conditions.[14] To date, two vaccines with different protective mechanisms and two therapeutic agents have been approved for use in Canada.[15]

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.[16] 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.[17] CP therapy involves transfusion of a blood product and is therefore associated with a risk of adverse events including anaphylaxis, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and transmission of infections.[18] 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.[19] Among them, TACO was the most common adverse transfusion reaction (18.1 per 100,000 units transfused).[19] To mitigate the risk of TRALI due to donor-derived human leukocyte antigen (predominantly found in females who have been pregnant), male plasma donors may be preferred.[20,21] 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.[22] A possible molecular mechanism for antibody dependent enhancement has been described in other coronaviruses like the Middle East respiratory syndrome coronavirus.[23]

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).[24] The FDA also issued an Emergency Use Authorization (EUA) for CP therapy for hospitalized COVID-19 patients in the US on August 23, 2020.[25] In Canada, CP therapy for COVID-19 is currently available only as an investigational drug treatment for participants in the CONCOR-1 clinical trial.[26] 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.[27] The CONCOR-1 clinical trial is currently underway and involves more than 50 hospitals across Canada with the intention to recruit 1,500 participants.[24] 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.[28] 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).[24] The plasma will be collected by apheresis from donors who have recovered from COVID-19.[24] 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.[24] 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.[27] 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.[27] 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.[26] 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.[24] 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.[27] Potential donors are also able to self-identify through a questionnaire that is accessible via social media.[24]

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.[29] 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 regular basis.

Research Question

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

Methods

Study Design

This report will be conducted as a living review, following the Cochrane guidance for living systematic reviews.[30] 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,[29] 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 regular basis. Between May 2020 and October 2020, searches were updated monthly. Going forward, searches will be updated quarterly, since conclusions have remained largely consistent from one version of the report to the next between May 2020 and October 2020 and to balance the timely incorporation of emerging evidence with resource constraints. 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[31] 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 January 13, 2021; the focused internet search was last conducted on October 13, 2020.

In total, 3,649 citations were identified in the literature searches. Following screening of titles and abstracts, 3,528 citations were excluded and 121 potentially relevant reports from the electronic searches were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search or via hand searching for full-text review. Of these potentially relevant articles, 108 publications were excluded for various reasons, and 16 publications met the inclusion criteria and were included in this report. These comprised 4 randomized controlled trials (RCT)[4,7,32-34] and 12 non-randomized studies (NRS).[1-3,5,6,35-41] Appendix 1 presents the PRISMA[42] 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

Four eligible RCTs[4,7,32,33] and 12 NRSs[1-3,5,6,35-41] were identified and included in this report. Detailed study characteristics are available in Appendix 2, Table 2.

Study Design

Among the RCTs, 1[7] was a multicenter double-blinded trial and 3 were open label multicenter trials.[4,32-34] Twelve NRSs were included in this report.[1-3,5,6,33-41] One study[37] was a pilot observational study in which the CP therapy group was observed prospectively and the control group was a retrospective historic control. Eight NRSs were retrospective observational studies,[2,3,5,36,38-41] and 3 were prospective observational studies.[1,6,35] Four of these NRSs (1 prospective[6] and 3 retrospective[3,6,41]) selected controls using propensity score matching. Earlier versions of this report included interim results from an ongoing study.[8] The final results of this study are now published; the interim results have been removed and the final results are included in this update of the report.[6] One study was a real-world experience of COVID-19 patients in Poland receiving several treatments, including CP.[5] Only the characteristics and results relevant to this report (i.e., pertaining to patients who were treated with CP) are summarized in the report.

Country of Origin

The RCTs were conducted in Argentina,[4,7] China[32] and India.[33] The NRSs were conducted in China,[2,3,37,39,40] Iran,[35] Kuwait,[1] Poland,[5] Turkey[36] and US.[6,38,41]

Patient Population

Randomized Controlled Trials

The RCT by Li et al.[32,34] 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; partial pressure of O_2 (PaO_2) < 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). There were no significant differences in demographics, baseline laboratory results and severity of disease or coexisting conditions between the groups.

The RCT by Agarwal et al.[33] enrolled adult patients with moderate COVID-19, confirmed by a positive reverse transcriptase PCR test. The study excluded patients who were pregnant or lactating, had IgA deficiency, known hypersensitivity to blood products or PaO_2:FiO_2 <200, received immunoglobulin in the previous 30 days, or were in shock. Based on these criteria, 464 patients were enrolled (CP group, n = 235, control group, n = 229). The prevalence of diabetes was significantly higher in the CP group compared to the control group, and significantly more patients in the control group reported the symptom cough. There were no other significant differences in demographics, clinical characteristics, comorbidities, or concomitant medications between the groups.

The RCT by Libster et al.[4] enrolled patients with mild COVID-19 (confirmed by RT-PCR) who were 75 years of age or older with two or more clinical features of COVID-19. Patients between the ages of 65 and 74 were also included if they had at least one co-existing condition such as hypertension, diabetes, obesity (BMI> 30 kg/m^2), chronic renal failure, cardiovascular disease, or chronic obstructive pulmonary disease. The study excluded patients with severe disease, blood disorders, allergy to blood products, HIV or Hepatitis C infection, solid organ transplant and other comorbidities. Accordingly, 160 patients (CP group, n = 80, control group, n = 80) were enrolled in the study. There were no significant differences in demographics, clinical characteristics, or comorbidities between the groups.

The RCT by Simonovich et al.,[7] (PlasmAr trial) enrolled adult patients with severe COVID-19 infection confirmed by RT-PCR. The study excluded patients who were pregnant, lactating or not on contraceptives, had history of allergic reactions to blood products, multiorgan failure or were on mechanical ventilation. Based on these criteria, 334 patients were enrolled (CP group, n = 228, control group, n = 105). Baseline characteristics such as demographics, clinical features, and comorbidities were numerically similar between the groups (but not compared statistically).

Non-Randomized Studies

The pilot study by Duan and colleagues[37] enrolled adult COVID-19 patients (diagnosed based on the WHO interim guidance[43] 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[40] enrolled 21 contemporaneous patients with COVID-19 from two referral hospitals who were diagnosed based on the interim guidance from WHO.[43]. 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).

In the NRS by Xia et al.,[39] 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,[35] 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). There were no significant differences in demographics, baseline laboratory results, or comorbidities and clinical conditions between the group.

In the study by Salazar and colleagues,[6] patients with severe or life-threatening COVID-19 (diagnosed with RT-PCR) were considered eligible. Patients who had a previous history of definite or probable reaction to blood or blood products, underlying end-stage diseases, fluid overload, or any contraindication to plasma transfusion were excluded. Based on these criteria, 351 patients received CP transfusion. They were then were matched with controls using two levels of propensity score matching. Primary matching was based on age, sex, body mass index (BMI), demographic variables, comorbidities, concomitant medications, and baseline ventilation requirement at 48 hours from admission. Secondary matching included the addition of ventilation status at day 0 (defined as the day of transfusion for

cases and the corresponding day of hospitalization for controls). Thus, the final sample included 903 patients (CP group, n = 341; control group, n = 594). There were no significant differences in age, sex, race, ethnicity, baseline laboratory results, vital signs, baseline clinical features, comorbidities and concomitant medications between the groups. Compared to control group, significantly more patients in the CP group were given supplemental O_2 or were on mechanical ventilation at baseline.

In the study by Altuntas et al.,[36] adult patients with severe or critical COVID-19 (laboratory confirmed) were considered eligible for the study. CP recipients were matched to controls based on age, sex, comorbidity and concomitant medications. No additional exclusion criteria were reported. Accordingly, 1,776 patients were enrolled (CP group, n = 888; control group, n = 888). There were no significant differences in age, sex, baseline comorbidities and use of concomitant medications (favipravir, lopinavir + litonavir, hydroxychloroquine and azithromycin) between the groups.

In the study by Liu et al.,[41] adult COVID-19 patients with severe or immediately life-threatening illness were enrolled. CP recipients were selected from patients who applied for CP transfusion through the FDA eIND program. CP recipients were propensity score matched (1:4) with controls based on baseline characteristics, clinical data, and treatment received on admission and up to the day of transfusion. Thus, the final sample included 195 patients (CP group, n = 39; control group, n = 156). There were no significant differences in age, sex and baseline comorbidities between the groups. Use of therapeutic anticoagulation was significantly higher in the CP group but use of other concomitant medications was similar between the groups.

In the study by Rogers et al.,[38] adult patients with confirmed or clinically suspected COVID-19, who were admitted to an acute care facility with severe or life-threatening illness and who received CP as a part of the Expanded Access program of the FDA, were considered eligible for the CP group. Patients who had a positive molecular test for COVID-19 and did not receive CP were considered for the control group. Additional inclusion criteria, for both the CP and control groups were: symptom onset within the previous 10 days, administration of supplemental O_2 (but not mechanical ventilation), and no evidence of hypercoagulability. Accordingly, 241 patients were included in the study (CP group, n = 64, control group, n = 177). There were no significant differences in age, sex, race or ethnicity, or baseline comorbidities between CP group and control group. Corticosteroid use was significantly higher in the CP group. Use of other concomitant medications (remdesivir and hydroxychloroquine) were similar between the groups.

In the study by Alsharidah et al.,[1] adult patients with confirmed moderate or severe COVID-19 were enrolled. Patients who had a contraindication to transfusion, acute severe multiorgan failure, hemodynamic instability, shock, disseminated intravascular coagulation, or were expected to survive less than 48 hours were excluded. Based on these criteria, 368 patients (CP group, n = 135; control group, n = 233) were included in the study. There were no significant differences between the groups in demographics, baseline laboratory results, severity of disease or concomitant treatment.

In the study by Dai et al.,[2] patients with COVID-19 and diabetes were considered eligible. No other eligibility criteria were reported. The study included 367 patients (CP group, n = 39; control group, n = 328). Compared to the CP group, numerically more patients in the control group had mild disease, and fewer patients had critical illness (statistical comparison not reported).

In the study by Jiang et al.,[3] 326 patients with COVID-19 (CP group, n = 163, control group, n = 163) were enrolled. No other inclusion and exclusion criteria were reported. Approximately 48% of patients in the CP group and 47% of patients in the control group were reported to have comorbidities such as hyperlipidemia, diabetes, coronary heart disease and tumor.

In the study by Moniuszko-Malinowska et al.,[5] patients with RT-PCR confirmed COVID-19 along with clinical symptoms and lesions on Chest Xray, who needed continuous O_2 therapy and had SpO_2 < 94% anytime after hospital admission, were included. Patients who received CP within 7 days of onset of disease were considered for the comparative analysis relevant to this report. Accordingly, 1,006 patients (CP group, n = 55, control group I, n = 236, control group II, n = 715) were included in the analysis.

Interventions and Comparators

Randomized Controlled Trials

The intervention in all studies included in this report was administration of CP collected from recovered COVID-19 patients who donated their plasma.[1-7,32,33,35,37-41] Patients who received CP in most studies received plasma compatible with their blood group (ABO compatible).[1-6,32,33,35-41] No CP therapy was administered to patients in control groups.

In the RCT by Li et al.,[32] 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 RCT by Agarwal et al.,[33] two doses of CP (200 mL each) were transfused 24 hours apart with the first dose at the time of randomization. Median time from symptom onset to enrolment was 8 days (IQR: 6 to 11 days). The median neutralizing antibody titre of the transfused CP, which was measured retrospectively after transfusion, was 1:40 (IQR: 1:30 to 1:80). Participants in both groups received standard care which included antivirals (remdesivir, lopinavir/ritonavir, oseltamivir), antibiotics, hydroxychloroquine, immunomodulators (steroids, tocilizumab) and supportive management (O_2, invasive or mechanical ventilation, and prone positioning while awake).

In the study by Libster and colleagues,[4] 250 mL (one unit) of CP with an IgG titre >1:1000 was transfused over 1.5 to 2 hours. CP was administered within 72 hours of symptom onset. Patients in the control group received similar volumes of placebo (0.9% saline).

In the RCT by Simonovich et al.,[7] CP with a mean neutralizing antibody titre of 1:300 (IQR 1:136 to 1:511) was transfused from either a single donor or from a plasma pool (4-5 donors) independently of ABO compatibility. CP was administered at a rate of 5 to 10 mL/kg/hour, for a median volume of 500 mL. The median time from symptom onset to enrolment was 8 days. Patients in the control group received similar volumes of placebo (normal saline). Patients in both groups received supportive care and medications including antivirals, glucocorticoids, tocilizumab, ivermectin and hydroxychloroquine.

Non-Randomized Studies

In the pilot study by Duan and colleagues,[37] 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[40] 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 study by Xia et al.,[39] 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 to 2 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.,[35] 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.

In the study by Salazar et al.,[6] among the CP recipients (n = 351), 278 received one unit of CP. For most of the patients, the first (or only) unit of CP had an Anti-RBD IgG titre >1:1350. Control group patients received standard care alone. Patients in both study groups received standard care and other medications such as steroids, hydroxychloroquine, antivirals (lopinavir and ritonavir, or remdesivir), antibiotics and tocilizumab.

In the study by Altuntas et al.,[36] the intervention was CP plus antiviral drugs. There was no standardized CP protocol; the median volume transfused was 600 mL and 228 patients in the CP group (among whose data was available) received transfusions within 10 days from symptom onset. Patients in both groups received symptomatic control and supportive care including antivirals (Favipravir or a combination of lopinavir and ritonavir), hydroxychloroquine, Azithromycin, and high dose vitamin C.

In the study by Liu et al.,[41] two units of CP with a serum IgG titre ≥ 1:320 (about 250 mL each) were transfused over one to two hours with monitoring every 15 minutes for adverse events. Patients were hospitalized for a median duration of 4 days (range 0 to 7) prior to transfusion. Patients in both groups received symptomatic and supportive care including therapeutic anticoagulants, antibiotics, hydroxychloroquine, antivirals, corticosteroids and other anti-inflammatory agents.

In the study by Rogers et al.,[38] two units of CP were prescribed. The median time from symptom onset to CP transfusion was 7 days (IQR: 5 to 9 days). The antibody index of the transfused CP was not assayed prior to transfusion. Patients in both groups received symptomatic control and supportive care including antivirals, steroids and hydroxychloroquine.

In the study by Alsharidah and colleagues,[1] a unit (200 mL) of CP was transfused within 24 hours of admission, and most patients received a second unit 24 hours later. Patients in

both groups received standard care and most patients received antibiotics and low molecular weight heparin.

In the study by Dai et al.,[2] one unit (200 mL) of CP was transfused, the timing of which was dependent on CP availability. The comparator was conventional treatment. Concomitant medications given to patients in each group were not reported.

In the study by Jiang et al.,[3] CP was compared to standard care. No details regarding the volume or timing of CP administration were reported.

In the study by Moniuszko-Malinowska et al.,[5] the clinical effectiveness of CP was compared to remdesivir or other medications. In the CP group, one or two units of CP was administered within a mean of 6.6 days (standard deviation 9.7 days) from symptom onset. Patients who received remdesivir were grouped as control group I and those who received other medications were considered in control group II. Other medications included tocilizumab (6%); dexamethasone (9.7%); chloroquine (43.7%); hydroxychloroquine (8.8%); lopinavir/ritonavir (28.2%); azithromycin (36%) and fractioned heparin (43.6%).

Outcomes

The primary end point in the RCT by Li et al.[32] was the time to clinical improvement within 28 days. Clinical improvement was defined as either hospital discharge or 2-point reduction in a 6-point disease severity scale used in other COVID-19 trials (scores ranged from 1 [hospital discharge] to 6 [death]).[44] 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 primary outcome in the RCT by Agarwal et al.[33] was a composite outcome that included progression to severe disease (defined as Pao_2:FiO_2 <100) or all-cause mortality by 28 days. If disease progression or death was prevented, the outcome was considered good; otherwise, the outcome was considered poor. Secondary outcomes included rate of symptom resolution, negative seroconversion, duration of hospital stay, duration of respirator support, mechanical ventilatory support, vasopressor support, and adverse events. Participants were followed for 28 days with outcome assessments at seven time points.

The primary endpoint in the RCT by Libster et al.,[4] was the development of severe disease which was defined as RR > 30/min or SpO_2 < 93% on ambient air. Secondary endpoints were development of life-threatening illness or critical systemic illness. Patients were followed up at 12 hours, 15 days, and 25 days post-intervention.

In the study by Simonovich et al.,[7] the primary outcome was clinical status at 30 days after intervention, measured using a 6-point clinical scale (range from 1 [death] to 6 [discharge with full return to baseline physical function]). Clinical improvement was defined as 2-point difference in the 6-point severity scale. Other outcomes of interest were clinical status at days 7 and 14, time to discharge from ICU, time to discharge from the hospital, time to clinical improvement, time to death, and time to full recovery. Adverse events related and non-related to the intervention were also recorded.

The pilot study by Duan and colleagues[37] 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,[40] 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.,[39] the primary outcome was mortality rate. Relevant to the current report, additional outcomes were clinical improvement based on the 6-point disease severity scale[44] 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.[35] 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.

The primary outcome in the study by Salazar and colleagues[6] was 60-day mortality. Other outcomes were overall mortality, clinical status at day 60, length of hospital stay, requirement of ICU and length of time in ICU (if applicable), requirement of mechanical ventilation and O_2 supplementation and their duration, and clinical improvement (defined as 1 point improvement in the 6-point severity scale relative to day 0).

In the study by Altuntas et al.,[36] the outcomes of interest were duration of hospital stay, duration of stay in the ICU, rates of mechanical ventilation and vasopressor support, and case fatality rate. The length of follow up was not reported.

The outcomes of interest in the study by Liu et al.[41] were oxygenation status and in-hospital mortality. The definition of the outcome "oxygenation status" was not reported. Patients were followed until the end of the study (May 1, 2020). For CP recipients, "day 0" was defined as the day of transfusion. For those in the control group, "day 0" was defined as same hospital day (i.e., number of days following admission) that corresponded to the hospital day on which their matched CP recipient received transfusion. Median follow up time was 11 days in the CP group and 9 days in the control group.

The primary outcome in the NRS by Rogers et al.[38] was in-hospital all-cause mortality. Time to discharge from the hospital was the secondary outcome. Outcomes were censored on day 28 from the date of admission.

The outcomes of interest in the study by Alsharidah et al.,[1] were clinical improvement measured as 2-point decrease in a 7-point disease severity scale (range from 1 [hospital discharge] to 7 [death]), in-hospital mortality, and changes in O_2 saturation. Patients were followed up for 30 days.

In the study by Dai and colleagues,[2] the outcomes were clinical improvement (1 point and 2 point reduction in the 6-point disease severity scale), clinical status, and the duration of illness. Length of follow up was not reported.

In the Jiang et al. study,[3] the primary outcome was discharge condition ("cure," "improve," "death," or "transfer to another hospital"). The definitions of "cure" or "improve" were

unclear. Another outcome of interest was the duration of hospital stay. Length of follow up was not reported.

The outcomes of interest in the study by Moniuszko-Malinowska et al.,[5] were need for constant O_2 therapy, duration of O_2 therapy, need for artificial ventilation, duration of hospitalization, mortality, and clinical improvement measured as 2-point reduction in an 8-point disease severity scale (range from 1 [hospital discharge] to 8 [death]). Patients were followed up for 28 days with assessment at days 7, 15, 21, and 28.

Summary of Critical Appraisal

The strengths and limitations of the studies[1-7,32,33,36-41] 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 Trials

The included RCTs[4,7,32,33] had clearly-described objectives, and detailed reporting regarding the population, intervention, comparator, and outcomes. The participants were enrolled from multiple study sites in Argentina,[4,7] China[32] and India[33] over the same period and were representative of the population and treatment. Baseline characteristics including age, demographics, severity of disease, and concomitant treatments (antivirals, steroids, immunoglobulins) were similar across groups. There was random allocation of participants to each group. 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 by Li et al.[32] Two RCTs were double-blinded and placebo controlled.[4,7] Outcome assessors were blinded to participant group in the RCT by Li et al.[32] but not the RCT by Agarwal et al.[33] For all RCTs,[4,7,32,33] main study findings were reported clearly with simple outcome data. Random variability in data was considered in reporting using IQRs and 95% confidence intervals.

The number of participants who dropped out of the studies after randomization, and reasons for drop-out were as follows. In the Li et al. study, one patient in CP group withdrew and one patient in control group was given CP.[32] In the Agarwal et al study, one patient each in each group was lost to follow-up, and two CP recipients discontinued the intervention.[33] In the study by Libster et al., 5 patients (3 in CP group and 2 in control group) received intervention (CP or placebo) after they had the primary end point event. One other patient in the CP group did not receive CP transfusion due to hypoxemia.[4] The authors conducted intent-to-treat analysis in these 3 RCTs.[4,32,33] In the study by Simonvich et al., the analysis was conducted excluding the participant who withdrew from the study before receiving the study intervention. There were no other patients reported as lost to follow up.[7]

The main limitation of the study by Li et al.[32] was that it was terminated early due to a decline in the number of patients resulting in underpowered analysis. A total of 103 patients were enrolled, which was half of the intended number of participants (200), leading to inadequate power for statistical analysis. Additionally, the median time between onset of symptoms to CP therapy was 30 days. It has been suggested that administration of CP early in the disease could be more beneficial in diseases with viral etiology.[45] In the study by Agarwal et al.,[33] about a third of patients screened for the study were not enrolled. It was unclear whether the patients excluded due to non-eligibility and those who declined to

participate were different from the enrolled patients. The antibody titre of the donor CP and the serum antibody titre of the patients were not assessed prior to transfusion. When assayed retrospectively, it was found that median antibody titre in the donor CP was 1:40 (IQR: 1:30 to 1:80) and that of the participants at enrolment was 1:90 (IQR: 1:30 to 1:240). Therefore, the patients were transfused with CP with a lower antibody titre than their own baseline levels. Though the optimal antibody titre for clinical effectiveness is not yet known, FDA eIND guidelines suggest using CP with a titer of > 1:160.[46,47] Additionally, only 160 patients (68%) in the CP arm received plasma with detectable levels of antibodies; according to the power calculation 226 patients were needed to detect significant effects of present. The RCT by Libster et al.[4] was terminated early due to a decline in the number of cases, resulting in a study enrolment of 76% of the targeted sample size. It is possible that the study was underpowered for the primary end point (i.e., development of severe disease). Considering the uncertainties and lack of scientific knowledge in the minimal important difference of the outcome (progression to severe disease) the internal validity of the results is unclear. There was also a risk of confounding bias in the study as concomitant treatments were not reported.[4] Lastly, in the RCT by Simonovich et al., although the patients who were excluded from the study due to various reasons were described, it was unclear whether the patients excluded due to non-eligibility and those who declined to participate were different from the enrolled patients. Conflict of interest of the study authors were not reported.[7]

As the time to recovery and long-term effects of COVID-19 are still unclear, it is unknown whether patients may have improved or deteriorated after the 28-day or 30 day follow-up time periods.[7,32,33] For 2 studies, the open label design meant neither participants nor the treating clinicians were blinded to the intervention groups. Standard treatment including steroids and antivirals were given to patients in both groups as needed, which could affect the outcomes.[4,7,32,33] Furthermore, the trials were conducted in Argentina,[4,7] China[32] and India[33] making the generalizability to Canadian settings unclear.

Non-randomized Studies

The 12 included NRSs had some strengths.[1-3,5,6,35-41] The study objectives were clearly described in 10 studies.[1,3,5,35-38,40,41] Ten studies reported estimates of random variability (e.g., IQR or SD), and used appropriate statistical tests to compare intervention and treatment groups.[1,2,35-41] All studies except 1[41] reported simple outcome data for the study findings,[1-3,5,6,35-40] had no patients lost to follow-up, and had reliable compliance with the interventions. Ten studies [1,2,5,6,35-39,41] reported the methods of plasma collection and the dosage and timing of the CP transfusion. The incidence of adverse events in those who received CP transfusion was reported in 10 studies.[1-3,5,6,35,37-41] Baseline characteristics of patients in each group were described and compared in 10 studies,[1-3,6,35,36,38-41] and no significant differences in potential confounders like comorbidities or baseline clinical symptoms between the two groups were found in 7 of them.[1,2,6,35,39,40] Two NRSs used propensity score matching to select controls based on predefined variables,[6,41] and one[6] of them used predefined case control ratios and clipper width. The variables used to match cases and controls were reported. The number of patients and controls excluded due to unmatching were reported in one study.[6] It is unclear whether these excluded patients could have impacted the results. Confounders that were not balanced well in the score matching (concomitant medications) were adjusted for in the multivariate analysis.[6,41]

The included NRSs[1-3,5,6,35,37,39,40] 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.[1-3,5,6,35-41] There was also a risk of sampling

bias, without clear random selection of patients. It was unclear whether the authors of the NRSs[1-3,5,6,35-40] performed power calculations prior to recruiting participants. The studies by Zeng et al.[40] and Duan et al.[37] had small sample sizes, with a combined total of 16 patients receiving CP therapy. In 5 studies,[2,3,5,35,36,39] it was unclear how long the participants were followed, including for the outcome all-cause mortality. Without a specific follow up period, outcomes such as case fatality rate and mortality have limited clinical relevance. 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.[1-3,5,6,35-41] None of the included NRSs reported incidence of adverse events in the control group.[1-3,5,6,35-41]

Additionally, in the NRS by Xia et al.,[39] 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[39] 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.[37] 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.,[40] 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.

Two propensity score-matched studies had some additional limitations.[6,41] It was unclear whether testing for proportional hazards assumption prior to Cox regression was done in either study.[6,41] In both studies, there were a number of statistical comparisons performed without control for type 1 error; therefore, it is unclear if the statistically significant comparisons are valid or just due to the inflated type 1 error risk.[6,41] Since the treatment groups were defined based on exposure to treatment (CP), there was a risk of immortal time bias which was not corrected in the studies with a time-dependent variable.[6,41] Immortal time bias occurs when by design, participants in the exposed group are considered immortal prior to the exposure to treatment (CP), since they must survive in

order to receive the treatment and be included in the treatment group. As a result of the incorrect management of immortal time, the benefit of CP may be overestimated in all of the comparisons.

In the Liu et al. study, the main limitation was that it was unclear how the variables to be included in the propensity score matching were determined.[41] In this study, the caliper width of the propensity score for matching was not reported. This is important because there were clinically important differences in covariates included in the propensity score between patients who received CP and their controls. Potential confounders like concomitant medications, sex, and diabetes were not equally distributed between groups.[41] Even though not reported as statistically significant, the differences in distribution could be clinically important. The study authors[41] did not consider other important potential confounders like race and ethnicity and hypertension in matching, and there was significantly higher use of therapeutic anticoagulation in the CP group compared to the control group. It is possible that these differences may have contributed to some of the differences in outcomes between the groups. Furthermore, [41] the outcomes of interest were not reported in this study, and it was unclear if they were planned a priori. The incidence of adverse events was not reported. The authors reported the results of "worsening oxygenation" and worsening "clinical condition", but the definitions of these outcomes were not reported and thus unclear. Six patients (out of 45) who submitted eIND application and were approved to receive CP therapy did not receive CP. These patients were excluded from the study. It is possible that those who were excluded were different from those included in the study since the characteristics of excluded patients were not reported. The matched controls were different from the overall population of potential controls available from the study site (as evidenced by the lack of overlap in the distribution of the logit of the propensity score). This lowered the generalizability of the results to the overall population with COVID-19. Follow-up duration was different between the CP group (median 11 days) and control group (median 9 days). For outcomes such as mortality, these short and varying follow up times between the groups have limited clinical relevance. Lastly, although the objective of the study was to evaluate the effects of "early" CP therapy, the definition of "early" was not reported by the study authors. The CP group patients had symptoms for up to 2 weeks (median 7 days) prior to hospital admission, and the median duration between hospitalization and CP transfusion was 4 days (range 0 to 7 days).[41]

In the NRS by Rogers et al.,[38] 82 patients received CP (based on the FDA Expanded Access program) at the study hospital, however only 64 of these were enrolled in the study based on the additional inclusion criteria. This limited the generalizability of the findings as it is possible that the patients who were excluded from study could have had different outcomes from those who were included. Additionally, patients in the control group were not selected based on disease severity, whereas all patients in the CP group had severe or life-threatening illness. The CP group also had a significantly higher rates of corticosteroid use compared to those in the control group. Because of these reasons it is possible that the patients in the CP group were different from those in the control group thereby lowering the internal validity of the study. The SARS-CoV-2 antibody titre of the administered CP was not measured before transfusion. The antibody index measure used for subgroup analyses was based on retrospective assays of thawed samples, which were not available for all the CP units transfused. Therefore, the specific characteristics of the intervention were unknown.

In the study by Alsharidah et al., patients in the control group were selected from a national registry based on disease severity and date of hospital admission.[1] It is possible that the

supportive care received by the control group patients were different from their CP group counterparts.[1] This could lead to selection bias as well as reduce the internal validity of the results. In another NRS by Dai and colleagues, there were limitations in reporting (no reporting of effect sizes, estimates of random variability and the statistical tests used, and ambiguity in the definitions of outcome measures).[2] The study by Jiang et al., lacked sufficient details in the study methods and results sections.[3] Although the study was described as "propensity score matched", without any additional details on patient selection, matching variables, propensity score, or caliper width, any assessment of methodology was not possible. The definitions for the outcome measures (e.g., "cure", "improve") were unclear, and it was unclear whether the outcomes were determined a priori. These limitations along with the observational study design, lack of a defined follow up period, and non-reporting of effect sizes lowered the quality of the study.[3] Lastly, in the study by Moniuszko-Malinowska et al.,[5] the inclusion and exclusion criteria for patient selection were not reported. The results relevant to the current report were from a subgroup analysis and it was unclear if the analysis was planned a priori. There was no description of any matching process to identify controls from the database. The second comparator group included a combination of other medications of different types used for the management of COVID-19. This grouping of other medications could make the interpretation of comparative results challenging and lower the clinical relevance.[5]

Overall, the evidence from 9 NRSs[2,3,5,36-41] was considered low-quality and the evidence from 3 NRSs[1,6,35] 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,[2,3,37,39,40] Iran,[35] Kuwait,[1] Poland,[5] Turkey,[36] and the US[6,38,41] making the generalizability to Canadian settings unclear due to differences in clinical practices and care.

Summary of Findings

Clinical Effectiveness of Convalescent Plasma Therapy

The 16 included studies in this report provided evidence regarding the clinical effectiveness of CP therapy in patients with COVID-19.[1-7,32,33,35-41] Study findings relevant to this report are summarized below. Appendix 4 presents the main study findings and authors' conclusions.

Mortality

Compared to standard care alone or placebo, 7[4,32,33,35,36,38,40] studies (3 RCTs[4,32,33] and 4 NRSs[35,36,38,40]) found that CP therapy was associated with no significant difference in mortality. However, 5[1,6,37,39,41] studies found significantly lower mortality with CP therapy compared to standard care alone, and 1 study[5] found significantly higher mortality with CP compared to remdesivir.

In terms of the studies that identified significantly lower mortality with CP therapy compared to standard care alone, the study by Liu et al.[41] found significant survival benefits in CP recipients compared to propensity score matched controls (HR = 0.39; 95% CI = 0.15 to 0.99). However, due to limitations in follow up (short duration of follow-up and varying duration of follow up in both groups) and other methodological limitations described earlier, the clinical importance and validity of the results is uncertain. In the NRS by Duan and colleagues[37] 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 by Xia et al.[39] 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). The study Alsharidah et al.,[1] found that among all patients, 30-day mortality was significantly lower in the CP group compared to the control group (OR = 0.32, 95%CI = 0.18 to 0.58), adjusted for age, baseline oxygen status, lymphocyte levels, and C-reactive protein. A similar significant difference in mortality was observed in the subgroup of patients with moderate illness, but not in those with severe illness. Lastly, Salazar et al.,[6] found that 60-day mortality was significantly lower in CP recipients compared to propensity score matched controls (data were not shown in the publication). There were no significant differences in 60-day mortality between the CP and propensity-matched control groups in the subset of patients who received CP was administered more than 72 hours after admission, or the subset of patients who were intubated on day 0. In subgroup analysis of patients who received CP with an antibody titre ≥ 1:1350, mortality rates at days 28 and 60 were significantly lower in CP group compared to the matched control group.[6]

In contrast, in the study by Moniuszko-Malinowska et al., compared to patients who were treated with remdesivir, those who received CP therapy had a significantly higher rate of mortality (3.4% vs 11.2%, P < 0.05).[5] There were no significant differences in mortality between those who were treated with CP and those who were treated with other drugs (Tocilizumab, dexamethasone, chloroquine, hydroxychloroquine, lopinavir/ritonavir, azithromycin or fractioned heparin).[5]

Clinical Improvement

Clinical improvement was reported in 7 studies,[1,2,5-7,32,37] and was defined as a decrease of 1 or 2 points on 6-point,[2,6,7,32,39] 7-point[1] or 8-point disease severity scales.[5] It was unclear whether a 1 or 2-point difference in the scale denoted a clinically significant improvement.

Four studies found that a significantly higher proportion of patients who received CP therapy achieved clinical improvement compared to those who received standard care alone.[1,2,6,37] One study found no significant differences in the proportion of clinically improved patients in CP group and control group (standard care alone).[32]

Specifically, two studies[1,6] found that significantly higher proportion of patients who received CP therapy achieved clinical improvement at 30 days[1] and up to 60 days[6] compared to those who received standard care alone. One NRS also found a significantly higher percentage of patients with clinical improvement in the CP group compared to the control group (standard care alone) among patients with COVID-19 and diabetes, although the length of follow up was unclear.[2] Another NRS reported that 7 patients (70%) in the CP treatment group improved compared to 1 in the historic control group.[37] Though reported as statistically significant, the definition of “improved” and the time of outcome measurement was unclear in the control group.[32] One RCT found no significant differences in the proportion of patients achieving clinical improvement between CP and control groups at 28 days.[32] This RCT was terminated early based on decreasing case numbers.[32] Lastly, compared to remdesivir or other medications, there were no significant differences in the proportion of clinically improved patients among those who received CP therapy.[5]

Four studies[1,2,7,32] compared the median time to clinical improvement between CP and control groups. Among them, 3 studies[1,2,32] found that CP therapy was associated with a

significantly shorter time to clinical improvement while the fourth study[7] did not find any significant difference between the groups.

Specifically, in the study by Alsharidah et al.,[1] the median time to clinical improvement was significantly shorter in CP recipients with moderate disease and those with severe disease, compared to similar subgroups of patients who received standard care alone. In the RCT by Li et al., among patients with severe disease, the median time to clinical improvement was significantly shorter in patients who received CP therapy (13 days) compared to those who received standard care alone (19 days).[32] No significant differences were found in patients with life-threatening illness. Among patients with COVID-19 and diabetes (study by Dai et al.), the median time to clinical improvement was significantly shorter in the CP group compared to the control group (standard care alone).[2] However, the RCT by Simonovich and colleagues found no differences in median time to clinical improvement (2-point difference in the 6-point scale), or time to complete restoration of physical function, between patients with severe COVID-19 who received CP and those who received placebo.[7] It was noted that these studies used different scales to measure clinical improvement which had different between-point intervals. Additionally, the required change in the scales to denote clinical improvement was also not consistent across studies. It is possible that these inconsistencies in outcome measurement contributed to the inconsistency in results.

Clinical Status at Follow-Up

Five studies compared the clinical status or disposition of study participants at various time points of follow up or at the end of the study.[3,6,7,37,39] Two studies found that the clinical status or disposition of patients at follow up was not significantly different between CP and control groups.[3,7] Three other studies[6,37,39] (1[6] was a sub-group analysis) reported significant differences in clinical status (in favor of CP therapy) at the time of follow up.

Specifically, a placebo-controlled RCT among patients with severe COVID-19 did not find any significant differences in clinical status between those who received CP and those who received placebo at 7, 14, and 30 days after intervention. Clinical status was defined as the patient's status on a 6-point disease severity scale. One observational study[3] also did not find any significant differences (between CP and control groups) in patients' discharge condition ("cure", "improve", "death" or "transfer to another hospital"); however, the length of follow up and the definitions of these outcomes were not reported.

In a sub-group analysis of one propensity score matched study,[6] clinical disposition (death, still admitted, or discharged) at 60 days was significantly different between patients who received CP (with an antibody titre ≥ 1:1350) compared to matched controls who received standard care alone. More patients in the CP group were discharged (92.2%) compared to control group (86.4%), whereas fewer patients in CP group were deceased or still admitted.[6] In another study, the clinical outcomes at the follow up date (death, discharge or hospitalization) were also reported as significantly different between CP recipients and those who received standard care alone. However, study participants were not followed for a specific duration, but rather the clinical outcomes were assessed on a particular day for all patients, making it unclear whether the results were due to differences in intervention or differences in follow-up duration.[39] In the NRS by Duan and colleagues,[37] all CP recipients (n = 10) were either discharged or had improved by the time of follow up assessments whereas one patient in the historic control group was discharged or improved. Though described as statistically significant, there was ambiguity in the definition and measurement of the outcomes and a small sample size (10 patients each in CP therapy and control groups).

Disease Progression

Findings from one RCT[4] showed that, among elderly patients with mild COVID-19, significantly fewer patients in the CP group progressed to severe respiratory disease (defined as RR > 30/min or SpO_2 < 93% on ambient air) compared to those in the placebo group. The median time to development of severe respiratory distress was 15 days (IQR 15 to 15) in the CP group and15 days (IQR 9 to 15) in the control group (P = 0.03). Number needed to treat to avert one episode of severe illness was estimated as 7 (95%CI = 4 to 50). There were no significant differences in rates of life-threatening disease, critical systemic illness, acute respiratory failure, shock, or multiple organ dysfunction syndrome between CP and placebo groups, although the number of patients was low for most of these outcomes (less than 5 in each group).

One NRS reported that significantly fewer patients in the CP group had "worsening oxygenation" by day 14 compared to those in the control group.[41] However, the definition of "worsening oxygenation" and how it was measured were not reported, and the clinical importance of this result was unclear.

Resolution of Symptoms

Findings from the RCT by Agarwal et al.[33] showed that patients who received CP therapy had higher rates of symptom resolution (shortness of breath and fatigue) compared to those who received standard care alone.

Need for Oxygen Therapy

Three studies[4-6] compared the need for O_2 associated with CP therapy compared to standard care,[6] placebo[4] or remdesivir.[5]

Compared to standard care, O_2 requirement was significantly higher in CP group (P < 0.001). The risk ratio was 0.99 (95% CI 0.99 to 0.99), suggesting a small effect.[6] Among those who received supplemental O_2, there was no significant difference in the duration of O_2 requirement.[6]

One RCT in elderly patients with mild COVD-19 found no significant differences in O_2 requirement in those treated with CP compared to those treated with placebo.[4]

Compared to patients who received remdesivir, a significantly greater proportion of patients who received CP required constant O_2 therapy.[5] Among patients who needed constant O_2 therapy, the duration of O_2 supplementation was significantly shorter for patients who were treated with remdesivir. The necessity of constant O_2 therapy was also significantly less frequent in patients who received other medications (i.e., Tocilizumab, dexamethasone, chloroquine, hydroxychloroquine, lopinavir/ritonavir, azithromycin or fractioned heparin) compared to CP, although the duration of supplementation was not statistically different between the groups.[5]

Respiratory Support (Need for Non-Invasive Ventilation)

Evidence from two RCTs showed that there were no differences in the rates or duration of non-invasive ventilation between patients who received CP and those who received standard care alone[33] or placebo.[4]

Respiratory Support (Need for Mechanical Ventilation, Time To and Duration of Mechanical Ventilation)

Compared to standard care alone, 3 studies[4,6,33] found no significant differences in the rates of requirement of mechanical ventilation in the CP group, whereas one study found that significantly more patients in the control group (55%) needed mechanical ventilation compared to those in the CP group (49.3%); P = 0.02.[36]

Time to mechanical ventilation was not significantly different between the CP and placebo groups in patients with severe COVID-19 in 1 RCT.[7] Salazar and colleagues[6] found that among patients who required mechanical ventilation, CP recipients were mechanically ventilated for around 9 days longer (–9.15; 95% CI: –16.91 to –1.38; P = 0.02) compared to those in a matched control group.[6]

The rate of mechanical ventilation was significantly higher in patients treated with CP than those treated with remdesivir (Remdesivir group 4%; CP group 11.2%) There were no differences in the rates of mechanical ventilation between patients who received CP and those who received other medications (i.e., tocilizumab, dexamethasone, chloroquine, hydroxychloroquine, lopinavir/ritonavir, azithromycin, or fractioned heparin).[5]

Respiratory Support (Intubation)

In one study among patients with COVID-19 who were not intubated at baseline, significantly fewer patients who received CP therapy (7%) were subsequently intubated compared to those who received standard care alone (20%).[35]

Respiratory Support (Ventilation Status)

The study by Salazar et al.[6] examined the ventilation status of patients during the study measured using the percentage of patients on room air, low flow O_2, high flow O_2, mechanical ventilation or extracorporeal membrane oxygenation (ECMO). All ventilation status measures were not statistically different between patients in the CP group (who received CP with antibody titre ≥ 1:1350) and those in the propensity score matched control group on days 7, 14, 28, and 60.

ICU Admission

Three studies found no differences in the rates of ICU admission between patients who were treated with CP and those who received standard care alone.[4,6,39]

Among the patients who were admitted to the ICU, 2 studies found no difference in the duration of ICU stay,[6,7] but 1 retrospective study[36] found that CP recipients stayed in the ICU for a shorter duration compared to those who received standard care alone.

Length of Hospital Stay

There were no significant differences in the rates of hospital discharge at 28 days (1 study) [32,34] or the overall length of hospital stay (6 studies) [6,7,32,33,36,38] between patients who received CP therapy and those who received standard care alone. In contrast, compared to standard care alone, 1 study found significantly shorter hospital stay[35] and another study found significantly longer hospital stay[3] in those treated with CP. Specifically, the results from the former NRS[35] showed that patients in the CP group remained in the hospital around 3 days fewer compared to standard care group. Significantly more patients in the CP group were discharged within 5 days of hospitalization than those in the control group. This NRS[35] only enrolled patients whose disease was not severe enough to warrant

intubation or mechanical ventilation.[38] Results from the latter NRS showed that CP recipients remained hospitalized for a median 23 days whereas the median length of hospital stay in the control group was 15 days.[3] However, this study had several limitations such as unclear follow up time and lack of adequate reporting.

In subgroup analysis in one propensity score matched study, it was found that patients in the CP group over 65 years of age had increased rates of hospital discharge, compared to those in the control group.[38] In that age group, compared to standard care alone, patients who received transfusion with high antibody titre CP had significantly higher rates of discharge from the hospital, whereas patients who received a low antibody titre CP had no significant difference in discharge rates. No significant differences between patients treated with CP or standard care were found in any other age groups (18 to 49 years or 50 to 64 years).

Compared to patients treated with remdesivir, those who received CP therapy had a significantly longer duration of hospitalization.[5] Similarly, patients who received CP were hospitalized significantly longer than those who received other medications (i.e., tocilizumab, dexamethasone, chloroquine, hydroxychloroquine, lopinavir/ritonavir, azithromycin or fractioned heparin).[5]

Viral Clearance

Evidence from one RCT[32] showed that the rates of negative PCR tests at 24, 48 and 72 hours were significantly higher in the CP group compared to the control group suggesting higher rates of viral clearance. 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.[32] Similarly, findings from the other RCT[33] also showed significantly higher rates of negative seroconversion at 7 days after transfusion in the CP group. However, since the median antibody titre of the transfused CP was lower than the median titre in the recipients, it is possible that the improvement was not directly due to CP therapy.

According to the findings from one NRS,[40] 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. 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

Two studies found that the duration of illness was longer in patients who received CP compared to those who received standard care alone.[39,40] The NRS by Zeng et al.[40] 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[39] 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 RCT by Simonovich et al.,[7] there was no significant difference in the time to complete restoration of physical function between patients in the CP and placebo groups.

In two of these studies [7,40] there was no significant difference in mortality between CP therapy and control groups, while in the NRS by Xia et al.,[39] 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

Whether there were adverse events in the CP group was reported in 14 of the included studies.[1-7,32,33,35,37-40] Whether there were adverse events in the control groups (both placebo) was reported in 2 RCTs.[4,7].

One RCT (by Simonovich et al.) compared the rates of adverse events between CP and control groups, and found no significant differences in the rates of overall adverse events, serious adverse events, or infusion-related adverse events between the groups.[7]

The RCT by Agarwal et al.[33] reported that there were 3 deaths in the CP group (out of a total 235 participants) that were "possibly related" to CP transfusion. No additional details were reported. Across the studies, there were 2 instances of TACO[6,38], 2 of TRALI,[38] 1 of severe transfusion reaction,[32] and 7 of allergic reactions recorded among CP recipients.[1,7]

Other adverse events in patients who received CP were fever (n = 6),[7,35] fever and tachycardia (n = 1),[33] local skin reactions, redness or rashes (n = 15)[3,6,32,33,37,39] shortness of breath (n = 1),[6] and unexplained or technical events (n = 2).[7] Four studies reported that there were no adverse events associated with CP transfusions.[2,4,5,40]

Overall, in the 14 studies in which adverse events were reported, among 1,686 CP recipients, there were 40 incidences of adverse events in various levels of severity.[1-7,32,33,35,37-40] Whether there were adverse events was not reported in 2 publications.[36,41] Most of the included studies did not report whether there were adverse events in the control groups.[1-3,5,6,32,33,35-41] In two studies in which adverse events in the placebo (saline) group were reported, 1 RCT[7] recorded 2 incidences of infusion related events (both allergic reaction) and another RCT reported that there were no adverse events in the control group.[4]

Limitations

The main limitation of this report was the lack of high-quality evidence regarding the clinical effectiveness of CP therapy in COVID-19. In most of the included studies,[1-3,6,32,33,35-41] 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. Additionally, there was lack of uniformity in study outcomes and their definitions across the studies, which made drawing overall inferences about the results challenging. For example, 7 studies measured the outcome "clinical improvement" using disease severity scales that had 6,[2,6,7,32,39] 7,[1] or 8 points.[5] The required change in the scale to denote clinical improvement was also not consistent across these studies. The included studies had moderate to high risk of bias and provided limited quality evidence based on the methodological limitations outlined earlier.

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 outside Canada, so the generalizability to Canadian settings is unclear given the differences in clinical practice and care. As COVID-19 is a

novel 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. In total, 4 RCTs[4,7,32,33] and 12 NRSs[1-3,5,6,35-41] were included in this report that provided limited-quality evidence regarding the clinical effectiveness of CP therapy in adults with COVID-19. No evidence was found regarding the effectiveness of CP therapy in pediatric populations or the effectiveness of CP therapy in lowering the SARS-CoV-2 viral load. The summarized evidence should be interpreted with caution considering the low-to-moderate quality of included studies, high heterogeneity (such as the differences in study populations, settings, concomitant treatments and outcome assessment across the studies), lack of clear reporting, and low generalizability to Canadian settings.

Overall, it was unclear whether there is a survival benefit associated with CP therapy compared to standard care. Evidence from 7 of the included studies showed no significant differences in mortality between patients who received CP and those who received standard care alone[32,33,35,36,38,40] or placebo,[4] and 5 studies[1,6,37,39,41] found statistically significant survival benefits in CP recipients compared to controls; however, all studies had substantial methodological limitations outlined earlier and the validity of the results is uncertain.

Findings regarding "clinical improvement" were also somewhat mixed. For instance, four studies found that a significantly greater proportion of patients who were treated with CP achieved clinical improvement compared to those who were treated with standard care alone,[1,2,6,37] however one study[32] (which was terminated early) found no significant difference between those treated with CP and standard care.[32] Similarly, the time to clinical improvement significantly reduced in patients treated with CP therapy compared to those treated with standard care in three studies,[1,2,32] but there were no significant differences between treatment groups in an RCT.[7] Clinical improvement was defined differently and measured using different scales in the included studies, which may have contributed to some of the observed differences. In terms of other measures of symptom severity, significantly fewer elderly patients with mild COVID-19 who received CP recipients progressed to severe respiratory disease compared to those who received placebo.[4] Among patients with moderate COVID-19, more patients in the CP group achieved symptom resolution (self-reported) compared to those who received standard care alone.[33]

The evidence suggested that there were no meaningful differences between CP and standard care for a number of additional outcomes. Specifically, compared to standard care or placebo, CP therapy was not associated with a beneficial effect regarding requirement of respiratory support such as O_2 therapy,[4,6] non-invasive ventilation[4,33] or mechanical ventilation.[4,6,33] One limited-quality study[36] found that fewer patients in the CP group required mechanical ventilation, and a moderate quality study found that fewer patients in the CP group required intubation,[35] both compared to standard care alone. Similarly, the rates of hospital discharge[32,34] and the length of hospital stay[6,7,32,33,36,38] were not significantly different between patients who received CP therapy and those who received standard care alone. Two studies found significant differences in the duration of hospitalization between CP and control groups (one favorable to CP[35] and the other favorable to standard care[3]). The inconsistencies in these results could be due in part to

overall heterogeneity of the studies (e.g., differences in participant inclusion criteria, outcome measurement and follow up period, standard care given, use of concomitant medications, discharge criteria), and methodological limitations.

Limited quality evidence from two RCTs [32,33] and an NRS[40] showed that CP recipients had higher rates of viral clearance (indicated by negative PCR tests) compared to those who received standard care. Low- to moderate-quality evidence from two NRSs[39,40] showed that duration of illness (defined as time between onset of symptoms to discharge or death) was longer in patients who received CP compared to those who received standard care alone. Taken together with the findings regarding mortality (one study found lower mortality among CP recipients[39] and the other found no differences between the groups[40]), this suggests that patients may have survived longer with CP therapy.

One relevant low-to-moderate-quality study was identified that compared the effectiveness of CP with that of other active therapies.[5] In general, the evidence suggested that CP may be less effective than remdesivir and other medications. Compared to remdesivir, CP therapy was associated with significantly higher mortality, longer duration of hospitalization, and a higher proportion of patients requiring O_2 supplementation and mechanical ventilation.[5] Additionally, significantly more CP recipients needed O_2 supplementation, and stayed in the hospital longer, compared to those who received other medications (i.e., tocilizumab, dexamethasone, chloroquine, hydroxychloroquine, lopinavir/ritonavir, azithromycin or fractioned heparin).

In the 14 studies in which adverse events were reported, among 1,686 patients who were treated with CP there were 40 incidences of adverse events at various levels of severity. This suggested that although adverse events due to CP therapy were relatively infrequent, CP therapy was not free of risks.[1-7,32,33,35,37-40] One study[33] reported three deaths that were "possibly related" to CP transfusion (out of 235 patients). As for the important adverse events related to CP transfusion,[18] there were 2 incidences of TACO,[6,38] 2 of TRALI,[38] 1 of severe transfusion reaction,[32] and 7 of allergic reactions among CP recipients.[1,7] Most of the included studies did not report whether there were adverse events in the control groups.[2,3,5,6,32,33,35-41]

Overall, limited low-quality evidence exists regarding the clinical effectiveness of CP therapy in patients with COVID-19. A 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 information regarding the potential utility and safety of CP therapy.[48-52] 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.[53-56] 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 19 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.[57] 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 who 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[58] 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 for the disease, immediate well-designed research on the management of COVID-19 is of paramount importance.

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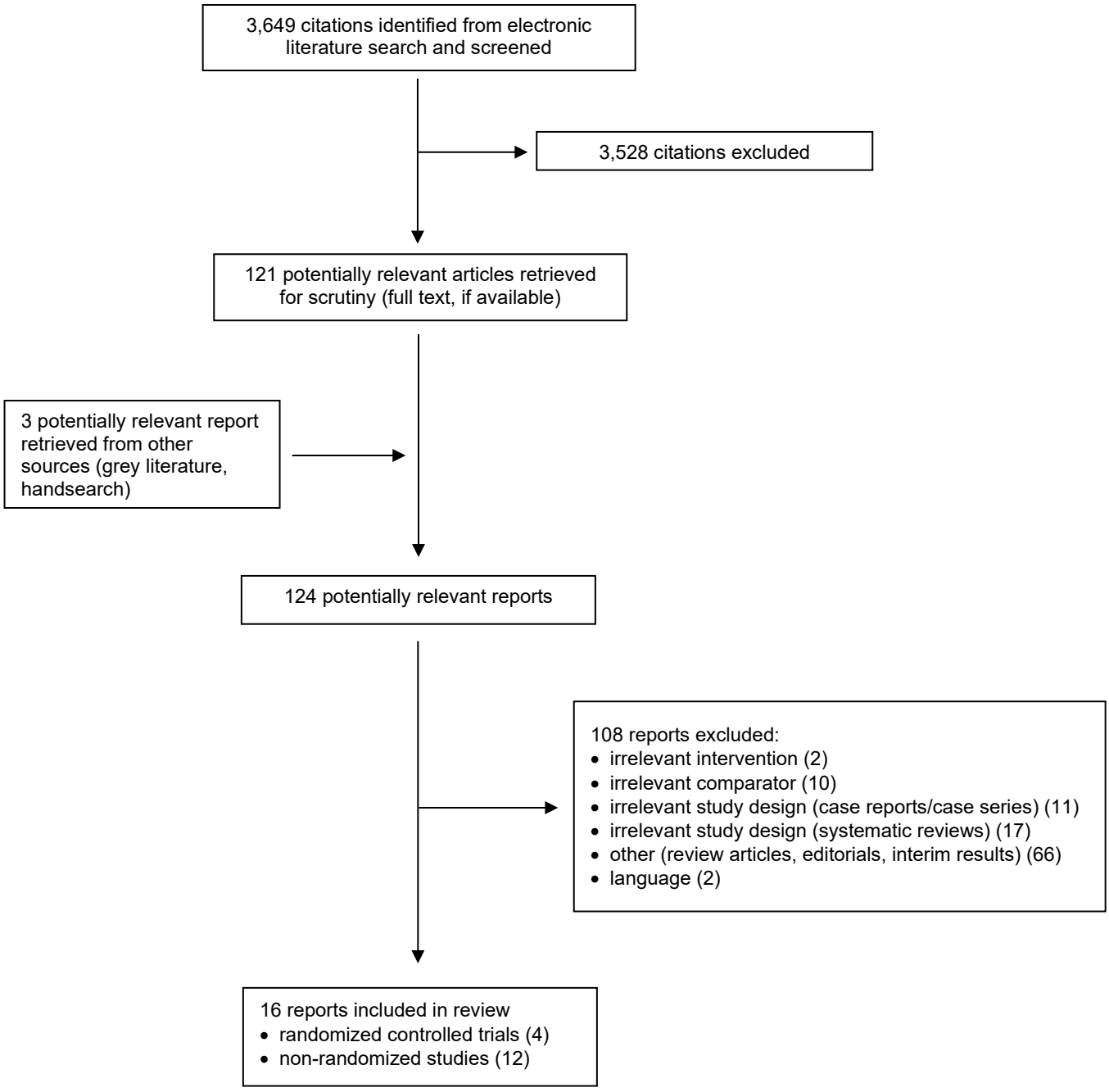
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies

3,649 citations were identified, 3,528 were excluded, while 121 electronic literature and 3 grey literature potentially relevant full text reports were retrieved for scrutiny. In total 16 reports are included in the review.



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				
Libster et al., 2021[4] **Country:** Argentina **Funding source:** Bill and Melinda Gates Foundation and the Fundación INFANT Pandemic Fund.	**Study design:** Open label, parallel arm, phase II, multi center randomized controlled trial. **Objective:** To investigate the effectiveness and safety of CP therapy within 72 hours of onset of mild symptoms	Patients with mild COVID-19 confirmed by RT-PCR who were 75 years or older, or those between 65 and 74 years of age with at least one coexisting condition. Coexisting conditions included: hypertension, diabetes, obesity (BMI> 30 kg/m2), chronic renal failure, cardiovascular disease, COPD) **Inclusion criteria:** At least one clinical symptom or sign from following two categories: a) Fever (> 37.5 degree C), sweating, chills b) Dry cough, dyspnea, anosmia, dysgeusia, fatigue, myalgia, anorexia, sore throat, rhinorrhea, **Exclusion criteria:** Severe respiratory disease (RR > 30/min; SpO2 < 93%), heart failure, renal insufficiency, primary hypogammaglobulinemia, IgA deficiency, blood disorders (e.g., myelodysplastic syndromes, lymphoma), known hypersensitivity to blood products, HIV or HCV infection, recent use of immunosuppressants, solid organ transplant, O2 requirement for lung disease, anticoagulant treatment, physician determined contraindications. **Number of participants:** Total number of participants, N = 160 CP group, n = 80 Control group, n = 80	**Intervention:** CP with an IgG titre >1:1000 *Volume:* 250 mL *Administratio*n: One dose transfused over 1.5 to 2 hours. *Timing*: Within 72 hours of symptom onset. **Comparator:** Placebo (250 mL of 0.9% saline) **Concomitant medications:** Not reported. (89% of patients in the CP group and 80% of patients in the control group used medications in the previous 15 days, although it was unclear whether these were for COVID symptoms)	**Primary end point:** Development of severe respiratory disease (RR >30/min or SpO2 < 93% on ambient air) **Secondary end points:** Life threatening illness (O2 supplementation, invasive or noninvasive ventilation, ICU admission), critical systemic illness (respiratory failure with PaO_2:FiO_2 < 200, shock, multi organ dysfunction), death. **Length of follow-up:** 12 hours after transfusion and at day 15. Final outcome assessment at 25 days.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Mean age (SD), years: CP group = 76.4 (8.7) Control group = 77.9 (8.4) **Sex:** CP group: 68% females Control group: 58% females		
Simonovich et al., 2020[7] (PlasmAr trial) **Country:** Argentina **Funding source:** Supported by the participating institutions and Research Council of the Hospital Italiano de Buenos Aires.	**Study design:** Double blinded, placebo controlled multi center randomized controlled trial. **Objective:** To investigate the effectiveness and safety of CP therapy in patients with severe SARS-CoV-2 pneumonia	Adult patients with severe COVID-19 confirmed by RT-PCR **Inclusion criteria:** Radiologically confirmed pneumonia, no previous directives rejecting advance life support and at least one of the severity criteria fulfilled. *Severe COVID-19* was defined as SaO2< 93% on ambient air, PaO_2: FiO_2 < 300 mmHg, SOFA score or modified SIFA score of two or more above baseline status. **Exclusion criteria:** pregnancy, lactation, absence of contraceptive measures for 30 days after enrollment (for patients of reproductive age), history of allergy to blood components, pneumonia due to other infections, mechanical ventilation, multiorgan failure, other reasons impeding giving informed consent. **Number of participants:** Total number of participants, N = 334 CP group, n = 228 Control group, n = 105 **Median age (IQR), years:** CP group = 62.5 (53 to 72.5) Control group = 62 (49 to 71) **Sex:** CP group: 29.4% females Control group: 39% females	**Intervention:** CP with median neutralizing antibody titre of 1:300 (IQR: 1:136 to 1:511) from a plasma pool. *Volume:* median : 500 mL (IQR: 415 to 600). Dose: 5 to 10 mL/kg with minimum 400 mL and maximum 600 mL. *Administration:* 5 to 10 mL/Kg per hour *Timing*: Median time from symptom onset to enrolment: 8 days (IQR 5 to 10) **Comparator:** Placebo (normal saline) **Concomitant medications:** Patients received supportive care and medications including antivirals, glucocorticoids tocilizumab, Ivermectin and hydroxychloroquine.	**Primary end point:** Clinical status at 30 days after intervention measured using WHO clinical scale. *Clinical scale:* 1: Death, 2: invasive ventilatory support, 3: hospitalized with supplemental oxygen, 4: hospitalized without supplemental oxygen, 5: discharged without full return to baseline physical function, 6: discharged with full return to baseline physical function **Secondary end points:** Clinical status at day 7 and 14, time to discharge from ICU, time to discharge from hospital, time to clinical improvement (2 points on scale), time to death and time to full recovery, adverse events. **Length of follow-up:** 30 days
Agarwal et al., 2020[33] (PLACID trial)	**Study design:** Open label, parallel arm, phase II, multi center	Adult patients with confirmed COVID-19 based on positive RT-PCR test.	**Intervention:** ABO compatible CP with standard of care	**Primary outcome:** Composite progression to severe disease

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Country: India **Funding source:** Indian Council of Medical Research (ICMR)	randomized controlled trial. **Objective**: To investigate the effectiveness and safety of CP therapy in moderate COVID-19	**Inclusion criteria:** moderate illness and availability of matched donor at the time of enrolment. *Moderate COVID-19* was defined as PaO_2:FiO_2 between 200 and 300 mmHg, respiratory rate > 24/min or SaO2 ≤ 93% on room air. **Exclusion criteria**: Pregnancy/lactation, IgA deficiency, known hypersensitivity to blood products, immunoglobulin administration in the past 30 days, patients in other clinical trials, PaO_2: FiO_2 < 200, or shock (requiring vasopressor support). **Number of participants:** Total number of participants, N = 464 CP group, n = 235 Control group, n = 229 **Median age (IQR), years:** CP group = 52 (42 to 60) Control group = 52 (41 to 60 **Sex:** CP group: 25% females Control group: 23% females	*Volume:* two doses of 200 mL CP. *Administratio*n: Frist dose at randomization, second dose 24 hours later. *Timing*: Median time from symptom onset to study enrolment: 8 days (IQR: 6 to 11 days) **Comparator:** Standard care alone All patients received standard care which included antivirals (remdesivir, lopinavir/ritonavir, oseltamivir), antibiotics, hydroxychloroquine, immunomodulators, steroids, tocilizumab) and supportive management (O_2, invasive or mechanical ventilation and prone positioning while awake).	(defined as PaO_2:FiO_2 <100) or all-cause mortality. If progression to severe disease or death was prevented, the outcome was considered “good”, otherwise it was considered “poor”. **Secondary outcomes:** Symptom resolution, O_2 requirement, duration of respiratory support, need for mechanical ventilation and safety outcomes within 6 hours of CP transfusion. **Length of follow-up:** 28 days with outcome assessments done at 0, 1, 3, 5, 7 and 14 days.
Li et al., 2020[32,34] **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, PaO_2 < 100, severe CHF, High titer of	**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 300 mL), 96% of patients received single dose *Timing:* Median time from onset of	**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

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		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 PaO_2 ≤ 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 **Median age (IQR):** CP group: 70 years (62 to 80) Control group: 69 years (63 to 76) **Sex:** CP group: 48.1% females Control group: 35.3% females	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.	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
Non-randomized studies				
Salazar et al., 2021[6,8] **Country:** US **Funding source:** Fondren Foundation, Houston Methodist Hospital	**Study design:** Prospective propensity score matched study **Objective:** To evaluate the efficacy of CP therapy in severe and/or critical COVID-19 patients. **Note:** Earlier versions of the current report included interim results of this study.[8]	**Inclusion criteria:** Patients with severe or life-threatening COVID-19 disease (diagnosed as positive RT-PCR test) Patients with available 60-day outcome data were included for analysis. **Exclusion criteria:** Previous history of severe reactions to blood or blood products (probable or definite), underlying and uncompensated end-stage disease, fluid overload or any condition	**Intervention:** ABO compatible CP *Volume:* one or two units. Among CP recipients (n = 351), 278 (79%) received a single unit, and 75 (21%) received a second unit of CP. *Anti-RBD IgG titer*: Among first or sole unit of CP: ≥ 1:1350 - 321 (91%) patients Between 1:150 and 1:1350 – 24 patients	**Primary outcome:** 60-day mortality Secondary outcomes: Overall mortality, clinical improvement, disposition at day 60, length of hospital stay, ICU requirement, length of ICU stay, mechanical ventilation requirement and

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	This version includes the final results.	contraindicating plasma transfusion *Severe COVID-19* was defined as one or more of these features: shortness of breath, respiratory rate ≥ 30/min; resting state oxygen saturation level less than 93% in room air; PaO_2 ≤ 300 mmHg; pulmonary infiltrates > 50% within 24 to 48 hours of screening assessment. *Life-threatening COVID-19* was defined as one or more of the following: respiratory failure, septic shock or multiple organ dysfunction/failure. CP recipients were matched with controls using a ratio of 1:3 and caliper of ≤ 1 based on age, sex, BMI, demographics, comorbidities and ventilation requirement, and concomitant medications (steroid, azithromycin, hydroxychloroquine, remdesivir, ribavirin and tocilizumab). A secondary propensity score matching was conducted using a ratio of 1:2 or 1:1 and caliper of ≤ 1 based on ventilation status at day 0. **Number of participants:** Total number of CP recipients: N = 351 Total number of patients not-transfused, n = 4944 After matching: Total number of participants, N = 903 CP group, n = 341 Control group, n = 594 **Median age (IQR):** Not reported **Sex:** CP group:42.8 % females Control group: 45.1% females	<1:150 – 6 patients Among second unit: ≥ 1:1350 – 71 (95%) patients Between 1:150 and 1:1350 – 4 patients <1:150 – 0 patients **Comparator**: Standard care All patients received symptomatic control and supportive care including antivirals, steroids, hydroxychloroquine, Tocilizumab and azithromycin according to physician's decision.	status, need for supplemental O2. *Clinical improvement definition:* Decrease of one point 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 **Length of follow-up:** 60 days after Day 0, with outcome assessments at days 7, 14, 28 and 60. Day 0 was the day of transfusion for CP group and corresponding day of admission for control group.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Alsharidah et al., 2020[1] **Country:** Kuwait **Funding source:** Kuwait Ministry of Health	**Study design:** Prospective observational **Objective:** To study the efficacy of CP in the treatment of moderate and severe COVID-19.	Adult patients with confirmed COVID-19 based on positive RT-PCR test. **Inclusion criteria:** Moderate or severe COVID-19 illness. *Moderate COVID-19* was defined as clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) and SpO2 >90% on room air. *Severe COVID-19* was defined as clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) along with RR>30/min, SpO2 < 90% on room air and/or ICU admission for respiratory support (non-invasive mechanical ventilation or intubation) **Exclusion criteria:** Contraindication to transfusion (volume overload, or history of anaphylaxis to blood products), acute severe multiorgan failure, hemodynamic instability, shock, DIC or expected survival of < 48 hours. For each CP patient, 2 control group patients who were admitted on the same calendar date were selected based on disease severity. **Number of participants:** Total number of participants, N = 368 CP group, n = 135 Control group, n = 233 *Moderate disease:* CP group, n= 89, control group, n= 155 *Severe disease:* CP group, n= 46, control group, n=78 **Median age (IQR), years:** CP group = 54 (48 to 60) Control group = 54 (45 to 62) P = 0.74 **Sex:** CP group: 22.2% females Control group: 15% females	**Intervention:** ABO compatible CP and standard care *Volume:* 107 patients received 2 units (200 mL each), 28 patients received one unit. *Administration*: 12 hours apart *Timing:* within 24 hours of admission **Comparator:** Standard care alone Most patients received antibiotics and low molecular weight heparin. No patients received antivirals or hydroxychloroquine. Steroids and Tocilizumab were given as per physician decision. including antivirals.	**Outcomes:** Clinical improvement, hospital mortality, changes in O2 saturation *Clinical improvement definition:* Decrease of two points on the WHO disease severity scale. *Disease severity scale:* Hospital discharge: 1 point; Not hospitalized but unable to resume normal activities: 2 points, Hospitalization with no supplemental oxygen: 3 points; Hospitalization plus supplemental oxygen (not high-flow or noninvasive ventilation: 4 points; Hospitalization plus noninvasive ventilation or high-flow supplemental oxygen: 5 points; Hospitalization plus ECMO or invasive mechanical ventilation: 6 points; Death: 7 points **Length of follow up:** 30 days

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Dai et al., 2020[2] **Country:** China **Funding source:** Medical Innovation Project of Logistics Service, Grant/Award Number: 18JS005; Foundation of Jiangsu Population Association, Grant/Award Number: JSPA2019017; Key Foundation of Wuhan Huoshenshan Hospital, Grant/Award Number: 2020[18]; Key Research & Development Program of Jiangsu Province, Grant/Award Number: BE2018713; Jiangsu Provincial Association for Maternal and Child Health Studies Commissioned Research Project Funding, Grant/Award Number: JSFY202005	**Study design:** Retrospective observational **Objective:** To study the efficacy of CP in the treatment of COVID-19 patients with diabetes	Patients with COVID-19 and diabetes mellitus **Number of participants:** Total number of participants, N = 367 CP group, n = 39 Control group, n = 328 **Median age (range), years:** CP group = 68 (21 to 93) Control group = 64 (33 to 90) **Sex:** CP group: 41.03% females Control group: 45.43% females	**Intervention:** ABO compatible CP *Volume:* 200 mL (one unit) *Administration:* Slow transfusion for the first 15 min, with close monitoring *Timing:* dependent on CP availability **Comparator:** Conventional treatment	**Outcomes:** Clinical improvement (1 and 2-point reduction in the 6-point scale), clinical outcome, duration of illness *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 **Time to follow-up:** Not reported
Jiang et al., 2020[3] **Country:** China **Funding source:** Scientific Research Project of Jiangsu Commission of Health (H2019065), Key Foundation of Wuhan Huoshenshan Hospital (2020[18]), Key Research & Development Program of Jiangsu Province (BE2018713), and Medical Innovation	**Study design:** Retrospective observational study by propensity score matching analysis **Objective:** To estimate the clinical efficacy and safety of CP treatment in COVID-19 patients.	**Inclusion criteria:** Patients with COVID-19 **Exclusion criteria**: Not reported **Number of participants:** Total number of participants, N = 326 CP group, n = 163 Control group, n = 163 **Mean age (SD), years:** CP group = 64.22 (12.42) Control group = 63.93 (14.25) P = 0.930 **Sex:** CP group: 44.17% females Control group: 68.71% females	**Intervention:** CP *Volume:* Not reported *Administration:* Not reported *Timing:* Not reported **Comparator:** Standard care	**Primary end point:** Discharge conditions (Cure, Improve, death or transfer to another hospital); duration of hospital stay **Time to follow-up:** Not reported

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Project of Logistics Service (18JS005).		P < 0.0001		
Moniuszko-Malinowska et al., 2020[5] **Country:** Poland **Funding source:** The Polish Association of Epidemiologists and Infectiologists and Medical University of Bialystok, Poland	**Study design:** Real-world retrospective observational study from the SARSTer database **Objective**: To study the effectiveness of CP in the treatment of COVID-19 in Poland.	Patients with confirmed COVID-19 based on positive RT-PCR test. **Inclusion criteria:** Cough, dyspnea or fever; typical lesions on Chest Xray or CT scan; need for continuous O2 therapy and SpO2 ≤ 94 any time after admission Patients who received CP within 7 days of onset of disease were considered for comparative analysis. **Number of participants:** Total number of CP recipients in the database, n = 78 Total number of participants, N = 1006 CP group, n = 55 (CP received within 7 days of disease onset) Remdesivir group, n = 236 Other drugs group, n = 715 **Mean age (SD), years:** CP group = 59.9 (18.2) Control group I = 58.6 (14.4) Control group II = 52.2 (21.5) **Sex:** CP group: 36.3% females Remdesivir group = 39.4% females Other drugs group = 46.8% females	**Intervention:** CP *Volume:* Among all CP recipients (n = 79) 55 patients received one unit (200-267 mL); and 24 patients received a second unit. *Timing: M*edian time from onset of symptoms to CP transfusion, days (SD) = 6.6 (9.7) – (Among all CP recipients) **Comparator:** *Control group I:* Remdesivir *Control group II:* Other medications including Tocilizumab (6%); dexamethasone (9.7%); chloroquine (43.7%); hydroxychloroquine (8.8%); lopinavir/ritonavir (28.2%); azithromycin (36%); fractioned heparin (43.6%)	**Outcomes:** Need for constant O2 therapy; duration of O2 therapy, need for artificial ventilation; duration of hospitalization; mortality; clinical improvement. *Clinical improvement definition:* Decrease of 2 points on the disease severity scale. *Disease severity scale:* Hospital discharge: 1 point; Not hospitalized but impaired activity and/or require O2 support: 2 points, Hospitalization with no supplemental oxygen or medical care: 3 points; Hospitalization not requiring oxygen support but requiring medical care (connected or not connected with COVID-19): 4 points; Hospitalization plus supplemental oxygen: 5 points; Hospitalization plus noninvasive ventilation or high-flow supplemental oxygen: 6 points; Hospitalization plus ECMO or invasive mechanical ventilation: 7 points; Death: 8 points

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
				Length of follow up: 28 days (assessment at days 7, 15, 21 and 28)
Altuntas et al., 2020[36] **Country:** Turkey **Funding source**: Non-funded	**Study design:** Retrospective observational **Objective:** To study the efficacy of CP in the treatment of severe and critically ill COVID-19 patients in Turkey	**Inclusion criteria:** Severe or critically ill patients with COVID-19. *Severe COVID-19* was defined as dyspnea, oxygen saturation level less than 93%, PaO_2: FiO_2 < 300; and > 50% progression of lung infiltrates within 24-48 hours. *Critical COVID-19* was defined as respiratory failure, septic shock, and/or multiple organ dysfunction Control group patients were with severe or critical illness and selected based on matching age, sex, comorbidity and concomitant medications. **Number of participants:** Total number of participants, N = 1776 CP group, n = 888 Control group, n = 888 **Median age (range), years:** CP group = 61 (19 to 96) Control group = 61 (21 to 91) P = 0.31 **Sex:** CP group: 30.6% females Control group: 28.6% females	**Intervention:** CP along with antiviral treatments *Dose*: NR *Administration*: NR *Volume:* Maximum volume administered was 600 mL (no standardized dosing reported) *Timing:* Among CP recipients whose data is available, 69 (11.3%) received CP within 5 days of symptom onset, 159 (25.9%) between 6-10 days, 171 (27.9%) between 11 to 15 days, 87 (14.2%) between 16 to 20 days and 127 (20.7%) after 20 days of symptom onset. **Comparator:** Standard care All patients received symptomatic control and supportive care including antivirals (Favipravir, Lopinavir+ Ritonavir). hydroxychloroquine, Azithromycin, and high dose vitamin C.	**Outcomes:** Duration of hospital stay, duration in ICU, rate of mechanical ventilation, case fatality rate. **Time to follow-up:** Not reported

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Liu et al., 2020[41] **Country: USA** **Funding source:** Internal funding from Mount Sinai Hospital and Icahn School of Medicine at Mount Sinai	**Study design:** Retrospective study with a propensity score-matched control group (selected using 1:4 ratio with replacement) **Objective:** To evaluate if treatment with CP early in the disease would reduce morbidity and mortality associated with COVID-19.	**Inclusion criteria for receiving CP:** Adult COVID-19 patients with severe or immediately life-threatening illness. *Severe COVID-19* was defined as dyspnea, respiratory rate ≥ 30 per minute, SaO_2 ≤ 93%, PaO_2: FiO_2 < 300; and >50% progression of lung infiltrates within 24-48 hours. *Life-threatening COVID-19* was defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure. CP recipients were matched with controls based on baseline characteristics (age, sex, smoking status, comorbidities, D dimer and C-reactive protein at admission), clinical status from the day of transfusion (O_2 requirement, length of hospital stay, SaO_2, heart rate, blood pressure respiratory rate), and chronological data up to the day of transfusion (ventilation requirement and duration and concomitant medications such as hydroxychloroquine and azithromycin) **Number of participants:** CP group, n = 39 Control group n = 156 **Mean age (SD), years:** CP group = 55 (13) Control group = 56 (14) **Sex:** CP group: 35.9 % females Control group: 28.85% females	**Intervention:** ABO compatible CP with a serum IgG titre ≥ 1:320 *Volume:* two units (about 250 mL each) *Administration:* infused over 1-2 hours, with monitoring every 15 min for adverse events *Timing:* Mean duration of hospitalization before transfusion: 4 days (range: 0 to 7 days) **Comparator**: Standard care Patients in both groups received symptomatic control and supportive care including therapeutic anticoagulants, antibiotics, hydroxychloroquine, antivirals, corticosteroids and other anti-inflammatory agents.	**Outcomes:** oxygenation status, in-hospital mortality. **Length of follow-up:** Until the end of study (May 1, 2020) Median follow up time in CP group was 11 days (range 1 to 28 days) and that in control group was 9 days (range: 0 to 31 days)
Rogers et al., 2020[38] **Country**: US **Funding source:** Non-funded	**Study design:** Retrospective observational with matched controls **Objective:** To describe the clinical outcomes of COVID-19 patients who received CP.	**Inclusion criteria:** *Inclusion criteria for receiving CP*: Adult patients with COVID-19 (confirmed or clinically suspected) admitted to an acute care facility with severe or life-threatening illness and had:	**Intervention:** ABO compatible CP *Volume:* Two units *Timing:* Median time from onset of symptoms to CP transfusion = 7 days (IQR: 5 to 9 days)	**Primary outcome:** All cause in-hospital mortality **Secondary outcome:** Time to hospital discharge

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		1) Symptom onset within 10 days prior, 2) supplemental O_2 (but not mechanical ventilation) and 3) no evidence of hypercoagulability (D-dimer < 1000 µg/L, no clinical signs of thrombosis) *Inclusion criteria for the control group*: Adult patients with a positive molecular test for COVID-19 who were admitted to the hospital and had 1) Symptom onset within 10 days prior to admission, 2)supplemental O_2 (but not mechanical ventilation) within 48 hours of hospitalization, and 3) no evidence of hypercoagulability (D-dimer <1000 µg/L within 48 hours of hospitalization). *Severe COVID-19* was defined as dyspnea, respiratory rate ≥ 30/min; SaO_2< 93%, PaO_2: FiO_2 < 300; and >50% progression of lung infiltrates within 24-48 hours. *Life-threatening COVID-19* was defined as respiratory failure, septic shock, and/or multiple organ dysfunction **Number of participants:** Total number of CP recipients: N = 241 CP group, n = 64 Control group, n = 177 **Median age (IQR), years:** CP group = 61 (47 to 70) Control group = 61 (50 to 75) P = 0.17 **Sex:** CP group: 42.2 % females Control group: 46.3% females P = 0.57	**Comparator:** Standard care Patients in both groups received symptomatic control and supportive care including antivirals, steroids and hydroxychloroquine	**Length of follow-up:** 28 days
Abolghasemi et al., 2020[35] **Country:** Iran	**Study design:** Prospective observational study	Adult patients with confirmed COVID-19 through laboratory (qRT-PCR) or CT imaging.	**Intervention:** ABO compatible CP, 500 mL (one unit) transfused over 4 hours, during the first	**Primary outcomes:** Patient survival and length of hospital stay

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding source: Baqiyatallah Medical Science University, Tehran, Iran Blood Transfusion Organization, Tehran, Iran and Darman Ara Company, Tehran, Iran.		**Inclusion Criteria:** Presence of some or all of disease clinical symptoms such as dyspnea, respiratory rate ≥20/ min, fever and cough; SpO_2 ≤ 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	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.	**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.
Xia et al., 2020[39] **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	**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 PaO_2 ≤ 300 mmHg. Chest imaging with obvious lesion progression over 24 to 48 hours >50% was also considered as severe.	**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)	**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
(Grant No. 18JS005) and Basic Research Program of Jiangsu Province (Grant No. BK20180036).		*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	**Comparator:** Standard care All patients received antivirals, traditional Chinese medicine and respiratory support.	
Duan et al., 2020[37] **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[43] 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[40] **Country:** China	**Study design:** Retrospective observational study	**Inclusion criteria:** Patients with COVID-19 (based on WHO interim guidance[43])	**Intervention:** CP therapy. Mean volume	**Outcomes measured:** Clinical outcomes,

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
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 Higher Education Institutions of China (No. 20B320028)	**Objective:** To analyze the efficacy of CP treatment in COVID-19 patients	**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.	300 mL (range 200 to 600 mL). **Comparator:** Standard care All patients received supportive care, antivirals, steroid and immunoglobulins as appropriate.	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.

BMI = Body Mass Index; COVID-19 = coronavirus disease; CHF: congestive heart failure; CP = convalescent plasma; CT = computerized tomography; DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenation; FiO^2 = fraction of inspired oxygen; IQR = interquartile range; PaO_2 = partial pressure of oxygen; PCR = polymerase chain reaction; RT = reverse transcriptase; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; S-RBD-specific IgG = S-receptor binding domain- specific immunoglobulin G; SpO_2 = oxygen saturation; 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[31]

Strengths	Limitations
Randomized controlled trials	
Libster et al. 2021[4]	
• 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 randomized allocation to intervention or control group. • The study participants and outcome assessors were blinded to the intervention (double blinded study) • The interventions of interest including dosage, timing 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. • Main study findings were reported with simple outcome data, estimates of random variability were reported and appropriate statistical tests were used. • Adverse events possibly related to the intervention were reported (there were none). • The authors used intention to treat analysis. 5 patients (3%) received CP or placebo after they had a primary end point event. One patient in the CP group did not receive CP due to hypoxemia. • Study participants were enrolled from multiple hospitals and geriatric centers in Argentina, increasing the representativeness. • Participants in the CP and control groups were enrolled from the same population over the same period of time, increasing the internal validity. • A sample size calculation was conducted and reported. • Conflicts of interest of the authors were reported (and there were no concerns).	• A list of potential confounders such as concomitant treatments were not reported. Although around 84% of patients used medications within 15 days prior to transfusion, additional details were not reported. • A secondary end point was added in later that included any of the other secondary end points alone or in combination. It was not planned at the study outset. • 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 study enrolled 76% of the target population. It is possible that the study was underpowered for the primary end point. Considering the uncertainties and lack of scientific knowledge in the minimal important difference of the outcome the internal validity of the results is unclear.
Simonovich et al. 2020[7]	
• The objectives of the study were clearly described. • There was randomized allocation to intervention or control groups. • The study participants and outcome assessors were blinded to the intervention (double-blinded study) • Well-described inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of the patients were reported in detail. • 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.	• It was reported that a sample size of 333 patients (222 in CP group and 111 in control group) were required to ensure adequate power. The study enrolled 334 patients with only 105 in placebo group. • Intention-to-treat analysis was not conducted. • Although the patients excluded from the study due to various reasons were described, it was unclear whether the patients excluded due to non-eligibility and those who declined to participate were different from the enrolled patients. • Participants in both groups received concomitant standard treatments including antivirals and steroids.

Strengths	Limitations
• The interventions of interest including dosage, volume and timing of CP and placebo were reported. Standard care given to both groups were described. • Potential confounders like age, comorbidities (e.g., diabetes, obesity), and trial site were adjusted for in the subgroup analyses. • Main study findings were reported with simple outcome data, estimates of random variability (95%CI, IQR) were reported and appropriate statistical tests were used. Actual probability values were reported for the primary outcome. • Important adverse events in both groups were reported and compared. • One patient in the control group were discontinued from study prior to intervention (withdrew consent). The analysis was conducted excluding that participant. • Study participants were enrolled from multiple hospitals in Argentina, increasing the representativeness. • Participants in the CP and control groups were enrolled from the same population over the same period of time, increasing the internal validity.	• Numerical values were reported inconsistently in different parts of the publication (tables versus text). • Conflicts of interest of the authors were not reported.
Agarwal et al. 2020[33]	
• 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 randomized allocation to intervention or control group. • The interventions of interest including dosage, timing 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 • Main study findings were reported with simple outcome data, estimates of random variability was reported and appropriate statistical tests were used. • The authors used intention to treat analysis to account for participants lost to follow up. Three patients (1%) were either lost to follow up or did not receive full dose of CP. • Adverse events possibly related to the intervention were reported. • Potential confounders like trial site and diabetes status were adjusted for in the analyses.	• This was an open-label study where the patients and treating clinicians were not blinded to the intervention. • The outcomes such as fatigue, and shortness of breath symptoms could be subjective, and the non-blinded assessment of them could have influenced the results. • About a third of patients admitted to the study sites and screened were enrolled in the study. It was unclear whether the patients excluded due to non-eligibility and those who declined to participate were different from the enrolled patients. • The antibody titre of the transfused CP and the serum antibody titre of the patients were not assessed prior to transfusion. When assayed retrospectively it was found that median antibody titre in the donor CP was 1:40 (IQR: 1:30 to 1:80) and the median antibody titre of participants at enrolment was 1:90 (IQR: 1:30 to 1:240). Therefore, the patients were transfused with CP with a lower antibody titre, than their own baseline levels. • Additionally, only 160 patients in the CP arm received CP with detectable levels of antibodies. According to the power calculation, the sample size required to detect significant effects if any was 226. • Participants in both groups received standard treatments including antivirals, steroids, and hydroxychloroquine, which may have contributed to the observed outcomes.

Strengths	Limitations
Li et al. 2020[32,34]	
• 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 • Conflicts 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.
Non-randomized studies	
Salazar et al. 2021 [6]	
• The objectives of the study were clearly described. • Well-described inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of all patients were reported in detail. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. Patients were followed up to the same time in both groups. • The interventions (including dosage, timing and the standard care given to both groups) were well described. • Potential confounders like age, severity of disease, comorbid conditions and other medications were addressed. Control group patients were selected based on two levels of propensity score matching which accounted for several confounders. Additional confounders were adjusted for in the multivariate analysis. • Two levels of propensity score matching were done to select controls based on predefined case control ratios and caliper width. The variables used to match cases and controls were reported and included the key known potential confounders • 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	• The study was observational in design with no randomized allocation or blinding. • Patients with a 60 day outcome were considered for the analysis. It was unclear whether the patients excluded due to this reason were different from the included patients. Excluded patients could have impacted the results and lowered the generalizability of results. • It was unclear whether testing of proportional hazards assumption was done prior to analyses. • Since the treatment group was defined based on exposure to treatment (CP), there was a risk of immortal time bias which was not corrected in the study with a time dependent variable. • Excluded patients could have impacted the results and lowered the generalizability of results. • There were a number of statistical comparisons performed without control for type 1 error; therefore, it is unclear if the statistically significant comparisons are valid or just due to the inflated type 1 error risk. • It was unclear whether a sample size calculation was performed.

Strengths	Limitations
tests were used) • Adverse events in the CP group were reported. • The authors recruited participants from seven hospitals, which were representative of the population, care and treatment of interest • Conflict of interest of the authors were reported (and there were no concerns)	
Alsharidah 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 and reported in detail. • The interventions of interest including dosage, timing, and the standard care given to both groups were described. • The distribution of potential confounders such as comorbidities, concomitant medications and demographics were similar between the groups. Adjusted analyses were conducted. • The outcomes of interest were reported with definitions. They were appropriate to the study. Patients were followed up to the same time in both groups • Incidence of adverse events was described. • 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. • Participants were recruited from four centers, over the same period and were representative of the population. • Conflicts of interest of the authors were reported (and there were no concerns).	• The study was prospective observational in design with no randomized allocation or blinding. • It was unclear whether the investigators conducted a sample size calculation. • It was unclear whether any patients were withdrawn from the study or lost to follow up. • Patients in the control group were not randomly selected. They were selected from the national registry based on disease severity and date of admission. It is possible that they were treated at a different hospital than their CP group counterparts. • Antibody titers in the transfused plasma were not measured
Dai et al. 2020[2]	
• Inclusion criteria were reported for the eligible patients. Baseline characteristics of the patients were reported. • The interventions of interest including dosage were described. • Adjusted subgroup analysis based on some confounders was conducted. • Participants of CP group and control group were recruited from same hospital over the same period of time. • Main study findings were reported with simple outcome data (medians and IQRs for the continuous outcomes, numbers and percentages for categorical outcomes) • Conflicts of interest of the authors were reported (and there were no concerns).	• The study was retrospective observational in design with no randomized allocation or blinding. • The objectives of the study were not clearly described. • Exclusion criteria for the study were not reported • The study outcomes and their definitions were not reported. The definitions for the outcome measures (e.g., “hospital transfer”) used to compare CP group and the control group were unclear. • Comparator was described as “conventional treatment” but no additional details were reported. • Potential confounders such as co-morbidities and concomitant medications were not adjusted for in the analysis. • Where comparative analyses were conducted, effect sizes (e.g., OR) or estimates of random variability (95% CI) were not reported. Actual P values were not reported for the outcomes. For clinical status outcomes, only descriptive results were reported. Statistical tests used for comparison were unclear.

Strengths	Limitations
	• The follow up time for patients in both groups was not reported. Without a specific follow up period, outcomes have limited clinical relevance. • It was unclear whether a sample size calculation was performed to ensure adequate power.
Jiang et al. 2020[3]	
• The objectives of the study were described. • Baseline characteristics of the patients were compared and reported. • Simple outcome data for the study outcomes were reported.	• The study was retrospective observational in design with no randomized allocation or blinding. • The study included a meta-analysis and was published as a letter to the editor Therefore, several reporting issues such as lack of clear methods and results sections were present. • The study outcomes and their definitions were not reported clearly. The definitions for the outcome measures (e.g., “cure”, “improve”) used to compare CP group and the control group were unclear. It was unclear whether they were determined a priori. It was unclear which outcome was considered primary. • Details of the intervention, such as dosage and administration of CP, were not reported. The details of standard care given to the control group patients were not reported. • Potential confounders such as co-morbidities and concomitant medications were not adjusted for in the analysis. • Where comparative analyses were conducted, effect sizes (e.g., OR) or estimates of random variability (95% CI) were not reported. Statistical tests used for comparison were unclear. • The number of patients lost to follow up, if any, were not reported. • The selection process of study participants was unclear. • Although reported as a propensity score matched study, no details about the matching process or the matched variables were reported. • The follow-up time for patients in both groups was not reported. Without a specific follow up period, outcomes have limited clinical relevance. • It was unclear whether a sample size calculation was performed to ensure adequate power.
Moniuszko-Malinowska et al. 2020[5]	
• The objectives of the study were clearly described. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. Patients were followed up to the same time in both groups • The details of the intervention of interest, including dosage and timing of CP therapy, were reported. Comparators of interest were described. • Main study findings were reported with simple outcome data. • Participants in the treatment and control groups were selected from a database from 30 centers in Poland over the same period of time. • Conflicts of interest of the authors were reported (and there were no concerns).	• The study was retrospective observational in design with no randomized allocation or blinding. • Baseline characteristics of the study participants were not reported other than mean age and sex. Potential confounders such as co-morbidities, other treatments received were not reported. • Inclusion and exclusion criteria for the control group participants were not reported. They were selected from a national database. There was no description of any matching process to identify controls. • Where comparative analyses were conducted, effect sizes (e.g., OR) or estimates of random variability (95% CI) were not reported. Actual probability values were not reported.

Strengths	Limitations
	• Characteristics of patients lost to follow up were not reported. The number of patients (if any) who discontinued treatment was unclear. • It was unclear whether a sample size calculation was performed.
Altuntas et al. 2020[36]	
• The objectives of the study were clearly described. • Well-described inclusion criteria were reported for the eligible patients. Baseline characteristics of the patients were compared and reported in detail. The distribution of potential confounders such as comorbidities, concomitant medications and demographics were similar between the groups. • Main study findings were reported with simple outcome data. Appropriate statistical tests were used. Actual probability values were reported when P value was < 0.001. • All patients who received a CP transfusion during the study period were included in the study, and a matched control group was selected based on predetermined variables. Patients were identified from a country-wide database in Turkey.	• The study was retrospective observational in design with no randomized allocation or blinding. • Exclusion criteria for the study were not reported • The main outcomes of the study were not reported in the introduction or methods section, and it was unclear whether they were determined a priori. It was unclear which outcome was considered primary. • Certain details of the intervention, such as dosage and administration of CP, were not reported. The study reported having no predetermined dosing schedule or volume of CP to be administered. • The follow-up time for patients in both groups was not reported. Without a specific follow up period, outcomes such as case fatality rate have limited clinical relevance. • Measures of distribution of outcomes (median, range etc.) were not clearly mentioned in tables and in the results section. • Adverse events in CP group and control group were not reported. • Participants in both groups received standard treatments including antivirals, hydroxychloroquine, or azithromycin. It is possible that the observed effects were due in part to these medications and immunoglobulins. • It was unclear whether the investigators conducted a sample size calculation to ensure adequate power.
Liu et al. 2020[41]	
• The hypothesis of the study was 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. • The interventions (including volume, administration and timing of CP) were well-described. • The study provided estimates of random variability for the data (mean, SD and ranges for the continuous outcomes, effect estimates and 95% confidence intervals). Actual probability values were reported when the P value was < 0.001. • The authors attempted to measure important adverse events. There were none. • The staff, places and facilities where the patients were treated were representative of the care majority of patients received.	• The study was observational in design with no randomized allocation or blinding. • The outcomes of interest were not reported in introduction or methods section and it was unclear if they were planned a priori. The authors reported the results of “worsening oxygenation” and worsening “clinical condition”, but the definitions of these outcomes were not reported and thus unclear. Simple outcome data of the study findings (e.g., oxygenation status) were not clearly reported in tabular form. • Although potential confounders were listed and matched using propensity-scores, variables like therapeutic anticoagulation were not equally distributed between the groups. Some important clinically relevant variables were not considered in matching (e.g., race and ethnicity, hypertension). • The distribution of confounders such as sex and diabetes status were different between the groups. Even though not reported as statistically significant, the differences in distribution could be clinically important. • Not all patients who applied to receive CP therapy received CP and thus were not included in the study. It is possible

Strengths	Limitations
	that these excluded patients were different from those included. Their characteristics were not reported. • The matched controls were different from the overall population of potential controls available from the study site (as evidenced by evidenced by the lack of overlap in the distribution of the logit of the propensity score) This lowered the generalizability of the results to the overall population with COVID-19. • Patients in the CP group and control group were not followed up for the same time. For outcomes such as mortality, varying follow up times between the groups lowered the internal validity of the results. • It was unclear whether proportional hazards assumption was tested for and met. Caliper width of the PS score for matching was not reported making drawing clinically relevant conclusions from the study challenging. • Since the treatment group was defined based on exposure to treatment (CP), there was a risk of immortal bias which was not corrected in the study with a time-dependent variable. • Lastly, even though the objective of the study was to evaluate the effects of "early" CP therapy, the median duration between hospitalization and CP transfusion was 4 days (range 0 to 7 days). • One of the co-authors had a potential conflict of interest related to a patent for an assay to select plasma donors.
Rogers et al. 2020[38]	
• 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. • The interventions (including volume and timing of CP) were well described. • Potential confounders like age, severity of disease, comorbid conditions and concomitant medications were addressed. Comparative analyses adjusting for potential confounders were done for the duration of hospital stay outcome. • 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 were reported when the P value was < 0.001, and appropriate statistical tests were used) • The incidence of adverse events in the CP group was described in detail. • The staff, places and facilities were representative of the care majority of patients receive. • Follow up data from patients in both groups were collected until 28-days from the day of admission.	• The study was observational in design with no randomized allocation or blinding. • The antibody index (AI) of the administered CP was not measured before administration. The AI measure used for subgroup analyses was based on retrospective assay of thawed samples, which was available for 88.9% of the CP units. Therefore, the specific characteristics of the intervention were unknown. • The study did not use random sampling. Among 82 patients who received CP at the study hospital, 64 were enrolled in the study based on the inclusion criteria. It is possible that the patients not included in the study were different from those who were included. • Participants in both groups received standard treatments including remdesivir, hydroxychloroquine and corticosteroids. Rates of corticosteroid use were significantly greater in the CP group compared to control group. It is possible that the observed effect was due to these medications leading to potential confounding. • It was unclear whether the investigators conducted a sample size calculation to determine the number of required participants to ensure adequate power. • The primary study author reported receiving grants from another company researching other potential therapeutics for COVID-19

Strengths	Limitations
Abolghasemi et al. 2020[35]	
• 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. • Potential confounders like age, comorbid conditions, baseline laboratory parameters, severity of disease and other medications were similar between the groups.	• 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.
Xia et al. 2020[39]	
• 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.

Strengths	Limitations
Duan et al. 2020[37]	
• 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), 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[40]	
• 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.	• 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.

Strengths	Limitations
• 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.	• 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; OR = odds ratio; 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
Randomized controlled trials	
Libster et al. 2021[4]	

A double-blinded placebo-controlled RCT to evaluate the effectiveness of CP therapy in elderly patients with mild COVID-19.
CP group, n = 80; Control group, n = 80
 	
There were no significant differences in demographics, clinical characteristics, or comorbidities between the groups.
 	
Study findings:
• **Severe respiratory disease**
  ○ CP group, n (%) = 13 (16)
  ○ Control group, n (%) = 25 (31)
  ○ Relative risk (95% CI) = 0.52 (0.29 to 0.94); P = 0.03
  ○ Time to development of severe respiratory disease
  ○ CP group, median (IQR) = 15 days (15 to 15)
  ○ Control group, median (IQR) = 15 days (9 to 15)
  ○ P = 0.03
  ○ Number needed to treat to avoid one episode of severe illness = 7 (95% CI = 4 to 50)
• **Life threatening respiratory disease**
  ○ CP group, n (%) = 4 (5)
  ○ Control group, n (%) = 10 (12)
  ○ Relative risk (95% CI) = 0.40 (0.13 to 1.22)
• **Oxygen supplementation at FiO2 of 100%**
  ○ CP group, n (%) = 4 (5)
  ○ Control group, n (%) = 6 (8)
  ○ Relative risk (95% CI) = 0.67 (0.20 to 2.27)
• **Noninvasive ventilation**
  ○ CP group, n (%) = 1 (1)
  ○ Control group, n (%) = 6 (8)
  ○ Relative risk (95% CI) = 0.17 (0.02 to 1.35)
• **ICU admission**
  ○ CP group, n (%) = 2 (2)
  ○ Control group, n (%) = 6 (8)
  ○ Relative risk (95% CI) = 0.33 (0.07 to 1.60)
• **Mechanical ventilation**
  ○ CP group, n (%) = 2 (2)
  ○ Control group, n (%) = 4 (5)
  ○ Relative risk (95% CI) = 0.50 (0.09 to 2.65)
• **Critical systemic illness**
  ○ CP group, n (%) = 5 (6)
  ○ Control group, n (%) = 6 (8)
  ○ Relative risk (95% CI) = 0.83 (0.27 to 2.62)
• **Acute respiratory failure**
  ○ CP group, n (%) = 2 (2)
  ○ Control group, n (%) = 5 (6)
  ○ Relative risk (95% CI) = 0.40 (0.08 to 2.00)
• **Shock**
  ○ CP group, n (%) = 2 (2)
	"In our randomized, controlled trial, the administration of high-titer convalescent plasma against SARS-CoV-2 to infected older adults within 72 hours after the onset of mild symptoms reduced the progression of Covid-19 to severe illness. This simple and inexpensive intervention can reduce demands on the health care system and may save lives. Early infusions of convalescent plasma can provide a bridge to recovery for at-risk patients until vaccines become widely available. (p. 8)"[4]

Main study findings	Authors' conclusion
○ Control group, n (%) = 1(8) ○ Relative risk (95% CI) = 2.00 (0.19 to 21.6) • **Multiple organ dysfunction syndrome** ○ CP group, n (%) = 3 (4) ○ Control group, n (%) = 5 (6) ○ Relative risk (95% CI) = 0.60 (0.15 to 2.43) • **Death from COVID-19** ○ CP group, n (%) = 2 (2) ○ Control group, n (%) = 4 (5) ○ Relative risk (95% CI) = 0.50 (0.09 to 2.65) • **Life-threatening respiratory disease, critical systemic illness, or death, alone or in combination:** ○ CP group, n (%) = 7 (9) ○ Control group, n (%) = 12 (15) ○ Relative risk (95% CI) = 0.58 (0.24 to 1.41) **Adverse events in the CP group, n = 0** **Adverse events in the Control group, n = 0** **Solicited adverse events included volume overload, allergic reaction, thrombophlebitis, vasovagal syndrome, hematoma at site, nerve injury and tetany (hyperventilation).**	
Simonovich et al. 2020[7]	
A double-blinded placebo-controlled RCT to evaluate the effectiveness of CP therapy in patients with severe COVID-19 pneumonia. CP group, n = 228; Control group, n = 105 Baseline characteristics such as demographics, comorbidities, previous medications used, laboratory values were comparable between the groups. **Study findings:** **Clinical status at Day 30, n (%)** • **Death** ○ CP group: 25 (11%); Control group: 12 (11.4%) • **Invasive ventilatory support** ○ CP group: 19 (8.3%); Control group: 10 (9.5%) • **Hospitalized with supplemental oxygen requirement** ○ CP group: 5 (2.2%); Control group: 2 (1.9%) • **Hospitalized without supplemental oxygen requirement** ○ CP group: 8 (3.5%); Control group: 1 (1%) • **Discharged without full return to baseline physical function** ○ CP group: 30 (13.2); Control group: 8 (7.6) • **Discharged with full return to baseline physical function** ○ CP group: 141 (61.8); Control group: 72 (68.6) • **Overall OR (95% CI) = 0.81 (0.50 to 1.31); P = 0.396** **Secondary outcomes reported as median time from intervention to outcome in days, (IQR):** • **Time to hospital discharge** ○ CP group: 13 (8 to 30); Control group: 12 (7 to ND) ○ Subhazard ratio (95% CI) = 1 (0.76 to 1.32) • **Time to discharge from the ICU** ○ CP group: ND (8 to ND); Control group: ND (6 to ND) ○ Subhazard ratio (95% CI) = 0.94 (0.48 to 1.82)	"In our trial, the use of convalescent plasma therapy in addition to standard treatment in patients with severe pneumonia due to Covid-19 did not reduce mortality or improve other clinical outcomes at day 30 as compared with placebo. We believe the use of convalescent plasma as a standard of care in such patients should be reevaluated. Further studies regarding antibody therapy may be best focused on other populations or on interventions with other types of preparations, such as intravenous immunoglobulin or anti-SARS-CoV-2 monoclonal antibodies. (p.9)"[7]

Main study findings	Authors' conclusion

• **Time to complete restoration of physical function**
  ○ CP group: 15 (9 to ND); Control group: 15 (7 to ND)
  ○ Subhazard ratio (95% CI) = 0.89 (0.66 to 1.18)
• **Time to start of invasive ventilation**
  ○ CP group: ND (9 to ND); Control group: ND
  ○ Subhazard ratio (95% CI) = 1.14 (0.72 to 1.81)
• **Time to death**
  ○ CP group: ND; Control group: ND
  ○ Subhazard ratio (95% CI) = 0.93 (0.47 to 1.86)
• **Time to improvement of 2 categories in the ordinal outcome or hospital discharge within 30 days**
  ○ CP group: 12 (7 to 29); Control group: 12 (6 to ND)
  ○ Subhazard ratio (95% CI) = 1 (0.76 to 1.32)
 	
Clinical status at Day 7, n (%)
• **Death**
  ○ CP group: 3 (1.3%); Control group: 4 (3.8%)
• **Invasive ventilatory support**
  ○ CP group: 53 (23.3%); Control group: 21 (20%)
• **Hospitalized with supplemental oxygen requirement**
  ○ CP group: 66 (29%); Control group: 34 (32.4%)
• **Hospitalized without supplemental oxygen requirement**
  ○ CP group: 57 (25%); Control group: 14 (13.3%)
• **Discharged without full return to baseline physical function**
  ○ CP group: 16 (7); Control group: 4 (3.8)
• **Discharged with full return to baseline physical function**
  ○ CP **group: 33 (14**.5); Control group: 28 (26.7)
• **Overall OR (95% CI) = 0.88 (0.58 to 1.34)**
 	
Clinical status at Day 14, n (%)
• **Death**
  ○ CP group: 7 (3.1%); Control group: 7 (6.7%)
• **Invasive ventilatory support**
  ○ CP group: 38 (16.7%); Control group: 18 (17.1%)
• **Hospitalized with supplemental oxygen requirement**
  ○ CP group: 27 (11.8%); Control group: 10 (9.5%)
• **Hospitalized without supplemental oxygen requirement**
  ○ CP group: 25 (11%); Control group: 7 (6.7%)
• **Discharged without full return to baseline physical function**
  ○ CP group: 24 (10.5); Control group: 11 (10.5)
• **Discharged with full return to baseline physical function**
  ○ CP group: 107 (46.9); Control group:52 (49.5)
• **Overall OR (95% CI) = 1.00 (0.65 to 1.55)**
 	
Adverse events, n (%)
• **Any event**
  ○ CP group: 153 (67.1); Control group: 66 (62.9)
  ○ OR (95% CI) = 1.21 (0.74 to 1.95)
• **Serious event**
  ○ CP group: 54 (23.7); Control group: 19 (18.1)
  ○ OR (95% CI) = 1.40 (0.78 to 2.51)
  ○ **Infusion related event**
  Different values were reported in the text and tables in this publication.
  Values in the text:
  ▪ CP group: 11 (4.8); Control group: 2 (1.9)	

Main study findings	Authors' conclusion
▪ OR (95% CI) = 2.62 (0.57 to 12.04) **Values in the tables:** ▪ CP group: 13 (5.7); Control group: 2 (1.9) ▪ OR (95% CI) = 3.13 (0.69 to 14.11) • **Infusion related events were:** CP group: Non-hemolytic febrile reaction, n = 5; Allergic reaction, n = 4; Unexplained event, n = 1; Technical resolution event, n = 1 Control group: Allergic reaction, n = 2	
Agarwal et al. 2020[33]	
An open label RCT to evaluate the effectiveness of CP therapy compared to standard care alone in moderately ill COVID-19 patients. CP group, n = 235; Control group, n = 229 There were no significant differences in demographics, clinical characteristics, comorbidities (except diabetes, which was significantly more prevalent in the CP group) and concomitant medications between the groups. Significantly more patients in the control group reported the symptom cough compared to the CP group. **Study findings:** • **All-cause mortality at 28 days or progression to severe disease:** ○ CP group, n (%) = 44 (19) ○ Control group, n (%) = 41 (18) ○ Unadjusted Risk Difference RD (95% CI) = 0.008 (–0.062 to 0.078) ○ Unadjusted risk ratio (RR) (95% CI) = 1.04 (0.71 to 1.54) ○ Adjusted RR (95% CI) = 1.07 (0.73 to 1.58) ○ (adjusted for study site and diabetes status) • Resolution of symptoms on day 7 *(N = number with symptoms at baseline):* ○ *Shortness of breath, n (%); N = 362* ▪ CP group = 140 (76%); Control group = 119 (66%) ▪ RR (95% CI) = 1.16 (1.02 to 1.32) ○ *Fever, n (%); N = 138* ▪ CP group = 66 (98%); Control group = 65 (92%) ▪ RR (95% CI) = 1.08 (0.99 to 1.16) ○ *Cough, n (%); N = 274* ▪ CP group = 102 (80%); Control group = 111 (76%) ▪ RR (95% CI) = 1.06 (0.94 to 1.2) ○ *Fatigue, n (%); N = 306* ▪ CP group = 114 (73%); Control group = 92 (60%) ▪ RR (95% CI) = 1.21 (1.02 to 1.42) • Negative seroconversion of SARS-CoV-2 RNA, n (%) ○ *Day 3:* ▪ CP group = 79 (43%); Control group = 67 (37%) ▪ RR (95% CI) = 1.2 (0.9 to 1.5) ○ *Day 7:* ▪ CP group = 117 (68%); Control group = 93 (55%) ▪ RR (95% CI) = 1.2 (1.04 to 1.5) • **Duration of hospital stay, median (IQR):** ○ CP group = 14 (10 to 19); Control group = 13 (10 to 18) ○ P = 0.2 • **Duration of respiratory support, median (IQR):** ○ CP group = 6 (3 to 9); Control group = 6 (4 to 10) ○ P = 0.5 • **Type of mechanical ventilation needed during hospital stay, n (%):** ○ Invasive ventilation:	"Although the use of convalescent plasma seemed to improve resolution of shortness of breath and fatigue in patients with moderate covid-19 and led to higher negative conversion of SARS-CoV-2 RNA on day 7 post-enrolment, this did not translate into a reduction in 28 day mortality or progression to severe disease. Areas of future research could include effectiveness of convalescent plasma among neutralising antibody negative patients and the use of convalescent plasma with high neutralising antibody titres. The challenge will be to find both suitable patients and suitable plasma donors. Additionally, this challenge could limit the use of convalescent plasma to a small subset of patients." (p. 9) [33]

Main study findings	Authors' conclusion
▪ CP group = 19 (8); Control group = 19 (8) ▪ RR (95% CI) = 0.99 (0.54 to 1.81) ○ *Non-invasive ventilation:* ▪ CP group = 31 (14); Control group = 37 (16) ▪ RR (95% CI) = 0.8 (0.5 to 1.3) • **Vasopressor support, n (%):** ○ CP group = 10 (4); Control group = 8 (4) ○ RR (95% CI) = 1.2 (0.5 to 3.05) **Adverse events:** **CP group:** ○ In three patients (1%) death was "possibly related" to CP transfusion. ○ Pain at infusion site, chills, nausea, bradycardia and dizziness, n = 1 ○ Fever and tachycardia, n = 3 ○ Dyspnea and blockage of intravenous catheter, n =2 **Control group:** Not reported.	
Li et al. 2020[32,34]	
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 severity of disease or 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) = 1.85 (0.83 to 4.10)[a] ○ P value = 0.13 ○ Median time from hospitalization to discharge, days ▪ CP group: 41.00 (IQR 31 to indeterminate)	"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."[32] (p. E10)

Main study findings	Authors' conclusion
▪ Control group: 53.00 (IQR 35.00 to indeterminate) ▪ HR = 1.68 (0.92 to 3.08) ▪ P value = 0.09 • **Patients with severe disease** ○ CP group: 21/23 (91.3%) ○ Control group:15/22 (68.2%) ○ OR (95%CI) = 4.90 (0.89 to 26.97)[a] ○ 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) • **Patients with life-threatening disease** ○ CP group: 5/28 (17.9%) ○ Control group:3/28 (10.7%) ○ OR (95%CI) = 1.81 (0.39 to 8.44)[a] ○ 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) = 0.59 (0.22 to 1.59)[a] ○ P value = 0.30 • **Patients with severe disease** ○ CP group: 0/23 ○ Control group: 2/22 (9.1%) ○ P value = 0.23 • **Patients with life-threatening disease** ○ CP group: 8/28 (28.6%) ○ Control group:10/28 (35.7%) ○ OR (95%CI) = 0.72 (0.23 to 2.22)[a] ○ P value = 0.57 **Viral nucleic acid negative rate, n/N (%)** • **All patients:** ○ At 24 hours ▪ 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 24 hours ▪ CP group**:** 7/21 (33.3%) ▪ Control group: 2/17 (11.8 %)	

Main study findings	Authors' conclusion
▪ 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%) ▪ 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	
Non-randomized studies	
Salazar et al. 2021[6]	
A prospective propensity-score matched study comparing the efficacy of CP therapy and standard care in patients with COVID-19. Total number of CP recipients: N = 351; Total number of patients not-transfused, n = 4,944 After propensity score matching: CP group, n=341; Control group, n=594 **Baseline characteristics:** There were no significant differences between groups in the following baseline characteristics: age, sex, baseline laboratory results, vital signs, baseline clinical features, comorbidities, and concomitant medications. **BMI ≥ 40 kg/m^2, n (%)** *Secondary matched, all plasma titers* ○ CP group = 45 (13.2); Control group = 108 (18.2); P = 0.047 *Secondary matched, plasma titer ≥ 1:1350* ○ CP group = 47 (14.6); Control group = 97 (16.7); P = 0.43 **Baseline ventilation status, n (%)** *Secondary matched, all plasma titers* **Room air**: CP group = 0; Control group = 23 (3.9) Supplemental O2: CP group = 294 (86.2); Control group = 538 (90.6) Mechanical ventilation: CP group = 21 (6.2); Control group = 33 (5.6) P = 0.04 *Secondary matched, plasma titer ≥ 1:1350* Room air: CP group = 24 (7.5); Control group = 19 (3.93) Supplemental O2: CP group = 282 (87.9); Control group = 539 (92.6)	"To summarize, this propensity score-matched analysis of a large patient cohort confirms and extends our previous findings and suggests that transfusion of convalescent plasma containing high-titer anti-RBD IgG early in hospitalization reduces mortality in COVID-19 patients. (p.101)"[6]

Main study findings	Authors' conclusion
Mechanical ventilation: CP group = 15 (4.7); Control group = 24 (4.1) P = 0.02 **Interleukin-6 (pg/mL) median (IQR)** *Secondary matched, all plasma titers* ○ CP group = 63.5 (28.5 to **133**); Control group = 52.5 (20 to 125); P = 0.03 *Secondary matched, plasma titer ≥ 1:1350* ○ CP group = 59 (28 to 123.5); Control group = 52 (20.5 to 122.5); P = 0.17 **D-dimer (µg/mL FEU) median (IQR)** *Secondary matched, all plasma titers* ○ CP group = 0.8 (0.6 to 1.5); Control group = 1.1 (0.6 to 2.0); P = 0.004 *Secondary matched, plasma titer ≥ 1:1350* ○ CP group = 0.8 (0.6 to 1.5); Control group = 1.0 (0.6 to 1.7); P = 0.06 **Study findings** *Secondary matched, all plasma titers* • **60-day mortality** "Kaplan-Meier curves showed significantly decreased mortality within 60 days after day 0 in the transfused cohort relative to propensity score-matched controls (P = 0.02) (data not shown). (p.96)"[6] "Mortality was not significantly different within 60 days after day 0 between cases and controls in patients who were intubated at day 0 or in patients who were transfused >72 hours after admission, even when the analysis was restricted to patients who received plasma with an anti-RBD IgG titer of ≥ 1:1350. (p.96-97)"[6] ***Secondary matched, plasma titer ≥ 1:1350*** **Disposition at 60 days** **Death** ○ CP group: 20 (6.2%); Control group: 73 (12.5%) ○ Risk ratio (95% CI) = 2.15 (1.30 to 3.54); P = 0.003 **Still admitted** ○ CP group: 5 (1.6%); Control group: 6 (1%) ○ Risk ratio (95% CI) = 0.71 (0.19 to 2.56); P = 0.003 **Discharged (base outcome)** ○ CP group: 296 (92.2%); Control group: 503(86.4%) **Overall mortality within 28 days, n (%)** ○ CP group: 12 (3.7%); Control group: 57 (9.8%) ○ Risk ratio (95% CI) = 2.62 (1.46 to 4.70); P = 0.001 **Overall mortality within 60 days, n (%)** ○ CP group: 20 (6.2%); Control group: 72 (12.4%) ○ Risk ratio (95% CI) = 1.99 (1.25 to 3.15; P = 0.004 **Duration of hospital stay in days, median (IQR)** ○ CP group: 5.9 (3.2 to 11.7); Control group: 5.9 (3.1 to 12.9) ○ Point estimate (95% CI) = –0.15 (–1.82 to 1.52); P = 0.86 **Requirement of ICU after day 0, n (%)** ○ CP group: 106 (33%); Control group: 190 (32.6%) ○ Risk ratio (95% CI) = 0.99 (0.84 to 1.16); P = 0.89 **Duration of ICU stay in days, mean (SD)** ○ CP group: 12.7 (13.6); Control group: 11.6 (12.3) ○ Point estimate (95% CI) = –1.07 (–4.01 to 1.88); P = 0.48	

Main study findings	Authors' conclusion
Required mechanical ventilation after day 0, n (%) ○ CP group: 46 (14.3%); Control group: 105 (18%) ○ Risk ratio (95% CI) = 1.26 (0.97 to 1.63); P = 0.08 **Duration of mechanical ventilation in days, mean (SD)** ○ CP group: 27.1 (25.4); Control group: 17.9 (16.2) Point estimate (95% CI) = –9.15 (–16.91 to –1.38); P = 0.02 **Required supplemental O_2 after day 0, n (%)** ○ CP group: 299 (93.1%); Control group: 527 (90.5%) ○ Risk ratio (95% CI) = 0.99 (0.99 to 0.99); P <0.001 **Duration of supplemental O_2 in days, mean (SD)** ○ CP group: 6.3(6.9); Control group: 6.5 (7.1) ○ Point estimate (95% CI) = 0.23 (–0.65 to 1.12); P = 0.61 **Ventilation status at day 0, n (%)** Room air (base outcome) ○ CP group: 27 (8.4%); Control group: 54 (9.3%) Low flow O_2 ○ CP group: 196 (61.1%); Control group: 353 (60.7%) ○ Risk ratio (95% CI) = 0.90 (0.55 to 1.48); P = 0.68 High flow O_2 ○ CP group: 85 (26.5%); Control group: 149 (25.6%) ○ Risk ratio (95% CI) = 0.90 (0.53 to 1.54); P = 0.70 Mechanical ventilation ○ CP group: 12 (3.7%); Control group: 24 (4.1%) ○ Risk ratio (95% CI) = 0.87 (0.41 to 1.83); P = 0.70 ECMO ○ CP group: 1 (0.3%); Control group: 2 (0.3%) ○ Risk ratio (95% CI) = 0.52 (0.07 to 3.89); P = 0.52 Death ○ CP group:0; Control group: 0 **Ventilation status at day 7, n (%)** Room air (base outcome) ○ CP group: 193 (60.1%); Control group: **339** (58.2%) Low flow O^2 ○ CP group: 42 (13.1%); Control group: 63 (10.8%) ○ Risk ratio (95% CI) = 0.85 (0.56 to 1.31); P = 0.47 High flow O_2 ○ CP group: 49 (15.3%); Control group: 102 (17.5%) ○ Risk ratio (95% CI) = 1.19 (0.85 to 1.65); P = 0.31 Mechanical ventilation ○ CP group: 33 (10.3%); Control group: 62 (10.7%) ○ Risk ratio (95% CI) = 1.07 (0.76 to 1.51); P = 0.70 ECMO ○ CP group: 2 (0.6%); Control group: 4 (0.7%) ○ Risk ratio (95% CI) = 1.14 (0.21 to 6.26); P = 0.88 Death ○ CP group: 2 (0.6%); Control group: 12 (2.1%) ○ Risk ratio (95% CI) = 3.42 (0.75 to 15.52); P = 0.11 **Ventilation status at day 14, n (%)** Room air (base outcome)	

Main study findings	Authors' conclusion
◦ CP group: 261(81.3%); Control group: 435 (74.7%) Low flow O_2 ◦ CP group: 8 (2.5%); Control group: 31 (5.3%) ◦ Risk ratio (95% CI) = 2.33 (1.11 to 4.86); P = 0.03 High flow O_2 ◦ CP group: 17(5.3%); Control group: 23 (4.0%) ◦ Risk ratio (95% CI) = 0.81 (0.43 to 1.52); P = 0.51 Mechanical ventilation ◦ CP group: 28 (8.7%); Control group: 59 (10.1%) ◦ Risk ratio (95% CI) = 1.26 (0.84 to 1.90); P = 0.26 ECMO ◦ CP group: 1 (0.3%); Control group: 4 (0.7%) ◦ Risk ratio (95% CI) = 2.40 (0.27 to 21.65); P = 0.44 Death ◦ CP group: 6 (1.9%); Control group: 30 (5.2%) ◦ Risk ratio (95% CI) = 3.00 (1.22 to 7.37); P = 0.02 **Ventilation status at day 28, n (%)** Room air (base outcome) ◦ CP group: 285(88.8%); Control group: 478 (82.1%) Low flow O_2 ◦ CP group: 4 (1.2%); Control group: 9 (1.5%) ◦ Risk ratio (95% CI) = 1.34 (1.11 to 4.86); P = 0.63 High flow O_2 ◦ CP group: 17(5.3%); Control group: 23 (4.0%) ◦ Risk ratio (95% CI) = 0.81 (0.4 to 4.44); P = 0.64 Mechanical ventilation ◦ CP group: 17 (5.3%); Control group: 30(5.2%) ◦ Risk ratio (95% CI) = 1.05 (0.60 to 1.84); P = 0.86 ECMO ◦ CP group: 1 (0.3%); Control group: 3 (0.5%) ◦ Risk ratio (95% CI) = 1.79 (0.18 to 17.34); P = 0.62 Death ◦ CP group: 12 (3.74%); Control group: 57 (9.8%) ◦ Risk ratio (95% CI) = 2.83 (1.54 to 5.22); P = 0.001 **Ventilation status at day 60, n (%)** Room air (base outcome) ◦ CP group: 296 (92.6%); Control group: 201(86.1%) Low flow O_2 ◦ CP group: 0; Control group: 1 (0.2%) ◦ Risk ratio (95% CI) = not determinable High flow O_2 ◦ CP group: 0; Control group: 0 ◦ Risk ratio (95% CI) = not determinable Mechanical ventilation ◦ CP group: 5 (1.6%); Control group: 8(1.4%) ◦ Risk ratio (95% CI) = 0.95 (0.29 to 3.11); P = 0.93 ECMO ◦ CP group: 0; Control group: 0	

Main study findings	Authors' conclusion
○ Risk ratio (95% CI) = not determinable Death ○ CP group: 20 (6.2%); Control group: 72 (12.4%) ○ Risk ratio (95% CI) = 2.13 (1.29 to 3.50); P = 0.003 **Clinical improvement at day 7, n (%) (relative to day 0)** ○ CP group: 206 (64.2%); Control group: **333** (57.2%) ○ Risk ratio (95% CI) = 0.89 (0.81 to 0.98); P = 0.02 **Clinical improvement at day 14, n (%) (relative to day 0)** ○ CP group: 266 (82.9%); Control group: 428 (73.5%) ○ Risk ratio (95% CI) = 0.89 (0.83 to 0.95); P <0.001 **Clinical improvement at day 28, n (%) (relative to day 0)** ○ CP group: 289 (90%); Control group: 461 (79.2%) ○ Risk ratio (95% CI) = 0.88 (0.83 to 0.93); P <0.001 **Clinical improvement at day 60, n (%) (relative to day 0)** ○ CP group: 296 (92.2%); Control group: 482 (82.8%) ○ Risk ratio (95% CI) = 0.90 (0.85 to 0.94); P <0.001 **Adverse events in the CP group**: Among all CP recipients (n = 351) Mild allergic reaction (transient rash), n = 5 Transient worsening of shortness of breath (resolved with treatment), n = 1 Possible TACO (resolved with treatment), n= 1 **Adverse events in the Control group:** Not reported	
Alsharidah et al. 2020[1]	
A prospective observational study to evaluate the efficacy and safety of CP therapy compared to standard care alone. Total number of participants, N=368 CP group, n=135; Control group, n=233 There were no significant differences in demographics, baseline laboratory results, severity of disease, or concomitant treatment between the groups. **Study findings:** **Clinical improvement at 30 days, n (%)** • **All patients**: ○ CP group: 100 (80.6%) ○ Control group: 133 (58.6%) ○ Adjusted HR (95% CI) = 1.9(1.4 to 2.7); P <0.001 ○ Median time to improvement, days (IQR) ▪ CP group: 7 (5 to 9) ▪ Control group: 10 (6 to 15) ▪ P <0.001 • **Patients with moderate disease** ○ CP group: 77 (86.5%) ○ Control group:106 (68.4%) ○ Adjusted HR (95% CI) = 1.9 (1.3 to 2.8); P = 0.001 ○ Median time to improvement, days (IQR) ▪ CP group: 7 (4 to 9) ▪ Control group: 8 (6 to 12) ▪ P = 0.006 • **Patients with severe disease** ○ CP group: 28 (60.8%) ○ Control group:27 (34.6%) ○ Adjusted HR (95% CI) = 2.5 (1.2 to 5.2); P = 0.012	In our prospective interventional study including patients with moderate and severe COVID-19, CCP administration was significantly associated with improved clinical outcomes. Thirty-day survival was significantly improved in the moderate group. In addition, administration of CCP in both moderate and severe cases was also associated with improved oxygen saturation, and recovery of lymphocytes and CRP levels. Larger multicenter controlled randomized trials to further evaluate the effectiveness of CCP in COVID-19 patients with particular emphasis on CCP donor qualification based on neutralizing antibody levels are warranted. (p.445)"[1]

Main study findings	Authors' conclusion
○ Median time to improvement, days (IQR) ▪ CP group: 7 (5 to 12) ▪ Control group: 15.5 (10 to 20) ▪ P = 0.003 **Mortality at 28 days, n (%)** • **All patients:** ○ CP group: 24 (17.8%) ○ Control group: 90 (38.8%) ○ Adjusted OR (95%CI) = 0.32 (0.18 to 0.58) ○ P value = 0.001 • **Patients with moderate disease** ○ CP group: 10 (11.4%) ○ Control group: 46 (29.7%) ○ Adjusted OR (95%CI) = 0.27 (0.12 to 0.62) ○ P value = 0.02 • **Patients with severe disease** ○ CP group: 14(30.4%) ○ Control group:44 (57.1%) ○ OR (95% CI) = 0.38 (0.14 to 1.02) ○ P value = 0.06 **Oxygen saturation at 14 days:** "Relative to baseline, CCP treatment improved oxygen saturation by 5.4% [95% CI 3.3–7.4] on day 1 and 4.1% [95% CI 2.3– 5.9] on day 3 in patients with moderate disease, but not among those with severe disease. (p.443)" [1] **Adverse events in the CP group:** ○ Allergic skin reaction, n = 3 (all three resolved) **Adverse events in the CP group:** Not reported	
Dai et al. 2020[2]	
A retrospective observational study to evaluate the efficacy and safety of CP therapy compared to standard care alone among patients with diabetes. Total number of participants, N=367 CP group, n=39; Control group, n = 328 **Study findings:** **Clinical improvement (one-point reduction), n (%)** ○ CP group: 27 (69.2%); Control group: 80 (24.4%) ○ **Mean time to improvement, days (range)** ▪ CP group: 10 (1 to 28); Control group: 17 (1 to 45) ▪ P <0.001 **Clinical improvement (two-point reduction), n (%)** ○ CP group: 11 (28.2%); Control group: 9 (2.7%) ○ **Mean time to improvement, days (range)** ▪ CP group: 14 (1 to 28); Control group: 27 (2 to 39) ▪ P <0.05 **Clinical outcome, n (%)** • **Death** ○ CP group: 3 (7.69%); Control group: 12 (3.66%) • **Discharge** ○ CP group: 35 (89.74%); Control group: 288 (87.80%) • **Hospitalization (transfer)** ○ CP group: 1 (2.56%); Control group: 28 (8.23%)	"CPT was an efficacious and beneficial therapy for COVID‐19 patients with DM, including those with a severe or critical illness. Obvious adverse effects were not observed during the CPT process. The latter significantly improved the clinical outcomes of COVID‐19 patients with DM compared with that in COVID‐19 patients with DM receiving conventional treatment. (p.9)"[2]

Main study findings	Authors' conclusion

• **Duration of illness, median (range)**
  ○ CP group: 24 (7 to 62); Control group: 14 (4 to 47)
 	
Subgroup analysis of matched patients (age, sex and disease severity): CP group, n = 39; Control group, n = 39
 	
Clinical improvement (one-point reduction), n (%)
  ○ CP group: 27 (69.2%); Control group: 14 (35.9%)
  ○ Mean time to improvement, days (range)
  ▪ CP group: 10 (1 to 28); Control group: 18 (5 to 35)
  ▪ P <0.01
 	
Clinical improvement (two-point reduction), n (%)
  ○ CP group: 11 (28.2%); Control group: 2 (5.1%)
  ○ Mean time to improvement, days (range)
  ▪ CP group: 14 (1 to 28); Control group: 38 (37 to 39)
  ▪ P <0.01
 	
Clinical outcome (%)
• **Death**
  ○ CP group: 7.7%; Control group: 10.2%
• **Discharge**
  ○ CP group: 92.3%; Control group:74.4%
• **Hospitalization (transfer)**
  ○ CP group:0; Control group: 15.4
 	
Subgroup analysis of matched noncritical patients (age, sex and disease severity):
CP group, n = 29; Control group, n = 29
 	
Clinical improvement (one-point reduction), n (%)
  ○ CP group: 25 (86.2%)
  ○ Control group: 10 (34.5%)
  ○ Mean time to improvement, days (range)
  ▪ CP group: 10 (1 to 28); Control group: 20 (5 to 27)
  ▪ P <0.001
 	
Clinical improvement (two-point reduction), n (%)
  ○ CP group: 5 (37.9%) (Note: This value was reported in the publication; however, the percentage calculation appears to be arithmetically incorrect since 5/29 = 17.2%)
  ○ Control group: 2 (6.9%)
  ○ Mean time to improvement, days (range)
  ▪ CP group: 8 (3 to 15); Control group: 29 (18 to 39)
  ▪ P – NS
 	
Clinical outcome, n (%)
• **Death**
  ○ CP group: 0; Control group:0
 	
• **Discharge**
  ○ CP group: 100%; Control group:74.4%
 	
• **Hospitalization (transfer)**
  ○ CP group:0; Control group: 3.4%
 	
Adverse events in the CP group: "No obvious adverse events"
 	
Adverse events in the CP group: Not reported	

Main study findings	Authors' conclusion
Jiang et al. 2020[3]	
A retrospective observational study to evaluate the efficacy and safety of CP therapy compared to standard care among patients with COVID-19. Total number of participants, N= 326 CP group, n= 163; Control group, n = 163 **Study findings:** **Discharge conditions, n (%)** • **Death** ○ CP group: 8 (4.91%); Control group: 15 (9.2%) • **Cure** ○ CP group: 140 (85.89%); Control group: 135 (82.82%) • **Improve** ○ CP group: 11 (6.75%); Control group: 12 (7.36%) • **Transfer to another hospital** ○ CP group: 4(2.45%); Control group: 1(0.62%) ○ P = 0.255 • **Duration of hospital stay, median (IQR) days** ○ CP group: 23 (16 to 32); Control group: 15 (10 to 22) ○ P <0.0001 **Adverse events in the CP group:** Slight transfusion related symptoms (red, itchy and inflamed skin), n = 4 **Adverse events in the CP group:** Not reported	"We found that CPT significantly decreased the rate of mortality in COVID-19 patients in our matched control study and meta-analysis. Our results showed that CPT could significantly reduce the mortality in COVID-19 patients, and there was no significant increase the incidence of adverse events. These data provide evidence favoring the efficacy and safety of CPT as a therapeutic agent in COVID-19 patients and provide comprehensive reference for COVID- 19 treatment. (p.3)"[3]
Moniuszko-Malinowska et al. 2020[5]	
A retrospective observational study to evaluate the efficacy and safety of CP therapy compared to remdesivir and other drugs among COVID-19 patients. Total number of participants, N= 1,006 CP group, n= 55; Control group I, n = 236 (Remdesivir); Control group II, n = 715 (Other drugs) **Study findings:** • **Need for constant O_2 therapy, n (%)** ○ CP group: 41 (74.5%) ○ Control group I: 108 (46%); P < 0.05 ○ Control group II: 276 (38.6%); P < 0.05 "The necessity of constant oxygen therapy was less frequent in CG I than in the Plasma Group (41/55 (74.5%) vs. 108/235 (46%); p < 0.05). (p.8)"[5] "The comparison between the Plasma Group and CG II showed that the necessity of constant oxygen therapy was less frequent in CG II (41/55 (74.5%) vs. 276/715 (38.6%); p < 0.05). (p.9)"[5] • **Duration of Oxygen therapy, days – mean, (SD)** ○ CP group: 11.3 (6.6) ○ Control group I: 8.3 (8.6); P < 0.05 ○ Control group II: 10.2 (8.5); P = not significant • **Duration of hospitalization, days – mean, (SD)** ○ CP group: 19 (7.1) ○ Control group I: 14.4 (7.5); P < 0.05 ○ Control group II: 15.7 (10.4); P < 0.05	"1. Convalescent plasma efficacy is inferior to remdesivir when treating COVID-19 patients. 2. The addition of remdesivir to plasma does not improve treatment effectiveness. 3. Convalescent plasma may be used as a supportive treatment in COVID-19 patients, but must be given as early as possible from the diagnosis. 4. Convalescent plasma might be considered as a safe alternative for other COVID-19 therapies because of the low frequency of adverse effects. (p.11)" [5]

Main study findings	Authors' conclusion

• **Need for mechanical ventilation, n (%)**
  ○ CP group: 6 (11.2%)
  ○ Control group I: 10 (4%); P = 0.05
  ○ Control group II: 30 (4.2%); P = not significant
 	
• **Mortality**
  ○ CP group: 6 (11.2%)
  ○ Control group I: 8 (3.4%); P < 0.05
  ○ Control group II: 43 (6%); P = not significant
 	
• **Clinical improvement, n (%)**
  ○ Day 7:
  ▪ CP group: 3 (5.4%)
  ▪ Control group I: 16 (6.77%); P = not significant
  ▪ Control group II: 101 (14%); P = not significant
 	
  ○ Day 14
  ▪ CP group: 20 (36.36%)
  ▪ Control group I: 131 (55.5%); P = not significant
  ▪ Control group II: 381 (53.3%); P = not significant
 	
  ○ Day 21
  ▪ CP group: 39 (70.9%)
  ▪ Control group I: 194 (82.2%); P = not significant
  ▪ Control group II: 551 (77.06%); P = not significant
 	
  ○ Day 28
  ▪ CP group: 48 (87.3%)
  ▪ Control group I: 208 (88.13%); P = not significant
  ▪ Control group II: 630 (88.11%); P = not significant
 	
Adverse events in the CP group: No incidents of severe allergic transfusion reactions, TRALI, TACO were observed.
Adverse events in the control group: Not reported	

Altuntas et al. 2020[36]	

A retrospective study evaluating the efficacy of CP therapy in severe and critically ill COVID-19 patients.
CP group, n = 888; Control group, n = 888
 	
Baseline characteristics:
There were no significant differences in age, sex, baseline comorbidities (diabetes, hypertension, cardiovascular disease, respiratory disease, chronic renal disease, chronic liver disease, and malignancies) and use of concomitant medications (Favipravir, Lopinavir + Ritonavir, hydroxychloroquine and Azithromycin) between the groups.
 	
Study findings:
• **Duration of hospital stay, days (measure not reported; possibly median and range)**
  ○ CP group = 17 (0 to 74)
  ○ Control group = 18 (0 to 77)
  ○ P = 0.860
• **Duration in ICU, days (measure not reported; possibly median and range)**
  ○ CP group = 9 (0 to 68)
  ○ Control group = 12 (0 to 74)
	"CP therapy seems to be effective for a better course of COVID-19 in severe and critically ill patients. CP transfusion can reduce the ICU stay, and the rate of MV support, and also can ease the workload of healthcare professionals, especially when transfused within the first 20 days of COVID-19. Finally, the optimal dose and transfusion time, as well as the safety and efficacy of CP transfusion, need to be investigated in detail with well-designed randomized clinical studies." (p. 4)[36]

Main study findings	Authors' conclusion
○ P = 0.001 • **Need for Mechanical ventilation, n (%)** ○ CP group = 438 (49.3%) ○ Control group = 488 (55 %) ○ P = 0.02 • **Case fatality rate, n (%)** ○ CP group = 219 (24.7%) ○ Control group = 246 (27.7%) ○ P = 0.150 • **Need for vasopressor support, n (%)** ○ CP group = 219 (24.7%) ○ Control group = 305 (34.3%) ○ P = 0.001 **Adverse events in the CP group**: Not reported **Adverse events in the Control group:** Not reported	
Liu et al. 2020[41]	
A retrospective study evaluating the effect of CP therapy in reducing mortality and morbidity associated with COVID-19. **CP group, n = 39** **Control group, n = 139** **Baseline characteristics:** There were no significant differences in age, sex, baseline comorbidities (such as diabetes, obesity, smoke status) and clinical status at admission between CP group and control group. Use of therapeutic anticoagulation was significantly higher in the CP group. Use of other concomitant medications (antibiotics, anti-inflammatory agents, corticosteroids, antivirals and hydroxychloroquine) were similar between the groups. **Study findings:** • **Oxygenation status:** "By day 14, clinical conditions had worsened in 17.9% of the convalescent plasma recipients and in 28.2% of the control patients. The covariates-adjusted OR for worsening oxygenation on day 14 was 0.86 (95% CI, 0.75–0.98; chi-square test, P = 0.025)." (p. 3) [41] • **Mortality** "As of the end of the study (1 May 2020), 12.8% of convalescent plasma recipients and 24.4% of the 1:4 matched control patients had died (21.6% in the 1:2 matched dataset), and 71.8% and 66.7% (68.9%) had been discharged alive, respectively." (p. 3) [41] "Without covariate adjustment, the survival benefit of convalescent plasma was significant in the 1:4 matched dataset (HR, 0.39; 95% CI 0.15–0.99; chi-square test P = 0.048" (p. 3) [41]	"…additional studies are needed to confirm these findings and draw more definitive conclusions about the efficacy of convalescent plasma transfusion for the treatment of COVID-19 in different populations." (p. 5)[41]
Rogers et al., 2020[38]	
A retrospective study evaluating the efficacy of CP therapy in COVID-19 patients. CP group, n = 64; Control group, n = 177 **Baseline characteristics:** There were no significant differences in age, sex, race or ethnicity, or baseline comorbidities (such as diabetes, hypertension, cardiovascular disease, respiratory disease, chronic renal disease, chronic liver disease) between the CP group and control group. Corticosteroid use was significantly higher in the CP	**"**Though our study had several limitations, we found no significant overall difference in the risk for in-hospital mortality or in the rate of hospital discharge for those patients who received CP as compared to those who did not. A secondary analysis showed a significantly increased rate of hospital discharge for CP given to patients 65-years-old or greater." (p. 12) [38]

Main study findings	Authors' conclusion
group. Use of other concomitant medications (remdesivir and hydroxychloroquine) were similar between the groups. **Study findings:** • **In-hospital all-cause mortality:** ○ CP group, n (%) = 8 (12.5) ○ Control group, n (%) = 28 (15.8) ○ P = 0.52 ○ Unadjusted HR (95% CI) = 0.73 (0.32 to 1.69) ○ Adjusted HR (95% CI) = 0.93 (0.39 to 2.20) ○ (Adjusted for age, sex, race, baseline O_2 requirement, remdesivir use and corticosteroid use) • **Duration of hospital stay, median (IQR)** ○ CP group = 8 (5 to 10.5) days ○ Control group = 8 (5 to 13) days ○ P = 0.76 ○ RR (95% CI) = 1.28 (0.91 to 1.81) **Subgroup analysis based on the antibody index of CP received:** AI ≥ 1.4, n = 32 (at least one unit with AI ≥ 1.4, but not two units both with AI ≥ 5.0) AI ≥ 5.0, n = 18 (Two units both with AI ≥ 5.0) • **In-hospital all-cause mortality compared to control group:** ○ AI ≥ 1.4: Unadjusted HR (95% CI) = 1.08 (0.41 to 2.80) ○ AI ≥ 5.0: Unadjusted HR (95% CI) = 0.35 (0.05 to 2.62) • **Time to hospital discharge compared to control group:** ○ AI ≥ 1.4: rate ratio (RR) (95% CI) = 1.14 (0.72 to 1.83) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.63 (0.92 to 2.88) **Sex** *Female* ○ Overall: rate ratio ((95 % CI) = 1.28 (0.75 to 2.19) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.31 (0.66 to 2.60) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.21 (0.40 to 3.68) *Male* ○ Overall: rate ratio (95 % CI) = 1.27 (0.80 to 2.00) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.00 (0.52 to 1.91) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.85 (0.94 to 3.64) **Age group, years** *18 to 49 years* ○ Overall: rate ratio (95 % CI) = 0.90 (0.48 to 1.70) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.77 (0.70 to 4.48) ○ AI ≥ 5.0: rate ratio (95% CI) = 0.81 (0.29 to 2.29) *50 to 64 years* ○ Overall: rate ratio (95 % CI) = 0.82(0.43 to 1.55) ○ AI ≥ 1.4: rate ratio (95% CI) = 0.80 (0.37 to 1.75) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.57 (0.25 to 9.93) *Above 65 years* ○ Overall: rate ratio (95 % CI) = 1.86 (1.03 to 3.36) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.28 (0.58 to 2.85) ○ AI ≥ 5.0: rate ratio (95% CI) = 2.70 (1.16 to 6.28) **Race/ethnicity** *Black or African-American* ○ Overall: rate ratio (95 % CI) = 1.49 (0.56 to 3.93) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.19 (0.34 to 4.14) ○ AI ≥ 5.0: rate ratio (95% CI) = 3.00 (0.67 to 13.4)	

Main study findings	Authors' conclusion
Hispanic or Latino ○ Overall: rate ratio (95 % CI) = 0.88 (0.51 to 1.54) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.09 (0.48 to 2.51) ○ AI ≥ 5.0: rate ratio (95% CI) = 0.95(0.44 to 2.05) *White or Caucasian* ○ Overall: rate ratio (95 % CI) = 1.51 (0.82 to 2.76) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.05 (0.52 to 2.14) ○ AI ≥ 5.0: rate ratio (95% CI) = 6.67 (1.39 to 32.1) *Others/Unknown* ○ Overall: rate ratio (95 % CI) = 1.38 (0.54 to 3.51) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.85 (0.44 to 6.91) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.20 (0.14 to 10.5) **Baseline oxygen requirement** *Low flow supplemental oxygen:* ○ Overall: rate ratio (95 % CI) = 1.34 (0.89 to 2.03) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.15 (0.68 to 1.94) ○ AI ≥ 5.0: rate ratio (95% CI) = 2.03 (0.90 to 4.56) *NIPPV or HFNC* ○ Overall: rate ratio (95 % CI) = 1.52 (0.78 to 2.96) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.00 (0.33 to 3.02) ○ AI ≥ 5.0: rate ratio (95% CI) = 2.36 (0.97 to 5.74) **Days from symptom onset to admission** *≤ 5 days* ○ Overall: rate ratio (95 % CI) = 1.31 (0.79 to 2.16) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.03 (0.52 to 2.04) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.82 (0.66 to 5.06) *> 5 days* ○ Overall: rate ratio (95 % CI) = 1.16 (0.71 to 1.89) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.21 (0.63 to 2.35) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.30 (0.64 to 2.65) **Remdesivir use** *No* ○ Overall: rate ratio (95 % CI) = 1.20 (0.79 to 1.82) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.04 (0.60 to 1.78) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.66 (0.83 to 3.33) *Yes* ○ Overall: rate ratio (95 % CI) = 1.41 (0.75 to 2.66) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.68 (0.63 to 4.50) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.37 (0.50 to 3.77) **Corticosteroids use** *No* ○ Overall: rate ratio (95 % CI) = 1.25 (0.81 to 1.93) ○ AI ≥ 1.4: rate ratio (95% CI) = 0.97 (0.52 to 1.83) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.94 (0.94 to 4.01) *Yes* ○ Overall: rate ratio (95 % CI) = 1.66 (0.81 to 1.93) ○ AI ≥ 1.4: rate ratio (95% CI) = 1.74 (0.82 to 3.69) ○ AI ≥ 5.0: rate ratio (95% CI) = 1.66 (0.63 to 4.37) **Adverse events in the CP group:** ○ TRALI, n = 2 ○ TACO, n = 1 **Adverse events in the control group:** Not reported	

Main study findings	Authors' conclusion
Abolghasemi et al. 2020[35]	

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
• **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
	"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)"[35]

Xia et al. 2020[39]	
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 (%)**	"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

Main study findings	Authors' conclusion

• **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
• **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)
	practice and monoclonal antibody development for COVID-19. (p. 6-7)"[39]

Main study findings	Authors' conclusion
○ 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** **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. (p. 4)"[39]	
Duan et al.2020 [37]	
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)	"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

Main study findings	Authors' conclusion
○ 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	to be further investigated in randomized clinical studies. (p. 9496)"[37]
Zeng et al. 2020[40]	
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) • 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)	"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 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. (p. 10)"[40]

Main study findings	Authors' conclusion
○ 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 (%)** ○ 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	

Main study findings	Authors' conclusion

• **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	

AI = SARS-CoV-2 IgG antibody index; 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; PE = Point Estimate; RBD = receptor binding domain; RCT= randomized controlled trial; RD = risk difference; RR = risk ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. TACO = Transfusion Associated Circulatory Overload; TRALI = Transfusion Related Acute Lung Injury

[a] Indicates revised estimates as reported in the erratum.[34]

Appendix 5: Further Information

Systematic Reviews and Meta-Analyses

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Single-Arm Studies

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PubMed: PM33140056

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	
Observational Study of Convalescent Plasma for Treatment of Veterans With COVID-19 (NCT04545047) https://clinicaltrials.gov/ct2/show/NCT04545047?term=plasma	USA VA Office of Research and Development	Retrospective observational	NA	4,000 participants	18 Years and older	June 30, 2022
Study on the Safety and Efficacy of Convalescent Plasma in Patients With Severe COVID-19 Disease (PC-COVID-HCM) (NCT04542967) https://clinicaltrials.gov/ct2/show/NCT04542967?term=plasma	Mexico Hospital Central Militar	Double blinded RCT	Phase II	150 participants	18 Years to 90 Years	September 30, 2020
Assessment of Safety and Efficacy of CCP (COVIDIT) (NCT04542941) https://clinicaltrials.gov/ct2/show/NCT04542941?term=plasma	Uganda Makerere University	Open Label RCT	N/A	136 participants	18 Years to 100 Years	October 31, 2020

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
COVID-19 (VA CURES-1) (VA CURES-1) (NCT04539275) https://clinicaltrials.gov/ct2/show/NCT04539275?term=plasma	USA VA Office of Research and Development	Triple blinded RCT	Phase III	702 participants	18 Years and older	June 30, 2022
Convalescent Plasma as Potential Therapy for Severe COVID-19 Pneumonia (NCT04535063) https://clinicaltrials.gov/ct2/show/NCT04535063?term=plasma	Argentina Centro de Educación Medica e Investigaciones Clínicas Norberto Quirno	Single group, open label	Phase III	200 participants	18 Years and older	February 25, 2021
Efficacy and Safety of Recovered Covid 19 Plasma Transfusion to Covid 19 Severly Ill Patients (NCT04530370) https://clinicaltrials.gov/ct2/show/NCT04530370?term=plasma	Egypt South Valley University	Quadruple blinded RCT	Early Phase I	30 participants	18 Years and older	September 1, 2020
COVID-19 Antibody Plasma Research Study in Hospitalized Patients (UNC CCP RCT) (NCT04524507) https://clinicaltrials.gov/ct2/show/NCT04524507?term=plasma	USA University of North Carolina, Chapel Hill	Double blinded RCT	Phase II	56 participants	18 Years to 99 Years	May 2021
Convalescent Plasma for COVID-19 Patients (CPCP) (CPCP) (NCT04521036) https://clinicaltrials.gov/ct2/show/NCT04521036?term=plasma	Vietnam Vinmec Research Institute of Stem Cell and Gene Technology	Open Label RCT	Phase I Phase II	44 participants	18 Years to 75 Years	October 30, 2021
SARS-CoV-2 Antibodies Based IVIG Therapy for COVID-19 Patients (NCT04521309) https://clinicaltrials.gov/ct2/show/NCT04521309?term=plasma	Pakistan Dow University of Health Sciences	Single blinded RCT	Phase I Phase II	50 participants	18 Years and older	March 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 COVID-19 Patients (CPCP) (NCT04516954) https://clinicaltrials.gov/ct2/show/NCT04516954?term=plasma	Vietnam Vinmec Research Institute of Stem Cell and Gene Technology	Open Label RCT	Early Phase I	10 participants	18 Years to 75 Years	December 30, 2020
Therapeutic Use of Convalescent Plasma in the Treatment of Patients With Moderate to Severe COVID-19 (NCT04516811) https://clinicaltrials.gov/ct2/show/NCT04516811?term=plasma	South Africa South African National Blood Service	Triple blinded RCT	Phase III	600 participants	18 Years to 75 Years	July 31, 2022
Convalescent Plasma in the Early Treatment of High-Risk Patients With SARS-CoV-2 (COVID-19) Infection (NCT04513158) https://clinicaltrials.gov/ct2/show/NCT04513158?term=plasma	USA Joseph M. Flynn, D.O., MPH	Single group, open label	Phase II	100 participants	18 Years to 99 Years	December 31, 2021
Open-label Treatment of Severe Coronavirus Disease 2019 (COVID-19) With Convalescent Plasma (Inova-CCP) (NCT04502472) https://clinicaltrials.gov/ct2/show/NCT04502472?term=plasma	USA Inova Health Care Services	Single group, open label	Phase II Phase III	100 participants	18 Years and older	December 31, 2021
Clinical Protocol for Convalescent Plasma and Remdesivir Therapy in Nepal (CPT-R-Nepal) (NCT04570982) https://clinicaltrials.gov/ct2/show/NCT04570982?term=plasma	Nepal Dr. Pradip Gyanwali,MD	Observational Case-crossover	N/A	200 participants	18 Years and older	December 30, 2020
Convalescent Plasma in COVID-19 Elderly Patients (RESCUE) (NCT04569188) https://clinicaltrials.gov/ct2/show/NCT04569188?term=plasma	Italy Azienda Socio Sanitaria Territoriale di Mantova	Single group, open label	Phase II	21 participants	65 Years and older	September 3, 2020

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Convalescent Plasma as Adjunctive Therapy for Hospitalized Patients With COVID-19 (Co-CLARITY) (NCT04567173) https://clinicaltrials.gov/ct2/show/NCT04567173?term=plasma	Philippines University of the Philippines	Open Label RCT	Phase II Phase III	136 participants	19 Years and older	June 30, 2021
Convalescent Plasma Therapy for COVID-19 Patients (NCT04565197) https://clinicaltrials.gov/ct2/show/NCT04565197?term=plasma	Pakistan Lahore General Hospital	Single group, open label	Early Phase I	20 participants	15 Years to 80 Years	October 30, 2020
Efficacy of CONvalescent Plasma in Patients With COVID-19 Treated With Mechanical Ventilation (CONFIDENT) (NCT04558476) https://clinicaltrials.gov/ct2/show/NCT04558476?term=plasma	Belgium University of Liege	Open Label RCT	Phase II	500 participants	18 Years and older	September 1, 2022
Convalescent Plasma for the Treatment of COVID-19 (NCT04554992) https://clinicaltrials.gov/ct2/show/NCT04554992?term=plasma	USA The Methodist Hospital System	Single group, open label	Phase I	350 participants	18 Years and older	June 2022
Convalescent Plasma for Severe COVID-19 Patients (PLACOVID) (NCT04547660) https://clinicaltrials.gov/ct2/show/NCT04547660?term=plasma	Brazil Hospital de Clinicas de Porto Alegre	Open Label RCT	Phase III	160 participants	18 Years and older	October 2021
Reconvalescent Plasma/Camostat Mesylate Early in SARS-CoV-2 Q-PCR (COVID-19) Positive High-risk Individuals (RES-Q-HR) (NCT04681430) https://clinicaltrials.gov/ct2/show/NCT04681430?term=plasma	Germany Heinrich-Heine University, Duesseldorf	Quadruple blinded RCT	Phase II	1094 participants	18 Years and older	November 2021
Remdesivir and Convalescent Plasma Therapy for Treatment of COVID-19 Infection in Nepal: A Registry Study (NCT04669990) https://clinicaltrials.gov/ct2/show/NCT04669990?term=plasma	Nepal Nepal Health Research Council	Prospective observational study	N/A	2000 participants	18 Years and older	November 19, 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 Open Randomised Controlled Trial (NCT04649879) https://clinicaltrials.gov/ct2/show/NCT04649879?term=plasma	Sweden Joakim Dillner	Open Label RCT	Phase II Phase III	920 participants	18 Years and older	February 1, 2022
Convalescent Plasma Transfusion in Severe COVID-19 Patients in Jamaica (NCT04644198) https://clinicaltrials.gov/ct2/show/NCT04644198?term=plasma	Jamaica The University of The West Indies	Open label non-randomized	Phase II	30 participants	18 Years to 65 Years	December 1, 2021
Application of Convalescent Plasma in the Treatment of SARS CoV-2 Disease (COVID-19) With Evaluation of Therapy Effectiveness (EPIC-19) (NCT04642014) https://clinicaltrials.gov/ct2/show/NCT04642014?term=plasma	Poland Wroclaw Medical University	Single group, open label	N/A	500 participants	18 Years and older	May 1, 2022
Plasma Exchange (PLEX) and Convalescent Plasma (CCP) in COVID-19 Patients With Multiorgan Failure (COVID-PLEX) (NCT04634422) https://clinicaltrials.gov/ct2/show/NCT04634422?term=plasma	Denmark Wladimir Szpirt	Open Label RCT	N/A	220 participants	18 Years and older	June 30, 2022
plasmApuane CoV-2 : Efficacy and Safety of Immune Covid-19 Plasma in Covid-19 Pneumonia in Non ITU Patients (NCT04622826) https://clinicaltrials.gov/ct2/show/NCT04622826?term=plasma	Italy Azienda USL Toscana Nord Ovest	Open label non-randomized	Phase II	50 participants	18 Years and older	December 31, 2020
Plasma for Early Treatment in Non-hospitalised Mild or Moderate COVID-19 Patients (NCT04621123) https://clinicaltrials.gov/ct2/show/NCT04621123?term=plasma	Spain Fundación FLS de Lucha Contra el Sida, las Enfermedades Infecciosas y la Promoción de la Salud y la Ciencia	Double blinded RCT	Phase II	474 participants	50 Years and older	October 2021
COVID-19 With Convalescent Plasma (NCT04616976) https://clinicaltrials.gov/ct2/show/NCT04616976?term=plasma	China Southeast University, China	Case-control study	N/A	78 participants	18 Years and older	November 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 in the Treatment of Covid-19 (COP20) (NCT04600440) https://clinicaltrials.gov/ct2/show/NCT04600440?term=plasma	Sweden Skane University Hospital	Open Label RCT	N/A	100 participants	18 Years and older	February 28, 2022
Early Convalescent Plasma Therapy for High-risk Patients With COVID-19 in Primary Care (the CoV-Early Study) (CoV-Early) (NCT04589949) https://clinicaltrials.gov/ct2/show/NCT04589949?term=plasma	The Netherlands Erasmus Medical Center	Quadruple blinded RCT	Phase III	690 participants	50 Years and older	November 1, 2023

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[37,40]
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[32] **Total number of included studies:** Three[32,37,40] **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[39] **Total number of included studies:** Four[32,37,39,40] **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[35] **Total number of included studies:** Five[32,35,37,39,40] **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 5.0	September 29, 2020	**Date of literature search update:** September 11, 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:** Six[8,32,35,37,39,40]

Version Number	Date of Publication	Report Version Details
		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, and a published erratum for a previously included study did not meaningfully alter the overall conclusions. 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 6.0	November 12, 2020	**Date of literature search update:** October 13, 2020 **Date of focused internet search:** October 13, 2020 **Number of new relevant studies included in this update:** Four[33,36,38,41] **Total number of included studies:** Ten [8,32,33,35-41] **What is new:** New evidence was found and the overall conclusions have not changed. Findings from one randomized study and three non-randomized studies 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. This report has been updated on a monthly basis since May 2020 until November 2020 for a total of six report versions. Going forward, this report will be updated quarterly, since conclusions have remained largely consistent from one version of the report to the next and to balance the timely incorporation of emerging evidence into the report with resource constraints.
Version 7.0	February23, 2021	**Date of literature search update:** January 13, 2021 **Date of focused internet search:** October 13, 2020 **Number of new relevant studies included in this update:** 7[1-7] **Total number of included studies:** 16[1-7,32,33,35-41] **What is new:** New evidence was found and the overall conclusions have not changed. Findings from two randomized studies and three non-randomized studies were similar to those from the previously included studies. Interim results of a study included in the previous have been updated to the now-published final results. One new study that compared convalescent plasma to remdesivir and other medications (i.e., new comparisons) was identified and included. 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.