CADTH COVID-19 PANDEMIC

COVID-19 CADTH Health Technology Review

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

This report was originally published on May 28, 2020, and updated on a regular basis until its last publication on July 5, 2021. This is the final version of the report.

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.

Version: 6.0
Publication Date: July 5,2021
Report Length: 168 Pages

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

Cite As: Convalescent plasma therapy for the treatment of COVID-19: a review of clinical effectiveness. Ottawa: CADTH; 2021 Jun. (CADTH Technology Review).

ISSN: 1922-8147 (online)

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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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

Abbreviations

BMI	body mass index
COVID-19	coronavirus disease
CI	confidence interval
CP	convalescent plasma
eIND	emergency investigational new drug
FiO_2	fraction of inspired oxygen
ICU	intensive care unit
IPTW	inverse probability of treatment weight
IQR	interquartile range
NRS	non-randomized study
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
RCT	randomized controlled trial
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SpO_2	saturation of peripheral oxygen
TACO	transfusion-associated circulatory overload
TRALI	transfusion-related acute lung injury

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, as of July 2021, CP therapy for COVID-19 is available only as an investigational drug treatment.
- Nine randomized controlled trials and 28 non-randomized studies were included in this report. The included studies had several methodological limitations, unclear reporting, high heterogeneity, and limited generalizability to Canadian settings; overall, the evidence was of low-to-moderate quality.
- There were mixed findings regarding a survival benefit associated with CP therapy compared to standard care or placebo (15 studies found no significant effects and 13 studies found favourable effects on mortality with CP). Given the limitations of the evidence as aforementioned, the potential survival benefit is unclear.
- Whether CP was more effective than standard care or placebo for other outcomes (e.g., clinical improvement, disease progression, viral clearance, 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 favourable and, in a few instances, CP was comparatively unfavourable (e.g., 1 study for the outcome duration of hospitalization). However, because of 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, as observed in 2 non-randomized studies of limited quality. Evidence from a non-randomized study of limited quality showed that that CP therapy and tocilizumab were equally effective in improving the clinical status of patients.
- The incidence of adverse events was similar between patients treated with CP therapy or standard care alone in the few studies in which adverse events were assessed in patients who received either treatment. Adverse events were reported in 30 studies and were relatively infrequent. The most common adverse events in patients who received CP were fever and allergic reactions. Most of the included studies did not report whether there were adverse events in the control groups (e.g., patients who received standard care, remdesivir, or other medications).
- This report includes a list of ongoing clinical trials that could provide additional evidence regarding the clinical effectiveness of CP therapy for COVID-19.
- This report was conducted as a living review from May 2020 until July 2021. This is the final version of this report. A list of ongoing clinical trials is provided in Appendix 6. Key information regarding each version of this report can be found in Appendix 7.

Context and Policy Issues

The novel coronavirus disease (COVID-19) is a highly infectious zoonotic disease, which emerged toward the end of 2019 and has rapidly spread all over the world.[1] COVID-19 is caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] With more than 176 million confirmed cases and more than 3.8 million deaths globally as of June 16, 2021,[2] COVID-19 has emerged as one of the biggest global public health concerns in recent history. The WHO declared COVID-19 a pandemic on

March 11, 2020.[3] In Canada, the first case of COVID-19 was reported on January 25, 2020, and 1,405,146 confirmed cases and 26,001 deaths were reported as of June 16, 2021.[4]

The clinical presentation of COVID-19 varies considerably. Up to half of infected individuals remain asymptomatic. Many patients have mild symptoms, with around 15% developing severe disease requiring hospitalization.[5] In those with moderate illness, there is evidence of lower respiratory disease in chest examination and peripheral oxygen saturation (SpO_2) levels are 94% or more on room air. Severe illness is defined as shortness of breath, with a respiratory rate of more than 30 breaths per minute, SpO_2 of less than 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) of less than 300 mm hg, or the presence of pulmonary infiltrates in more than 50% of the lungs. Critical or life-threatening illness is defined as the presence of respiratory failure, septic shock, and/or multiple organ dysfunction.[6] Several antiviral agents and vaccines are currently being actively researched for the prevention and treatment of COVID-19.[7] On December 9, 2020, Health Canada authorized the Pfizer-BioNTech COVID-19 mRNA (i.e., messenger ribonucleic acid) vaccine to be used, with conditions.[8] To date, 4 vaccines with different protective mechanisms and 3 therapeutic agents have been approved for use in Canada.[9]

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.[10] 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.[11] CP therapy involves the 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.[12] The Public Health Agency of Canada reported an overall risk of adverse events related to the transfusion of blood components as 1 in 2,405 transfusions during the period of 2011 to 2015.[13] Among them, TACO was the most common adverse transfusion reaction (18.1 per 100,000 units transfused).[13] 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.[14,15] 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.[16] A possible molecular mechanism for antibody-dependent enhancement has been described in other coronaviruses like the Middle East respiratory syndrome coronavirus.[17]

Regulatory Status

The use of CP as a treatment for COVID-19 was first approved by the US FDA on March 25, 2020 as an emergency investigational new drug (eIND).[18] The FDA also issued an Emergency Use Authorization for CP therapy for hospitalized COVID-19 patients in the US on August 23, 2020.[19] In Canada, as of June 2021, CP therapy for COVID-19 is available only as an investigational drug treatment for participants in the CONCOR-1 clinical trial.[20] 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.[21] The CONCOR-1 clinical trial is currently underway and involves more than 50 hospitals across Canada. Recruitment for the study has been completed.[18] 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 CA$719.[22] 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 (1 500 mL unit from 1 donor or 2 250 mL units from 1 or 2 donors).[18] The plasma will be collected by apheresis from donors who have recovered from COVID-19.[18] The plasma will be infused over a period of 4 hours. If 2 units are used, the second unit will be infused within 12 hours of the first.[18] Different treatment protocols are being used in other ongoing trials (Appendix 6).

Implementation Issues

If CP is found to be effective, a major barrier to its implementation as a treatment for COVID-19 is likely to be the availability of both donors and plasma.[21] For this reason, its use as a treatment will be prioritized to patients with active illness rather than being tested as a preventive treatment for those at high risk of exposure.[21] CP is collected in the same way as a standard plasma donation, so existing infrastructure can be used in its production. In Canada, CP 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.[20] 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.[18] 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.[21] Potential donors are also able to self-identify through a questionnaire accessible via social media.[18]

A report published by CADTH in May 2020 identified evidence regarding the clinical effectiveness of CP therapy in COVID-19, together with detailed information on ongoing clinical trials.[23] 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 was conducted as a living review, with updates published on a regular basis until July 2021.

Research Question

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

Methods

Study Design

This report was conducted as a living review, following the Cochrane guidance for living systematic reviews.[24] This model allowed for ongoing assessment of the clinical

effectiveness and safety of CP therapy, incorporating the results from several ongoing clinical trials[23] and any other relevant studies that were published.

CADTH reviewed the appropriateness of continuing to maintain the review in living mode on an ongoing basis. The review was regularly updated, as described, until: the research question was no longer a priority for decision-making, a reasonable level of certainty was reached in the existing evidence, or research that might impact the conclusions of the review was no longer emerging (e.g., the research area is no longer active). CADTH considered the research question to no longer be a priority for decision-making in situations where the intervention was superseded or withdrawn. Additionally, CADTH sought input from decision-makers in Canadian jurisdictions to determine whether there was continued interest in this topic. This was 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. It was further planned that this report would transition out of living mode if there was a 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 comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were CP 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 CP therapy for the treatment of COVID-19 were also handsearched for potentially relevant primary studies.

Living Updates

After the initial literature search was 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) were updated on a regular basis. Between May 2020 and October 2020, searches were updated monthly. Between October 2020 and May 2021, searches were updated quarterly. Websites of Canadian and international health technology agencies and a focused internet search were updated every 6 months. A final update of the literature search was conducted on May 20, 2021.

Selection Criteria and Methods

Baseline Review

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

Living Updates

Relevant publications identified in each subsequent search were incorporated into the corresponding version updates. In addition, relevant publications that were identified via other means (e.g., handsearching) were incorporated. The selection criteria and methods were 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 they were published prior to January 2019.

Critical Appraisal of Individual Studies

Baseline Review

The included publications were critically appraised by 1 reviewer using the Downs and Black checklist[25] 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 involved the same processes as the baseline review and were conducted when updating the review.

Table 1: Selection Criteria

Population	Individuals (of all ages) with confirmed or presumptive 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

Transition Out of Living Mode

With each updated version of this report, CADTH reviewed the appropriateness of continuing to maintain the review in living mode. With the current update, it was clear that, despite the continued publication and incorporation of new studies, and the limited quality of the existing evidence, a reasonable level of certainty has been reached in the existing evidence. Over the course of 8 versions of the report, the overall conclusions have remained consistent. In addition, with the shift in focus to vaccinations, this topic is no longer a top priority for decision-making. Therefore, per our protocol, the decision was made to transition this report out of living mode. This is the final version of this report.

Quantity of Research Available

The updated search of the databases and trial registry was last conducted on May 20, 2021; the focused internet search was last conducted on May 10, 2021.

In total, 5,114 citations were identified in the literature searches. Following the screening of titles and abstracts, 4,942 citations were excluded and 172 potentially relevant reports from the electronic searches were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search or via handsearching for full-text review. Of these 176 potentially relevant articles, 139 publications were excluded for various reasons and 37 publications met the inclusion criteria and were included in this report. These comprised 9 randomized controlled trials (RCTs)[26-35] and 28 non-randomized studies (NRSs).[36-63]

Appendix 1 presents the PRISMA[64] flow chart 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

Nine eligible RCTs[26-35] and 28 NRSs[36-63] were identified and included in this report. The studies were published in 2020[26,27,29,33,35-42,44-47] and 2021.[28,31,32,34,43,48-63] Detailed study characteristics are available in Appendix 2, Table 2.

Study Design

Two[29,33] of the RCTs were double-blinded and 6[26-28,31,32,35] were open-label studies. One of the open-label RCTs, the RECOVERY trial, [32] is an adaptive platform trial evaluating the efficacy of multiple therapeutic options for patients with COVID-19.[65] The results of efficacy and safety of CP therapy is summarized and presented in the current report.[32] The authors of the final RCT[33] described the study as single-blinded and the randomized allocation was conducted by a centralized system that was blinded; however, patients and treating physicians were aware of the treatment assignments. It was unclear from the publication whether the treating physicians were the outcome assessors.

Among the NRSs, 8[36,38,43,44,50,53,56,59] were prospective observational and 20[37,39-42,45-49,51,52,54,55,57,58,60-63] were retrospective observational in design. Six of these NRSs (2 prospective[43,59] and 4 retrospective[42,46,55,63]) selected controls using propensity score matching. One study used inverse probability of treatment weight (IPTW) for adjustment using propensity scores.[53] One study was a real-world experience of COVID-19 patients in Poland receiving several treatments, including CP.[47] 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,[28,29] Bahrain,[31] China,[26] Egypt,[33] India,[27] Iran,[34] Iraq[35] and the UK.[32] The included NRSs were conducted in China,[38,40,41,45,46,60] Europe,[37,47,51,53,59] India,[52] the Middle East,[36,44,48-50,57] South America,[56,61] and the US.[39,42,43,54,55,58,62,63] None of the included studies were conducted in Canada.

Patient Population

Randomized Controlled Trials

Six of the included RCTs enrolled adult patients (aged 18 years or older, or older than 21 years).[26,27,29,31,33,35] One study included patients who were either older than 75 years of age, or were 65- to 74-years-old and had 1 or more coexisting conditions.[28] One RCT (the RECOVERY trial) included patients of all ages[32] and 1 study did not specify age as an eligibility criterion.[34]

Regarding disease severity, 1[28] study enrolled patients with mild COVID-19, 1[27] with moderate illness, 4[29,31,33,34] with severe disease, and 2[26,35] with critical or severe/life-threatening illness. Lastly, the RECOVERY trial enrolled all hospitalized patients irrespective of disease severity.[32]

Overall, the included RCTs enrolled 12,792 patients, with sample sizes in individual studies ranging from 30[33] to 11,558[32] patients (in the RECOVERY trial). Of the included patients, 6,476 were randomized to CP and 6,321 to control. The mean age of the patients ranged from approximately 52 years of age [27] to 78 years of age[28] across studies. The proportion of female participants ranged from 15%[31] to 68%[28] in CP groups and 23%[27] to 58%[28] in control groups.

Non-randomized Studies

Among the included NRSs, 14 studies enrolled adult patients (18 years of age and older),[36,38,39,42,44,48-50,52,53,58,59,61,62] whereas the other studies did not specify any specific age criteria for inclusion. Two studies[44,52] included patients with moderate-to-severe COVID-19, 5 studies[36,57,47,38,49] included those with severe COVID-19, and 14 studies[37,39,40,42,43,48,50,54,58-63] included patients with severe or life-threatening illness. One NRS[56] included all patients admitted to the intensive care unit (ICU) with COVID-19 and 1[53] enrolled patients in the ICU with respiratory failure and acquired or inborn immunodeficiency. One NRS enrolled COVID-19 patients with hematological malignancies[51] and 1 included COVID-19 patients with diabetes.[45] Three studies enrolled all COVID-19 patients who were identified as eligible during the study periods, irrespective of disease severity and comorbidities.[41,46,55]

Overall, the NRSs enrolled 22,238 patients — 5,061 patients of whom received CP. The number of study participants in individual studies ranged from 20[38] to 9,565.[55] The mean age of the study patients ranged from 47.5 years[57] to 73 years[41] across studies. The mean age was not reported in one study.[43] The proportion of female participants were lowest in the study by Omrani et al.[57] (CP group 15% and control group, 12.5%) and highest in the study by Jiang et al.[46](CP group 44.1% and control group, 68.7%).

Interventions and Comparators

The intervention in all studies included in this report was the administration of CP collected from recovered COVID-19 patients who donated their plasma.[26-29,31-63] Patients who received CP in most studies received plasma compatible with their blood group (ABO compatible).[26-28,31,32,35,36,39,40,42-45,49,50,54,56,57,59,60,62,63] No CP therapy was administered to patients in control groups.

Randomized Controlled Trials — Interventions

In the included RCTs, the intervention was up to 2 doses (most patients received 1 dose) of CP, with volumes ranging from 200 mL[28] to 500 mL.[29,34] The neutralizing antibody titer of the transfused CP was >1:1000 in 2 studies,[28,32] ≥1:1280 in 1 study,[26] and a median of 1:300 (interquartile range [IQR]: 1:136 to 1:511) in 1 study.[29] Neutralizing antibody titers of the CP were not reported or measured in 5 RCTs.[27,31,33-35] The median time from symptom onset to CP therapy ranged from 8 days[27,29] to 30 days.[26] In 1 RCT, CP therapy was given within 4 hours of admission[34] and within 72 hours of admission in another.[28] The timing of CP therapy was not reported in 1 study.[31]

Non-randomized Studies — Interventions

In most of the included NRSs,[38-40,42-45,47,48,51,52,56,60-63] the intervention was 1 or 2 doses of CP, with volumes ranging from 200 mL to 300 mL per unit. In one study, up to 5 doses of CP of 300 mL were transfused (each a day apart).[50] The volume and dose of CP was not reported in 2 studies.[46,55]

The neutralizing antibody titer of the transfused CP in the NRSs varied considerably, ranging from ≥1:40[52] to ≥1:1350[43] in the 14 studies in which this was reported. The antibody titer was not reported in the remaining 14 studies.[37,41,44,46-50,54-58,62] In one study, CP with at least 30 AU/mL of neutralizing anti-SARS-CoV-2 S1/S2 IgG antibodies was used.[53] In 3 studies, an assay called EUROIMMUN SARS-CoV-2 ELISA that detects IgG antibodies against the S1 protein of the virus was used to determine antibody levels in the donor plasma.[36,39,59] Results of the assay are denoted as a ratio of the optical density of the test trip to that of the calibrator strip. A ratio of ≥1.1 is considered positive for IgG antibodies.[66] In 1 study,[36] CP units with a ratio of >1.1 were used for transfusion and, in 1 study, CP units with a ratio of >1.4 were used.[39] The median level ratio of transfused CP units was 3.42 in the other study.[59] Where reported, the timing of CP transfusion also varied widely, ranging from within 24 hours of hospital admission in 1 study[44] to a median 45 days from symptom onset in another.[40] The timing of CP therapy was not reported in 11 studies.[38,41,43,46,50,52,55,58,60-62]

Randomized and Non-Randomized Studies — Comparators

The majority of included RCTs (n = 7)[26,27,31-35] and NRSs (n = 25)[36-46,49-57,59-63] compared CP with standard care alone. Two of the RCTs were placebo-controlled (saline) and patients in both groups received standard care.[28,29] Two NRSs[47,58] compared CP therapy with remdesivir. One of these studies also compared CP with “other medications.” The “other medications” group included tocilizumab, dexamethasone, chloroquine, hydroxychloroquine, lopinavir-ritonavir, azithromycin, and/or fractioned heparin.[47] Lastly, one NRS compared CP therapy with tocilizumab (dosage not reported).[48]

Standard care varied across the included RCTs and NRSs but generally included a wide range of therapies and medications such as antivirals (e.g., lopinavir-ritonavir), antibiotics (e.g., azithromycin, doxycycline), systemic corticosteroids (e.g., dexamethasone, methylprednisolone), hydroxychloroquine, remdesivir, tocilizumab, or therapeutic anticoagulation, in addition to respiratory and other supportive treatments. In 2 studies, standard care also included the use of traditional Chinese medicines.[26,40] Concomitant medications given to study participants were not reported in 7 NRSs.[28,45,46,49,50,60,61]

Outcomes

Mortality was measured in 7 RCTs[26-28,31,32,34,35] and 24 NRSs.[36,37,39-44,47,49-63] Among the RCTs, all-cause mortality within 28 days post-randomization was the primary outcome in 4 studies.[26,27,31,32] The assessment time was 25 days in 1 study[28] and 2 months in another.[34] Among the NRSs, 7-day mortality was assessed in 1 study,[54] 4-week or 30-day mortality was assessed in 6 studies,[37,49,52,61-63] in-hospital mortality was assessed in 5 studies,[39,42,44,47,55] and 60-day mortality was assessed in 1 study.[43] Overall survival was assessed in 3 studies[51,56,59] at 28 days and 1 study[53] at 3 months. The follow-up period for assessing mortality was unclear in 5 studies.[35,36,41,58,60]

Clinical improvement was reported in 11 studies,[26,29,34,35,43-45,47,48,56,57] and was defined as a decrease of 1 or 2 points on 6-point,[26,29,40,43,45,57] 7-point,[44] 8-point,[34,47] or 10-point[56] disease severity scale. The categories in the scales ranged from "discharged from hospital" to "death," with different levels of respiratory status in-between. It was unclear whether a 1- or 2-point difference in the scales denoted a clinically significant improvement. Recovery time from critical illness was a secondary outcome in 1 study.[35] Recovery time from critical illness was defined as the time (in days) to improvement in the signs and symptoms of critical illness such as resolution of dyspnea (to less than 30 breaths per minute) and fever, non-requirement of ventilators or O_2 therapy, increase of SpO_2 to greater than 93%, together with a negative SARS-Cov-2 test and allowing patients to be discharged from the ICU. The disease severity categories used to define clinical improvement were unclear in 3 studies.[33,48,50]

Clinical status at follow-up was assessed in 12 studies.[29,32,40,42-46,57-59,63] Four studies reported results on disease progression[28,49,51,54] and 1 study reported symptom resolution.[27]

Several outcomes related to the need for, and the duration of, various respiratory supports such as O_2 therapy,[28,43,47,54,62] non-invasive ventilation,[28,31,49,57] mechanical ventilation,[27,28,31,37,47,49,50,52,56,58] and intubation [28,32,36,59] were reported in 13 studies. Need for, or duration of, ICU admission was measured in 6 studies.[37,40,50,58,59,61]

The duration of hospitalization or length of stay was reported in 19 studies.[27,29,31,32,34,36,37,39,41,46-50,56,58-60,62]

Measures of viral clearance such as negative nasopharyngeal swab testing or negative reverse transcriptase-polymerase chain reaction tests were reported in 7 studies.[26,33,35,41,51,57,59] The antibody response after treatment was measured in 2 studies.[33,35]

Renal complications such as the occurrence of acute kidney injury were reported in 2 NRSs.[55,57] One of these studies[57] reported the outcome as an adverse event. The need for renal replacement therapy was reported in 1 RCT.[32]

The need for vasopressor support was reported in 1 RCT.[27]

The question of whether there were adverse events in the CP groups was reported in 30 studies.[26-29,31-36,38-41,43-47,49-54,56-59,62] Whether there were adverse events in the control groups was reported in 3 RCTs[28,29,32] and 2 NRSs.[57,58] Among them, 2 studies reported adverse events in patients who received standard care alone,[28,29,32,57] 2 studies in patients who received placebo,[28,29] and 1 study in patients who received remdesivir.[58]

The duration of follow-up in the included studies ranged from 3 days[38] to 3 months[53] post-CP transfusion. The most common follow-up duration was 28 to 30 days (17 studies).[26,27,29,31,32,39,44,47,49-52,56,57,61-63] Nine studies followed patients either until the end of the study,[40,42,58,59] or until they were discharged or deceased.[34,36,41,46,60] The length of follow-up was unclear in 5 studies.[35,37,45,48,55]

Summary of Critical Appraisal

The key strengths and limitations of the studies[26-29,31-35,37-63] included in this report are summarized herein. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 3.

Randomized Controlled Trials

Overall, the evidence from 6 RCTs[26-29,31,32] were considered moderate to high quality and the evidence from 3 RCTs[33-35] were considered low-to-moderate quality. Strengths and limitations of the RCTs are subsequently summarized.

Strengths

The included RCTs[26-29,31-35] had clearly described objectives, and detailed reporting regarding the population, intervention, comparator, and outcomes. In each RCT, the participants were enrolled from multiple study sites over the same time period and were representative of the population who would be eligible for treatment with CP. Details on the volume, dose, timing, and administration of CP were provided, together 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 (≥ 1:1000) was used in 3 trials.[26,28,32] Although the optimal antibody titer for clinical effectiveness is not yet known, FDA eIND guidelines suggest using CP with a titer of > 1:160.[67,68] Two RCTs were double-blinded and placebo-controlled.[28,29] Outcome assessors were blinded to participant groups in the RCT by Li et al.[26] but not the RCT by Agarwal et al.[27] For all RCTs,[26-29] the main study findings were reported clearly, with simple outcomes data. Random variability in data were considered in reporting using IQRs and 95% confidence intervals (CIs).

The number of participants who dropped out of the studies after randomization was relatively small. Specifically, in the largest trial (RECOVERY), 39 patients (less than 1%) withdrew consent but were included in the intention-to-treat analysis.[32] In 2 trials, one patient each, in each group, was lost to follow-up.[27,34] In the Li et al. study, 1 patient in the CP group withdrew and 1 patient in control group was given CP; they were included in the CP and control groups, respectively, for the primary analysis.[26] In the study by Libster et al., 5 patients (3 in the CP group and 2 in the control group) received CP or placebo after they had the primary end point event (i.e., progression to severe disease) and 1 patient in the CP group did not receive CP transfusion due to hypoxemia.[28] The authors conducted intention-to-treat analysis in 3 of these RCTs.[26-28] In 2 studies, 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.[29,34]

Limitations

The main limitation of the study by Li et al.[26] was that it was terminated early because of 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 the onset

of symptoms to CP therapy was 30 days. It has been suggested that the administration of CP early in the disease could be more beneficial in diseases with viral etiology.[69]

In the study by Agarwal et al.,[27] about a third of patients screened for the study were not enrolled. It was unclear whether the patients who were excluded because of non-eligibility and those who declined to participate were different from the enrolled patients. The antibody titer of the donor CP and the serum antibody titer of the patients were not assessed prior to transfusion. When assayed retrospectively, it was found that the median antibody titer 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 titer than their own baseline levels. 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 if present.

The RCT by Libster et al.[28] 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.[28]

In the RCT by Simonovich et al., although the patients who were excluded from the study due to various reasons 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.[29]

In the study by Pouladzadeh et al., participants in the CP group had a significantly higher proportion of underlying disease compared to those in the control group; however, this was assessed using adjusted analyses. In addition, some outcomes (e.g., clinical improvement) were poorly defined and the antibody titer in the administered CP was not measured.[34] These factors could lower the internal validity of the results.

Regarding the RCT by Hamdy Salman and Ail Mohamed, although the study was reported as double-blinded, there was no placebo control and it was unclear how blinding was maintained. Second, the categories of the 4-point scale used to measure the clinical improvement was unclear. Third, the relatively short follow-up time of 5 days was likely not enough to identify patient improvement. Lastly, although it was reported that patients were randomized based on a 2:1 ratio to the control and CP groups, the final randomized sample included an equal number of participants in each group.[33]

In the RCT by Rasheed et al., it was unclear whether appropriate randomization methods were used. Overall, the available information was insufficient to appraise the methodology.[35]

Lastly, although the RECOVERY trial was well-designed with few limitations, 965 patients were excluded from the study because of the unavailability of CP. It is possible that these excluded patients were different from those who were included.[32]

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 study follow-up time points. In 5 studies, the open-label design meant neither participants nor the treating clinicians were blinded to the intervention groups.[26,27,31,32,34] Standard treatment, including steroids and

antivirals, was given to patients in both groups, as needed, which could affect the outcomes.[26-29,31-35] Furthermore, none of the trials were conducted in Canada; therefore, the generalizability to Canadian settings was unclear.

Non-randomized Studies

Overall, the evidence from 14 NRSs[37-42,45-49,51,55,60] was considered of low-quality and the evidence from 14 NRSs[36,43,44,50,52-54,56-59,61-63] was considered of moderate quality. Strengths and limitations of the NRSs are summarized, as follows.

Strengths

The 28 included NRSs had some strengths. [36-63] The study objectives were clearly described in 26 studies.[36-39,41-44,46-63] Twenty studies reported estimates of random variability (e.g., IQR or standard deviation) and used appropriate statistical tests to compare treatment groups.[36-42,44,45,49,50,52-55,58,59,61-63] The prospective studies had reliable compliance with the interventions and had no patients lost to follow-up.[36,38,43,44,50,53,56,59]

Details of the intervention, such as methods of plasma collection and dose and timing of CP transfusion, were reported in 16 studies. [36,37,39,40,42,44,45,47,49,51,53,54,56,57,59,63] The incidence of adverse events in those participants who received CP transfusion was reported in 23 studies.[36,38-47,49-54,56-59,62,63] Baseline characteristics of patients in each group were described and compared in 24 studies,[36,37,39-46,50-63] and no significant differences in potential confounders like comorbidities or baseline clinical symptoms between the 2 groups were found in 11 of them.[36,40,41,43-45,50,57-59,63] In most studies, as all eligible patients were enrolled in the study, participants were likely to be representative of the entire population from which they were recruited.[36-38,41,43,44,47,48,52,53,55-59,61-63] Overall, the staff, facilities and care received were likely to be representative of the treatment the majority of patients would receive.[36,37,39,42-44,47-59,61-63]

Nine NRSs used propensity score–matching to select controls.[42,43,46,49,50,53,55,59,63] Four studies reported the predefined case control ratios[43,55,59,63] and selected controls without replacement[43,55,59,63] or nearest neighbour.[63] Three studies selected based on predefined variables.[42,43,59] The variables used to match cases and controls were reported in 4 studies.[42,43,59,63] The number of patients and controls excluded due to unmatching was reported in 3 studies.[43,59,63] It is unclear whether these excluded patients could have impacted the results.

Limitations

The included NRSs 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.[36-63] In 6 studies, patients in the control group were selected from a pool of patients treated earlier in the pandemic (historic controls). [38,49,51,54,56,62] Due to the rapidly evolving nature of the pandemic, it is possible that patients treated earlier could have received different standards of care and supportive care.

The antibody titer of the CP used in 14 studies were not reported or not assessed,[37,41,44,46-50,54-58,62] and the timing of CP therapy was not reported in 11 studies.[38,41,43,46,50,52,55,58,60-62] 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.[36-63] In 5 studies, it was unclear how long the participants were followed, including for the all-cause mortality outcome.[35,37,45,48,55] In 9 studies, the outcomes were assessed either at the end of the study,[40,42,58,59] or at the day of discharge or death. [34,36,41,46,60] Therefore, the duration of

standard care for patients in both groups, and the duration between CP therapy and the date of assessment in the CP group, were unclear. Without a specific follow-up period, outcomes such as case fatality rate and mortality have limited clinical relevance. The definitions of outcomes were unclear, limiting the interpretation of results in several studies.[38,42,45,46,48,51,63] For example, in the study by Al Harthi et al., patient status at follow-up was measured as "improved" or "worsened," but how these were defined was unclear.[48] Except for 2 studies,[57,58] none of the included NRSs reported the incidence of adverse events in the control group.

A key limitation that could affect the internal validity of results was the significant differences in baseline characteristics between CP and control groups in the included studies. Baseline characteristics of patients in each group were described and compared in 24 studies.[36,37,39-46,50-63] Characteristics such as age, sex, comorbidities, and disease severity have been shown to affect disease prognosis and outcomes in patients with COVID-19[70] and these factors were significantly different between groups at baseline in 8 studies.[40,51-53,56,58,60,61] These differences could bias the results in favour of CP therapy or in favour of standard care alone. For example, in the Biernat et al. study, significantly more patients in the control group had severe disease compared to those in the CP group; because disease severity is an independent risk factor for mortality, this could skew the results in favour of CP therapy.[51] In 4 studies, patients in the CP group were significantly younger than those in the control group, which could bias prognostic outcomes in favour of CP therapy.[53,56,60,61] The use of concomitant medications could also affect study outcomes. For example, in 2 studies, significantly more patients in the CP group received treatment with systemic corticosteroids compared to those in the control group.[39,62] It is possible that the use of systemic corticosteroids could have affected the study outcomes.

The propensity score-matched studies had some additional limitations.[42,43,46,49,50,53,55,59,63] In 3 of these studies, no details regarding patient selection, matching variables, propensity score, or caliper width were provided.[46,49,50] It was unclear whether testing for proportional hazards assumption prior to Cox regression was done in any of the studies.[42,43,55,59,63] 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.[42,43] As 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. [42,43,46,49,50,53,55,59,63] Immortal time bias occurs when, by design, participants in the exposed group are considered immortal prior to the exposure to treatment (CP), as 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 3 studies it was unclear whether the variables to be included in the propensity score-matching were predetermined or data-driven.[42,55,63] In the study by Kuno et al., the matching variables were not reported.[55]The caliper width of the propensity score for matching was not reported in 2 studies.[55,63] This is important because there were clinically important differences in covariates included in the propensity score between patients who received CP and their controls.[42] The study authors did not consider other important potential confounders like race and ethnicity, and hypertension, in matching[42,59] and in 1 study there was significantly higher use of therapeutic anticoagulation in the CP group compared to the control group.[42] It is possible that these differences may have contributed to some of the differences in outcomes between the groups. It is also possible that those who were excluded (due to unmatching) were different from those included in the study, as the characteristics of excluded patients were not reported. [42,59] In the study by Liu et al., 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.[42] Biernat et al. reported that a principal component analysis was conducted to assess the "correlations between analyzed factors."[51] As very limited details were available in the published article, the appropriateness of such analysis is unclear. In the study by Hatzl et al., IPTW analysis was used to conduct adjusted analysis using propensity scores.[53] IPTW analysis has an advantage over propensity score-matched analysis in preserving power; however, there were some issues in this study that could lower the validity of this analysis. First, the distribution of weights showed that there were high weights (up to 15) that could disproportionately influence the weighted analysis. Second, the variables for adjustment were selected based on a data-driven method, were not predefined, and key variables such as race were not considered. Third, it is possible that there were clinically meaningful differences between groups that were not statistically significant; however, weighted means were not reported.[53]

In the NRS by Rogers et al.,[39] 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.[39] In the study by Moniuszko-Malinowska et al.,[47] 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.[47] The studies by Zeng et al.[41] and Duan et al.[38] had small sample sizes, with a combined total of 16 patients receiving CP therapy.

In several studies, sufficient details were unavailable or unreported to adequately appraise the study methodology.[38,40,41,46,48,55,60] No conclusions can be made based on these results because of unclear and incomplete reporting in the published articles. literature. None of the included studies were conducted in Canada, making the generalizability to Canadian settings unclear because of differences in clinical practices and care.

Summary of Findings

Clinical Effectiveness of Convalescent Plasma Therapy

The 37 included studies in this report provided evidence regarding the clinical effectiveness of CP therapy in patients with COVID-19.[26-29,31-63] Study findings relevant to this report are summarized herein. Appendix 4 presents the main study findings and authors' conclusions.

Mortality

Compared to standard care alone or placebo, 15 studies[26-28,31,32,34,36,37,39,41,50,54-57] (6 RCTs[26-28,31,32,34] and 9 NRSs[36,37,39,41,50,54-57]) found that there were no significant differences in mortality associated with CP therapy. In 13 studies[35,42-44,49,51-53,59-63] (1 RCT[35] and 12 NRSs[42-44,49,51-53,59-63]) CP therapy was associated with significantly lower mortality

compared to standard care alone. Two studies found that time to death was not significantly different between those treated with CP and standard care alone[60] or placebo.[29]

Among the 13 studies that found significantly lower mortality with CP therapy compared to standard care alone, the baseline characteristics were significantly different between the CP and control groups in 5 studies. Specifically, patients in the control group were significantly older,[60,61] had more severe disease,[51] or had more comorbidities,[52] all of which have been shown as factors associated with poorer outcomes in COVID-19;[70] results may have been biased in favour of CP therapy. In 1 NRS, there was a significantly higher rate of use of steroids, remdesivir and tocilizumab in the CP group, which could have affected the outcomes.[62] In 2 studies in which mortality rates were significantly lower in the CP group, it was unclear how long patients were followed in each group.[35,42] In 2 NRSs, there were several methodological limitations such as questionable analyses and reporting issues.[49,51] Therefore, no conclusions can be made based on these results because of methodological limitations and/or unclear and incomplete reporting.

The study by Alsharidah et al.[44] found that 30-day mortality was significantly lower in the CP group compared to the control group (odds ratio = 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.[44] In a subgroup analysis of 1 NRS,[63] among patients younger than 65 years of age, CP therapy was associated with a survival benefit at 28 days compared to propensity score–matched controls (odds ratio = 0.23; 95% CI, 0.05 to 0.95; P = 0.03). However, no similar benefit was observed in the entire study population, even adjusting for variables such as demographics, clinical and laboratory factors, and concomitant treatments.[63] In a study using IPTW analysis to adjust for immunosuppression, SARS-CoV-2 antibody positivity, PaO_2/FiO_2 ratio and the period of infection (first wave versus second wave), there was a significantly lower risk of death in the CP group (adjusted hazard ratio = 0.44; 95% CI, 0.21 to 0.95).[53] Methodological limitations such as excessive weights and a data-driven variable selection process, as previously discussed, could affect the validity of these results. In another propensity score–matched study, CP therapy was associated with a statistically significant small benefit in overall survival (hazard ratio = 0.05; 95% CI, 0.01 to 0.43).[59] Lastly, Salazar et al.(2021)[43] 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 score–matched control groups in the subset of patients who received CP more than 72 hours after admission or in the subset of patients who were intubated on day 0. In the subgroup of patients who received CP with an antibody titer of ≥ 1:1350, mortality rates at days 28 and 60 were significantly lower compared to those in the matched control group.[43]

Compared to remdesivir, those who received CP therapy had a higher rate of mortality.[47,58] This result was statistically significant in 1 NRS[47](3.4% versus 11.2%, P < 0.05) but not the other (27.3% versus 28.3%, P = 0.052).[58] 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).[47]

Clinical Improvement

Five studies found that a significantly higher proportion of patients who received CP therapy achieved clinical improvement compared to those who received standard care alone.[34,38,43-45] Three studies found no significant differences in the proportion of clinically improved patients in CP and control (standard care alone) groups. [26,56,57]

Specifically, 2 studies[43,44] found that a significantly higher proportion of patients who received CP therapy achieved clinical improvement at 30 days[44] and up to 60 days[43] compared to those who received standard care alone. In 1 RCT, significantly more patients in the CP group were clinically improved (on an 8-point scale) by the date of follow-up.[34] CP group patients showed significant improvement in WHO scores from baseline to follow-up; however, the difference in clinical improvement between the groups was not statistically significant.[34] Among COVID-19 patients with diabetes, significantly more patients in the CP group showed clinical improvement compared to the control group (standard care alone), although the length of follow-up was unclear.[45] Another NRS reported that 7 patients (70%) in the CP treatment group improved compared to 1 (10%) in the historic control group.[38] Though reported as statistically significant, the definition of "improved" and the time of outcome measurement was unclear in the control group.

Compared to tocilizumab,[48] remdesivir, or other medications,[47] there were no significant differences in the proportion of clinically improved patients among those who received CP therapy. In the study comparing CP and tocilizumab,[48] the definitions of "improved" or "worsened" were unclear.

Five studies[26,29,35,44,45] compared the median time to clinical improvement between CP and control groups (standard care alone or placebo). Among them, 4 studies[26,35,44,45] found that CP therapy was associated with a significantly shorter time to clinical improvement, while the fifth study[29] did not find any significant difference between the groups.

Specifically, in the study by Alsharidah et al.,[44] 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).[26] No significant differences were found in patients with life-threatening illness. Among patients with COVID-19 and diabetes, the median time to clinical improvement was significantly shorter in the CP group compared to the control group (standard care alone).[45] One RCT found that the mean recovery time from critical illness was almost 4 days shorter in CP recipients compared to those who received standard care alone; this difference was statistically significant. However, the RCT by Simonovich et al. 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.[29] It was noted that these studies used different scales to measure clinical improvement, with 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

Eight studies compared the clinical status or disposition of study participants at various time points of follow-up or at the end of the study.[29,38,40,43,46,58,59,63] Five studies found that the clinical status or disposition of patients at follow-up was not significantly different between CP and the control groups.[29,46,58,59,63] Two studies[38,40,43] (and a subgroup analysis in a third study)[43] reported significant differences in clinical status (in favour of CP therapy) at the time of follow-up.

In studies that showed significant differences, in a subgroup analysis of 1 propensity score–matched study,[43] clinical disposition (death, still admitted, or discharged) at 60 days was significantly different between patients who received CP (with an antibody titer ≥ 1:1350) compared to matched controls who received standard care alone. More patients in the CP group were discharged (92.2%) compared to the control group (86.4%), whereas fewer patients in the CP group were deceased or still admitted.[43] 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.[40] In the NRS by Duan et al.,[38] 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. Although 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).

One NRS that compared CP with remdesivir reported the discharge disposition of patients. The proportion of patients who were discharged from the hospital (to home or a long-term acute care facility) was numerically similar between groups; however, a statistical comparison was not done.[58]

Disease Progression

Five studies found statistically significant differences in favour of CP therapy in disease progression between patients who received CP therapy and those who received standard care alone[28,33,42,49,51] or placebo.[28] Two studies (including the RECOVERY trial) found that disease progression was not different between the 2 groups.[32,54]

In studies in which significant between-group differences were observed, findings from one RCT[28] showed that, among elderly patients with mild COVID-19, significantly fewer patients in the CP group progressed to severe respiratory disease (defined as respiratory rate of > 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 and 15 days (IQR 9 to 15) in the control group (P = 0.03). The number needed to treat to avert 1 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).[28]

The results from 1 trial showed that the proportion of patients with a respiratory rate of > 24/min, SpO_2 ≤ 93% on room air, PaO_2: FiO_2 < 300 mm hg, and pulmonary infiltrates > 50% of both lungs, were all significantly higher in the control group from day 1 to day 5

after randomization, suggesting a comparative decrease in disease severity associated with CP therapy.[33] In 1 study of patients with acute respiratory distress syndrome, by the day of discharge/death, patients in the CP group had less severe illness compared to those in the control group. The PaO_2: FiO_2 was significantly higher and the Acute Physiology And Chronic Health Evaluation (APACHE) scores were significantly lower in the CP group.[49] One NRS reported that significantly fewer patients in the CP group had "worsening oxygenation" by day 14 compared to those in the control group.[28,42] However, the definition of "worsening oxygenation" and how it was measured were not reported and the clinical importance of this result was unclear. One study found no significant differences between CP and control groups in "worsening of O2 support" among patients who were not on ventilator support at baseline.[54] Lastly, in 1 study it was reported that CP recipients had a "milder course of infection" compared to those who received standard care alone.[51] However, unclear definitions pertaining to the course of infection, baseline differences between the groups, and methodological limitations lowered the validity of this finding.

Symptoms

Findings from the RCT by Agarwal et al.[27] 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. Additionally, 1 NRS with methodological limitations and baseline differences between CP and control groups suggested that patients in the CP group had less severe symptoms (fever, shortness of breath, and cough), which were resolved faster.[51]

Respiratory Support (O_2 Therapy)

Evidence from 1 RCT showed that, compared to placebo, the proportion of patients requiring O_2 supplementation was not significantly different in the CP group.[28] However, in a propensity score–matched study, compared to those who received standard care alone, the proportion of patients requiring O_2 supplementation was significantly higher in those who received CP. The risk ratio was 0.99 (95% CI, 0.99 to 0.99), suggesting a small effect.[43] Among those who received supplemental O_2, there was no significant difference in the duration of O_2 requirement.[43]

One study found that the mean duration of the use of non-rebreather masks (a type of high-flow oxygen device) was significantly longer (by an average of 9.6 days) in the CP group compared to standard care group.[62] The duration of the use of nasal cannulas for O_2 was also longer in the CP group; however, this was not statistically significant.[62] These findings could be due to significantly longer survival in CP recipients in this study. Among patients using a non-rebreather or a nasal cannula, there were no differences in the time to improvement in O_2 delivery devices (defined as a decrease of 1 point in O_2 delivery device categories) between CP and standard care groups.[62] The categories ranged from "not on supplemental O_2"(category 1) to "invasive mechanical ventilation" (category 5).[62] In another study, among patients who were not on a ventilator pre-transfusion, the proportion of patients who experienced a "worsening" of O_2 support by 7 days was not significantly different between the CP and standard care groups.[54] Worsening was defined as 2-point deterioration on a 5-point scale that ranged from "no O_2 support" to "mechanical ventilation."[54]

Compared to patients who received remdesivir, a significantly greater proportion of patients who received CP required constant O_2 therapy.[47] Among patients who needed constant O_2 therapy, the duration of O_2 supplementation was significantly longer for patients who were treated with CP. 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 patients who received CP, although the duration of supplementation was not statistically different between the groups.[47]

Respiratory Support (Need for Non-Invasive Ventilation)

Evidence from 4 studies showed that there were no differences in the rates or duration of non-invasive ventilation use between patients who received CP and those who received standard care alone [27,32,49] or placebo.[28] In one NRS, patients in the CP group received non-invasive positive pressure ventilation for a significantly longer duration (by 5 days) compared to those who received standard care alone, possibly due to increased survival time in CP group. The median time to improvement was not significantly different between the groups irrespective of the timing of CP therapy.[62]

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

Compared to standard care alone[27,28,32,43,52,62] or placebo,[28] 6 studies[27,28,32,43,52,62] 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.[37]

Time to mechanical ventilation was not significantly different between the CP and placebo groups in patients with severe COVID-19 in 1 RCT.[29] In the RECOVERY trial, among patients who were on invasive ventilation at baseline, the rate of successful cessation of mechanical ventilation was not different between the CP and control groups.[32] Salazar et al.(2021a)[43] 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.[43]

The rate of mechanical ventilation was numerically higher in patients treated with CP than in those treated with remdesivir; however, this was not statistically significant (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).[47] The median duration of mechanical ventilation was found to be similar in the CP and remdesivir groups in 1 study.[58]

Respiratory Support (Intubation)

Four studies compared the need for and duration of intubation between patients who received CP and those who received standard care alone.[36,49,50,59] Two studies found that the proportion of patients who required intubation,[49,59] and the time to intubation,[59] were not statistically different between the CP group and the control group (standard care alone). In one study among patients with COVID-19 who were not intubated at baseline, however, significantly fewer patients who received CP therapy (7%) were subsequently intubated compared to those who received standard care alone (20%).[36]

In one of the studies in which there was no difference between groups in the proportion of patients who required intubation, among those who did require intubation, significantly more patients in the CP group (22% versus 1.7% in control group) were able to get extubated (suggesting improvement).[59] In the same study, among those who were extubated, time to extubation was not different between the groups.[59] Results from another NRS found that

the duration of intubation was also not different between the CP and standard care groups.[50]

Respiratory Support (Ventilation Status)

Two studies examined the ventilation or respiratory support status of patients using the percentage of patients on respiratory support such as room air, supplemental O_2, non-invasive ventilation, or invasive ventilation.[43,57] Ventilation status measures were not statistically different between patients in the CP group and the control group (standard care alone) at day 28[57] or on days 7, 14, 28, and 60.[43]

Three studies examined the requirement for non-invasive or invasive ventilation among patients who did not require ventilatory support at baseline.[27,31,32] No significant differences were found between the CP and standard care groups in the proportion of patients requiring any ventilator (invasive or non-invasive) support[31,32] or in the duration of such support.[27,31]

ICU Admission

Four studies found no differences in the rates of ICU admission between patients who were treated with CP and those who received standard care alone[28,40,43,59] or placebo.[28]

Among the patients who were admitted to the ICU, 4 studies found no difference in the duration of ICU stay,[29,43,50,58] but 3 retrospective studies[37,61,62] found that CP recipients stayed in the ICU for a significantly shorter duration (by 2 to 3 days) compared to those who received standard care alone[43,50,58,59] or placebo.[29] In one of these studies, significantly more patients in the CP group were admitted to the ICU at study baseline, which could affect the average duration of ICU stay.[61] In one NRS, significantly more patients in the CP group (22%) were able to be discharged from the ICU compared to those in the standard care group (3.4%).[59]

Compared to patients treated with remdesivir, there was statistically no difference in the length of stay in ICU in CP recipients. In the CP group, the median duration of stay in the ICU was 6 days (IQR 5 to 10.5 days); however, there was only 1 patient in the remdesivir group who was admitted to ICU (whose ICU stay was 27 days).[58]

Length of Hospital Stay

Overall, CP therapy was not associated with a shorter stay in the hospital compared to standard care alone. There were no significant differences in the rates of hospital discharge at 28 days (3 studies)[26,32,57] or the overall length of hospital stay (11 studies) [26,27,29,31,34,37,39,43,49,56,59] between patients who received CP therapy and those who received standard care alone or placebo. Four studies found a significantly longer hospital stay[46,50,60,62] in those treated with CP. In these studies, CP recipients were hospitalized for a median of 1.5 days[50] to 8 days[46] longer than their control group counterparts. One study with methodological limitations (unclear dosage and volume of CP, unclear follow-up time) found a significantly shorter hospital stay among CP recipients compared to those in the control group.[36]

In the 2 studies that compared CP therapy with remdesivir, 1 study found that patients treated with CP were hospitalized for a significantly shorter duration[47] and the other found no significant difference in length of hospital stay between the groups.[58] The former study also found that 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).[47]

Viral Clearance

Six studies examined the rate of viral clearance (measured as negative polymerase chain reaction [PCR] tests or negative nasopharyngeal swab test) following CP or standard care.[26,27,33,41,57,59] Three studies (2 RCTs[26,27] and 1 NRS[41]) found that CP therapy was associated with significantly higher rates of SARS-CoV-2 viral clearance, whereas 2 NRSs found no difference between the groups.[57,59] Lastly, one study found that by day 5, none of the patients (in either group) had a negative nasopharyngeal swab test to indicate viral clearance.[33]

Regarding studies that indicated a significant result, 1 RCT[26] 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. 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 3 times.[26] Similarly, findings from another RCT[27] also showed significantly higher rates of negative seroconversion at 7 days after transfusion in the CP group. However, since the median antibody titer of the transfused CP was lower than the median titer in the recipients, it is possible that the improvement was not directly due to CP therapy. According to the findings from 1 NRS,[41] all patients in the CP therapy group (n = 6) obtained viral clearance by the study end point compared to 26.7% of patients (n = 4) in the control group.

The duration of infection, defined as time to SARS-CoV-2 negativity together with improvement in signs and symptoms, was reported in 1 RCT. Compared to the standard care group, the duration of infection was 4.1 days shorter in the CP group.[35] The duration of infection was also significantly shorter in the CP group versus the standard care group (by 19 days) in another study among COVID-19 patients with hematological malignancies, although the definition of “duration of infection” was unclear.[51] This study also had several methodological limitations (e.g., baseline differences between groups in disease severity and concomitant treatments, reporting issues), as outlined in earlier sections. Therefore, these results should be interpreted with caution. [51] Lastly, in 1 NRS, the duration of viral shedding was not significantly different between the CP and standard care groups.[41]

Antibody Response

Two RCTs measured the antibody response in study participants.[33,35] One study found that, by day 3 post-baseline, significantly more patients in the CP group (n = 21/21; 100%) tested weakly, moderately, or strongly positive for SARS-CoV-2 IgG antibodies compared to those in the standard care group (n = 7/28; 25%).[35] Similarly, all CP recipients tested positive for SARS-CoV-2 IgM antibodies by day 3 compared to 28.6% of those who received standard care alone.[35] In another RCT, 60 to 80% of patients in the CP group had neutralizing antibodies from day 1 to day 5, whereas these were undetected in any of the control group patients.[33]

Duration of Illness

Two studies found that no significant difference in the median duration of illness (defined as time to complete restoration of health or recovery) between CP and control (standard care alone or placebo) groups (15[29] to 16.5[50] days and 15 days[29,50] in the CP and control groups, respectively). In contrast, 2 studies found that the duration of illness was longer in patients who received CP compared to those who received standard care alone.[40,41] The NRS by Zeng et al.[41] 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 or death) was 45.5 days (IQR: 37.8 days to 59 days), which was significantly longer than that in the control group (31 days; IQR: 30 days to 36 days). Similarly, results from the study by Xia et al.[40] 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 3 of these studies,[29,41,50] there was no significant difference in mortality between CP therapy and control groups, while in the NRS by Xia et al.,[40] mortality was lower in the CP group compared with the control group, as previously described. Taken together, these findings suggest that patients may have survived longer with CP therapy.

Vasopressor Support

One RCT found that the proportion of moderately ill patients with COVID-19 who required vasopressor support was not significantly different between those who received CP and those who received standard care alone.[27]

Renal Complications

Findings from 2 NRSs showed that there was no significant difference in the rate of occurrence of acute kidney injury between patients who received CP and those who received standard care alone.[55,57] In one of these studies, acute kidney injury was reported as an adverse event.[57] Additionally, results from the RECOVERY trial showed that there were no significant differences in the proportion of patients who required renal replacement therapy in the CP and standard care groups.[32]

Adverse Events

Adverse events in the CP and control groups (standard care[32,57] or placebo[28,29]) were reported in 4 studies.[28,29,32,57] Among them, 2 studies[29,57] statistically compared the rates of adverse events between CP and respective comparators, and found no significant differences in the rates of overall, serious, or infusion-related adverse events compared to placebo,[29] or any adverse changes in laboratory parameters (e.g., bilirubin rise, hypernatremia, hypokalemia) compared to standard care alone.[57] In the RECOVERY trial in which approximately 11,500 patients were enrolled, 21% of patients in the CP group and 22% of patients in the standard care group reported a “sudden worsening” of respiratory status within 72 hours after starting treatment. Occurrences of other adverse events (e.g., sudden hypotension, clinical hemolysis, thrombotic events) were reported (in ≤ 3% of patients) and were similar between the groups.[32] Lastly, in 1 study, several adverse events (e.g., allergic reaction, thrombophlebitis, vasovagal syndrome, hematoma at site) were measured in the CP and placebo groups; however, no adverse events were reported in either group.[28]

The RCT by Agarwal et al.[27] reported that there were 3 deaths in the CP group (out of a total of 235 participants) that were “possibly related” to CP transfusion. No additional details were reported. Across the studies, there were 2 instances each of TACO[39,43] and TRALI.[39] Severe adverse events reported across the studies included transfusion-related dyspnea (n = 3),[26,43,59] severe transfusion reaction (n = 3),[26,32,58] and severe allergic reaction (n = 23).[29,32,44]

Other non-severe or transient adverse events in patients who received CP were fever (n = 206),[27,29,32,36,54,59] local skin reactions, redness or rashes (n = 21),[26,27,35,38,40,43,46,52,59] shortness of breath (n = 3),[27,43] or unexplained or technical events (n = 3).[27,29] Thirteen

studies reported that there were no adverse events associated with CP transfusions.[28,33,34,41,45,47,49-51,53,56,62,63] There were 2 instances of infusion-related events (both allergic reactions) in the placebo group of an RCT.[29]

Lastly, 1 study measured adverse events in both the CP and remdesivir groups.[58] There were 4 instances of transaminitis and 2 instances of acute kidney injury among patients treated with remdesivir (out of 11 patients). Two patients in the CP group (out of 53 patients) reported infusion reactions. In the same study, there were 3 instances of QT prolongation (in an electrocardiogram) because of azithromycin; however, it was unclear if these patients received CP or remdesivir.[58]

Limitations

The main limitation of this report was the lack of high-quality evidence regarding the clinical effectiveness of CP therapy in patients with COVID-19. In most of the included studies,[26,27,36-46] patient outcomes could also have been affected by the provision of standard care, which was not standardized and was given to both groups based on the decisions of the treating physicians 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,10 studies measured the outcome "clinical improvement" using disease severity scales that had 6,[26,29,40,43,45,57] 7,[44] 8,[34,47] or 10[56] points. 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 previously.

No evidence was found for the effectiveness of CP therapy in pediatric populations. 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. Nine eligible RCTs[26-35] and 28 NRSs[36-63] were identified and included in this report. They 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. 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 15 of the included studies showed no significant differences in mortality between patients who received CP and those who received standard care alone[26,27,31,32,34,36,37,39,41,50,54-57] or placebo,[28] and 13 studies[35,42-44,49,51-53,59-63] found statistically significant survival benefits in CP recipients compared to controls; however, most of the studies had substantial methodological limitations, as previously outlined, and the validity of the results is uncertain.

Findings regarding “clinical improvement” were also somewhat mixed. For instance, 5 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.[34,38,43-45] However, 3 studies found no significant difference between those treated with CP and standard care.[26,56,57] Similarly, the time to clinical improvement was significantly shorter in patients treated with CP therapy compared to those treated with standard care in 4 studies,[26,35,44,45] but there were no significant differences between treatment groups in an RCT.[29] 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 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.[28] 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.[27]

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 the requirement of respiratory support such as O_2 therapy,[28,43,62] non-invasive ventilation,[27,28,32,49] mechanical ventilation,[27,28,33,43,52,62] or intubation.[49,59] One limited-quality study[37] 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;[36] both studies compared to standard care alone. Similarly, the rates of hospital discharge[26,30,32,57] and the length of hospital stay[26,27,29,31,34,37,39,43,49,56,59] were not significantly different between patients who received CP therapy and those who received standard care alone or placebo. Four studies found significant differences in the duration of hospitalization between the CP and control groups (1 favourable to CP[36] and the others favourable to standard care[46,50,62]). 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 3 studies[26,27,41] showed that CP recipients had higher rates of viral clearance (indicated by negative PCR tests) compared to those who received standard care, while 2 NRSs found no difference between the groups.[57,59] Low- to moderate-quality evidence from 2 NRSs[40,41] 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 (1 study found lower mortality among CP recipients[40] and the other found no differences between the groups[41]), this suggests that patients may have survived longer with CP therapy.

Three relevant low- to moderate-quality studies were identified that compared the effectiveness of CP with that of other active therapies.[47,48,58] In general, the evidence suggested that CP may be less effective than remdesivir or other medications. Compared to remdesivir, CP therapy was associated with significantly higher mortality,[47,58] longer duration of hospitalization,[47] and a higher proportion of patients requiring O_2 supplementation[47] and mechanical ventilation.[47] Evidence from 1 low-quality study suggested that the proportion of patients who improved or worsened were similar in those treated with CP compared to those treated with tocilizumab.[48] 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).[47]

Overall, although adverse events due to CP therapy were relatively infrequent, CP therapy was not free of risks. Compared to standard care alone[32,57] or placebo,[29] the rates of adverse events were similar in the CP group, as found in 3 studies.[29,32,57] In another study in which adverse events in CP and placebo groups were measured, no adverse events were reported in either group. In the RECOVERY trial, in which approximately 11,500 patients were enrolled, 21% of patients in the CP group and 22% of patients in the standard care group reported a "sudden worsening" of respiratory status within 72 hours of treatment.[32] The most common adverse events in CP recipients (n = 8,540) across all studies in which they were reported were fever (n = 206)[27,29,32,36,54,59] and allergic skin rashes, itching, or redness (n = 21).[26,27,35,38,40,43,46,52,59] One study[27] reported 3 deaths that were "possibly related" to CP transfusion (out of 235 patients). As for the important adverse events related to CP transfusion,[12] there were 2 incidences of TACO,[39,43] 2 of TRALI,[39] 3 of severe transfusion-related dyspnea,[26,43,59] 3 of severe transfusion reaction,[26,32,58] and 23 of allergic reactions among CP recipients.[29,32,44] In 1 study,[58] out of 11 patients who received remdesivir, there were 4 instances of transaminitis and 2 instances of acute kidney injury. There were also 2 instances of infusion reactions reported among CP recipients (out of 53 patients) and 3 instances of QT prolongation reported among all study participants (patients' treatment arms unclear) in that study.[58] Most of the included studies did not report whether there were adverse events in the control groups.[26,27,31,33-43,45-56,59-63]

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.[71-75] 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.[76-79] 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 and meta-analysis included 13 studies (12 RCTs and 1 NRS). The authors concluded that treatment with CP therapy is not associated with a reduction in all-cause mortality and has no effect on clinical improvement.[80] This is consistent with the conclusions of this report. 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, together 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[81] of CP therapy (donor-related issues like autonomy, consent, and the medical and psychosocial condition of the convalescent patients) are other factors that may be considered in decision-making regarding the use of CP.[82]

COIVID-19 is a highly infectious disease that 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.

References

1. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). Geneva (CH): World Health Organization; 2020: www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report. Accessed 2020 May 15.
2. World Health Organization. WHO Coronavirus disease (COVID-19) dashboard 2020; https://covid19.who.int/. Accessed 2021 Jun 16.
3. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. 2020; https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed 2020 May 15.
4. Public Health Agency of Canada. Coronavirus disease (COVID-19): outbreak update. 2020; https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection.html. Accessed 2021 Jun 16.
5. Clinical management of patients with COVID-19: second interim guidance. Ottawa (ON): Public Health Agency of Canada; 2020: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html#a1. Accessed 2021 June 16.
6. National Institutes of Health. Clinical spectrum of SARS-CoV-2 infection. 2021; https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed 2021 Jun 16.
7. WHO R&D blueprint: COVID 19 landscape of experimental treatments. Geneva (CH): World Health Organization; 2020: https://www.who.int/publications-detail/covid-19-landscape-of-experimental-treatments. Accessed 2020 May 15.
8. Health Canada. Pfizer-BioNTech COVID-19 vaccine: authorization information. 2020; https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/vaccines/pfizer-biontech/authorization.html. Accessed 2021 Jan 29.
9. Health Canada. Drug and vaccine authorizations for COVID-19: list of authorized drugs, vaccines and expanded indications. 2020; https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/list-drugs.html. Accessed 2021 Jun 16.
10. Position paper on use of convalescent plasma, serum or immune globulin concentrates as an element in response to an emerging virus. Geneva (CH): WHO Blood Regulators Network (BRN); 2017: https://www.who.int/bloodproducts/brn/2017_BRN_PositionPaper_ConvalescentPlasma.pdf?ua=1 Accessed 2020 May 15.
11. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest.* 2020 Apr 7.
12. Pandey S, Vyas GN. Adverse effects of plasma transfusion. *Transfusion.* 2012;52 Suppl 1(Suppl 1):65S-79S.
13. Transfusion transmitted injuries surveillance system 2011 - 2015 summary report. Vol 2020. Ottawa (ON): Public Health Agency of Canada 2019: https://www.canada.ca/en/public-health/services/publications/drugs-health-products/transfusion-transmitted-injuries-surveillance-system-ttiss-2011-2015-summary-results.html. Accessed 2020 May 22.
14. Roubinian N. TACO and TRALI: biology, risk factors, and prevention strategies. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):585-594.
15. Petraszko T. Transfusion-related acute lung injury (TRALI). *Canadian Blood Services* 2019; https://professionaleducation.blood.ca/en/transfusion/publications/transfusion-related-acute-lung-injury-trali. Accessed 2020 Jun 10.
16. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest.* 2020;130(4):1545-1548.
17. Wan Y, Shang J, Sun S, et al. Molecular mechanism for antibody-dependent enhancement of Coronavirus entry. *J Virol.* 2020;94(5):e02015-02019.
18. Hamilton Health Sciences Corporation. NCT04348656: CONvalescent plasma for hospitalized adults with COVID-19 Respiratory illness (CONCOR-1). *Clinicaltrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2020: https://clinicaltrials.gov/ct2/show/NCT04348656?id=NCT04348656&draw=2&rank=1&load=cart. Accessed 2020 May 13.
19. U.S Food and Drug Administration. Recommendations for investigational COVID-19 convalescent plasma. 2020; https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. Accessed 2020 Aug 24.
20. Canadian Blood Services. COVID-19 and convalescent plasma. 2020; https://blood.ca/en/convalescentplasma. Accessed 2020 May 13.
21. Rashid A. Canadian researchers lead world's largest convalescent plasma therapy trial for COVID-19. *Xtalks* 2020; https://xtalks.com/canadian-researchers-lead-worlds-largest-convalescent-plasma-therapy-trial-for-covid-19-2202/. Accessed 2020 May 13.
22. Dalal M, Doig C, Laupacis A. Paying for plasma – Canada's double standard? *HealthyDebate* 2014; https://healthydebate.ca/2014/04/topic/cost-of-care/paying-plasma. Accessed 2020 May 13.

23. Convalescent plasma therapy for the treatment of COVID-19: clinical effectiveness. *(CADTH Rapid response report: reference list)*. Ottawa (ON): CADTH; 2020: https://cadth.ca/sites/default/files/covid-19/RA1113%20Convalescent%20Plasma%20COVID.pdf. Accessed 2020 May 15.

24. Brooker J, Synnot A, McDonald S, Elliott J, Turner T. Guidance for the production and publication of Cochrane living systematic reviews: Cochrane reviews in living mode (version December 2019). London (UK): Cochrane Community; 2019: https://community.cochrane.org/sites/default/files/uploads/inline-files/Transform/201912_LSR_Revised_Guidance.pdf. Accessed 2020 May 26.

25. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.

26. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA.* 2020;324(5):460-470.

27. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ.* 2020;371:m3939.

28. Libster R, Perez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med.* 2021;06:06.

29. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med.* 2020.

30. Liu Z. Errors in trial of effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19. *JAMA.* 2020;324(5):518-519.

31. AlQahtani M, Abdulrahman A, Almadani A, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. *Sci Rep.* 2021;11(1):9927.

32. Recovery Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet.* 2021;14:14.

33. Hamdy Salman O, Ail Mohamed HS. Efficacy and safety of transfusing plasma from COVID-19 survivors to COVID-19 victims with severe illness. A double-blinded controlled preliminary study. *Egypt J Anaesth.* 2020;36(1):264-272.

34. Pouladzadeh M, Safdarian M, Eshghi P, et al. A randomized clinical trial evaluating the immunomodulatory effect of convalescent plasma on COVID-19-related cytokine storm. *Intern Emerg Med.* 2021;10:10.

35. Rasheed AM, Fatak DF, Hashim HA, et al. The therapeutic potential of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. *Infezioni in Medicina.* 2020;28(3):357-366.

36. Abolghasemi H, Eshghi P, Cheraghali AM, et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study. *Transfus Apher Sci.* 2020:102875.

37. Altuntas F, Ata N, Yigenoglu TN, et al. Convalescent plasma therapy in patients with COVID-19. *Transfus Apher Sci.* 2020:102955.

38. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A.* 2020;117(17):9490-9496.

39. Rogers R, Shehadeh F, Mylona EK, et al. Convalescent plasma for patients with severe COVID-19: a matched cohort study. *Clin Infect Dis.* 2020;10:10.

40. Xia X, Li K, Wu L, et al. Improved clinical symptoms and mortality on severe/critical COVID-19 patients utilizing convalescent plasma transfusion. *Blood.* 2020;23:23.

41. Zeng QL, Yu ZJ, Gou JJ, et al. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *J Infect Dis.* 2020;29:29.

42. Liu STH, Lin H-M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study. *Nat Med.* 2020.

43. Salazar E, Christensen PA, Graviss EA, et al. Significantly decreased mortality in a large cohort of Coronavirus disease 2019 (COVID-19) patients transfused early with convalescent plasma containing high-titer anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spike protein IgG. *Am J Pathol.* 2021;191(1):90-107.

44. Alsharidah S, Ayed M, Ameen RM, et al. COVID-19 convalescent plasma treatment of moderate and severe cases of SARS-CoV-2 infection: a multicenter interventional study. *Int J Infect Dis.* 2020;04:04.

45. Dai W, Wu J, Li T, et al. Clinical outcomes for COVID-19 patients with diabetes mellitus treated with convalescent plasma transfusion in Wuhan, China. *J Med Virol.* 2020;07:07.

46. Jiang W, Li W, Xiong L, et al. Clinical efficacy of convalescent plasma therapy on treating COVID-19 patients: evidence from matched study and a meta-analysis. *Clin Transl Med.* 2020;10(8):e259.

47. Moniuszko-Malinowska A, Czupryna P, Zarębska-Michaluk D, et al. Convalescent plasma transfusion for the treatment of COVID-19-experience from Poland: a multicenter study. *J Clin Med.* 2020;10(1).

48. Al Harthi S, Osali MA, Kindi NA, et al. Characteristics of the first 102 severe COVID-19 cases treated with convalescent plasma or tocilizumab or both in Al-Nahdha Hospital, Oman. *Health Serv Res Manag Epidemiol.* 2021;8:2333392820986639.

49. Allahyari A, Seddigh-Shamsi M, Mahmoudi M, et al. Efficacy and safety of convalescent plasma therapy in severe COVID-19 patients with acute respiratory distress syndrome. *Int Immunopharmacol.* 2021;93:107239.

50. AlShehry N, Zaidi SZA, AlAskar A, et al. Safety and efficacy of convalescent plasma for severe COVID-19: interim report of a multicenter phase II study from Saudi Arabia. *Saudi J Med Med Sci.* 2021;9(1):16-23.

51. Biernat MM, Kolasinska A, Kwiatkowski J, et al. Early administration of convalescent plasma improves survival in patients with hematological malignancies and COVID-19. *Viruses.* 2021;13(3):08.

52. Budhiraja S, Dewan A, Aggarwal R, et al. Effectiveness of convalescent plasma in Indian patients with COVID-19. *Blood Cells Mol Dis.* 2021;88:102548.

53. Hatzl S, Posch F, Sareban N, et al. Convalescent plasma therapy and mortality in COVID-19 patients admitted to the ICU: a prospective observational study. *Ann Intensive Care.* 2021;11(1):73.

54. Klapholz M, Pentakota SR, Zertuche JP, et al. Matched cohort study of convalescent COVID-19 plasma treatment in severely or life threateningly ill COVID-19 patients. *Open Forum Infect.* 2021;8(2):ofab001.

55. Kuno T, Takahashi M, Egorova NN. The association between convalescent plasma treatment and survival of patients with COVID-19. *J Gen Intern Med.* 2021;13:13.

56. Kurtz P, Righy C, Gadelha M, et al. Effect of convalescent plasma in critically ill patients with COVID-19: an observational study. *Front Med (Lausanne).* 2021;8:630982.

57. Omrani AS, Zaqout A, Baiou A, et al. Convalescent plasma for the treatment of patients with severe coronavirus disease 2019: a preliminary report. *J Med Virol.* 2021;93(3):1678-1686.

58. Padilla R, Arquiette J, Mai Y, Singh G, Galang K, Liang E. Clinical outcomes of COVID-19 patients treated with convalescent plasma or remdesivir alone and in combination at a community hospital in California's Central Valley. *J Pharm Pharm Sci.* 2021;24:210-219.

59. Pappa V, Bouchla A, Terpos E, et al. A phase II study on the use of convalescent plasma for the treatment of severe COVID-19- a propensity score-matched control analysis. *Microorganisms.* 2021;9(4):11.

60. Pei S, Yuan X, Zhang Z, et al. Convalescent plasma to treat COVID-19: clinical experience and efficacy. *Aging (Albany N Y).* 2021;13(6):7758-7766.

61. Salazar MR, Gonzalez SE, Regairaz L, et al. Risk factors for COVID-19 mortality: the effect of convalescent plasma administration. *PLoS ONE.* 2021;16(4):e0250386.

62. Shenoy AG, Hettinger AZ, Fernandez SJ, Blumenthal J, Baez V. Early mortality benefit with COVID-19 convalescent plasma: a matched control study. *Br J Haematol.* 2021;192(4):706-713.

63. Yoon HA, Bartash R, Gendlina I, et al. Treatment of severe COVID-19 with convalescent plasma in Bronx, NYC. *JCI Insight.* 2021;6(4):22.

64. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.

65. RECOVERY collaborative group. 2021; https://www.recoverytrial.net/. Accessed 2021 Jun 16.

66. U.S. Food & Drug Administration. EUA Authorized Serology Test Performance-EUROIMMUN SARS-COV-2 ELISA (IgG). 2021; https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance. Accessed 2021 Jun 21.

67. Clinical memorandum: COVID-19 convalescent plasma (EUA 26382). Silver Spring (MD): U.S. Food & Drug Administration; 2020: https://www.fda.gov/media/141480/download. Accessed 2020 Nov 4.

68. Psaltopoulou T, Sergentanis TN, Pappa V, et al. The emerging role of convalescent plasma in the treatment of COVID-19. *HemaSphere.* 2020;4(3):e409.

69. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis.* 2015;211(1):80-90.

70. Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review. *PLoS One.* 2020;15(11):e0241955-e0241955.

71. Ahn JY, Sohn Y, Lee SH, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. *J Korean Med Sci.* 2020;35(14):e149.

72. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA.* 2020;27:27.

73. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol.* 2020;15:15.

74. Zhang B, Liu S, Tan T, et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. *Chest.* 2020;31:31.

75. Salazar E, Perez KK, Ashraf M, et al. Treatment of COVID-19 patients with convalescent plasma. *Am J Pathol.* 2020;190(8):P1680-1690.

76. AminJafari A, Ghasemi S. The possible of immunotherapy for COVID-19: a systematic review. *Int Immunopharmacol.* 2020;83:106455.

77. Devasenapathy N, Ye Z, Loeb M, et al. Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis. *CMAJ.* 2020;22:22.

78. Rajendran K, Narayanasamy K, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: systematic review. *J Med Virol.* 2020;01:01.

79. Valk SJ, Piechotta V, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *Cochrane Database Syst Rev.* 2020;5:CD013600.

80. Piechotta V, Iannizzi C, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database Syst Rev.* 2021;5:CD013600.

81. Ethics of using convalescent whole blood and convalescent plasma during the Ebola epidemic. Interim guidance for ethics review committees, researchers, national health authorities and blood transfusion services. Geneva (CH): World Health Organization; 2015: https://apps.who.int/iris/bitstream/handle/10665/161912/WHO_HIS_KER_GHE_15.1_eng.pdf;jsessionid=89438F40209D3EDE3C58183513BF66E5?sequence=1. Accessed 2020 May 22.

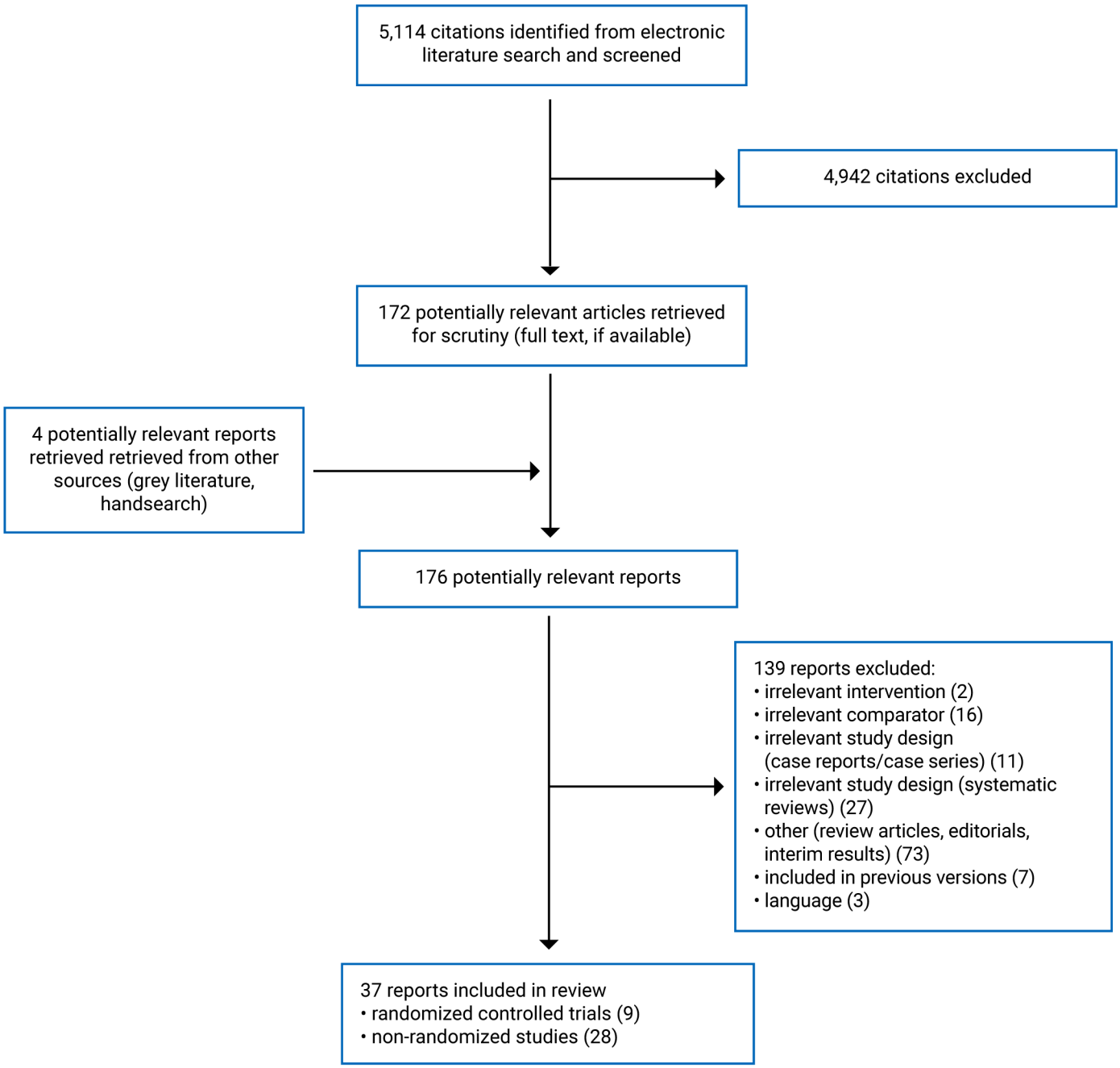
82. Munir MA, Tandiabang PA, Setyawati T, Basry A, Cyio AD, Rahman N. Bioethical perspective of convalescent plasma therapy for COVID-19: a systematic review. *Transfus Clin Biol.* 2021:S1246-7820(1221)00043-00044.

83. Salazar E, Christensen PA, Graviss EA, et al. Treatment of COVID-19 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol.* 2020.

84. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. Geneva (CH): World Health Organization; 2020: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed 2020 May 14.

Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has been formatted for accessibility but has not been copy-edited.

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				
AlQahtani et al., 2021[31] **Country: Bahrain** **Funding source:** Ministry of Health Bahrain and the College of Surgeons in Ireland-Bahrain	**Study design:** Open-label randomized controlled study **Objective**: To compare the effectiveness of CP therapy and standard therapy in COVID-19 patients with pneumonia and hypoxia	Patients (≥ 21 years) with PCR-confirmed COVID-19 **Inclusion criteria**: hypoxia (as SaO2< 92% on air); PO2<60mmHG arterial blood gas, PaO_2: FiO_2 < 300 mm hg or needing O2 therapy; pneumonia confirmed by chest imaging **Exclusion criteria**: mild disease, normal chest imaging, need for ventilatory support (non-invasive or mechanical), negative PCR test, history of allergy to plasma, autoimmune disease or IgA deficiency. **Number of participants**: Total number of participants, N = 40 CP group, n = 20 Control group, n = 20 **Mean age (SD), years:** CP group = 52.6 (14.9) Control group = 50.7 (12.5)	**Intervention:** ABO compatible CP *Dose:* 2 doses over 2 consecutive days *Volume:* 200 mL per dose **Comparator**: Standard therapy alone **Concomitant medications**: All patients received standard care including antivirals, tocilizumab and antibiotics	**Primary outcome:** Need for invasive or mechanical ventilation and the duration **Secondary outcome:** improvement in biomarkers, 28-day mortality **Length of follow-up:** 28 days

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Sex: CP group: 15% females Control group: 25% females		
Libster et al., 2021[28] **Country:** Argentina **Funding source:** Bill and Melinda Gates Foundation and the Fundación INFANT Pandemic Fund	**Study design:** Open-label, parallel arm, phase II, multi centre 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 2 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	**Intervention:** CP with an IgG titer >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 (Respiratory rate >30/min or SpO2 < 93% on ambient air) **Secondary end points:** Life-threatening illness (O2 supplementation, invasive or non-invasive 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
		disease, anticoagulant treatment, physician determined contraindications. **Number of participants**: Total number of participants, N = 160 CP group, n = 80 Control group, n = 80 **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		
Pouladzadeh et al., 2021[34] **Country:** Iran **Funding source:** NR	**Study design:** Parallel group, single blind, randomized controlled trial **Objective**: To evaluate the impact of CP therapy on modulation of cytokine storm	Patients with severe COVID-19 confirmed with PCR and CT scan. **Inclusion criteria**: Less than 7 days since onset of symptoms, WHO severity score >4, SpO2 <93% on room air, no hypersensitivity to plasma administration. **Exclusion criteria**: NR **Number of participants**: Total number of participants, N = 60 CP group, n = 30 Control group, n = 30	**Intervention:** *Dose:* At least one dose, with second dose if no improvement *Volume:* 500 mL *Timing*: First unit within 4 hours after admission, second dose after 24 hours if there was no improvement (physicians' decision) **Comparator**: Standard care alone **Concomitant medications**: All patients received standard care including Ritonavir/Lopinavir and chloroquine phosphate	**Primary outcome:** Levels of cytokine storm indices (not relevant to the current report) **Secondary end points:** Length of hospital stay, 2-month mortality (after admission), Clinical improvement as measured with 8-point WHO scale, adverse events. **Length of follow-up:** Outcomes were measured on date of discharge from the hospital

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 = 53.5 (10.3) Control group = 57.2 (17) **Sex:** CP group: 46.7 % females Control group: 43.3% females		
RECOVERY Collaborative group, 2021[32] **RECOVERY** **Country:** UK **Funding source:** University of Oxford from UK Research and Innovation and NIHR(MC_PC_19056), Department of Health and Social Care (DHSC), UKRI, and NIHR COVID 19 Rapid Response Grant (COV19-RECPLA), NIHR Oxford Biomedical Research Centre, Wellcome Trust, Bill & Melinda Gates Foundation, Department for International Development, Health Data Research UK, Medical Research Council Population Health Research Unit, NIHR Health Protection Unit in Emerging and Zoonotic Infections, NHS Blood and Transplant Research and Development Funding, EUs Horizon 2020 research and innovation programme	**Study design:** Multicenter, open-label, adaptive platform RCT **Objective**: To evaluate the efficacy and safety of CP therapy in patients hospitalizes with COVID-19.	Patients (of any age) hospitalized with COVID-19 **Inclusion criteria:** Clinically suspected or lab confirmed COVID-19 **Exclusion criteria:** Medical history that could put patients ats significant risk (physicians' judgment) **Number of participants**: Total number of participants, N = 11,558 CP group, n = 5795 Control group, n = 5763 **Mean age (SD), years:** CP group = 63.5 (14.7) Control group = 63.4 (14.6) **Sex:** CP group: 37% females Control group: 34% females	**Intervention:** ABO compatible CP *Dose:* 5mL/kg, up to 2 doses *Volume*: 275 (200 to 350 mL) *Timing*: first dose at randomization and second dose at least 12 h later. CP with EUROIMMUN sample to cut-off ratio of ≥6 were used, which correlates with 1:1000 antibody titer **Comparator**: Usual care **Concomitant medications**: Patients in both groups received supportive care and medications including corticosteroids, lopinavir/ritonavir, dexamethasone, hydroxychloroquine, azithromycin, colchicine aspirin.	**Primary outcome:** all-cause mortality **Secondary outcome:** time to discharge from hospital, composite outcome of need for invasive ventilation/ECMO/ death (among patients not mechanically ventilated at baseline) **Other outcomes:** need for any ventilation and duration, renal replacement therapy and thrombotic events **Safety outcomes:** bleeding, new major cardiac arrythmias, sudden worsening in respiratory status, severe allergic reaction, significant fever, sudden hypotension, and clinical hemolysis. **Length of follow-up:** Patients were followed up till death, discharge or 28 days post-randomization (whichever is earlier)

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
(SUPPORT-E - 101015756), and NIHR Clinical Trials Unit Support Funding				
Agarwal et al., 2020[27] (PLACID trial) **Country:** India **Funding source:** Indian Council of Medical Research (ICMR)	**Study design:** Open-label, parallel arm, phase II, multi centre randomized controlled trial. **Objective**: To investigate the effectiveness and safety of CP therapy in moderate COVID-19	Adult patients with confirmed COVID-19 based on positive RT-PCR test. **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 mm hg, 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:**	**Intervention:** ABO compatible CP with standard of care *Volume:* 2 doses of 200 mL CP. *Administration*: 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).	**Primary outcome:** Composite progression to severe disease (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.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		CP group: 25% females Control group: 23% females		
Hamdy Salman et al., 2020 [33] **Country: Egypt** **Funding source:** Not reported	**Study design:** Double-blinded preliminary RCT **Objective**: To assess the efficacy and safety of CP therapy in patients with severe COVID-19	Patients (≥ 18 years) with COVID-19 confirmed with nasopharyngeal swab **Inclusion criteria**: Respiratory rate ≥24/min, SaO2< 93% on room air, PaO_2: FiO_2 < 300 mm hg, pulmonary infiltrates >50% of both lungs **Exclusion criteria**: prior allergic history to plasma or plasma products, septic shock, multiple organ failure. **Number of participants**: Total number of participants, N = 30 CP group, n = 15 Control group, n = 15 **Median age (IQR), years:** CP group = 58 (49 to 68) Control group = 57 (50 to 67) **Sex:** CP group: 26.67% females Control group: 33.3% females	**Intervention:** CP and standard care *Volume: 250mL* *Timing: days from hospitalization to randomization, median (IQR), days: 13 (11 to 16)* **Comparator**: Standard care alone Standard care included supplemental O2, non-invasive/invasive ventilation, antibiotics, inotrope drugs, renal replacement therapy, anticoagulants, glucocorticoids, intravenous fluids, interferon, ECMO	**Primary end point:** At least 50% improvement in severity of illness within 5 days after transfusion (defines as 2-point reduction on the 4 category illness scale) **Secondary end points:** improvement of laboratory parameters, detection of neutralizing antibodies within 5 days after transfusion, adverse events **Length of follow-up:**5 days after transfusion with assessment at every day.
Li et al., 2020[26,30] **Country:** China **Funding source:** Chinese Academy of Medical Sciences Innovation Fund for	**Study design:** Open-label randomized clinical trial **Objective**: To evaluate the	**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,	**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	**Primary end point:** Time to clinical improvement. *Clinical improvement definition:* Decrease of 2 points on the disease severity scale. *Disease severity scale:*

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
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	efficacy and safety of CP therapy using a standardized approach in donor selection and CP quality control	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 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 mm hg *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	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 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.	Hospital discharge: 1 point; Hospitalization with no supplemental oxygen: 2 points; Hospitalization plus supplemental oxygen (not high-flow or non-invasive ventilation: 3 points; Hospitalization plus non-invasive ventilation or high-flow supplemental oxygen: 4 points; Hospitalization plus ECMO or invasive mechanical ventilation: 5 points; Death: 6 points **Secondary outcomes:** 28-day mortality, duration of hospitalization, viral clearance from nasopharyngeal swab **Time to follow-up:** 28 days from randomization

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		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 to76) **Sex:** CP group: 48.1% females Control group:35.3% females		
Rasheed et al., 2020[35] **Country: Iraq** **Funding source:** Alkharkh General Directorate of Health, Alkadymia, Baghdad, Iraq under fund order CC-104	**Study design:** Open-label RCT **Objective**: To assess the safety and efficacy of CP	Patients (≥ 21 years) with COVID-19 **Inclusion criteria**: Critical illness, pneumonia, admitted to respiratory care units within previous 3 days, receiving O2 therapy or on ventilation **Exclusion criteria**: previous history of allergy to plasma or its ingredients, serious general condition such as severe organ dysfunction, very late stage of ARDS **Number of participants**: Total number of participants, N = 43 CP group, n = 21 Control group, n = 28 **Mean age (SD), years:** CP group = 55.66 (17.83) Control group = 47.82 (15.36)	**Intervention:** ABO compatible plasma with an IgG index >1.25 and standard care *Volume:* 400 mL *Administration*: transfused over 2 hours with continuous monitoring **Comparator**: Standard care alone **Standard care included:** *Hydroxychloroquine:* 200mg BD for at least 10 days *Azithromycin:* 500mg/day loading dose +250mg per day for 5 days *Oxygen therapy* *Methylprednisolone:* 40mg/day after admission to respiratory care unit.	**Primary end point:** Safety within 3 hours post-transfusion **Secondary end points:** time till viral clearance, improvement in signs and symptoms (relief od sever dyspnea, no need for ventilators or O2 therapy, resolution of fever, decrease in RR to <30/min, increase of SpO2 >93%), duration to clinical improvement (recovery time from critical illness), survival or death **Length of follow-up:** Total follow-up was unclear; safety assessment was done at 3 hours post-CP, viral clearance was assessed daily until 5 days post-CP.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Sex: CP group: 25% females Control group: 25% females		
Simonovich et al., 2020[29] (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 centre 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 mm hg, SOFA score or modified SOFA score of 2 or more above baseline status. **Exclusion criteria**: pregnancy, lactation, absence of contraceptive measures for 30 days after enrolment (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	**Intervention:** CP with median neutralizing antibody titer 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

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		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		
Non-randomized studies				
Al Harthi et al., 2021[48] **Country: Oman** **Funding source: Non-funded**	**Study design:** Retrospective case control **Objective**: to detail the characteristics of patients with severe COVID-19 treated with CP, tocilizumab or both	Patients (≥18 years) hospitalized with laboratory confirmed COVID-19 **Inclusion criteria:** severe or life-threatening COVID-19 or at high risk of severe or life-threatening COVID-19 (assessed by physician) *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 **Exclusion criteria**: NR **Number of participants**: Total number of participants, N = 102 CP group, n = 20 Tocilizumab group, n = 61 Both treatments, n = 21	**Intervention: CP** *Dose: 2 transfusions 24 hours apart* *Volume: 200 to 500 mL (overall)* *Timing: 3.7 days (SD 4.8) from admission* **Comparator**: Tocilizumab Timing: *7.8 days (SD 5.1) from admission* Tocilizumab was administered to patients with abnormal findings in Chest imaging, SaO_2< 93%, and or requiring >6L/min of O_2 **Concomitant medications**: All patients received supportive care, steroid, antibiotics and heparin. Hydroxychloroquine, ritonavir/lopinavir, interferons were also given.	**Primary end point:** clinical improvement grouped as improved (discharged) vs worsened (death or transferred for critical care) **Secondary end points:** length of hospital stay **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
		Mean age (SD), years: 52.2 (15.2) (mean age per group not reported) **Sex:** Overall: 18.6% females (proportion of females per group not reported)		
Allahyari et al., 2021[49] **Country: Iran** **Funding source: Mashhad University of Medical Sciences**	**Study design:** Retrospective observational with matched historic controls **Objective**: To investigate the efficacy of CP therapy in COVID-19 patients with ARDS	Adult patients with laboratory confirmed COVID-19 **Inclusion criteria**: ARDS resulted from COVID-19; PaO_2: FiO_2 < 250 despite first-line treatment with hydroxychloroquine, corticosteroid and broad-spectrum antibiotics; normal IgA levels; absence of uncontrolled hypertension; absence of comorbidities such as heart failure, chronic liver disease or COPD; systolic blood pressure ≥ 90 mm hg on admission; not intubated; Glasgow coma scale score ≥ 12 and a glomerular filtration rate ≥30. **Exclusion criteria**: allergy to plasma product; unwilling to provide consent Participants in the treatment group were those who were treated from September or November 2020. Participants in the control group were the historic group pf patients treated during March 2020.	**Intervention:** ABO compatible CP *Dose:* *Volume: 600 mL* *Administration*: slow with continuous monitoring *Timing*: Duration from admission to CP transfusion, mean = 4.41 days (range 3 to 11 days) **Comparator**: Standard care alone **Concomitant medications**: NR	**Primary end point:** Mortality at 4 weeks **Secondary end points:** length of hospital stay, need for mechanical ventilation, SOFA score, APACHE score **Length of follow-up:** 28 days with outcome assessments done at 0 and 3 days, and date of discharge or death

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Control group participants were randomly selected from previously treated patients-matched for disease severity, age, sex, first-line treatment, comorbidities (hypertension and diabetes) and "symptom day." **Number of participants**: Total number of participants, N = 64 CP group, n = 32 Control group, n = 32 **Mean age (SD), years:** CP group = 58.74 (14.67) Control group = 55.53 (14.10) **Sex:** CP group: 43.8 % females Control group: 43.8 % females		
Al Shehry et al., 2021[50] **Country: Saudi Arabia** **Funding source:** Ministry of Health, Kingdom of Saudi Arabia; King Abdullah International Medical Research Center, Riyadh, Saudi Arabia	**Study design:** Multi-centre, prospective open-label observational (interim results) **Objective**: To test the feasibility, safety, and efficacy of CP in treating patients with COVID-19.	Patients (≥18 years) with RT-PCR–confirmed COVID-19 **Inclusion criteria**: Severe symptoms, required ICU care or had life-threatening illness *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,	**Intervention:** ABO compatible CP *Dose:* at least once and up to 5 sessions (once daily) *Volume:* 300 mL *Administration*: monitored for adverse events **Comparator**: Standard care alone **Concomitant medications**: Not reported	**Primary end point:** Length of stay in ICU or designated are for critical patients; serious adverse events **Secondary end points:** Number of days on mechanical ventilation, 30-day mortality, days to clinical recovery (as defined by the Ministry of Health**)** **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
		septic shock, and/or multiple organ dysfunction **Exclusion criteria**: Negative or inconclusive RT-PCR test, mild symptoms, and non-requirement of ICU care Control group participants comprised those who either did not consent for CP therapy, did not receive CP due to lack of availability or historic control (matched for age, sex, intubation status, history of diabetes and hypertension) **Number of participants**: Total number of participants, N = 164 CP group, n = 40 Control group, n = 124 **Mean age (SD), years:** CP group = 50.25 (14.90) Control group = 52.59 (12.79) **Sex:** CP group: 17.5 % females Control group: 16.1 % females		
Biernat et al., 2021[51] **Country: Poland** **Funding source:** Medical Research Agency Poland, grant number 2020/ABM/	**Study design:** Retrospective observational study with a historic control	Patients with hematological malignances who have RT-PCR–confirmed COVID-19. **Inclusion criteria**: Not reported **Exclusion criteria**: Not reported	**Intervention:** CP *Dose:* one or more unit of CP with an IgG Titer > 1:1000 *Volume:* 200-250 mL per dose *Administration*: 10 mL for the first 10 min then increased to 200 mL per 30 min.	**Outcomes:** Overall survival, disease severity, symptom resolution, viral clearance **Length of follow-up:** follow-up assessments were done on days 0, 7, 14, 21 and 28 after disease onset.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Covid-19/0005	**Objective**: to evaluate the efficacy and safety of CP therapy in patients with hematological malignancies	Participants in the treatment group were those who were treated from September or November 2020. Participants in the control group were the historic group pf patients treated during March 2020. **Number of participants**: Total number of participants, N = 45 CP group, n = 23 Control group, n = 22 **Median age (range), years:** CP group = 57 (31 to 72) Control group = 62.5 (20 to 80) **Sex:** CP group: 39% females Control group: 36% females The hematological malignancies diagnosed in the participants included Acute Leukemia (51%), Chronic Lymphocytic Leukemia (13%), Aggressive lymphoma (18%) and multiple myeloma (13%). The distribution of these between the study groups were similar.	*Timing*: 48-72 hours after diagnosis of COVID-19 **Comparator**: "other therapy" **Concomitant medications, n (%)**: *hydroxychloroquine:* CP group = 0 Control group = 22 (100) *Dexamethasone:* CP group = 8 (34.8) Control group = 212 (54.8) P value = 0.18 *Other treatment (Tocilizumab, Remdesivir, Lopinavir/Ritonavir*): CP group = 3 (13) Control group = 9 (41) P value = 0.034	Patients were followed up until recovery or death.
Budhiraja et al., 2021[52] **Country: India** **Funding source: Not reported**	**Study design:** Multicenter, retrospective, observational case-control study	Patients (≥18 years) with RT-PCR–confirmed COVID-19. **Inclusion criteria**: Patients with moderate or severe disease requiring O2 therapy	**Intervention:** CP with plaque neutralizing antibody (IgG) titer 1:40 to 1:160 *Dose: 2 units* *Volume: 400 mL over 2 days* *Administration*: 1 unit per 1.5 hours	**Primary outcome:** 28-day mortality **Secondary outcomes:** need for invasive ventilation, mortality in critically ill patients

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	Objective: To investigate whether CP therapy is associated with a mortality benefit in COVID-19 patients	*Moderate COVID-19* was defined as pneumonia with no signs of severe disease and or more of the following: a) dyspnea, fever and cough, b) SPO_2< 94%, on room air and c) respiratory rate ≥ 24/min *Severe COVID-19* was defined as clinical signs of pneumonia and one or more of the following: respiratory rate ≥ 30/min, SPO_2< 90% on room air, severe respiratory distress requiring ventilation, ARDS, sepsis, septic shock. **Exclusion criteria**: pregnant and lactating women, patients not requiring O2 therapy **Number of participants**: Total number of participants, N = 1097 *In ICU*: Total number of participants, N = 694 CP group, n = 333 Control group, n = 361 **Mean age (SD), years:** CP group = 60 (12.1) Control group = 58.9 (13.8) **Sex:** CP group: 19.8% females Control group: 27.7% females	**Comparator**: Best supportive care **Concomitant medications**: patients in both groups received a range of medications including hydroxychloroquine, antibiotics, ivermectin, remdesivir, anticoagulants, steroids and tocilizumab	**Length of follow-up:** 28 days

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Hatzl et al., 2021[53] **Country: Austria** **Funding source: City of Graz Research Grant**	**Study design:** Prospective cohort study **Objective**: To evaluate the effects of CP therapy in overall survival in severely ill COVID-19 patients with acute respiratory failure	Patients (≥18 years) with PCR-confirmed COVID-19. **Inclusion criteria**: Respiratory failure of any grade, treatment in ICU **Exclusion criteria**: Selective IgA deficiency, end-stage renal or hepatic failure, prior history of allergic reaction to blood products, lack of consent. CP was restricted to eligible patients with acquired or inborn immunodeficiency or those with negative SARS-CoV-2 antibody status at the time of ICU admission. Patients with prior CP therapy, non-pulmonary reason for ICU admission, insufficient follow-up data, or with pulmonary co-infection with *P.jirovecci* were excluded from the analysis. **Number of participants**: Total number of participants, N = 120 CP group, n = 48 Control group, n = 72 **Median age (IQR), years:** CP group = 61 (53 to 72) Control group = 69 (55 to 76)	**Intervention:** CP with at least 30 AU/mL of neutralizing IgG antibodies *Dose:* 2-3 doses of CP with a median anti–SARS-CoV-2 antibody of 79.2 AU/mL (IQR: 77 to 150) *Volume:* Median volume 600 mL (IQR: 600 to 600) *Administration*: 400 mL on day 1 and 200 mL on day 2, or 200 mL/day for 3 days *Timing*: Median time from symptom onset to transfusion: 4 days (IQR 1 to 10 days) **Comparator**: Standard care alone **Concomitant medications**: Patients in both groups received hydroxychloroquine (13%) glucocorticoids (100%), remdesivir (17%) and tocilizumab (5%)	**Primary outcome:** 3 month overall survival, 30 day ICU survival (co-primary outcome) **Length of follow-up:** 3 months

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Sex: CP group: 25% females Control group: 33% females		
Klapholz et al., 2021[54] **Country: USA** **Funding source: No external funding**	**Study design:** Retrospective matched cohort study **Objective**: To report on the safety and efficacy of CP therapy.	Patients with severe or life-threatening COVID-19. CP group participants were those who received CP as part of the eIND and expanded access IND. Control group participants were recruited from those who were admitted when CP was not available. CP group was matched to control group 1:1 using individual level matching based on sex, race, ethnicity, age, level of O_2 support, duration of O_2 support prior to CP. *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 **Exclusion criteria**: contraindication to transfusion, severe multiorgan failure, other documented uncontrolled infections, severe DIC, acute renal failure needing dialysis, active	**Intervention:** ABO compatible CP *Dose: 1 unit at baseline and up to 2 additional units.* *Volume: 200mL per unit.* *Timing*: *Mean 4.9 days (SD 3.2) from admission* **Comparator**: Standard care alone **Concomitant medications**: Patients in both groups received a range of medications including IL-6 inhibitor, doxycycline or azithromycin, hydroxychloroquine, steroids and anticoagulants. Remdesivir was not given to any patients.	**Outcomes:** Mortality at day 7, worsening of O_2 support at day 7 (based on a 5 level O_2 support scale), composite outcome or both at day 7, laboratory markers O_2 worsening was defined as 2 point deterioration on a 5-level O_2 support scale: 1- Room air 2- Nasal cannula 3a- high-flow nasal cannula or face mask 3b- CPAP or BiPAP 4- Mechanical ventilation **Safety:** allergic reactions, TRALI, TACO **Length of follow-up:** 7 days

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		intracranial bleeding, or clinically significant myocardial ischemia **Number of participants**: Total number of participants, N = 94 CP group, n = 47 Control group, n = 47 **Mean age (SD), years:** CP group = 58 (13.0) Control group = 57.7 (13.7) **Sex:** CP group: 38.3% females Control group: 38.3% females		
Kuno et al.,2021[55] **Country: USA** **Funding source: Not reported**	**Study design:** Retrospective observational study **Objective:** to assess the association between CP therapy and mortality in COVID-19 patients	All patients with laboratory confirmed COVID-19 **Inclusion criteria**: Not reported **Exclusion criteria**: Not reported Patients in the control group were selected based on propensity score matching (1:1) without replacement. **Number of participants**: Total number of participants, N = 9565 CP group, n = 1113 Control group, n = 8452 *PS matched pairs:* CP group, n = 960 Control group, n = 960	**Intervention: CP** **Comparator**: Other treatment **Concomitant medications**: Patients in both groups received a range of medications including therapeutic anticoagulation, steroids, remdesivir, or Interleukin-6 inhibitor	**Primary outcome:** In-hospital mortality **Secondary outcomes:** acute kidney injury (creatinine ≥ 1.5 times the level at baseline or an increase of ≥ 0.3mg/dL) **Length of follow-up:** Unclear

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 = 64.8 (16.1) Control group = 65 (17.1) *PS matched pairs:* CP group =64.5 (16.2) Control group 64.9 (16.1) **Sex:** CP group: 40% females Control group: 46% females *PS matched pairs:* CP group: 40% females Control group: 39.1% females		
Kurtz et al., 2021[56] **Country: Brazil** **Funding source:** Fundação de Amparo a Pesquisa do Estado do Rio de Janeiro (FAPERJ), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Secretária de Estado de Saúde do Rio de Janeiro, Fundação Saúde do Estado do Rio de Janeiro and Instituto Serrapilheira	**Study design:** Prospective observational study **Objective**: to assess the effect of CP therapy in clinical improvement and 28-day mortality in critically ill COVID-19 patients.	RT-PCR–confirmed COVID-19 patients admitted to ICU Patients admitted between March 17 and April 18th were included in control group Patients admitted between April 18th and May 30th to ICU or were intubated for up to 3 days were considered for CP therapy **Exclusion criteria**: negative RT-PCR, life expectancy < 24 h **Number of participants**: Total number of participants, N = 113 CP group, n = 41 Control group, n = 72	**Intervention:** ABO compatible CP *Dose: Up to 2 doses* *Volume: 200-250 mL* *Timing*: Up to 3 days after ICU admission **Comparator**: Standard care alone **Concomitant medications**: Patients in both groups received medications including hydrocortisone, methylprednisolone, dexamethasone, and anticoagulants.	**Primary outcomes:** Clinical improvement (2-point reduction in a 10-point scale), 28-day survival **10-point scale:** <4- ambulatory 4- Hospitalized on room air 5- O2 my mask/prongs 6- Non-invasive ventilation or high-flow cannula 7- Intubated and mechanically ventilated PaO_2: FiO_2 ≥150 8- Mechanical ventilation and PaO_2: FiO_2 < 150 9- Mechanical ventilation and PaO_2: FiO_2 < 150, vasopressors, dialysis, or ECMO 10-Death

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Median age (IQR), years: CP group = 58 (45 to 64) Control group = 63 (49 to 71) **Sex:** CP group: 36.6 % females Control group: 40% females		**Secondary end points:** Safety, Biomarkers **Length of follow-up:** 28 days
Omrani et al., 2021[57] **Country: Qatar** **Funding source: Non-funded**	**Study design:** Retrospective observational **Objective**: To assess the clinical benefits of CP in patients with severe COVID-19	Patients with laboratory confirmed severe COVID-19 *Severe COVID-19* was defined as respiratory rate ≥ 30/min; SaO_2< 90%, PaO_2: FiO_2 < 300; hypotension or any organ failure. **Inclusion criteria**: requirement of mechanical ventilation, completed 28 day follow-up by June 1, 2020, CP recipients should have received CP within 7 days of ICU admission E**xclusion criteria**: Not reported **Number of participants**: Total number of participants, N = 80 CP group, n = 40 Control group, n = 40 **Median age (IQR), years:** CP group = 47.5 (39 to 60.5) Control group = 55.5 (46.5 to 60.5) **Sex:** CP group: 15% females Control group: 12.5% females	**Intervention:** ABO compatible CP *Volume: 400mL* *Timing*: within 7 days of ICU admission **Comparator**: Standard care alone **Concomitant medications**: Patients in both groups received medications including hydroxychloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, methylprednisolone (for ARDS).	**Primary outcome:** improvement in respiratory status (2 point difference on a 6-point scale) **6-point scale:** 6-Death 5- Invasive mechanical ventilation 4- non-invasive ventilation or high-flow nasal O2 3-O2 therapy 2-hospitalization without O2 1-discharge **Secondary outcomes:** viral clearance (2 consecutive negative RT-PCR tests 24 h or more apart), discharge status at day 28 **Length of follow-up:** 28 days

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Padilla et al.,2021[58] **Country: USA** **Funding source: Non-funded**	**Study design:** Retrospective observational **Objective**: to evaluate the clinical outcomes of COVID-19 patients treated with CP, Remdesivir or both	Patients (≥18 years) with RT-PCR–confirmed COVID-19. **Criteria for CP therapy**: shortness of breath, RR >30/min, $SpO_2 \leq 94\%$ on room air, PaO_2: $FiO_2 < 300$; progression of lung infiltrates within 24-48 hours, respiratory failure, septic shock, multiple organ dysfunction **Criteria for Remdesivir therapy:** Symptom onset ≤ 10 days, $SpO_2 \leq 94\%$ on room air or on supplemental O2, age <81 years, duration of mechanical ventilation <24 hours, GFR ≥ 30mL/min, AST/ALT <5 times upper limit normal **Number of participants**: Total number of participants, N = 106 CP group, n = 53 Remdesivir group, n = 11 CP + Remdesivir group, n = 42 (not relevant to the current report) **Median age (IQR), years:** CP group = 61 (48 to 67) Remdesivir group = 56 (54 to 68) **Sex:** CP group: 35.8% females Control group: 27.3% females	**Intervention:** CP therapy *Dose:* 1 to 2 doses *Volume:* 200mL per dose *Administration*: Infused over 30 min **Comparator**: Remdesivir ,Remdesivir +CP(not relevant to the current report) *Remdesivir dose*: 200 mg intravenous on day1, then 100 mg daily for the duration of the treatment. **Concomitant medications**: Patients in all groups received medications including azithromycin, steroids and high intensity statin	**Primary outcome:** Survival **Secondary outcome:** discharge disposition, length of hospital stay, length of ICU stay, duration of ventilation, adverse events **Length of follow-up:** From date of first positive PCR test (dates unclear) to end of data collection period (August 31, 2020)

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Pappa et al.,2021[59] **Country: Greece** **Funding source:** SYNENOSIS, Intramural Research Program of the National Cancer Institute, Federal funds from the National Cancer Institute, National Institutes of Health. No external funding	**Study design:** Multicenter Phase II prospective observational study with propensity score matched analysis **Objective**: To assess the efficacy and safety of CP treatment in hospitalized patients with COVID-19.	Patients (≥18 years) with ≥ grade IV COVID-19 disease (based on WHO criteria), diagnosis confirmed with RT-PCR test **Inclusion criteria**: symptom onset within 10 days, severe or life-threatening disease, signed informed consent to receive CP *Severe COVID-19* was defined as respiratory rate ≥ 30/min; SaO_2< 93% (FiO_2 = 0.21), CRP >1.5 (NR <0.4) or > 3x upper normal limit; Ferritin >100 ng/mL; PaO_2: FiO_2 < 300; pulmonary infiltrates on chest imaging *Life-threatening COVID-19* was defined as respiratory failure, septic shock, multiple organ dysfunction; intubation duration > 72 hours Patients in the control group included those with same criteria as above but did not provide consent for CP therapy. They were matched based on age, sex, SOFA score, time from symptom onset to diagnosis, and concomitant use of dexamethasone **Number of participants**: Total number of participants, N = 118	**Intervention:** single donor ABO compatible CP *Dose:* 3 doses in days 1, 3 and 5 *Volume:* 200 to 233mL each *Administration*: infusion over 30 to 60 min *Timing*: Median time from symptom onset to CP transfusion was 7 days Median level of IgG anti-S1 antibodies in the CP:3.42 (EUROIMMUN assay) **Comparator**: standard care alone **Concomitant medications**: Patients in both groups received medications including dexamethasone	**Primary end point:** Survival at 28 days **Secondary end points:** Time to clinical improvement (patients not fulfilling criteria for severe disease), safety, length of hospitalization, duration of stay in ICU, duration of ventilation/ECMO, time to negative SARS-CoV-2 PCR test. **Length of follow-up:** Day 1: day of hospitalization. *Median length of follow-up:* CP group: 29 days Control group: 10 days (P < 0.001) Outcomes were assessed at day 14, day 28 and end of follow-up.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		CP group, n = 59 Control group, n = 59 **Median age, years:** CP group = 59 Control group = 59 **Sex:** CP group: 32.2% females Control group: 37.3% females		
Pei et al., 2021[60] **Country: China** **Funding source: Not reported**	**Study design:** Retrospective observational study from **Objective**: to assess the effectiveness of CP therapy	Patients with severe or critical COVID-19 **Inclusion criteria** for CP: Duration of disease < 3 weeks, positive nucleic acid test, severe or critical illness as assessed by physicians, long-term (>4weeks) positivity of nucleic acid test. **Exclusion criteria** for CP: Congenital IgA deficiency, history of allergy to plasma products, irreversible multiple organ damage Control group patients were selected from 2 provinces (Hunan and Hubei) using a “stratified random sampling method” based on age, sex and disease severity. **Number of participants**: Total number of participants, N = 62 CP group, n =19 Control group:	**Intervention:** ABO compatible CP, with IgG antibody titer> 1:160 *Dose:* 4-5 mL/kg *Volume:* 200 to 500 mL *Administration*: slow infusion for the first 15 minutes **Comparator**: No treatment with CP **Concomitant medications**: Not reported	**Outcomes:** Fatality rate, length of stay **Length of follow-up:** Patients were followed up until discharge or death. Median follow-up time not reported.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		Hunan, n = 23 Hubei, n = 20 **Mean age (SD), years:** CP group = 66.3 (15.3) Control group: Hunan, n = 57.3 (15.0) Hubei, n = 69.1 (14.3) **Sex:** CP group: 42.1% females Control group: Hunan, n = 35.1% females Hubei, n = 40.1% females		
Salazar et al., 2021(a)[43,83] **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.[83] This version includes the final results.	**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 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	**Intervention:** ABO compatible CP *Volume:* one or 2 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 <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	**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 status, need for supplemental O2. *Clinical improvement definition:* Decrease of 1 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 non-invasive ventilation: 3 points; Hospitalization plus non-invasive ventilation or high-flow supplemental oxygen: 4 points; Hospitalization plus ECMO

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		saturation level less than 93% in room air; PaO_2 ≤ 300 mm hg; 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	including antivirals, steroids, hydroxychloroquine, Tocilizumab and azithromycin according to physician's decision.	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
		Median age (IQR): Not reported **Sex:** CP group:42.8 % females Control group:45.1% females		
Salazar et al., 2021 (b)[61] **Country: Argentina** **Funding source:** Not funded	**Study design:** Multicenter cohort study **Objective**: To determine the risk factors for 28-day mortality in COVID-19 patients who received CP and those who did not.	Patients (≥18 years) with RT-PCR–confirmed COVID-19 and are hospitalized. **Eligibility criteria for CP therapy**: Dyspnea with respiratory rate ≥ 30/min, SaO_2< 93%, O2 requirement, PaO_2: FiO_2 < 300, progression of lung infiltrates within 24-48 hours, altered consciousness, multiple organ dysfunction, age. 65 years, comorbidities such as arterial hypertension, diabetes, cardiovascular disease, COPD, immunodeficiency. **Number of participants**: Total number of participants, N = 3259 CP group, n = 868 Control group, n = 2661 **Mean age (SD), years:** CP group = 56 (13) Control group =64 (17) **Sex:** CP group: 41.9% females Control group: 30.9% females	**Intervention:** CP with IgG antibody titer ≥1:1400 *Dose:* 1 dose for patients <70 kg weight ,2 doses for those >70 kg. *Volume:* 200- 250 mL/unit **Comparator**: No CP therapy **Concomitant medications**: Not reported	**Primary Outcome:** 28-day mortality: **Secondary end points:** Length of ICU stay **Length of follow-up: 28 days**

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Shenoy et al., 2021[62] **Country: USA** **Funding source:** US Department of Health and Human Services, Biomedical Advanced Research and Development Authority grant, contract 75A50120C00096, National Center for Advancing Translational Sciences grant UL1TR002377, Schwab Charitable Fund, United Health Group, National Basketball Association (NBA), Millennium Pharmaceuticals, Octopharma USA, Inc., and the Mayo Clinic	**Study design:** Retrospective matched cohort study **Objective**: To assess the efficacy of CP for hospitalized COVID-19 patients	Patients (≥18 years) with RT-PCR–confirmed COVID-19. **Inclusion criteria**: Hospitalized patients who has severe or life-threatening illness CP group patients were matched by age, sex, preceding length of stay, and O2 delivery device. Control group patients were treated prior to CP recipients (mean 29 days prior) **Number of participants**: Total number of participants, N = 526 CP group, n = 263 Control group, n = 263 **Mean age (SD), years:** CP group = 55.93 (14.01) Control group = 56.1 (14.0) **Sex:** CP group: 36.5% females Control group: 36.5% females	**Intervention:** ABO compatible CP *Dose:* 1-2 doses *Volume, mean (SD)* = 245.6 (144.4)mL **Comparator**: Standard care alone **Concomitant medications**: Patients in both groups received medications including hydroxychloroquine, azithromycin, systemic steroids, remdesivir, tocilizumab, sarilumab.	**Primary outcome:** All-cause mortality **Secondary outcome:** Improvement in oxygenation, length of hospital stay. **Length of follow-up:** 28 days, with assessment at 7 and 14 days
Yoon et al., 2021[63] **Country: USA** **Funding source:** NR	**Study design:** Retrospective observational study with propensity scored matched controls. **Objective**: To report on the	Patients with nasopharyngeal PCR-confirmed COVID-19. **Inclusion criteria**: admitted within 3 days and symptomatic for ≤7 days, severe or life-threatening COVID-19.	**Intervention:** ABO compatible CP *Dose:* 1 dose, median neutralizing antibody titer was 1:938 (IQR 407 to 2784) *Volume:* 200mL *Administration:* Over 2to 3 hours and monitored *Timing*: within 72 hours of admission	**Primary outcome:** All-cause mortality **Secondary outcome:** improvement in oxygenation status, clinical status at day 28 **Length of follow-up:** 28 days from baseline

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	mortality and clinical and laboratory findings in patients with severe or life-threatening COVID-19 receiving CP therapy	*Severe COVID-19* was defined as respiratory symptoms with hypoxemia requiring ≥ 5L O2 support (nasal cannula) *Life-threatening COVID-19* was defined as respiratory failure, requiring mechanical ventilation, septic shock, multiple organ dysfunction Control group patients were selected based on propensity score matching by age, sex, BMI, race, ethnicity, comorbidities, steroids, anticoagulation, baseline O2 requirement, D-dimer, lymphocyte counts, week of admission **Number of participants**: Total number of participants, N = 146 CP group, n = 73 Control group, n = 73 **Median age (IQR), years:** CP group = 67 (55 to 75) Control group = 66 (56 to 77) **Sex:** CP group: 43.8% females Control group: 35.6% females	**Comparator**: Standard care alone **Concomitant medications**: Patients in both groups received standard care with medications including corticosteroids and therapeutic anticoagulation	*Baseline in CP group*: day of CP transfusion *Baseline in control group*: 2 days post-admission

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Abolghasemi et al., 2020[36] **Country:** Iran **Funding source:** Baqiyatallah Medical Science University, Tehran, Iran Blood Transfusion Organization, Tehran, Iran and Darman Ara Company, Tehran, Iran	**Study design:** Prospective observational study	Adult patients with confirmed COVID-19 through laboratory (qRT-PCR) or CT imaging. **Inclusion Criteria:** Presence of some or all of disease clinical symptoms such as dyspnea, respiratory rate ≥20/ min, fever and cough; 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	**Intervention:** ABO compatible CP, 500 mL (one unit) transfused over 4 hours, during the first 3 days of hospitalization. If no improvement, one more unit was transfused based on physician decision. **Comparator**: Standard care Patients in both groups received antiviral therapy including Lopinavir or Ritonavir, hydroxychloroquine, and an anti-inflammatory agent.	**Primary outcomes:** Patient survival and length of hospital stay **Secondary outcomes**: need for intubation, clinical symptom improvement such as tachypnea, “para clinical measured of the patients” and adverse events. **Length of follow-up:** Till discharge from hospital or death.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Alsharidah et al., 2020[44] **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	**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 2 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 non-invasive ventilation: 4 points; Hospitalization plus non-invasive 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
		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		
Altuntas et al., 2020[37] **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	**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 are 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,	**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
		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	Lopinavir+ Ritonavir). hydroxychloroquine, Azithromycin, and high dose vitamin C.	
Dai et al., 2020[45] **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 with antibody titer ≥1:160 *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 non-invasive ventilation: 3 points; Hospitalization plus non-invasive 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

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Duan et al., 2020[38] **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[84] 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 mm hg. **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**: Total number of participants, N = 20 CP group, n = 10 Control group, n = 10 **Median age, years:** CP group = 52.5 Control group = 53 **Sex:** CP group: 40% females Control group: 40% females	**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 *Clinical symptoms improvement was defined as*: symptom relief (fever, dyspnea), normal SpO2, and radiological improvement **Time to follow-up:** within 3 days of CP transfusion

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Jiang et al., 2020[46] **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 Project of Logistics Service (18JS005)	**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 P < 0.0001	**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
Liu et al., 2020[42] **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	**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.	**Intervention:** ABO compatible CP with a serum IgG titer ≥ 1:320 *Volume:* 2 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	**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)

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	mortality associated with COVID-19.	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	Patients in both groups received symptomatic control and supportive care including therapeutic anticoagulants, antibiotics, hydroxychloroquine, antivirals, corticosteroids and other anti-inflammatory agents.	

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Moniuszko-Malinowska et al., 2020[47] **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 (200-267mL); 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 non-invasive ventilation or high-flow supplemental oxygen: 6 points; Hospitalization plus ECMO or invasive mechanical ventilation: 7 points; Death: 8 points **Length of follow-up:** 28 days (assessment at days 7, 15, 21 and 28)

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Rogers et al., 2020[39] **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: 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.	**Intervention:** ABO compatible CP *Volume:* Two units *Timing:* Median time from onset of symptoms to CP transfusion = 7 days (IQR: 5 to 9 days) **Comparator**: Standard care Patients in both groups received symptomatic control and supportive care including antivirals, steroids and hydroxychloroquine	**Primary outcome:** All-cause in-hospital mortality **Secondary outcome:** Time to hospital discharge **Length of follow-up:** 28 days

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		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		
Xia et al., 2020[40] **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,	**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	**Intervention:** ABO compatible CP with titers ≥ 1: 160 *Dose*: 4 to 5 mL/kg of recipient body weight. *Administration*: Slow transfusion for the first 15 min, and then with monitoring. *Volume:* 117 (84.7%) patients received 1 to 2 units (200 to 400 mL); 81 patients (58.6%) received CP once. *Timing:* Median time from onset of symptoms to CP transfusion 45 days (IQR: 39 to 54) **Comparator**: Standard care	**Clinical outcomes:** Mortality rate, clinical improvement based on 6 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
BE2018713), Medical Innovation Project of Logistics Service (Grant No. 18JS005) and Basic Research Program of Jiangsu Province (Grant No. BK20180036)		PaO_2 ≤ 300 mm hg. Chest imaging with obvious lesion progression over 24 to 48 hours >50% was also considered as severe. *Critical COVID-19* was defined as respiratory failure requiring mechanical ventilation, shock, other organ failure requiring ICU monitoring **Number of participants**: Total number of participants, N = 1,568 CP group, n = 138 Control group, n = 1,430 **Median age (IQR):** CP group: 65 years (57 to 73) Control group: 63 years (53 to 71) **Sex:** CP group: 44.2% females Control group: 49.7% females	All patients received antivirals, traditional Chinese medicine and respiratory support.	
Zeng et al. 2020[41] **Country:** China **Funding source:** The National Natural Science Foundation of China (No. 81970517), Zhongyuan (Henan) Thousands Outstanding Talents Plan (No. ZYQR201912179), Foundation for Distinguished Young Talents of Zhengzhou University	**Study design:** Retrospective observational study **Objective:** To analyze the efficacy of CP treatment in COVID-19 patients	**Inclusion criteria:** Patients with COVID-19 (based on WHO interim guidance[84]) **Exclusion criteria**: Not reported **Number of participants**: Total number of participants, N = 21 CP group, n = 6 Control group, n = 15	**Intervention**: CP therapy. Mean volume 300 mL (range 200 to 600 mL). **Comparator**: Standard care All patients received supportive care, antivirals, steroid and immunoglobulins as appropriate.	**Outcomes measured:** Clinical outcomes, SARS-CoV-2 clearance, adverse events **Primary end point:** fatality or recovery **Follow-up**: Patients were followed up until they reached any of the end points.

Study citation, country, funding source	Study design, objective	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Medical School (No.2020ZQLMS), and The Key Scientific Research Project of Henan Higher Education Institutions of China (No. 20B320028)		**Median age:** CP group: 61.5 years Control group: 73 years **Sex:** CP group: 16.6% females Control group: 26.6% females		

APACHE = Acute Physiology And Chronic Health Evaluation; ARDS= acute respiratory distress syndrome; BMI = Body Mass Index; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; CHF = congestive heart failure; CP = convalescent plasma; CT = computerized tomography; DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenation; eIND = emergency investigational new drug; FiO^2 = fraction of inspired oxygen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICU = intensive care unit; IND = investigational new drug; IQR = interquartile range; n = number of participants; NR = not reported; PaO_2 = partial pressure of oxygen; PCR = polymerase chain reaction; PS = propensity score; RCT = randomized controlled trial; RT = reverse transcriptase; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2;SD = standard deviation; S-RBD-specific IgG = S-receptor-binding domain- specific immunoglobulin G; SOFA = Sequential Organ Failure Assessment; SpO_2 = oxygen saturation; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury; WHO = World Health Organization.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 3: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[25]

Strengths	Limitations
Randomized controlled trials	
AlQahtani et al., 2021[31]	
• 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 outcomes of interest were reported in detail with definitions. They were appropriate to the study. • Main study findings were reported with simple outcome data, estimates of random variability were reported and appropriate statistical tests were used. • Potential confounders such as age, comorbidities and concomitant treatments were similar between the groups. • Adverse events in the CP group were reported. • All study participants were included in the analysis. There were no issues related to compliance. • Participants were enrolled from 2 centres in Bahrain. They were likely to be representative of the population. The care and facilities at the study centre were also likely to be representative of the treatment the majority of patients receive. • 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 follow-up duration of the study participants was unclear. • The relatively small sample size (20 in each group) could have resulted in underpowered analysis. • Participants in both groups received concomitant standard treatments including antivirals and steroids. • Adverse events in the control group were not reported.
Libster et al., 2021[28]	
• 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	• 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.

Strengths	Limitations
event. One patient in the CP group did not receive CP due to hypoxemia. • Study participants were enrolled from multiple hospitals and geriatric centres 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).	
Pouladzadeh et al., 2021[34]	
• The objectives of the study were clearly described. • Inclusion criteria were reported for the eligible patients. • Baseline characteristics of the patients were compared and reported. • There was randomized allocation to intervention or control group. • The study was single-blinded; the outcome assessors were blind to the allocation. Although the patients were not blinded, the outcomes were not subjective and thus could have less impact on the results. • The interventions of interest including dosage, timing and the standard care given to both groups were well-described • The outcomes of interest were appropriate to the study. Main study findings were reported with simple outcome data, estimates of random variability were reported and appropriate statistical tests were used. Actual probability values were reported for the primary outcome. • One person in each group declined to participate in the study. They were not included in the analytical sample. • Patients in both groups were recruited from a single centre, over the same period and were likely representative of the population. • The staff, places and facilities where the patients were treated were representative of the care majority of patients received.	• Although clinical outcomes were adjusted for some potential confounders (e.g., age, sex), other possible confounders such as diabetes were unclear. • All comorbidities were grouped as basic or underlying diseases, and it was unclear which all conditions were considered. Participants in CP group had significantly higher proportion of underlying disease compared to control group, however this was assessed using adjusted analyses. • The antibody titer in the administered CP were not measured. • The duration of follow-up in both CP and control arms was unclear. The disease severity and laboratory values were measured on admission day and discharge day. Among patients who died, those in CP group had significantly longer stay in hospital compared to control group. Although length of hospital stay was considered as a variable in adjusted analysis, differences in treatment standards and guidelines in different settings could lower the generalizability of the results. • Participants in both groups received standard treatments including antivirals and chloroquine, which may have contributed to the observed outcomes. Concomitant treatments were not considered as a variable in adjusted analysis. • Clinical outcomes such as clinical improvement (in WHO score) and “frequency of side effects” were poorly defined. The units for clinical outcomes were unclear. • No sample size calculation was conducted due to limited literature. All eligible patients were enrolled. • Adverse events in the control group were not reported.
RECOVERY Collaborative group, 2021[32]	
• The objectives of the study were clearly described. • The outcomes of interest were reported in detail with definitions. They were appropriate to the study. • Patients in both groups were followed up for the same period. • Main study findings were reported with simple outcome data, estimates of random variability were reported and appropriate statistical tests were used. • Well-described inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of the patients were compared and reported in detail.	• This was an open-label study where the patients and treating clinicians were not blinded to the intervention. • Among the patients recruited to the overall study (n = 16,287), 965 patients were excluded due to unavailability of CP. It is possible that these excluded patients were different from those included. • Participants in both groups received concomitant standard treatments including antivirals and steroids.

Strengths	Limitations
• The interventions of interest including dosage, timing and the standard care given to both groups were described. • A list of potential confounders (age, sex, ethnicity, steroid treatment) were listed and adjusted for in the analysis. • Adverse events in the CP group and control group were reported. • Less than 1% of patients in each group withdrew consent from the study. However, they were included in the intention-to treat analysis. • The participants were enrolled from 177 centres in UK increasing the external validity of the results. The study participants and the care they received were likely to be representative of the entire patient population and the care majority of them would receive. • Although a sample size calculation was not done at the study onset, it was determined late that 2,500 participants in each arm would ensure 90% power to detect 20% mortality (primary outcome) • Conflicts of interest of the authors were reported (and there were no concerns).	
Agarwal et al., 2020[27]	
• 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 titer of the transfused CP and the serum antibody titer of the patients were not assessed prior to transfusion. When assayed retrospectively it was found that median antibody titer in the donor CP was 1:40 (IQR: 1:30 to 1:80) and the median antibody titer of participants at enrolment was 1:90 (IQR: 1:30 to 1:240). Therefore, the patients were transfused with CP with a lower antibody titer, 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. • Adverse events in the control group were not reported.
Hamdy Salman et al., 2020[33]	
• The objectives of the study were clearly described. • Inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of the patients were reported in detail. They were similar between the groups.	• The study was designed as a double-blinded RCT. However, since the study was not placebo-controlled it was unclear how the blinding was maintained in the patients and outcome assessors. • It was reported that patients were randomized based on a 2;1 ratio to control and CP groups. However, the final

Strengths	Limitations
• The interventions of interest including dosage, timing and the standard care given to both groups were described. • Main study findings were reported with simple outcome data. • Participants in the CP and control groups were enrolled from the same population over the same period of time, increasing the internal validity. • Treatment compliance was good and there were no dropouts from the study. • A sample size calculation was done at the study onset based on a pilot study. The study enrolled adequate number of participants based on the calculation. • Conflicts of interest of the authors were reported (and there were no concerns**).**	randomized sample included equal number of participants in each group. • The main outcome for the study was 50% improvement in severity of illness which was a 2-point reduction on a 4-category illness scale. However, the categories of the 4-point scale were unclear. Indicators of disease severity (e.g., proportion of patients with respiratory rate >24/min) were measured over the follow-up time. It was unclear how these indices contributed to improvement. • The follow-up time of 5 days was likely too short to detect changes in secondary outcome such as nasopharyngeal swab testing. • Patients in both groups received concomitant treatments including steroids, which could have impacted the outcomes. • Potential confounders were nor listed or adjusted for in the analysis. • Actual probability values were not reported, rather only statistical significance was indicated. Effect sizes or confidence intervals were not reported. • Adverse events in the control group were not reported.
Li et al., 2020[26,30]	
• 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. Estimates of random probability (medians and IQRs for the continuous outcomes, effect estimates and 95% confidence intervals) were reported, actual probability values when P value was > 0.001, and appropriate statistical tests were used) • Incidence of adverse events in the CP group was described. • Characteristics of patients lost to follow-up were described (one in each group) • Patients were recruited from 7 centres, over the same period and were representative of the population. • Outcome assessment was blinded. • There was intention-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. • Adverse events in the control group were not reported.
Rasheed et al., 2020[35]	
• The objectives of the study were clearly described. • Study participants were randomly allocated to receive CP therapy or standard care alone.	• It was unclear whether there was random selection patients or whether the participants or outcome assessors or blinded to allocation.

Strengths	Limitations
• The outcomes of interest were reported in detail with definitions. They were appropriate to the study. • Inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of the patients were compared and reported. • The interventions of interest including dosage, timing and the standard care given to both groups were clearly described. • Main study findings were reported with simple outcome data, estimates of random variability were reported and appropriate statistical tests were used. • Adverse events in the CP group were reported. • Participants in both groups were enrolled from the same population over the same period. The care and facilities at the study centre were likely to be representative of the treatment majority of patients receive.	• Potential confounders were not adjusted for in the analysis. • Actual probability values were not reported for the comparative analysis. • The follow-up time in patients were not mentioned. Without specific follow-up time, results of outcome such as mortality has limited clinical relevance. • It was unclear whether a sample size calculation was conducted. • Adverse events in the control group were not reported.
Simonovich et al., 2020[29]	
• 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. • 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.	• 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. • Numerical values were reported inconsistently in different parts of the publication (tables versus text). • Conflicts of interest of the authors were not reported.
Non-randomized studies	
Al Harthi et al.,2021[48]	
• The objectives of the study were described. • The interventions of interest including dosage, timings were well-described	• The study was retrospective observational in design with no randomized allocation or blinding. • Exclusion criteria for the study were not reported

Strengths	Limitations
• Participants were recruited from one centre, over the same period and were likely to be representative of the local population. • Conflict of interest of the authors were reported (there were no concerns).	• The baseline characteristics of the study participants were reported only for the whole study population and not reported for each study group separately. • Antibody titers in the transfused plasma were not measured. The details for the comparator such as dosage and duration of treatment were not described. • Potential confounders such as comorbidities 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. • Adverse events in any of the study groups were not reported. • The study outcomes and their definitions were not reported. The definitions for the outcome measures used to compare CP group and the control group were unclear. The “clinical status” outcome was measured as ”improved” or “worsened” based on their status at the time of discharge/transfer/death. • 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 the study outcomes were determined a priori. • No sample size calculation was conducted. All eligible patients were enrolled.
Allahyari et al., 2021[49]	
• The objectives of the study were 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 interventions of interest including dosage, timings were well-described • Main study findings were reported with simple outcome data. Actual probability values when P value was > 0.001 were reported and appropriate statistical tests were used. • It was reported that there were no adverse events during CP transfusion (additional details not reported) • Conflict of interest of the authors were reported (there were no concerns).	• The study was retrospective observational in design with no randomized allocation or blinding. • Participants of the historic control group were selected from previously treated patients identified from a registry. Due to the emerging nature of disease and treatments, it is possible that both groups received different standard of care. • Concomitant medications given to patients in both groups were not reported. • Adverse events in the control group were not reported. • Potential confounders such as comorbidities and concomitant medications were not adjusted for in the analysis. • It was unclear whether participants in both groups were followed up for the same duration. Control group patients were matched to with CP group using several variables including “symptom day” (definition unclear). Day of CP transfusion was considered as day 0 in the CP group, however the criteria for Day 0 in control group were unclear. • Though the study authors reported that a propensity score calculation was conducted based on the matched variables, no additional details were provided to appraise the methodology. • A sample size calculation was not conducted.
Al Shehry et al., 2021[50]	
• The objectives of the study were described. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study.	• The study was observational in design with no randomized allocation or blinding.

Strengths	Limitations
• Well-described inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of all patients were reported. • The interventions of interest including dosage, volume and administration were described. • Some potential confounders such as age, sex, intubation status and comorbidities were considered for generating matched controls. • Main study findings were reported with simple outcome data, estimates of random variability were reported (medians and IQRs for the continuous outcomes) actual probability values when P value was > 0.001, and appropriate statistical tests were used. • It was reported that there were no adverse events during CP transfusion (additional details not reported) • Conflict of interest of the authors were reported (there were no concerns).	• Participants in the control group consisted of patients who did not consent to CP therapy, who did not get CP due to non-availability and from a historic control group. It is unclear whether they were enrolled from the same hospitals. The number of patients in each of these categories were not reported. The time period of treatment of patients in the historic control group were not reported. These factors could introduce a selection bias and lower the generalizability of the results. • Though the study authors reported that a propensity score calculation was conducted based on the matched variables, no additional details were provided to appraise the methodology. • Concomitant medications given to patients in both groups were not reported. • Adverse events in the control group were not reported. • Sample size calculation was conducted based on the outcome 30-day mortality which was a secondary outcome. Based on that, 575 patients were required to ensure adequate power. In the published results of interim analysis, the sample size was 164 which could lead to underpowered analysis.
Biernat et al., 2021[51]	
• The objectives of the study were described. • Baseline characteristics of the participants were described. • The interventions of interest including dosage, volume and administration were described. • It was reported that there were no adverse events during CP transfusion (additional details not reported) • Conflict of interest of the authors were reported. Although one author received funding from pharmaceutical companies, it is unlikely that it posed any concerns.	• The study was observational in design with no random selection, randomized allocation or blinding. • Outcomes were not described in the methods section. Definitions of outcomes such as “course of infection” and “viral clearance” were unclear. It was unclear whether they were determined a priori. It was unclear which outcome was considered primary. • No inclusion and exclusion criteria for the study were reported other than confirmed COVID-19 in patients with hematological malignancies. • Participants in treatment and control groups were recruited over different periods of time. The control group participants were treated during the early phase of the pandemic when standard supportive treatments could be less defined. • There were significant differences in the treatments received by participants in each group. For example, medications such as Remdesivir and Tocilizumab were not given to CP group due to lack of availability. Hydroxychloroquine was not given to any patients in the CP group, while it was given to all patients in the control group. This distribution of other treatments lowers the internal validity of the results. • The disease severity of patients in CP and control groups were significantly different. More patients in control group had severe disease. • Potential confounders such as comorbidities and concomitant medications were not adjusted for in the analysis. • Adverse events in the control group were not reported. • The appropriateness of using principal component analysis was unclear due to lack of details reported.

Strengths	Limitations
	• Reporting of main findings of results was unclear. For outcomes such as “course of infection” and “symptom resolution” P values were reported without simple outcome data or effect sizes. No estimates of random variability were reported. • It was unclear whether a sample size calculation was performed.
Budhiraja et al., 2021[52]	
• The objectives of the study were described. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. • The interventions of interest including dosage, volume and administration were described. • Potential confounders such as age, sex and comorbidities were considered in the analysis. • Main study findings were reported with simple outcome data, estimates of random variability were reported (e.g., IQRs, confidence intervals) actual probability values were reported when P value was > 0.001, and appropriate statistical tests were used. • Adverse events in the CP group were reported • It was a multicenter study in which patients of both groups were recruited from same centres over the same period of time.	• The study was observational in design with no random selection, randomized allocation or blinding. • Although the study included patients admitted to ward and ICU, results of comparative analysis between the groups were reported for patients admitted to ICU. Baseline characteristics were reported only for these subgroup pf patients as well. • The study reported that 170 patients were excluded due to lack of availability of clinical data. It was therefore unclear whether the excluded patients were different from the study participants. • Various concomitant treatments were given to patients in both groups. It was unclear whether the distribution of these treatments was similar across the groups. Additionally, remdesivir was given to patients in both groups who were enrolled after few weeks of the start of the study. This could mean that patients enrolled before and after the introduction of remdesivir had different supportive care which could affect the outcomes. • Adverse events in the control group were not reported. • A sample size calculation was not performed and all patients that met in the inclusion criteria during the study period were enrolled. • Conflict of interest of the authors were not reported.
Hatzl et al., 2021[53]	
• The objectives of the study were described • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. Patients were followed up for the same duration. • Inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of all patients were reported in detail. • The interventions of interest including dosage, volume and administration were described. • A list of potential confounders was provided and were adjusted for in the analysis. • Adverse events in the CP group were reported. • The staff, places care the study participants received were likely representative of the care majority of patients would receive. • Conflict of interest of the authors were reported (there were no concerns).	• The study was observational in design with no random selection, randomized allocation or blinding. • Some patients were excluded from the analysis due to reasons that were not listed as exclusion criteria (e.g., patients with non-pulmonary reason for ICU admission). The rationale for this exclusion was unclear. It is also possible that these excluded patients (n = 51) were different from those included in the analysis, however their characteristics were not reported. • Patients in CP group were different from those in the control group. CP was only given to patients with immunosuppression or those who tested negative for SARS-CoV-2 antibody. • At baseline, there were significant differences between patients in both groups. Overall patients in CP group were younger, had more comorbidities and had more severe disease. Although analysis adjusted for these differences using inverse-probability- of-treatment-weight (IPTW), it is possible that these differences could affect the outcome. • The distribution of IPTW is suggestive of unstable weights (as high as 15) which could lower the validity of results. It

Strengths	Limitations
	was also unclear whether weighting balanced all key covariates as weighted means were not reported. • The variables used in this analysis were derived from data and not decided a priori. Factors such as sex, race, specific comorbidities (e.g., diabetes) were not considered as variables in the weighted analysis. • A higher number of patients in the control group were enrolled during the first wave of COVID-19. It is possible that, with the subsequent increase in research and knowledge about the disease, patient management could have been different then. • The study outcomes were not reported in a tabular form, with simple outcome data. • Adverse events in the control group were not reported. • 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.
Klapholz et al., 2021[54]	
• The objectives of the study were described. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. • Well-described inclusion and exclusion criteria were reported for the eligible patients. Baseline characteristics of all patients were reported in detail. They were similar between the groups. • The interventions of interest including dosage, volume and administration were described. • Potential confounders such as age, sex and race were considered in matching with controls. Other confounders such as comorbidities, concomitant treatment with tocilizumab were adjusted for in the analysis. • Main study findings were reported with simple outcome data, estimates of random variability were reported (e.g., SD, confidence intervals) actual probability values were reported when P value was >0.001, and appropriate statistical tests were used. • Adverse events in the CP group were reported. • Conflict of interest of the authors were reported (there were no concerns).	• The study was observational in design with no random selection, randomized allocation or blinding. • Patients in the control group were treated prior to the availability of CP therapy. Patients in the CP group were selected from those who received CP through the eIND program. Among 94 patients who received CP, 47 patients were excluded due to unavailability of matched controls. It is possible that the excluded patients were different from the included patients and could have had different outcomes. • Study participants were followed up for 7 days, which is a short period to assess mortality. The starting point for CP group was CP transfusion. For those in the control group, assigned start time was decided by matching the duration of pre-transfusion O_2 support (with the CP group). Therefore, it is possible that the disease duration could be different in both groups which can affect the outcomes. • The outcome “worsening of O2 support” was based on a 5-level O2 support scale. It is unclear whether this scale was validated, and the minimal clinically important difference was not known. • Adverse events in the control group were not reported. • It was unclear whether a sample size calculation was performed.
Kuno et al.,2021[55]	
• The objectives of the study were described. • The outcomes of interest were reported. • Baseline characteristics of all patients were reported in detail. • Potential confounders such as age, sex, comorbidities clinical features, and concomitant treatments were accounted for in selecting matched controls. • Main study findings were reported with simple outcome data, estimates of random variability were reported (e.g., IQR), actual probability values were reported when P value was > 0.001.	• The study was observational in design with no random selection, randomized allocation or blinding. • The inclusion and exclusion criteria for the study were unclear. • Additional, details about CP such as dose, volume, antibody titer or timing of transfusion were not reported. • The rationale of choosing “acute kidney injury” as a study outcome was not reported. The definition of the that outcome was not described. • Adverse events in groups were not reported.

Strengths	Limitations
• The staff, places care the study participants received were likely representative of the care majority of patients would receive. • Conflict of interest of the authors were reported (there were no concerns).	• The follow-up time for patients in both groups was not reported. • It was unclear whether the study outcomes were decided a priori. • Though the study authors reported that a propensity score calculation was conducted based on the matched variables, no additional details were provided to appraise the methodology. • The statistical tests used to compare the groups were not reported. • It was unclear whether a sample size calculation was performed.
Kurtz et al., year[56]	
• The objectives of the study were described. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. Patients in both groups were followed up for the same duration. • Baseline characteristics of all patients were reported in detail. • The interventions of interest including dosage, volume and administration were described. • Main study findings were reported with simple outcome data. Actual probability values were reported when P value was < 0.001 • All eligible patients were included in the analysis. • Adverse events in the CP group were reported.	• The study was observational in design with no random selection, randomized allocation or blinding. • Patients in CP group and control group were not enrolled during same period of time. Control group patients were treated a few weeks prior to CP group patients. • Study inclusion criteria for control group were not well-described. The definition of 'critically ill" was not reported. • There were significant differences between both groups at baseline in characteristics such as age, obesity and history of cardiac disease. Obesity and comorbidities were not adjusted for in the analysis. • Participants in both groups received standard treatments including steroids and anticoagulation which were not adjusted for in the analysis. • Effect sizes (e.g., odds ratio and CI) were not reported for any of the univariate outcomes. • Some outcomes (length of hospital stay) were not indicted as proposed outcomes in the methods section. It is possible that these were not decided a priori. • Adverse events in the control group were not reported. • It was unclear whether a sample size calculation was performed. • Conflict of interest of the authors were not reported.
Omrani et al., 2021[57]	
• The objectives of the study were described. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. Patients in both groups were followed up for the same duration. • Baseline characteristics of all patients were reported in detail. • The interventions of interest including dosage, volume and administration were described. • Potential confounders were adjusted for in the analysis. • Main study findings were reported with simple outcome data. Actual probability values were reported when P value was < 0.001 and appropriate statistical tests were used. • Adverse events in the CP group and control groups were reported. • Participants in both groups were enrolled from same centre over the same period of time.	• The study was observational in design with no random selection, randomized allocation or blinding. • Effect sizes (e.g., odds ratio and CI) were not reported for any of the univariate outcomes. • The outcome "respiratory improvement" was based on a 5-level O2 support scale. It is unclear whether this scale was validated, and the minimal clinically important difference was not known. • Although a sample size calculation was reported, it was conducted based on arbitrarily set values due to lack of data in the literature.

Strengths	Limitations
• Conflict of interest of the authors were reported (there were no concerns).	
Padilla et al.,2021[58]	
• The objectives of the study were described. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. • Baseline characteristics of all patients such as age, sex and disease severity were reported. • The interventions of interest including dosage, volume and administration were described. • Main study findings were reported with simple outcome data. Actual probability values were reported when P value was >0.001 • Adverse events in the study groups were reported. • All eligible patients from the study site were enrolled into this retrospective study. They were recruited over the same period. The staff, facilities and acre received by the participants were likely representative of most patients would receive. • Conflict of interest of the authors were reported (there were no concerns).	• The study was retrospective observational in design with no random selection, randomized allocation or blinding. • The eligibility criteria for CP therapy and remdesivir therapy were different. It appeared that CP was given to patients with more severe disease (e.g., respiratory failure, shock). Significantly more patients from the CP group were admitted to the ICU, suggesting, more severe disease. However, other clinical characteristics such as SOFA scores, baseline score of disease severity were balanced between the groups. • Potential confounding factors such as concomitant treatments, age, and sex were not adjusted for in the analysis. • For survival outcomes, a hazard ratio or confidence interval were not reported. • Follow-up assessment was done at the end of the study. Thus, it is possible that patients in different groups were followed up for different durations. Without specific follow-up period, outcomes such as survival have limited clinical relevance. • It was unclear whether a sample size calculation was performed.
Pappa et al.,2021[59]	
• The objectives of the study were described. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. • Study inclusion criteria cases and controls were provided. Baseline characteristics of all patients such as age, sex and disease severity, comorbidities were reported. • The interventions of interest including dosage, volume and administration were 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 were reported. • Adverse events in the CP group were reported. • All study patients were recruited over the same period from same sites. The staff, facilities and acre received by the participants were likely representative of most patients would receive. • Conflict of interest of the authors were reported (there were no concerns).	• The study was observational in design with no random selection, randomized allocation or blinding. • The details of standard care provided to Control group patients were not described. • Potential confounders were not listed. • One patient who received CP and died after 1 day was not included in the comparative analysis due to non-availability of a matched control. No other patient in the CP group was excluded from the study. • Among 144 patients who received standard care alone, 85 patients were excluded due to not matching. The characteristics of these excluded patients were not reported. 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. • 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. • The median follow-up time in control group (10 days) was significantly shorter compared to that in CP group (29 days). Therefore, outcomes assessed at the end of follow-up time has limited clinical relevance. • Adverse events in the control group were not reported.

Strengths	Limitations
	• It was unclear whether a sample size calculation was performed.
Pei et al., 2021[60]	
• The objectives of the study were described. • Baseline characteristics of all patients such as age, sex and disease severity were reported. • The interventions of interest including dosage, volume and administration were described. • Main study findings were reported with simple outcome data. Actual probability values were reported when P value was >0.001 • Conflict of interest of the authors were reported (there were no concerns).	• The study was observational in design with no random selection, randomized allocation or blinding. • The study outcomes and their definitions were not reported • Control group patients were selected from patients who did not receive CP from 2 provinces. The inclusion and exclusion criteria for control group patients were not reported. • The details of treatment provided for control group patients were not reported. Concomitant treatment given for all patients were not reported. • 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. • Potential confounders such as comorbidities 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. • Adverse events in CP and control groups were not reported. • It was unclear whether the study participants were representative of the population from which they were recruited. • It was unclear whether the study outcomes were decided a priori. • It was unclear whether a sample size calculation was performed
Salazar et al., 2021(a) [43]	
• 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 2 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	• 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. • Adverse events in the control group were not reported.

Strengths	Limitations
• 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) • Adverse events in the CP group were reported. • The authors recruited participants from 7 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)	• It was unclear whether a sample size calculation was performed.
Salazar et al., 2021 (b)[61]	
• The objectives of the study were described. • Main outcome was described. • Baseline characteristics of all patients such as age, sex and disease severity were reported • 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 were reported • All patients admitted during the study period were enrolled in the study. All study patients were recruited over the same period from same sites. The staff, facilities and care received by the participants were likely representative of most patients would receive. • Conflict of interest of the authors were reported (there were no concerns).	• The study was observational in design with no random selection, randomized allocation or blinding. • CP was administered based on eligibility criteria, which selected patients with severe or life-threatening disease. All other patients were included in the control group. This non-random selection of patients for each care lowered the internal validity of the results. • Patients in the CP and control groups were significantly different in characteristics such as age and comorbidities. • Although the primary outcome was assessed in 28 days. The starting point of the study was unclear. Without a specific follow-up period, outcomes have limited clinical relevance. • 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. • Details of standard care provided of the patients including concomitant treatments were not reported. They could have impacted the outcome. • Adverse events in CP and control group were not reported. • It was unclear whether the study outcomes were decided a priori. • It was unclear whether a sample size calculation was performed
Shenoy et al., 2021[62]	
• The objectives of the study were clearly described. • The outcomes of interest were reported clearly with definitions. They were appropriate to the study. Patients in both groups were followed up for the same duration. • Baseline characteristics of all patients were reported in detail. • The interventions of interest including dosage, volume and administration were described. • Main study findings were reported with simple outcome data. Actual probability values were reported when P value was > 0.001 • Adverse events in the CP group were reported (there were none) • Patients in both groups were recruited from same centres, and the care is likely to be representative of that general population would receive.	• The study was observational in design with no random selection, randomized allocation or blinding. • Patients in the control group were treated on average a month prior to their CP group counterpart. • Among all CP recipients, 31 (out of 294) patients were excluded from the study due to unavailability of matched control or lack of data. It was unclear whether these exclude patients were different from those included in the analysis. • 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. • It was unclear whether testing of proportional hazards assumption was done prior to analyses. • The use of systemic steroids, remdesivir and tocilizumab were significantly higher in the CP group. It is possible that

Strengths	Limitations
	the use of these medications affected the outcomes, lowering the internal validity of the results. • The distribution of race and ethnicity were significantly different between the groups. As African American race is associated with poorer race COVID-19 prognosis, this difference could affect outcomes. • Although potential confounders such as race, concomitant medications were different between the groups, these factors were not adjusted for in the analysis. • Where comparative analyses were conducted (e.g., HR) estimates of random variability (95% CI) were not reported. • Patients in the control group were matched to CP recipients based on their preceding length of hospitalization. They were not matched based on disease severity which could have affected the outcomes. • Adverse events in the control group were not reported. • Conflict of interest of the authors were not reported.
Yoon et al., 2021[63]	
• The objectives of the study were clearly described. • The main study outcomes were described in the methods section. Patients in both groups were followed up for the same duration • Baseline characteristics of all patients were reported in detail. They were similar between the groups. • The interventions of interest including dosage, volume and administration were described. • Potential confounders such as age, sex, race, ethnicity and comorbidities were balanced after PS matching. • Main study findings were reported with simple outcome data. Actual probability values were reported when P value was >0.001 • Adverse events in the CP group were reported (there were none) • All 103 patients who received CP from the study hospital were included in the study. Among them 30 were excluded either due to not meeting eligibility criteria (n =13) or due to lack of matched controls (n = 17). All patients (CP and control group) prior to PS sore matching were included in the analysis. PS matched pairs were compared separately. Thus, it is likely that participants were representative of the entire population from which they were recruited. The staff, facilities and acre received by the participants were likely representative of most patients would receive.	• The study was retrospective observational in design with no random selection, randomized allocation or blinding. • The definition of outcome “improvement in oxygenation status or mortality” was unclear. Results for this outcome were reported as “stable/better” and “worse/dead” for which the definitions were unclear as well. • Patients in both groups received concomitant treatments. Even through the use of corticosteroids and therapeutic anticoagulation were similar between the groups, use of other medications were not reported. • 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. • It was unclear whether a sample size calculation was performed. • It was unclear whether testing of proportional hazards assumption was done prior to analyses. • Adverse events in the control group were not reported. • Several study authors declared conflicts of interest related to SARS-CoV-2 assays and pharmaceutical companies. However, it was unclear whether this could have impacted the study findings.
Abolghasemi et al., 2020[36]	
• 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.	• 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. • Adverse events in the control group were not reported

Strengths	Limitations
• 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 in the CP group and no patients were lost to follow-up. • Study participants were recruited from 4 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.	
Alsharidah et al., 2020[44]	
• 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 in the CP group was describedi • Participants were recruited from 4 centres, 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. • Adverse events in the control group were not reported.
Altuntas et al., 2020[37]	
• 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.

Strengths	Limitations
	• 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.
Dai et al., 2020[45]	
• 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 comorbidities 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. • The follow-up time for patients in both groups was not reported. Without a specific follow-up period, outcomes have limited clinical relevance. • Adverse events in the control group were not reported. • It was unclear whether a sample size calculation was performed to ensure adequate power.
Duan et al.,2020[38]	
• 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

Strengths	Limitations
	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. Adverse events in the control group were not reported. • 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.
Jiang et al., 2020[46]	
• 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. • Adverse events in the CP 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 comorbidities and concomitant medications were not adjusted for in the analysis. • Adverse events in the control group were not reported. • 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.

Strengths	Limitations
	• 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.
Liu et al., 2020[42]	
• 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 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).

Strengths	Limitations
	• Adverse events in the control group were not reported. • One of the co-authors had a potential conflict of interest related to a patent for an assay to select plasma donors.
Moniuszko-Malinowska et al., 2020[47]	
• 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 centres 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 comorbidities, 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. • Characteristics of patients lost to follow-up were not reported. The number of patients (if any) who discontinued treatment was unclear. • Adverse events in the CP and control group were not reported. • It was unclear whether a sample size calculation was performed.
Rogers et al., 2020[39]	
• 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. • Adverse events in the control group were not reported. • 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
Xia et al., 2020[40]	
• 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 in the CP group 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. • Adverse events in the control group were not reported. • 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.
Zeng et al. 2020[41]	
• 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 2 groups. • Simple outcome data for all measured outcomes were reported clearly. • Median and IQR were reported for continuous variables. Actual probability values were reported for P > 0.001. • Adverse events of the intervention group were reported. • No patients were lost to follow-up. • Participants of both groups were recruited from 2 referral hospitals for COVID-19 over the same period. • There was no evidence of data-dredging by way of unplanned subgroup analysis. • Study end points was clearly described and were the same for both study arms.	• 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. • Adverse events in the control group were not reported. • 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.

Strengths	Limitations
• 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.	

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

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Table 4: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Randomized controlled trials	
AlQahtani et al., 2021[31]	
Open-label RCT to assess the effectiveness of CP therapy in COVID-19 patients with hypoxia compared to standard care alone. Total number of participants, N=40 CP group, n=20; Control group, n=20 **Baseline characteristics:** There were no significant differences in demographics, clinical characteristics, comorbidities or use of concomitant medications between the groups. **Study findings:** • **Need for non-invasive or mechanical ventilation, n (%)** ○ CP group = 4 (20) ○ Control group = 6 (30) ○ Risk ratio (95% CI) = 0.67 (0.22 to 2.0); P value = 0.72 • **Time to non-invasive or mechanical ventilation** ○ CP group vs. control group, log rank P = 0.52 • **Time on non-invasive or mechanical ventilation, mean (SD)** ○ CP group = 8.25 (4.42) ○ Control group = 10.5 (2.9) ○ P value = 0.809 • **Length of stay, mean (SD)** ○ CP group = 14.1 (1.25) ○ Control group = 18.05 (2.22) ○ P value = 0.12 • **Mortality, n (%)** ○ CP group = 1 (5) ○ Control group = 2 (10) ○ P value = 0.55 **Adverse events in the CP group:** diarrhea/ vomiting, n = 1 (resolved without treatment); transient desaturation, n = 1 **Adverse events in the Control group:** not reported	"In conclusion, there were no significant differences in the primary or secondary outcome measures between CP and standard therapy though fewer patients required ventilation (NIV or MV) and for a shorter period of time, although a larger definitive study is needed for confirmation. However, the study did show that CP therapy appears to be safe in hospitalized COVID-19 patients with hypoxia. (p.7)"[31]
Libster et al., 2021[28]	
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 **Baseline characteristics:** 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	"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)"[28]

Main study findings	Authors' conclusion
○ 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) • **Non-invasive 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) ○ 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**	

Main study findings	Authors' conclusion
Solicited adverse events included volume overload, allergic reaction, thrombophlebitis, vasovagal syndrome, hematoma at site, nerve injury and tetany (hyperventilation).	
Pouladzadeh et al., 2021[34]	
A single-blinded RCT to evaluate the effectiveness of CP therapy in patients with severe COVID-19. CP group, n = 30; Control group, n = 30 **Baseline characteristics:** There were no significant differences in demographics or disease severity between the groups. A higher percentage of patients in the CP group (66.7%) had "underlying disease" compared to control group (33.3.%), most commonly diabetes, hypertension and ischemic heart disease. **Study findings:** • Length of hospital stay, (unit not reported, likely days) • CP group, mean (SD)= 8.66 (3.94) • Control group, mean (SD) = 6.66 (4.30) • P = 0.06 • Adjusted hazard ratio (95% CI) = 0.368 (0.020 to 6.838); P = 0.502 • Adjusted for age, sex, laboratory markers of cytokine storm, basic diseases ***Among deceased patients:*** • CP group, mean (SD) = 10.3 (0.57) • Control group, mean (SD) = 3.4 (2.3) • P = 0.002 ***Among alive patients:*** • CP group, mean (SD) = 8.5 (4.11) • Control group, mean (SD) = 7.32 (4.31) • P = 0.32 **Mortality** • CP group, n (%) = 3 (10) • Control group, n (%) = 5 (16.7) • Adjusted OR (95% CI) = 0.305 (0.009 to 10.065) ; P = 0.505 • Adjusted for age, sex, laboratory markers of cytokine storm, basic diseases and length of hospital stay **Clinical improvement** • CP group, n (%) =16 (53.33) • Control group, n (%) = 8 (26.66) • Adjusted OR (95% CI) = 7.314 (1.622 to 32.969); P = 0.01 • Adjusted for age, sex, laboratory markers of cytokine storm, basic diseases and length of hospital stay **Adverse events:** **CP group:** CP therapy had "no serious side effects on patients. (p.7)"[34] **Control group: Not reported**	"The convalescent plasma has a remarkable immunomodulatory and antiviral potential to improve cytokine storm and 8-point WHO severity score in COVID-19 patients. (p. 9)"[34]
RECOVERY Collaborative group, 2021[32]	
Open-label RCT to assess the effectiveness of CP therapy in COVID-19 patients compared to standard care alone. Total number of participants, N=11,558 CP group, n=5,795; Control group, n=5,763	"In RECOVERY, the largest clinical trial of convalescent plasma for any infectious indication, we did not find evidence that high-titer convalescent plasma improved survival or other pre-specified clinical outcomes in

Main study findings	Authors' conclusion
Baseline characteristics: The demographics (age, sex, ethnicity), clinical characteristics, comorbidities or use of concomitant medications were similar between the groups. **Study findings:** • **Mortality at 28 days, n (%)** ○ CP group = 1,399 (24) ○ Control group = 1,408 (24) ○ Rate ratio (95% CI) = 1.00 (0.93 to 1.07); P value = 0.95 • **Length of hospitalization, median (IQR), days** ○ CP group = 12 (6 to >28) ○ Control group = 11 (6 to >28) • **Patients discharged from hospital within 28 days, n (%)** ○ CP group = 3,832 (66) ○ Control group = 3,822 (66) ○ Rate ratio (95% CI) = 0.99 (0.94 to 1.03); P value = 0.57 **Among patients not on invasive ventilation at baseline** CP group, n = 5,493; Control group, n = 5,448 • **Composite end point of mechanical ventilation, ECMO or death, n (%)** ○ CP group = 1568 (29) ○ Control group = 1568 (29) ○ Rate ratio (95% CI) = 0.99 (0.93 to 1.05); P value = 0.79 • **Invasive mechanical ventilation, n (%)** ○ CP group = 678 (12) ○ Control group = 690 (13) ○ Rate ratio (95% CI) = 0.97 (0.88 to 1.08); P value = 0.61 • **Death, n (%)** ○ CP group = 1241 (23) ○ Control group = 1263 (23) ○ Rate ratio (95% CI) = 0.97 (0.91 to 1.04); P value = 0.46 **Among patients not on invasive or non-invasive ventilation at baseline** CP group, n = 3,564; Control group, n = 3,441 • **Use of ventilation, n (%)** ○ CP group = 885 (25) ○ Control group = 876 (25) ○ Rate ratio (95% CI) = 0.98 (0.90 to 1.06); P value = 0.55 • **Non-invasive mechanical ventilation, n (%)** ○ CP group = 856 (24) ○ Control group = 845 (25) ○ Rate ratio (95% CI) = 0.98 (0.90 to 1.06); P value = 0.60 • **Invasive mechanical ventilation, n (%)** ○ CP group = 229 (6) ○ Control group = 238 (7) ○ Rate ratio (95% CI) = 0.93 (0.78 to 1.11); P value = 0.41 **Among patients on invasive ventilation at baseline** CP group, n = 302; Control group, n = 315 • **Successful cessation of invasive mechanical ventilation, n (%)** ○ CP group = 85/302 (28) ○ Control group = 108/315 (34) ○ Rate ratio (95% CI) = 0.79 (0.59 to 1.05); P value = 0.11	patients hospitalised with COVID-19. Whether convalescent plasma would benefit other patient groups is unknown and would need to be evaluated in other, adequately powered, randomized clinical trials. (p.9)"[32]

Main study findings	Authors' conclusion
Among patients not on renal replacement therapy at baseline CP group, n = 5707; Control group, n = 5697 • **Need for Renal replacement therapy, n (%)** ○ CP group = 250 (4) ○ Control group = 241 (4) ○ Rate ratio (95% CI) = 1.04 (0.87 to 1.23); P value = 0.69 **Adverse events (assessed 72 hours after randomization)** • **Sudden worsening of respiratory status, n (%)** ○ CP group = 1139 (21) ○ Control group = 1144 (22) • **Severe allergic reaction, n (%)** ○ CP group = 16 (<1) ○ Control group = 2 (<1) • **Sudden fever, n (%)** ○ CP group = 195 (4) ○ Control group = 169 (3) • **Sudden hypotension, n (%)** ○ CP group = 128 (2) ○ Control group = 143 (3) • **Clinical hemolysis, n (%)** ○ CP group = 90 (2) ○ Control group = 71 (1) • **Thrombotic event, n (%)** ○ CP group = 75 (1) ○ Control group = 87 (2)	
Agarwal et al., 2020[27]	
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 **Baseline characteristics:** 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*	"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 titers. 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) [27]

Main study findings	Authors' conclusion
▪ 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:* ▪ 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 3 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.	
Hamdy Salman et al., 2020 [33]	
A double-blinded RCT to evaluate the effectiveness of CP therapy in patients with severe COVID-19. Total number of participants, N=30 CP group, n=15; Control group, n=15 **Baseline characteristics:** Baseline characteristics such as age, sex, comorbidities, clinical status, concomitant treatments, days from onset of illness to hospitalization and days from hospitalization to randomization were similar between the groups.	"In conclusion, a single dose of 250 ml of RCP to severely ill COVID-19 patients, mitigated the severity of symptoms, endured by all patients with reliable safety and improved radiological findings and laboratory parameters. (p.271)"[33]

Main study findings	Authors' conclusion

Study findings:
• **Illness severity scale post-randomization**
 	
Respiratory rate >24/min, n (%)
• Baseline: CP group = 11 (73.33); Control group = 12 (80); P = NS
• Day 1: CP group = 7 (46.3); Control group = 12 (80); P <0.05
• Day 2: CP group = 5 (33.3); Control group = 10 (66.3); P <0.05
• Day 3: CP group = 5 (33.3); Control group = 8 (53.3); P <0.05
• Day 4: CP group = 6 (44); Control group = 10 (66.3); P <0.05
• Day 5: CP group = 4 (26); Control group = 8 (53.3); P <0.05
 	
Blood O2 saturation ≤93% on room air, n (%)
• Baseline: CP group = 9 (60); Control group = 10 (66.6); P = NS
• Day 1: CP group = 6 (40); Control group = 8 (53); P <0.05
• Day 2: CP group = 3 (20); Control group = 9 (60); P <0.05
• Day 3: CP group = 3 (20); Control group = 7 (46.3); P <0.05
• Day 4: CP group = 4 (26.4); Control group = 8 (53.3); P <0.05
• Day 5: CP group = 3 (20); Control group = 8 (53.3); P <0.05
 	
PaO_2: FiO_2 < 300mmHg, n (%)
• Baseline: CP group = 10 (66.6); Control group = 11 (73.33); P = NS
• Day 1: CP group = 7 (46.6); Control group = 10 (66.33); P <0.05
• Day 2: CP group = 5 (33.3); Control group = 10 (66.34); P <0.05
• Day 3: CP group = 4 (26.4); Control group = 9 (60); P <0.05
• Day 4: CP group = 3 (20); Control group = 8 (53.8); P <0.05
• Day 5: CP group = 4 (26.4); Control group = 9 (60); P <0.05
 	
Pulmonary infiltrates >50% of both lungs, n (%)
• Baseline: CP group = 10 (66.33); Control group = 11 (73.33); P = NS
• Day 1: CP group = 6 (40); Control group = 10 (66.33); P <0.05
• Day 2: No CT was taken
• Day 3: CP group = 5 (33); Control group = 10 (66.3); P <0.05
• Day 4: No CT was taken
• Day 5: CP group = 5 (33); Control group = 10 (66.3); P <0.05
 	
"…there was gradual decrease in illness severity during the study period in RCP group, P < 0.001, compared to baseline value. This trend was not apparent in the control group, Figure 2(b), compared to their baseline values, P > 0.05. (p.267)"[33]
 	
• **Neutralizing antibody detected (i.e., presence of any neutralizing antibody), n (%)**
  ○ Baseline: CP group = 0 Control group = 0
  ○ Day 1: CP group = 9 (60); Control group = 0
  ○ Day 2: CP group = 11 (73.3); Control group = 0
  ○ Day 3: CP group = 12 (80); Control group = 0
  ○ Day 4: CP group = 9 (60); Control group = 0
  ○ Day 5: CP group = 11 (73.3); Control group = 0
 	
• **Positive nasopharyngeal swab, n (%)**
  ○ Baseline: CP group = 15 (100); Control group = 15 (100)
  ○ Day 1: CP group = 15 (100); Control group = 15 (100)
  ○ Day 2: CP group = 15 (100); Control group = 15 (100)
  ○ Day 3: CP group = 15 (100); Control group = 15 (100)
  ○ Day 4: CP group = 15 (100); Control group = 15 (100)
  ○ Day 5: CP group = 15 (100); Control group = 15 (100)	

Main study findings	Authors' conclusion
Adverse events **CP group:** "no transfusion-related complications" **Control group:** not reported	
Li et al., 2020[26,30]	
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 **Baseline characteristics:** 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) ▪ 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)	"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."[26] (p. E10)

Main study findings	Authors' conclusion
▪ 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 24h ▪ CP group:21/47 (44.7%) ▪ Control group:6/40 (15 %) ▪ OR (95%CI) = 4.58 (1.62 to 12.96); P value = 0.003 ○ At 48 hours ▪ CP group:32/47 (68.1%) ▪ Control group:13/40 (32.5 %) ▪ OR (95%CI) = 4.43 (1.80 to 10.92); P value = 0.001 ○ At 72 hours ▪ CP group:41/47 (87.2%) ▪ Control group:15/40 (**37.5 %)** ▪ **OR (95%CI) = 11.39 (3.91 to 33.18); P value < 0.001** • **Patients with severe disease** ○ At 24h ▪ CP group**: 7/21 (33.3%)** ▪ **Control group:2/17 (11.8 %)** ▪ **OR (95%CI) = 3.75 (0.66 to 21.2); P value = 0.15** ○ **At 48 hours** ▪ **CP group:13/21 (61.9%)** ▪ Control group:6/17 (35.3%) ▪ OR (95%CI) = 2.98 (0.79 to 11.25); P value = 0.10 ○ At 72 hours ▪ CP group: 19/21 (90.5%) ▪ Control group: 7/17(41.2%) ▪ OR (95%CI) = 13.57 (2.36 to77.95); P value < 0.001	

Main study findings	Authors' conclusion
• **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	
Rasheed et al., 2020[35]	
RCT to assess the effectiveness of CP therapy in critically ill COVID-19 patients compared to standard care alone. Total number of participants, N=49 CP group, n=21; Control group, n=28 **Baseline characteristics:** There were no significant differences in demographics, clinical characteristics, comorbidities or use of concomitant medications between the groups. **Study findings:** • **Recovery time from critical illness, mean (SD), days** ○ CP group = 4.52 (2.35) ○ Control group = 8.45 (1.87) ○ P value <0.0001 • **Duration of infection, mean (SD), days** ○ CP group = 19.33 (6.90) ○ Control group = 23.42 (6.39) ○ P value = 0.037 • **Mortality, n (%)** ○ CP group = 1 (4.8) ○ Control group = 8 (28.6) ○ P value = 0.03 • **Antibody levels at Day3, n (%)** **SARS-CoV-2 IgG** ○ Negative: CP group = 0; Control group = 21 (75) ○ Weakly positive: CP group = 2 (9.5); Control group = 7 (25) ○ Moderately positive: CP group = 8 (38.1); Control group = 0 ○ Strongly positive: CP group = 11 (52.4); Control group = 0 ○ P value <0.0001 **SARS-CoV-2 IgM** ○ Negative: CP group = 0; Control group = 20 (71.4) ○ Positive: CP group = 21 (100); Control group = 8 (28.6) ○ P value <0.0001 **Adverse events in the CP group:** mild skin redness and itching, n=1 (resolved with treatment)	"CP therapy proved in this study to lower mortality and morbidity and to accelerate recovery. Therefore, the observed outcome of CP therapy is encouraging to be trialled on higher number of patients. (p.365)"[35]

Main study findings	Authors' conclusion
Adverse events in the Control group: not reported	
Simonovich et al., 2020[29]	
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:** 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) • **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%)	"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)"[29]

Main study findings	Authors' conclusion
• **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) ○ 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	
Non-randomized studies	
Al Harthi et al., 2021[48]	
A retrospective study to compare CP and Tocilizumab in patients with severe or life-threatening COVID-19. Total number of participants, N=102 CP group, n=20; Tocilizumab group, n=61 **Baseline characteristics:** Not reported.	"This is the first study in Oman that explored the compared the use of CP or Tocilizumab or both in severe cases of COVID-19. Despite lack of effect between the treatment groups on the proportion of patients who improved vs worsened, this study

Main study findings	Authors' conclusion
Study findings: • **Proportion of patients who improved versus worsened, n (%):** ○ *Within group:* ▪ CP group: improved = 12 (60); worsened = 8 (40); P value = 0.05 ▪ Tocilizumab group: improved = 36 (59); worsened = 25 (41); P value = 0.03 ▪ Both treatments: improved = 11 (52.4); worsened = 10 (47.2); P value = 0.7 ○ *Between groups: P value = 0.7* **Adverse events in the CP group**: Not reported **Adverse events in the Control group**: Not reported	showed significant within-group differences in the proportion of patients who improved vs worsened in mostly the Tocilizumab treatment group. Results from this study indicate that both treatments might be capable of reducing the risk of invasive mechanical ventilation in patients with severe COVID-19 pneumonia. However, despite promising results, randomised studies are warranted. (p.7)"[48]
Allahyari et al., 2021[49]	
Clinical trial comparing COVID-19 inpatients with ARDS who received CP therapy with a matched historic control group of patients who received standard care alone. Total number of participants, N=64 CP group, n=32; Control group, n=32 **Baseline characteristics:** Baseline characteristics such as demographics, comorbidities and disease severity were comparable between the groups. **Study findings:** • **4-weeks mortality, n (%)** ○ CP group = 7 (21) ○ Control group = 14 (43.8) ○ P value = 0.062 ○ OR = 1.30 (95% CI = 1.13 to 1.49); P value <0.001 **Patients with mild ARDS (PaO2/FiO2: 200 to 250), n = 19 in each group** ○ CP group = 0 ○ Control group = 5 (26.3) ○ P value = 0.046 **Patients with moderate ARDS (PaO2/FiO2: 100 to 200), n = 9 in each group** ○ CP group = 4 (44.4) ○ Control group = 6 (66.7) ○ P value = 0.637 **Patients with severe ARDS (PaO2/FiO2: <100), n = 4 in each group** ○ CP group = 3 (75) ○ Control group = 3 (75) ○ P value = >0.99 • **Need for non-invasive ventilation, n (%)** ○ CP group = 14 (43.8) ○ Control group = 19 (59.4) ○ P value = 0.211 • **Need for intubation, n (%)** ○ CP group = 8 (25) ○ Control group = 14 (43.8) ○ P value = 0.114 • **Length of hospitalization, mean (SD), days** ○ CP group = 13.91 (8.43) ○ Control group = 15.34 (10.11) ○ P value = 0.732	"Early administration of the convalescent plasma could successfully contribute to the treatment of severe COVID-19 patients with mild or moderate ARDS at risk of progressing to critical state. (p. 1)"[49]

Main study findings	Authors' conclusion
• **PO_2/FiO_2, mean (SD), mm hg** **Day zero** ○ CP group = 188.16 (58.48) ○ Control group = 190.63 (53.66) ○ P value = 0.666 **Day 3** ○ CP group = 181.28 (64.33) ○ Control group = 193.28 (58.83) ○ P value = 0.350 **Day of discharge/death** ○ CP group = 275.03 (142.54) ○ Control group = 213.41 (92.76) ○ P value = 0.034 • **SOFA score, mean (SD), units** **Day zero** ○ CP group = 3.25 (1.08) ○ Control group = 3.22 (1.76) ○ P value = 0.316 **Day 3** ○ CP group = 3.47 (2.03) ○ Control group = 3.59 (1.10) ○ P value = 0.761 **Day of discharge/death** ○ CP group = 3.34 (3.70) ○ Control group = 3.91 (2.79) ○ P value = 0.058 • **APACHE score, mean (SD), units** **Day zero** ○ CP group = 8 (2.60) ○ Control group = 8.28 (2.98) ○ P value = 0.995 **Day 3** ○ CP group = 6.53 (2.34) ○ Control group = 9.69 (4.28) ○ P value = 0.001 **Day of discharge/death** ○ CP group = 6.69 (4.17) ○ Control group = 9.25 (5.14) ○ P value = 0.023 **Adverse events in the CP group**: "No adverse effects or allergic responses associated with plasma transfusion were observed in recipients. (p.5)"[49] **Adverse events in the Control group:** Not reported	
Al Shehry et al., 2021[50]	
Open-label, multi centre observations study comparing CP therapy with standard care alone in patients with severe or life-threatening COVID-19. Total number of participants, N=164 CP group, n=40; Control group, n=124 **Baseline characteristics:** Baseline characteristics such as demographics, comorbidities and intubation status were comparable between the groups. **Study findings:** • **Length of stay in ICU, median (IQR), days**	"The preliminary findings of this trial suggest that CP is a safe strategy for COVID-19 disease and that it results in a nonsignificant absolute risk reduction in the 30-day mortality for CP recipients, and its effects are likely to be more profound when carried out earlier in their disease course. The final report of this trial would provide more clarity on the outcomes reported here. (p. 21)"[50]

Main study findings	Authors' conclusion
○ Overall = 8 (5 to 14) ○ CP group = 8 (5 to 20) ○ Control group = 8 (5 to 12.5) ○ P value =0.349 • **Length of hospitalization, median (IQR), days** ○ Overall = 15 (10 to 22) ○ CP group = 15.5 (11 to 31) ○ Control group = 14 (10 to 20) ○ P value =0.049 • **Duration of intubation, median (IQR), days** ○ Overall = 9 (5 to 14.5) ○ CP group = 10 (5 to 20) ○ Control group = 8.5 (5 to 13) ○ P value = 0.474 • **Time to clinical recovery, median (IQR), days** ○ Overall = 15 (11 to 24) ○ CP group = 16.5 (12 to 36.5) ○ Control group = 15 (11 to 21) ○ P value =0.101 • **30-day mortality, n (%)** ○ CP group = 10 (26.3) ○ Control group = 46 (39.3) ○ Absolute risk reduction, ARR = 13; P value =0.15 ○ Survival, HR (95% CI) = 0.554 (0.299 to 1.027); P value = 0.061 **Adverse events in CP group:** "The CP transfusion was safe, with no adverse effects reported. (p.19)"[50] **Adverse events in the Control group:** Not reported	
Biernat et al., 2021[51]	
Retrospective observational trial evaluating the efficacy of CP therapy in COVID-19 patients with hematological malignancies. Total number of participants, N=45 CP group, n=23; Control group, n=22 **Baseline characteristics:** Significantly more patients in the control group (59.1%) had severe COVID-19 compared to CP group (21.7%), P = 0.03. More patients in the CP group had COVID-19 pneumonia (82%) compared to CP group (74%), as well as symptoms such as fever, dyspnea, and others. The use of concomitant medications such as dexamethasone (CP group 34.8% vs. control group 54.5%), hydroxychloroquine (CP group 0 vs. control group 100%), and other treatments (remdesivir, Lopinavir/ritonavir, Tocilizumab) were significantly different between the groups. **Study findings:** • **Death, n (%)** ○ Overall = 12 (27) ○ CP group = 3 (13) ○ Control group = 9 (41) ○ OR = 4.615 (95% CI: not reported) ○ P value = 0.03460 • **Course of disease and symptom resolution:** ○ "… the group of patients who received convalescent plasma showed a statistically significant milder course of infection (p = 0.03807) (Figure 2), with less severe and faster resolution of symptoms such as fever (p = 0.00665), shortness of breath (p = 0.03008) and cough (p = 0.00763). (p.4)"[51]	"In conclusion, we have demonstrated that convalescent plasma is an effective treatment and its early administration leads to clinical improvement, increased viral clearance and longer overall survival in patients with hematological malignancies with COVID-19. (p. 6)"[51]

Main study findings	Authors' conclusion
• **Disease progression:** ○ "Moreover, patients treated with convalescent plasma had a faster clearance of the virus by day 14. Pulmonary infiltrates resolved after day 14, significantly faster than in the control group (p = 0.02480) and patients required oxygen therapy for a shorter time, on average 14 days (p = 0.02355), and more patients in the treatment group had recovered by day 14 (p = 0.00001). (p.4)"[51] [Data not reported in the publication] • **Duration of SARS-CoV-2 infection, median (range), days** ○ Overall = 21 (8 to 53) ○ CP group = 18 (8 to 28) ○ Control group = 37 (20 to 53) ○ OR = 6.056 (95% CI: not reported) ○ P value = 0.00001 **Adverse events in CP group:** "Convalescent plasma administration was well tolerated and no adverse events were reported in any case. (p. 4-5)"[51] **Adverse events in the Control group:** Not reported	
Budhiraja et al., 2021[52]	
Retrospective observational study comparing the efficacy of CP therapy compared to best supportive care in patients with moderate-to-severe COVID-19. Total number of participants, N= 1079 Total number of participants in the ICU, N= 694 CP group, n=333; Control group, n=361 **Baseline characteristics:** There were significantly more males in the control group than the CP group. Significantly more patients in the control group were in the ICU. As for comorbidities, there were more patients with hypertension in the control group and more patients with coronary artery disease in the CP group. **Study findings:** • **Mortality, n (%):** **Overall patients (N = 1079)** ○ CP group = 22.4% ○ Control group = 18.5% ○ OR (95% CI) = 1.27 (0.94 to 1.72); P value = 0.125 **ICU patients (N = 694)** ○ CP group = 85 (25.5) ○ Control group = 120 (33.2) ○ OR (95% CI) = 0.69 (0.50 to 0.96); P value = 0.026 ***Age group, years*** ***<45*** ○ CP group = 7(17.5); Control group =14 (22.6) ○ OR (95% CI) = 0.73 (0.26 to 2.00); P value = 0.536 ***45 to 59*** ○ CP group = 28 (23.0); Control group =27 (23.5) ○ OR (95% CI) = 0.97 (0.53 to 1.77); P value = 0.923 ***60 to 74*** ○ CP group = 36 (26.7); Control group =64 (43) ○ OR (95% CI) = 0.48 (0.29 to 0.80); P value = 0.004 ○ >75 ○ CP group = 14 (38.9); Control group =15 (42.9) ○ OR (95% CI) = 0.85 (0.33 to 2.19); P value = 0.734	"The use of convalescent plasma was associated with reduced mortality in severe COVID-19 elderly patients, above 60 years of age, particularly females, those with comorbidities and especially those who require some form of ventilation. This beneficial effect was lost when the entire cohort of patients across varying severity of illness was compared. Plasma did not seem to offer any mortality benefit in patients of moderate severity or those who were terminally ill. Further research into the mechanism of actions of CP in COVID-19 may help predict the good responders. (p.8)"[52]

Main study findings	Authors' conclusion
Sex ***Males*** ○ CP group = 72 (27); Control group =73 (28) ○ OR (95% CI) = 0.95(0.65 to 1.39); P value = 0.796 ***<45*** ○ CP group = 6 (18.8); Control group =9 (18)) ○ OR (95% CI) =1.05 (0.33 to 3.30); P value = 0.932 ***45 to 59*** ○ CP group = 24 (25); Control group =13 (16.3) ○ OR (95% CI) = 1.72 (0.81 to 3.65) P value = 0.156 ***60 to 74*** ○ CP group = 30 (27.5); Control group = 41 (38.7) ○ OR (95% CI) =0.60 (0.34 to 1.07); P value = 0.082 ***>75*** ○ CP group = 12 (40); Control group =10 (40) ○ OR (95% CI) = 1.00 (0.34 to 2.95); P value = 1.00 ***Females*** ○ CP group = 13 (19.7); Control group = 47 (47) ○ OR (95% CI) = 0.28 (0.13 to 0.57); P value <0.001 ***<45*** ○ CP group = 1 (12.5); Control group =5 (41.7) ○ OR (95% CI) = 0.20 (0.02 to 2.18); P value = 0.325 ***45 to 59*** ○ CP group = 4 (15.4); Control group =14 (40) ○ OR (95% CI) = 0.27 (0.08 to 0.96); P value = 0.037 ***60 to 74*** ○ CP group = 6 (23.1); Control group =23 (53.5) ○ OR (95% CI) = 0.26 (0.09 to 0.78); P value = 0.013 ***>75*** ○ CP group = 2 (33.3); Control group = 5 (50) ○ OR (95% CI) = 0.50 (0.06 to 4.09); P value = 0.633 ***Number of comorbidities*** ***None*** ○ CP group = 14 (19.4); Control group = 16(17.4) ○ OR (95% CI) = 1.15 (0.52 to 2.54); P value = 0.736 ***1*** ○ CP group = 37 (22.3); Control group = 66 (36.5) ○ OR (95% CI) = 0.50 (0.31 to 0.80); P value = 0.004 ***2*** ○ CP group = 26 (35.1); Control group =30 (49.2) ○ OR (95% CI) = 0.56 (0.28 to 1.12); P value = 0.099 ***3+*** ○ CP group = 8 (38.1); Control group =8 (29.6) ○ OR (95% CI) = 1.46 (0.44 to 4.89); P value = 0.537 **Males** ***None*** ○ CP group = 12 (19); Control group =8 (11.1) ○ OR (95% CI) = 1.88 (0.72 to 4.95); P value = 0.195 ***1*** ○ CP group = 35 (25.7); Control group = 40(31.3) ○ OR (95% CI) = 0.76 (0.45 to 1.30); P value = 0.321 ***2*** ○ CP group = 20 (37.7); Control group =19 (42.2) ○ OR (95% CI) = 0.83 (0.37 to 1.87); P value = 0.651	

Main study findings	Authors' conclusion
3+ ○ CP group = 5 (33.3); Control group =6 (37.5) ○ OR (95% CI) = 0.83 (0.19 to 3.64); P value = 0.809 **Females** ***None*** ○ CP group = 2 (22.2); Control group =8 (40) ○ OR (95% CI) = 0.43 (0.07 to 2.61); P value = 0.351 ***1*** ○ CP group = 2 (6.7); Control group =26 (49.1) ○ OR (95% CI) = 0.17 (0.02 to 0.34); P value <0.001 ***2*** ○ CP group = 6 (28.6); Control group =11 (68.8) ○ OR (95% CI) = 0.18 (0.04 to 0.75; P value = 0.015 ***3+*** ○ CP group = 3 (50); Control group =2 (18.2) ○ OR (95% CI) = 4.50 (0.49 to 41.25); P value = 0.169 **Specific comorbidity** ***Hypertension*** ○ CP group = 53 29.1); Control group =59 (37.6) ○ OR (95% CI) = 0.68 (0.43 to 1.08); P value = 0.099 ***Diabetes Mellitus*** ○ CP group = 18 (29.5); Control group =17 (25.8) ○ OR (95% CI) = 1.21 (0.55 to 2.63); P value = 0.636 ***Coronary artery disease*** ○ CP group = 11 (44); Control group =24 (47.1) ○ OR (95% CI) = 0.88 (0.34 to 2.31); P value = 0.802 ***Hypothyroidism*** ○ CP group = 8 (19); Control group =14 (42.4) ○ OR (95% CI) = 0.32 (0.11 to 0.90); P value = 0.027 **Ventilator and vasopressor status** ***No ventilator*** ○ CP group = 4 (3.5); Control group = 7 (5.3) ○ OR (95% CI) = 0.64 (0.18 to 2.26); P value = 0.488 ***Any ventilator*** ○ CP group = 81 (37.2); Control group =113 (49.3) ○ OR (95% CI) = 0.61 (0.42 to 0.89); P value = 0.009 ***Non-invasive ventilation*** ○ CP group = 42 (26.8); Control group =55 (34.6) ○ OR (95% CI) = 0.69 (0.43 to 1.12); P value = 0.131 ***Invasive ventilation*** ○ CP group = 39 (63.9); Control group =58 (82.9) ○ OR (95% CI) = 0.37 (0.16 to 0.83); P value = 0.014 ***Vasopressor with invasive ventilation*** ○ CP group = 21 (87.5); Control group = 33 (91.7) ○ OR (95% CI) = 0.64 (0.12 to 3.45); P value = 0.675 • **Need for invasive ventilation n (%)** ○ "Out of a total of 694 patients with severe COVID-19 in ICU, 101 (14.6%) patients worsened on non-invasive ventilation (NIV) and needed to be shifted to invasive ventilator. Fifty-four (53.46%) of these patients were given CP. The other 316 (45.5%) patients remained on NIV only and 157 (49.6%) of these received CP. Overall, CP did not affect the chances of being put on invasive ventilator from NIV (p = 0.508). (p.4)"[52]	

Main study findings	Authors' conclusion
Adverse events in CP group: minor allergic reactions (rashes), n = 2 **Adverse events in the Control group:** Not reported	
Hatzl et al., 2021[53]	
Prospective observational study comparing the efficacy of CP therapy compared to best supportive care in patients with critical COVID-19 with associated acute respiratory failure. Total number of participants, N= 120 CP group, n=78; Control group, n=72 **Baseline characteristics:** Patients in the CP group were significantly younger (median age 61 years vs. 69 years) and had a higher number of comorbidities (median number of comorbidities in CP group 3 (IQR 2 to 5) vs. control group 2 (IQR 1 to 4), higher proportion of patients with immunosuppression (CP group 30% vs. control group 4%), and significantly more patients with severe disease (CP group 88% vs. control group 47%). CP group patients also had significantly more severe disease as evidenced by SOFA score (CP group median 6 vs. control group median 4), PaO2/FiO2 ratio (CP group median 81 vs. control group median 113). Significantly more patients in the control group (35%) were treated during the "first wave" compared to CP group (6%) **Study findings**: • **Overall survival:** **Unadjusted analysis:** ○ "..after 1.3 months 50% of patients deceased in the non-CVP group, whereas patients allocated to CVP treatment did not reach this threshold (log-rank p = 0.049). (p.4)"[53] ○ 30-day OS: "…estimates 69% in the CVP group, and 54% in the non-CVP group. In univariable Cox regression, this corresponded to a Hazard Ratio (HR) of 0.56 (95% CI 0.31– 1.01, *p* = 0.054) by CVP therapy. (p.4)"[53] **Adjusted analysis (using an Inverse probability of treatment-weight [IPTW] analysis):** ○ Adjusted for immunosuppression, SARS-CoV-2 antibody positivity, PaO2/FiO2 ratio and whether patients were treated in the "first wave" of COVID-19. ○ "the 30-day OS after weighting the time-to event data which were 77% in the CVP group, and 59% in the non-CVP group. This corresponded to an estimated 2.3-fold lower risk of death (IPTW-adjusted HR = 0.44, 0.21–0.95, *p* = 0.035) after CVP therapy. (p.7)"[53] ○ Besides CP, "..the strongest multivariable independent predictor for a more favorable OS was positivity for SARS-CoV-2 antibodies at ICU admission. (p.7)"[53] **Adverse events in CP group:** "..no unexpected or serious adverse events related to CVP administration were observed..(p.4)" [53] **Adverse events in the Control group:** Not reported	"In this observational study comprising 120 critically ill patients and high proportion of immunocompromised patients with PCR-confirmed COVID-19 and associated acute respiratory failure admitted to our ICUs, we were able to demonstrate that CVP treatment is able to improve ICU outcomes especially in patients with absence of anti-SARS-CoV-2 antibodies at time of ICU admission. We could further strengthen this finding using propensity scores to balance the population for known and unknown risk factors. In summary, we report the utility of CVP in a "real-world" ICU-cohort of critically ill COVID-19 patients highlighting the potential relevance of our finding to the field of intensive care medicine. (p.9)"[53]
Klapholz et al., 2021[54]	
A retrospective matched cohort study assessing short-term efficacy and safety of CP therapy in patients with severe or life-threatening COVID-19. Total number of participants, N= 94 CP group, n=47; Control group, n=47 **Baseline characteristics:** Baseline characteristics such as demographics, comorbidities, medications used, and oxygen support were comparable between the groups.	"Convalescent plasma infused for severe or life threateningly ill COVID-19 inner-city, minority patients appears to be safe. Comparison with a matched contemporaneous control cohort suggested improvement in the treated population for 7-day outcomes but was not statistically

Main study findings	Authors' conclusion
Study findings: • **7-day composite outcome, n/N** ○ CP group = 14/47 ○ Control group = 17/47 ○ Adjusted HR = 0.70 (95% CI: 0.23 to 2.12) ○ P value = 0.52 • **7-day mortality, n/N** ○ CP group = 10/47 ○ Control group = 9/47 ○ Adjusted HR = 0.23 (95% CI: 0.04 to 1.51) ○ P value = 0.13 • **7-day worsening of O_2 support among patients not on ventilator pre-transfusion (N = 38 matched pairs), n/N** ○ CP group = 10/38 ○ Control group = 9/38 ○ Adjusted HR = 2.38 (95% CI: 0.47 to 12.1) ○ P value = 0.30 **Patients on mechanical ventilation pre-transfusion (N = 9 matched pairs)** • **7-day composite outcome, n/N** ○ CP group = 3/9 ○ Control group = 6/9 ○ Adjusted HR = 0.27 (95% CI: 0.04 to 1.77) ○ P value = 0.17 **Patients not on mechanical ventilation pre-transfusion (N = 38 matched pairs)** • **7-day composite outcome, n/N** ○ CP group = 11/38 ○ Control group = 11/38 ○ Adjusted HR = 0.97 (95% CI: 0.38 to 2.45) ○ P value = 0.94 **Adverse events in CP group:** transient fever, n = 1 (resolved after transfusion was discontinued and with acetaminophen) **Adverse events in the Control group:** Not reported	significant. Large multicenter randomized trials with CCP (alone or in combination with other anti-COVID-19 candidate drugs) that address timing relative to disease stage and dosing or the use of CCP as a preemptive strategy for protection against SARS-CoV-2 infection in high-risk patients appear to be warranted. (p. 7)"[54]
Kuno et al.,2021[55]	
A retrospective matched cohort study to assess the association of CP therapy and mortality in patients with COVID-19. Total number of participants, N= 9,565 CP group, n = 1,113; Control group, n=8,452 PS matched pairs: CP group, n = 960; Control group, n=960 **Baseline characteristics:** Patients in the CP group had a significantly higher proportion of males (CP group 59.9% vs. control group 54%) and patients with cancer (CP group 11.7% vs. control group 8.7%). CP group participants had clinical characteristics denoting significantly more disease severity as evidenced by lower median O2 saturation (CP group 88% vs. control group 90%) and higher respiratory rate (CP group 20/min vs control group 19/min). A higher proportion of CP group patients received therapeutic anticoagulation, steroids, remdesivir and IL-6 inhibitor. • **Steroid use during hospitalization, n (%)** ○ CP group = 949 (85.3); control group = 3,802 (45) ○ P value <0.001 • **Use of remdesivir, n (%)** ○ CP group = 530 (47.6); control group = 1,066 (12.6)	"In conclusion, convalescent plasma treatment was not associated with a lower risk of in-hospital mortality of COVID- 19 patients. Further investigation is required to confirm these findings. (p.2)" [55]

Main study findings	Authors' conclusion
○ P value <0.001 • **Use of Interleukin-6 inhibitor, n (%)** ○ CP group = 50 (4.5); control group = 274 (3.2) ○ P value <0.001 • **Therapeutic anticoagulation during hospitalization, n (%)** ○ CP group = 525 (47.2); control group = 2,604 (30.8) ○ P value <0.001 • **Needed ICU admission, n (%)** ○ CP group =332 (29.8); control group = 1,592 (18.8) ○ P value <0.001 ○ Needed endotracheal intubation, n (%) ○ CP group = 214 (19.2); control group = 1,052 (12.4) ○ P value <0.001 **All baseline characteristics were balanced between the groups in the cohort of PS matched pairs.** **Study findings:** • **In-hospital death, n (%)** **Overall:** ○ CP group = 279 (25.1) ○ Control group = 1,961 (23.2) ○ P value = 0.18 **PS matched pairs:** ○ CP group = 241 (25.1) ○ Control group = 250 (26) ○ P value = 0.68 ***Among patients with moderate or severe disease:*** • "In the analysis limiting patients to moderate or severe COVID-19 (N = 8295, 86.7%), in-hospital mortality was not significantly different in patients with and without convalescent plasma in the propensity-matched cohorts (N = 930 pairs; 26.1% versus 22.4%, p = 0.066). (p.1)" [55] • "..among severe patients (N = 278 pairs; 58.6% versus 60.8%, p = 0.67) as well as moderate patients (N = 6215 patients; 645 pairs; 10.5% versus 11.6%, p = 0.60) (p.1)" [55] ***Among patients> 75 years old*** **PS matched pairs:** • CP group = 108 (39.4) • Control group = 124 (45.3) • P value = 0.20 ***Among patients with steroid treatments:*** **PS matched pairs:** • CP group = 217 (26.6) • Control group = 205 (25.1) • P value = 0.53 ***Among patients who were discharged between February 18, 2021 and March 30, 2021*** • "…in-hospital mortality was not significantly different in patients with and without convalescent plasma treatment in the propensity-matched cohorts (171 pairs; 25.7% versus 19.3%, p = 0.20). (p.1)" [55]	

Main study findings	Authors' conclusion
• **Acute kidney injury, n (%)** **Overall:** ○ CP group = 319 (28.7) ○ Control group = 2313 (27.8) ○ P value = 0.56 **PS matched pairs:** ○ CP group = 261 (27.2) ○ Control group = 273 (28.4) ○ P value = 0.58 *Among patients> 75 years old* **PS matched pairs:** ○ CP group = 92 (33.6) ○ Control group = 98 (35.8) ○ P value = 0.65 ***Among patients with steroid treatments:*** **PS matched pairs:** ○ CP group = 231 (28.3) ○ Control group = 226 (27.7) ○ P value = 0.83 **Adverse events in CP group:** Not reported **Adverse events in the Control group:** Not reported	
Kurtz et al., 2021[56]	
Prospective observational study assessing the 28-day mortality and clinical improvement in critically ill COVID-19 patients who received CP compared to those who received standard care alone. Total number of participants, N= 113 CP group, n=41; Control group, n=72 **Baseline characteristics:** There were no significant differences between groups in the following baseline characteristics: sex, baseline disease severity, and concomitant medications. Patients in CP group were younger (P = 0.048), had lesser rates of vasopressor therapy (46% in CP group vs. 68% in control group), higher rates of obesity (27% in CP group vs. 14% in control group) and higher incidence of cardiac disease (10% in CP group vs. 4% in control group). **Study findings:** • **Clinical improvement in 28 days, n (%)** ○ CP group = 19 (46) ○ Control group = 23 (32) ○ P value = 0.13 ○ Univariate Kaplan- Meier curves showed "no significant differences in the probability of clinical improvement between groups. (p.4)"[56] • **28-day mortality, n (%)** ○ CP group = 20 (49) ○ Control group = 40 (56) ○ P value = 0.5 ○ Univariate Kaplan- Meier curves showed no significant differences between the groups. • **Hospital length of stay at 28 days, median (IQR), days** ○ CP group = 17 (7 to 28) ○ Control group = 14 (4 to 26) ○ P value = 0.16	"In summary, convalescent plasma therapy showed a nonsignificant reduction in short-term mortality,but was not associated with clinical improvement or survival at 28 days. These results may be explained by our small sample size, the inclusion of patients with life-threatening disease, and elevated baseline IgG titers. These findings may guide future trials to identify patients with early disease and without antibody response that may benefit from CP therapy. (p. 8)"[56]

Main study findings	Authors' conclusion
• **Ventilator free days, median (IQR), days** ○ CP group = 0 (0 to 8) ○ Control group = 0 (0 to 3) ○ P value = 0.24 • **Mortality at 7 days, n (%)** ○ CP group = 7 (17) ○ Control group = 21 (29) ○ P value =0.15 • **Mortality at 21 days, n (%)** ○ CP group = 17 (42) ○ Control group = 37 (51) ○ P value =0.3 **Patients with moderate-to-severe ARDS, N = 78** **CP group, n = 34, control group, n = 44** • **Hospital length of stay at 28 days, median (IQR), days** ○ CP group = 20 (10 to 28) ○ Control group = 14 (4 to 27) ○ P value = 0.05 • **Clinical improvement in 28 days, n (%)** ○ CP group = 12 (35) ○ Control group = 10 (23) ○ P value = 0.2 • **Mortality at 7 days, n (%)** ○ CP group = 7 (21) ○ Control group = 18 (41) ○ P value =0.06 • **Mortality at 21 days, n (%)** ○ CP group = 17 (50) ○ Control group = 28 (64) ○ P value =0.2 • **Mortality at 28 days, n (%)** ○ CP group = 20 (59) ○ Control group = 29 (66) ○ P value =0.5 **Multivariable analysis:** ○ adjusting for age, mechanical ventilation, SOFA score, SAPS3, frailty, and time from symptom onset to ICU admission. ○ "CP was not independently associated with clinical improvement [adjusted Hazard Ratio (aHR) 0.91 (0.49–1.69)] or 28-day mortality [aHR 0.90 (0.52–1.57)]. (p.5)"[56] **Adverse events in CP group:** no adverse events were identified **Adverse events in the Control group:** Not reported	
Omrani et al., 2021[57]	
Retrospective observational study to compare the efficacy of CP therapy in patients with severe COVID-19 compared to standard care alone. Total number of participants, N= 80 CP group, n=40; Control group, n=40 **Baseline characteristics:** There were no significant differences between groups in the following baseline characteristics: age, sex, baseline disease severity, comorbidities and concomitant medications. Patients in the CP group had significantly lower serum	"In conclusion, in this retrospective cohort study of critically ill COVID‐19 patients, convalescent plasma therapy was not associated with clinical benefit in terms of improvement in the respiratory support status within 28 days. It is not clear if the administration of convalescent plasma at an earlier stage may prevent the clinical progression of COVID‐19 and result in better

Main study findings	Authors' conclusion
creatinine at baseline than those in the control group (CP group, median = 81 µmol/L; control group, median = 90 µmol/L). **Study findings:** • **Improvement in respiratory support at day 28, n (%)** ○ CP group = 31 (77.5) ○ Control group = 57 (71.3) ○ P value =0.32 • **Proportion of patients discharged alive at day 28, n (%)** ○ CP group = 26(65) ○ Control group = 26(65) ○ P value >.99 • **Viral clearance, n (%)** ○ CP group = 22 (55) ○ Control group = 26 (65) ○ P value = 0.49 • **All-cause mortality at 28 days, n (%)** ○ CP group = 1 (2.5) ○ Control group = 5 (12.5) ○ P value = 0.22 • **Respiratory status at 28 days, n (%):** ○ Ambient room air: CP group = 6 (15); Control group = 3 (7.5) ○ Supplemental O2: CP group = 25 (62.5); Control group = 25 (62.5) ○ Non-invasive ventilation: CP group = 1 (2.5); Control group = 0 ○ Invasive ventilation: CP group = 8 (20); Control group = 12 (30) ○ P value = 0.42 ○ **Time to improvement in respiratory support CP group = 31 (77.5)** ○ Adjusted HR (95% CI) = 0.87 (0.51 to 1.49); P = 0.622 ○ Log rank P = 0.99 **Adverse events:** • **Acute kidney injury, n (%)** ○ CP group = 13 (32.5); Control group = 16 (40) ○ P value = 0.64 • **Anemia, n (%)** ○ CP group = 28 (70); Control group = 20 (50) ○ P value = 0.11 • **ALT rise, n (%)** ○ CP group = 31 (77.5); Control group = 35 (87.5) ○ P value = 0.38 • **Bilirubin rise, n (%)** ○ CP group = 15 (37.5); Control group = 13 (32.5) ○ P value = 0.81 • **Hypernatremia, n (%)** ○ CP group = 18 (45); Control group = 13 (32.5) ○ P value = 0.36 • **Hypokalemia, n (%)** ○ CP group = 9 (22.5); Control group = 7 (17.5) ○ P value = 0.78 • **QTc prolongation, n (%)** ○ CP group = 8 (20); Control group = 5 (12.5) ○ P value = 0.55	clinical outcomes. Randomized clinical trials are urgently required to address these questions. (p. 7)"[57]

Main study findings	Authors' conclusion
Padilla et al.,2021[58]	
Retrospective observational study to compare the efficacy of CP therapy in patients with severe COVID-19 compared to Remdesivir. Total number of participants, N=106 CP group, n=53; Control group, n=11 **Baseline characteristics:** There were no significant differences between groups in the following baseline characteristics: age, sex, baseline disease severity, comorbidities, and concomitant medications. A significantly higher proportion of patients in the CP were admitted to ICU (CP group 56.6% vs. Remdesivir group 9.1%) **Study findings:** • **Survival** ○ "…treatment with remdesivir monotherapy showed an increased chance of survival compared to combination therapy or CP monotherapy with this difference approaching statistical significance (p = 0.052). (p.213)"[58] ○ "Based on logistic regression, age (p = 0.036), initial SOFA score (p = 0.013), and intubation (p = 0.005) were found to be statistically significant predictors of mortality. (p.213)"[58] • **Discharge disposition, n (%)** **Death** ○ CP group = 15 (28.3) ○ Remdesivir group = 3 (27.3) **Hospice** ○ CP group = 0 ○ Remdesivir group = 0 **Long-term acute care facility** ○ CP group = 5 (9.4) ○ Remdesivir group = 1 (9.1) **Skilled Nursing facility** ○ CP group = 4 (7.6) ○ Remdesivir group = 0 **Home** ○ CP group = 29 (54.7) ○ Remdesivir group = 7 (63.6) • **Days on ventilation, median (IQR), days** ○ CP group = 8 (4.5 to 14)) ○ Remdesivir group = 26 days (one patient) ○ P value = 0.091 • **Duration of stay in ICU, median (IQR), days** ○ CP group = 6 (5 to 10.5) ○ Remdesivir group = 27 days (one patient) ○ P value = 0.220 • **Length of stay, median (IQR), days** ○ CP group = 11 (7 to 15.5) ○ Remdesivir group = 8 (5 to 10) ○ P value = 0.175 **Adverse events:** Overall, 13 adverse events were reported. Remdesivir group: transaminitis, n =4; acute kidney injury, n =2 CP group: infusion reactions, n = 2 QT prolongation due to azithromycin, n = 3 (patients' treatment arm unclear)	"No significant differences in survival or clinical outcomes were observed between patients treated with either remdesivir monotherapy, CP monotherapy, or the combination of remdesivir and CP. The possible benefit of remdesivir in patients with more mild disease and the apparent lack of benefit of CP should prompt providers to develop a more targeted approach to the use of COVID-19 treatments. Larger studies should be conducted to determine which patients may benefit the most from the available therapies. Elderly patients, those with a high initial SOFA score, and patients who require intubation are at increased risk of mortality associated with COVID-19. Blood type did not influence clinical outcomes. (p.217)" [58]

Main study findings	Authors' conclusion
Pappa et al.,2021[59]	
Observational study with propensity score–matched controls to assess the efficacy of CP therapy in patients hospitalized with severe or life-threatening COVID-19 compared to standard care alone. Total number of participants, N=118 CP group, n=59; Control group, n=59 **Baseline characteristics:** There were no significant differences between groups in the following baseline characteristics: age, sex, baseline disease severity, laboratory parameters, comorbidities, and concomitant use of dexamethasone. **Study findings:** • **Overall survival** Patients surviving at the end of follow-up, n (%) ○ CP group = 57 (98.3) ○ Control group = 51 (86.4) ○ Overall survival, HR (95% CI) = 0.05 (0.01 to 0.43) ○ Kaplan-Meir analysis: "statistically significant association between CP infusion and better OS (Logrank p < 0.001). (p.7)"[59] ○ **"**Factors associated with reduced OS were advanced age (HR: 1.08 (95% CI: 1.01–1.14), p: 0.024) and the percentage of infiltrates in the CT scan (HR: 2.53 (95% CI: 1.24–5.19), p: 0.011). (p.7)"[59] • **Status at day 14, n (%)** ○ Discharged: CP group = 21 (35.6); Control group = 31 (52.5) ○ Hospitalized: CP group = 30 (50.8); Control group = 18 (30.5) ○ In ICU: CP group = 8 (13.6); Control group = 5 (8.5) ○ Death: CP group = 0; Control group = 5 (8.5) ○ P value = 0.249 ○ OR (95% CI) = 1.50 (0.76 to 2.98), P value = 0.244 • **Status at day 28, n (%)** ○ Discharged: CP group = 48 (81.4); Control group = 46 (78) ○ Hospitalized: CP group = 5 (8.5); Control group = 5 (8.5) ○ In ICU: CP group = 5 (8.5); Control group = 3 (5.1) ○ Death: CP group = 1 (1.7); Control group = 5 (8.5) ○ P value = 0.566 ○ OR (95% CI) = 0.77 (0.31 to 1.88), P value = 0.565 • **Status at end of follow-up, n (%)** ○ Discharged: CP group = 56 (94.9); Control group = 51 (86.4) ○ Hospitalized: CP group =0; Control group = 0 ○ In ICU: CP group = 1 (1.7); Control group =0 ○ Death: CP group = 2 (3.4); Control group = 8 (13.6) ○ P value = 0.106 ○ OR (95% CI) = 0.33 (0.08 to 1.33), P value = 0.119 • **Length of hospital stay, median (IQR)** ○ CP group = 15 (10); Control group = 10 (11) ○ P value = 0.006 ○ Time to discharge: HR (95% CI) = 0.68 (0.46 to 0.99), P value = 0.05 ○ Hospital discharge: OR (95% CI) = 2.93 (0.74 to 11.64), P value = 0.127 • **ICU stay** **Admission to ICU, n (%)** ○ CP group = 16 (27.1); Control group = 9 (15.3) ○ P value = 0.116 **Exit from ICU, n (%)** ○ CP group = 13 (22); Control group = 2 (3.4)	"In conclusion, in this prospective multicenter phase II study, we show through multivariate analysis that CP infusion compared to a matched control group was associated with a significant reduction of the risk of death and a significantly improved overall survival by Kaplan-Meir analysis. Within a median follow-up of 28.5 days, 57/59 patients remained alive and 56 were discharged from hospital fully recovered, with a median hospital stay of 15 days. The death rate in the CP group was 3.4% vs. 13.6% in the control group. At the end of follow-up, 56/59 (94.9%) in the intervention group were discharged compared to 51/59 (86.4%) in the control group; however, this difference was not statistically significant. In addition, 13/59 (22.0%) of patients in the control group exited ICU vs. 2/59 (3.4%) (p = 0.014) in the control group. A significant association between CP infusion and extubation or exit from ICU was also noted. High antibody levels in the CP were also associated with significantly improved OS, as shown by multivariate analysis, and with a higher rate of extubation and exit from ICU. CP infusion was safe and side effects were mild and easily managed. These encouraging data need confirmation by randomized controlled trials. (p.16)"[59]

Main study findings	Authors' conclusion
○ P value = 0.014 ○ OR (95% CI) = 15.16 (2.02 to 113.3), P value = 0.0008 **Time to exit from ICU, median (IQR)** ○ CP group = 12.5 (37.25); Control group = 7 (NC) ○ P value = 0.824 ○ HR (95% CI) = 0.54 (0.07 to 4.41), P value = 0.566 • **Intubation, n (%)** ○ CP group = 16 (27.1); Control group = 8 (13.6) ○ P value = 0.068 ○ OR (95% CI) = 2.37 (0.93 to 6.01), P value = 0.072 ○ Time to intubation: HR (95% CI) = 0.48 (0.19 to 1.21), P value = 0.122 **Extubation, n (%)** ○ CP group = 13 (22); Control group = 1 (1.7) ○ P value = 0.006 ○ OR (95% CI) = 30.3 (2.64 to 348.9), P value = 0.006 **Time to extubation, median (IQR)** ○ CP group = 15 (35.5); Control group = 17.5 (NC) ○ P value = 0.837 ○ Time to extubation: HR (95% CI) = 0.68 (0.08 to 5.44), P value = 0.712 • **Duration of O2 support, median (IQR)** ○ CP group = 7 (11.5); Control group = NA • **Achievement of negative PCR, n (%)** ○ CP group = 37(62.7); Control group = 19 (52.8) ○ P value = 0.167 ○ OR (95% CI) = 1.84 (0.78 to 4.36), P value = 0.168 **Time to PCR negativity, median (IQR)** ○ CP group = 14 (14); Control group = 9.5 (14.8) ○ P value = 0.007 ○ HR (95% CI) = 0.74 (0.42 to 1.29), P value = 0.741 **Adverse events:** **CP group:** grade 3 adverse event (severe exacerbation of dyspnea and hypoxemia, resolved with treatment), n =1; mild erythema, n =1; mild dizziness, n =1; increased temperature, n = 1 **Control group: Not reported**	
Pei et al., 2021[60]	
Retrospective observational study assessing the effectiveness of CP therapy in patients with COVID-19. Total number of participants, N=62 CP group (Hunan), n=19; Control group, n= 43 (Hunan, n = 23; Hubei, n = 20) **Baseline characteristics:** CP group patients from Hunan were younger than the 2 other groups, with mean ages of 66.3, 69.1 and 57.3 years in CP group, Hubei control group and Hunan control group respectively. Distribution of sex and disease severity were similar between the groups. **Study findings:** • **Case fatality rate:** ○ "All the 19 patients treated with CP transfusion in our study were survived, and showed a significantly lower case-fatality rate compared to the control group (0% vs. 19%, p=0.031). (p.7760)"[60] • **Length of hospital stay among survivors, median (IQR) days** ○ CP group = 32.5 (24.5 to 37.7) ○ Control group (Hunan) = 20.0 (17.0 to 21.0)	"More importantly, all the patients in exposure group were survived and discharged, suggesting that the CP treatment was associated with a better outcome and a lower fatality. (p.7762)"[60]

Main study findings	Authors' conclusion
○ Control group (Hubei) = 29.0 (26.0 to 31.3) ○ P < 0.001 • **Time from hospitalization to death, median (IQR) days** ○ CP group = N/A (no deaths) ○ Control group (Hunan) = 10.0 (3.3 to 22.7) ○ Control group (Hubei) = 22.0 (19.0 to 22.0) ○ P = 0.157 **Adverse events:** **CP group:** Not reported **Control group:** Not reported	
Salazar et al., 2021(a)[43]	
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) 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	"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)"[43]

Main study findings	Authors' conclusion
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)"[43] "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)"[43] ***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 **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 O2** • 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 O2** • CP group: 85 (26.5%); Control group: 149 (25.6%)	

Main study findings	Authors' conclusion
• 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 O2** • 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 O2** • 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)** • CP group: 261(81.3%); Control group: 435 (74.7%) **Low flow O2** • 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 O2** • 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 O2** • 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 O2** • CP group: 17(5.3%); Control group: 23 (4.0%)	

Main study findings	Authors' conclusion
• 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 O2** • CP group: 0; Control group: 1 (0.2%) • Risk ratio (95% CI) = not determinable **High-flow O2** • 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 • 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	
Salazar et al., 2021 (b)[61]	
Retrospective cohort study comparing the effectiveness of CP therapy to standard care alone in hospitalized patients with COVID-19. Total number of participants, N= 3529 CP group, n=868; Control group, n=2661	"Our study suggests that the administration of convalescent plasma in COVID-19 pneumonia might be associated with better outcomes. Large, well-designed clinical trials are required to confirm these findings. (p.7)"[61]

Main study findings	Authors' conclusion
Baseline characteristics: Patients in the CP group were significantly younger (Mean age CP group 56 vs. control group 64) and had more of comorbidities (CP group mean number 1.55 vs. control group 1.11). Comorbidities such as arterial hypertension and diabetes were significantly more frequent in CP group. CP group had significantly higher proportion of males (CP group 69.1 vs. control group 58.1). More patients in the CP group (32.3%) were admitted to ICU compared to control group (25.4%). Requirement for mechanical ventilation at baseline was not statistically significant between the groups. **Study findings:** • **28-day mortality, n (%)** ○ CP group = 221 (25.5); Control group = 1010 (38) ○ OR (95% CI) = 0.59 (0.47 to 0.66), P <0.001 **Among patients admitted to general ward** ○ CP group = 57/406 (14.0); Control group = 421/1409 (29.9) ○ OR (95% CI) = 0.38 (0.28 to 0.62); P <0.001 **Among patients admitted to ICU** ○ CP group = 73/280 (26.1); Control group = 125/677 (31.8) ○ OR (95% CI) = 0.76 (0.56 to 1.04); P = 0.081 **Among patients admitted to ICU with mechanical ventilation** ○ CP group = 91/182 (50); Control group = 374/575(65) ○ OR (95% CI) = 0.54 (0.38 to 0.75); P <0.001 • **Length of ICU stay, days (units not reported, likely median and IQR)** ○ CP group =12 (7 to 18); Control group = 10 (4 to 17) ○ P <0.001 **Adverse events:** **CP group:** Not reported **Control group:** Not reported	
Shenoy et al., 2021[62]	
Retrospective matched cohort study comparing the effectiveness of CP therapy to standard care alone in patients with COVID-19. Total number of participants, N= 526 CP group, n=263; Control group, n=263 **Baseline characteristics:** The distribution of race and ethnicity were significantly different between the groups. There proportion of African American patients was higher in the control group. The use of concomitant medications was significantly different between the groups. Significantly more patients in the CP group received steroids, remdesivir and tocilizumab, whereas more patients in the control group received hydroxychloroquine. • **Azithromycin, n (%)** ○ CP group = 157 (59.7); Control group = 177 (67.3) ○ P = 0.07 • **Dexamethasone, n (%)** ○ CP group = 70 (26.62); Control group = 21 (7.98) ○ P < 0.001 • **Hydrocortisone, n (%)** ○ CP group = 33 (12.55); Control group = 25 (9.51) ○ P = 0.26	"In this retrospective, health system-based, matched control study, we found an early mortality benefit at seven and 14 days of CCP transfusion but not at 28 days compared to controls. There was also a trend toward a quicker improvement in the oxygen device category in patients transfused with CCP, reflecting a more rapid respiratory recovery. This is the largest study to date, demonstrating a mortality benefit from COVID-19 convalescent plasma compared to controls. Further studies controlling for patient characteristics and using high IgG titer plasma are needed. (p.712)"[62]

Main study findings	Authors' conclusion
• **Methylprednisolone, n (%)** ○ CP group = 85 (32.32); Control group = 32 (12.17) ○ P <0.001 • **Prednisone, n (%)** ○ CP group = 5 (1.90); Control group = 1 (0.38) ○ P = 0.21 • **Hydroxychloroquine, n (%)** ○ CP group = 12 (4.56); Control group = 123 (46.77) ○ P< 0.001 • **Remdesivir, n (%)** ○ CP group = 107 (40.68); Control group = 9 (3.42) ○ P <0.001 • **Sarilumab, n (%)** ○ CP group = 1 (0.38); Control group = 0 ○ P = 1 • **Tocilizumab, n (%)** ○ CP group = 76 (28.90); Control group = 47 (17.87) ○ P = 0.002 **Study findings:** • **Mortality** **28-day mortality, n (%)** ○ CP group = 67 (25.48); Control group = 71 (27) ○ P value = 0.06 **14-day mortality, n (%)** ○ CP group = 39 (14.83); Control group = 62 (23.57) ○ P value = 0.01 **7-day mortality, n (%)** ○ CP group = 24 (9.13); Control group = 52 (19.77) ○ P value <0.001 • **Length of stay, mean (SD), days** ○ CP group = 15.67 (13.65); Control group = 10 (10.86) ○ P value <0.001 • **Length of stay for discharged patients, mean (SD), days** ○ CP group = 19.18 (14.75) Control group = 14.56 (12.18) ○ P value <0.001 • **Length of use of Oxygen devices, mean (SD) days** **Mechanical ventilation** ○ CP group = 20.97 (16.07); Control group = 15.92 (16.03) ○ P value = 0.07 **NIPPV** ○ CP group = 15.04 (13.01); Control group = 10.17 (9.47) ○ P value = 0.005 **Non-rebreather** ○ CP group = 16.88 (11.43)); Control group = 7.28 (6.08) ○ P value<0.001 **Nasal cannula** ○ CP group = 8.13 (10.41); Control group = 5.41 (4.50) ○ **P value = 0.10** • **Improvement in Oxygen devices, median, days** **Overall** ○ CP group = 3; Control group = 6 ○ HR = 1.12; P value = 0.22	

Main study findings	Authors' conclusion
Mechanical ventilation ○ CP group = 11; Control group = 15 ○ HR = 1.43; P value = 0.11 **NIPPV** ○ CP group = 3; Control group = 4 ○ HR = 1.00; P value = 0.99 **Non-rebreather** ○ CP group = 2; Control group = 4 ○ HR = 1.10; P value = 0.58 **Nasal cannula** ○ CP group = 2; Control group = 3 ○ HR = 1.42; P value = 0.06 • **Improvement in Oxygen devices in patients transfused within 3 days, median, days** **Overall** ○ CP group = 4; Control group = 5 ○ HR = 1.00; P value = 0.99 **Mechanical ventilation** ○ CP group = 12; Control group = 14 ○ HR = 1.06; P value = 0.84 **NIPPV** ○ CP group = 4; Control group = 3 ○ HR = 0.93; P value = 0.72 **Non-rebreather** ○ CP group = 3; Control group = 4 ○ HR = 0.84; P value = 0.52 **Nasal cannula** ○ CP group = 1; Control group = 4 ○ HR = 1.64; P value = 0.02 **Adverse events in CP group: "no transfusion reactions occurred in our cohort. (p.708)"**[62] **Adverse events in the Control group:** Not reported	
Yoon et al., 2021[63]	
A propensity score matched observational study to study the effects of CP therapy in mortality among patients with severe or life-threatening COVID-19. Total number of participants, N= 146 CP group, n=73; Control group, n=73 **Baseline characteristics:** There were no significant differences between groups in the following baseline characteristics: age, sex, BMI, race, ethnicity, laboratory parameters, comorbidities, and concomitant use of corticosteroids and therapeutic anticoagulation. • **Mortality at 28 days, n (%)** **All matched pairs** ○ CP group = 23 (31.5); Control group = 28 (38.4) ○ OR (95% CI) = 0.74 (0.37 to 1.46); P value = 0.37 ○ Kaplan-Meir log rank p = 0.47 **Among patients not on mechanical ventilation** ○ CP group = 21 (32.8); Control group = 24 (37.5) ○ P value = 0.58	"In summary, we report that CCP administration within 72 hours of hospitalization demonstrated a possible signal of reduced mortality in patients younger than 65 years. Similar to others, we found CCP was safe with no adverse events directly attributable to transfusion (21, 71, 72). Although our data suggest possible effects of age and disease severity on CCP efficacy, prospective RCTs are needed to definitively establish its efficacy. (p.9)"[63]

Main study findings	Authors' conclusion
Among patients on mechanical ventilation ○ CP group = 2 (22.2); Control group = 4 (44.4) ○ P value =0.32 "Multivariable analysis of 90 CCP recipients and 258 controls adjusted for covariates age, sex, BMI, race, ethnicity, comorbid conditions, week of admission, baseline oxygen requirement, corticosteroids, anticoagulation use, D-dimer, and lymphocyte counts did not show any difference in outcome between the 2 groups. (p.3)"[63] • **Clinical status at 28 days, n (%)** ○ Stable/better: CP group = 47 (64.4); Control group = 42 (57.5) ○ Worse/dead: CP group = 26 (35.6); Control group = 31 (42.5) ○ P value = 0.39 ***Patients <65 years*** • **Mortality at 28 days, n (%)** **All matched pairs** ○ CP group = 3 (8.8); Control group = 10 (29.4) ○ OR (95% CI) = 0.23 (0.05 to 0.95); P value = 0.03 ○ Kaplan-Meir log rank p = 0.04 **Among patients not on mechanical ventilation** ○ CP group = 2 (7.1); Control group = 8 (28.6) ○ P value = 0.04 **Among patients on mechanical ventilation** ○ CP group = 1 (14.2); Control group = 3 (42.8) ○ P value =0.23 • **Clinical status at 28 days, n (%)** ○ Stable/better: CP group = 30 (88.2); Control group = 22 (64.7) ○ Worse/dead: CP group = 4 (11.8); Control group = 12 (35.3) ○ P value = 0.02 ○ Risk of deterioration in oxygenation or mortality, OR (95% CI) = 0.24 (0.06 to 0.87); P value = 0.03 ***Patients ≥65 years*** • **Mortality at 28 days, n (%)** **All matched pairs** ○ CP group = 20 (52.6); Control group = 17 (45.9); P = 0.56 ○ OR (95% CI) = 1.07 (CI not reported); P value = 0.89 ○ Kaplan-Meir log rank p = 0.61 **Among patients not on mechanical ventilation** ○ CP group = 19 (52.8); Control group = 16 (44.4) ○ P value = 0.48 **Among patients on mechanical ventilation** ○ CP group = 1 (33.3); Control group = 2 (66.7) ○ P value =0.41 • **Clinical status at 28 days, n (%)** ○ Stable/better: CP group = 17 (43.6); Control group = 20 (51.3) ○ Worse/dead: CP group = 22 (56.4); Control group = 19 (48.7) ○ P value = 0.49 **Adverse events in CP group:** "There were no adverse reactions, including no instances of transfusion-related acute lung injury or transfusion-associated circulatory overload attributable to CCP administration. (p.5)"[63] **Adverse events in the Control group:** Not reported	

Main study findings	Authors' conclusion
Abolghasemi et al., 2020[36]	

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)"[36]

Main study findings	Authors' conclusion
Alsharidah et al., 2020[44]	
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 ○ 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	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)"[44]

Main study findings	Authors' conclusion
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)" [44] **Adverse events in the CP group:** • Allergic skin reaction, n = 3 (all 3 resolved) **Adverse events in the CP group:** Not reported	
Altuntas et al., 2020[37]	
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) ○ 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	"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)[37]
Dai et al., 2020[45]	
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 (1-point reduction), n (%)** • CP group: 27 (69.2%); Control group: 80 (24.4%) • **Mean time to improvement, days (range)**	"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)"[45]

Main study findings	Authors' conclusion
○ CP group: 10 (1 to 28); Control group: 17 (1 to 45) ○ P <0.001 **Clinical improvement (2-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%) • **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 (1-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 (2-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 (1-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 (2-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	

Main study findings	Authors' conclusion
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	
Duan et al.,2020 [38]	
A non-randomized pilot study to assess the effectiveness of CP therapy. 10 COVID-19 patients received one dose of 200 mL CP infusion, compared with age- and sex-matched historic control. CP treatment group, n=10 Historic Control group, n=10 **Baseline characteristics** • Age, median (IQR) ○ CP treatment group = 52.5 (45 to 59.5) ○ Historic control group = 53 (46.5 to 60.5) • Sex, n (%) ○ CP treatment group = 4 (40%) female ○ Historic control group = 4 (40%) female • Comorbidity, n (%) ○ CP treatment group = 4 (40%) had comorbidities ○ Historic control group = 6 (60%) had comorbidities **Study findings** • **Death, n (%)** ○ CP treatment group = 0 ○ Historic control group = 3 (30) • **Stable, n (%)** ○ CP treatment group = 0 ○ Historic control group = 6 (60) • **Improved, n (%)** ○ CP treatment group = 7 (70) ○ Historic control group = 1 (10) • **Discharged, n (%)** ○ CP treatment group = 3 (30) ○ Historic control group = 0	"In conclusion, this pilot study on CP therapy shows a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients. One dose of CP with a high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes. The optimal dose and treatment time point, as well as the definite clinical benefits of CP therapy, need to be further investigated in randomized clinical studies. (p. 9496)"[38]
Jiang et al., 2020[46]	
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%)	"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

Main study findings	Authors' conclusion
• 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	provide comprehensive reference for COVID-19 treatment. (p.3)"[46]
Liu et al., 2020[42]	
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) [42] • **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) [42] "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) [42]	"…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)[42]
Moniuszko-Malinowska et al., 2020[47]	
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 O2 therapy, n (%)** ○ CP group: 41 (74.5%) ○ Control group I: 108 (46%); P <0.05 ○ Control group II: 276 (38.6%); 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)" [47]

Main study findings	Authors' conclusion
"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)"[47] "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)"[47] • **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 • **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	
Rogers et al., 2020[39]	
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) [39]

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 2 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) *Males* ○ 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*** *18-49 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 High-flow nasal cannula* ○ 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
Xia et al., 2020[40]	
A non-randomized study comparing CP therapy and standard care in COVID-19 patients. CP group, n=138 Control group, n=1,430 **Baseline characteristics:** **Degree of severity, n (%)** • **Severe disease, n (%)** ○ CP treatment group = 116 (84.1); Control group = 1,304 (91.2) • **Critical disease, n (%)** ○ CP treatment group = 22 (15.9); Control group = 126 (8.8) ○ P = 0.009 **Comorbidities:** • **Diabetes, n (%)** ○ CP treatment group = 31 (22.5); Control group = 218 (15.2) ○ P = 0.04 • **Hypertension, n (%)** ○ CP treatment group = 53 (38.4); Control group = 508 (35.5) ○ P = 0.5 • **Cardiovascular disease, n (%)** ○ CP treatment group = 27 (19.6); Control group = 210 (14.7) ○ P = 0.1 • **Cerebrovascular disease, n (%)** ○ CP treatment group = 12 (8.7); Control group = 75 (5.2) ○ P = 0.1 • **Malignancy, n (%)** ○ CP treatment group = 4 (2.9); Control group = 53 (3.7) ○ P = 0.8 • **Chronic obstructive pulmonary disease, n (%)** ○ CP treatment group = 12 (8.7); Control group = 91 (6.4) ○ P = 0.3 • **Chronic renal disease, n (%)** ○ CP treatment group = 4 (2.8); Control group = **33 (**2.3) ○ P = 0.6 • **Chronic liver disease, n (%)** ○ CP treatment group = 4 (2.9); Control group = 39 (2.7) ○ P = 0.8 • **Immunodeficiency, n (%)** ○ CP treatment group = 2 (1.4); Control group = 4 (0.28) ○ P = 0.09 • **Days from symptoms onset to admission, median (IQR)** ○ CP treatment group = 35 (18 to 40); Control group = 25 (14 to 35) ○ P < 0.001 • **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)	"Our results suggest that CCP, transfused even after 2 weeks (median of 45 days in our cohort) of symptom onset, could improve the symptoms and mortality in severe or critical COVID-19 patients. We anticipate that this study could shed new light in clinical practice and monoclonal antibody development for COVID-19. (p. 6-7)"[40]

Main study findings	Authors' conclusion
○ P = 0.8 • **Highest temperature (ºC), median (IQR)** ○ CP treatment group = 37.2 (37.0 to 37.4); Control group = 37.1 (36.9 to 37.3) ○ P = 0.008 • **Cough, n (%)** ○ CP treatment group = 83 (60.1); Control group = 863 (60.3) ○ P = 1 • **Shortness of breath, n (%)** ○ CP treatment group = 28 (20.3); Control group = 150 (10.5) ○ P = 0.001 • **Chest congestion, n (%)** ○ CP treatment group = 24 (17.4); Control group = 175 (12.2) ○ P = 0.1 • **Nausea or vomiting, n (%)** ○ CP treatment group = 2 (1.4); Control group = 13 (0.9) ○ P = 0.4 • **Diarrhea, n (%)** ○ CP treatment group = 4 (2.9); Control group = 39 (2.7) ○ P = 0.8 **ICU admission, n (%)** ○ CP treatment group (among 126 patients who were not admitted to ICU prior to CP therapy) = 3 (2.4) ○ Control group = 72 (5.1) ○ P = 0.2 **Highest 6 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 non-invasive 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)"[40]	

Main study findings	Authors' conclusion
Zeng et al. 2020[41]	

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)
  ○ 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
• **Dyspnea, 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)
	"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)"[41]

Main study findings	Authors' conclusion
○ 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) **Adverse events in the CP group: Not reported** **Adverse events in the control group: Not reported**	

AI = SARS-CoV-2 IgG antibody index; APACHE = Acute Physiology And Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; BMI = body mass index; CI = confidence interval; COVID-19 = coronavirus disease; CP = convalescent plasma; ECMO = extracorporeal membrane oxygenation; FiO2 = fraction of inspired oxygen; HR = hazard ratio; ICU = Intensive Care Unit; IQR = interquartile range; n = number of participants; ND = not determined; NIPPV = non-invasive positive pressure ventilation; OR = odd's ratio; PaO2 = partial pressure of oxygen; PCR = polymerase chain reaction; PE = Point Estimate; PS = propensity score; RBD = receptor binding domain; RCT= randomized controlled trial; RD = risk difference RR = risk ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; SOFA = Sequential Organ Failure Assessment; TACO = Transfusion-Associated Circulatory Overload; TRALI = Transfusion-Related Acute Lung Injury

[a] Indicates revised estimates as reported in the erratum.[30]

Appendix 5: Further Information

Note that this appendix has been formatted for accessibility but has not been copy-edited.

Systematic Reviews and Meta-Analyses

AminJafari A, Ghasemi S. The possible of immunotherapy for COVID-19: a systematic review. *Int Immunopharmacol*. 2020;83:106455.
PubMed: PM32272396

Meher BR, Padhy BM, Das S, Mohanty RR, Agrawal K. Effectiveness of convalescent plasma therapy in the treatment of moderate-to-severe COVID 19 patients: a systematic review and meta-analysis. *J Assoc Physicians India*. 2020;68(12):35-43.
PubMed: PM33247641

Rajendran K, Narayanasamy K, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: systematic review. *J Med Virol*. 2020;92(9):1475-1483.
PubMed: PM32356910

Sarkar S, Soni KD, Khanna P. Convalescent plasma is a clutch at straws in COVID-19 management! A systematic review and meta-analysis. *J Med Virol*. 2021;93(2):1111-1118.
PubMed: PM32776573

Valk SJ, Piechotta V, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *Cochrane Database Syst Rev*. 2020;5:CD013600
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013600

Wang Y, Huo P, Dai R, et al. Convalescent plasma may be a possible treatment for COVID-19: a systematic review. *Int Immunopharmacol*. 2020;91:107262.
PubMed: PM33338863

Wenjing L, Yuanzheng F, Li JY, Tang LV, Yu H. Safety and efficacy of convalescent plasma therapy in severely and critically ill patients with COVID-19: a systematic review with meta-analysis. *Aging (Albany NY)*. 2020;13(1):1498-1509.
PubMed: PM33323550

Zaffanello M, Piacentini G, Nosetti L, Franchini M. The use of convalescent plasma for pediatric patients with SARS-CoV-2: a systematic literature review. *Transfus Apher Sci*. 2021:60(2):103043.
PubMed: PM33388249

Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systematic review. *J Med Virol*. 2020 05;92(5):479-490.
PubMed: PM32052466

Review Articles

Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest*. 2020;130(6):2757-2765.
PubMed: PM32254064

Casadevall A, Grossman BJ, Henderson JP, et al. The assessment of convalescent plasma efficacy against COVID-19. *Med (N Y)*. 2020;1(1):66-77.
PubMed: PM33363284

Kumar GV, Jeyanthi V, Ramakrishnan S. A short review on antibody therapy for COVID-19. *New Microbes New Infect*. 2020:35;100682.
PubMed: PM32313660

Mehta N, Mazer-Amirshahi M, Alkindi N, Pourmand A. Pharmacotherapy in COVID-19; a narrative review for emergency providers. *Am J Emerg Med*. 2020;38(7):1488-1493.
PubMed: PM32336586

Sullivan HC, Roback JD. Convalescent plasma: therapeutic hope or hopeless strategy in the SARS-CoV-2 pandemic. *Transfus Med Rev*. 2020;34(3):145-150.
PubMed: PM32359788

Single-arm Studies

Hartman W, Hess AS, Connor JP. Hospitalized COVID-19 patients treated with convalescent plasma in a mid-size city in the Midwest. *Transl Med Commun*. 2020;5(1):17.
PubMed: PM33072871

Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc*. 2020;95(9):1888-1897.
PubMed: PM32861333

Perotti C, Baldanti F, Bruno R, et al. Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma. A proof of concept single arm multicenter trial. *Haematologica*. 2020;105(12):2834-2840.
PubMed: PM32703797

Wu Y, Hong K, Ruan L, et al. Patients with prolonged positivity of SARS-CoV-2 RNA benefit from convalescent plasma therapy: a retrospective study. *Virol Sin*. 2020;35(6):768-775.
PubMed: PM32865701

Case Reports and Case Series

Ahn JY, Sohn Y, Lee SH, et al. Use of convalescent plasma therapy in 2 COVID-19 patients with acute respiratory distress syndrome in Korea. *J Korean Med Sci*. 2020;35(14):e149.
PubMed: PM32281317

Anderson J, Schauer J, Bryant S, Graves CR. The use of convalescent plasma therapy and remdesivir in the successful management of a critically ill obstetric patient with novel coronavirus 2019 infection: a case report. *Case Rep Womens Health*. 2020;27:e00221.
PubMed: PM32426243

Cinar OE, Sayinalp B, Aladag Karakulak E, et al. Convalescent (immune) plasma treatment in a myelodysplastic COVID-19 patient with disseminated tuberculosis. *Transfus Apher Sci*. 2020:102821.
PubMed: PM32487513

Hegerova L, Gooley T, Sweerus KA, et al. Use of convalescent plasma in hospitalized patients with Covid-19 - case series. *Blood*. 2020;136(6):759-762.
PubMed: PM32559767

Im JH, Nahm CH, Baek JH, Kwon HY, Lee JS. Convalescent plasma therapy in Coronavirus disease 2019: a case report and suggestions to overcome obstacles. *J Korean Med Sci*. 2020;35(26):e239.
PubMed: PM32627442

Kong Y, Cai C, Ling L, et al. Successful treatment of a centenarian with coronavirus disease 2019 (COVID-19) using convalescent plasma. *Transfus Apher Sci*. 2020:59(5):102820.
PubMed: PM32467007

Salazar E, Perez KK, Ashraf M, et al. Treatment of COVID-19 patients with convalescent plasma. *Am J Pathol*. 2020;190(8):1680-1690.
PubMed: PM32473109

Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA*. 2020;323(16):1582-1589.
PubMed: PM32219428

Xu TM, Lin B, Chen C, Liu LG, Xue Y. Non-optimal effectiveness of convalescent plasma transfusion and hydroxychloroquine in treating COVID-19: a case report. *Virol J*. 2020;17(1):80.
PubMed: PM32560646

Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol*. 2020;92(10):1890-1901.
PubMed: PM32293713

Zhang B, Liu S, Tan T, et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. *Chest*. 2020;158(1):e9-e13.
PubMed: PM32243945

Zhang L, Pang R, Xue X, et al. Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of 6 donors who have recovered from COVID-19. *Aging (Albany NY)*. 2020;12(8):6536-6542.
PubMed: PM32320384

Preliminary Report – Not Peer-Reviewed

Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Convalescent plasma for COVID-19. A randomized clinical trial **[non peer-reviewed preprint].** *medRxiv*. 2020:2020.07.01.20139857.
https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1. Accessed 2020 Nov 11.

Avendano-Sola C, Ramos-Martinez A, Munez-Rubio, E et al. Convalescent plasma for COVID-19: a multicenter, randomized clinical trial **[non peer-reviewed preprint].** *medRxiv*. 2020:2020.08.26.20182444.
https://www.medrxiv.org/content/10.1101/2020.08.26.20182444v3. Accessed 2020 Nov 11.

Klassen SA, Senefeld JW, Johnson PW, et al. Evidence favoring the efficacy of convalescent plasma for COVID-19 therapy **[non peer-reviewed preprint]**. *medRxiv*. 2020:2020.07.29.20162917.
PubMed: PM33140056

Appendix 6: Ongoing Clinical Trials

Note that this appendix has been formatted for accessibility but has not been copy-edited.

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	January 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 (NCT04497324) https://clinicaltrials.gov/ct2/show/NCT04497324	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	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	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	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	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	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	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	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	USA Kashif Khan	Triple blinded RCT	Phase II	96 participants	18 years and older	December 2021
"NORPLASMA" Covid-19 Convalescent Plasma Treatment Monitoring Study (MONITOR) (NCT04463823) https://clinicaltrials.gov/ct2/show/NCT04463823	Norway Oslo University Hospital	Single arm prospective observational	NA	500 participants	18 years and older	May 31, 2025

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 as Prevention and Treatment for Children With Underlying Medical Conditions (NCT04462848) https://clinicaltrials.gov/ct2/show/NCT04462848	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	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	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	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	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	Uganda Makerere University	Open-Label RCT	N/A	136 participants	18 Years to 100 Years	October 31, 2020
COVID-19 (VA CURES-1) (VA CURES-1) (NCT04539275) https://clinicaltrials.gov/ct2/show/NCT04539275	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	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

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Efficacy and Safety of Recovered Covid 19 Plasma Transfusion to Covid 19 Severly Ill Patients (NCT04530370) https://clinicaltrials.gov/ct2/show/NCT04530370	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	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	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	Pakistan Dow University of Health Sciences	Single-blinded RCT	Phase I Phase II	50 participants	18 Years and older	March 2021
Convalescent Plasma for COVID-19 Patients (CPCP) (NCT04516954) https://clinicaltrials.gov/ct2/show/NCT04516954	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	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	USA Joseph M. Flynn, D.O., MPH	Single group, open-label	Phase II	100 participants	18 Years to 99 Years	December 31, 2021

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
Open-label Treatment of Severe Coronavirus Disease 2019 (COVID-19) With Convalescent Plasma (Inova-CCP) (NCT04502472) https://clinicaltrials.gov/ct2/show/NCT04502472	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	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	Italy Azienda Socio Sanitaria Territoriale di Mantova	Single group, open-label	Phase II	21 participants	65 Years and older	September 3, 2020
Convalescent Plasma as Adjunctive Therapy for Hospitalized Patients With COVID-19 (Co-CLARITY) (NCT04567173) https://clinicaltrials.gov/ct2/show/NCT04567173	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	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	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	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	Brazil Hospital de Clinicas de Porto Alegre	Open-Label RCT	Phase III	160 participants	18 Years and older	October 2021

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
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	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	Nepal Nepal Health Research Council	Prospective observational study	N/A	2000 participants	18 Years and older	November 19, 2021
Convalescent Plasma for Treatment of COVID-19: An Open Randomised Controlled Trial (NCT04649879) https://clinicaltrials.gov/ct2/show/NCT04649879	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	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	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	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	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	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

Trial Name (Registration Number); Link	Country; Primary Sponsor	Study Design	Trial Phase	Number of Expected Participants	Age	Expected Study Completion Date
COVID-19 With Convalescent Plasma (NCT04616976) https://clinicaltrials.gov/ct2/show/NCT04616976	China Southeast University, China	Case-control study	N/A	78 participants	18 Years and older	November 1, 2020
Convalescent Plasma in the Treatment of Covid-19 (COP20) (NCT04600440) https://clinicaltrials.gov/ct2/show/NCT04600440	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	The Netherlands Erasmus Medical Center	Quadruple blinded RCT	Phase III	690 participants	50 Years and older	November 1, 2023
Preemptive Use of Convalescent Plasma for High-risk Patients With COVID-19 (NCT04836260) https://clinicaltrials.gov/ct2/show/NCT04836260	Switzerland University Hospital, Geneva	Open-label non-randomized	Phase III	100 participants	18 Years and older	December 31, 2021
Clinical Efficacy of Early Administration of Convalescent Plasma Among COVID-19 Cases in Egypt (NCT04816942) https://clinicaltrials.gov/ct2/show/NCT04816942	Egypt Ministry of Health and Population	Open-label non-randomized	Phase III	102 participants	18 Years and older	October 12, 2020
Efficacy of Reinforcing Standard Therapy in COVID-19 Patients With Repeated Transfusion of Convalescent Plasma (NCT04803370) https://clinicaltrials.gov/ct2/show/NCT04803370	Spain Hospital Son Llatzer	Open-Label RCT	N/A	100 participants	18 Years and older	September 1, 2021
The Effectiveness of ACB-IP 1.0 Convalescent Plasma in COVID-19 Infection (NCT04769245) https://clinicaltrials.gov/ct2/show/NCT04769245	Turkey Acibadem University	Retrospective single arm	N/A	40 participants	18 Years to 75 Years	June 1, 2021
Effectiveness of Convalescent Plasma in Hospitalized Patients With COVID-19 (NCT04764747) https://clinicaltrials.gov/ct2/show/NCT04764747	Iraq Kufa University	Retrospective cohort	N/A	400 participants	18 Years to 95 Years	April 25, 2021
COVID-19 Convalescent Plasma Therapy (TPCC) (NCT04747158) https://clinicaltrials.gov/ct2/show/NCT04747158	Paraguay Universidad Nacional de Asunción	Single group, open-label	Phase II Phase III	350 participants	18 Years and older	January 10, 2021

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 (CP_COVID-19) (NCT04730401) https://clinicaltrials.gov/ct2/show/NCT04730401	Finland Helsinki University Central Hospital	Double-blinded RCT	Phase II	390 participants	18 Years and older	December 31, 2021
TranSfUsion of coNvalescent plAsma for the Early Treatment of pneuMonIa in COVID-19 Patients (NCT04716556) https://clinicaltrials.gov/ct2/show/NCT04716556	Italy Istituto Superiore di Sanità	Open-Label RCT	N/A	474 participants	18 Years and older	May 2021
Assessment of Efficacy and Safety of Therapy With COVID-19 Convalescent Plasma in Subjects With Severe COVID-19 (IPCO) (IPCO) (NCT04712344) https://clinicaltrials.gov/ct2/show/NCT04712344	Germany University of Erlangen-Nürnberg Medical School	Open-Label RCT	Phase II	58 participants	18 Years and older	September 2021
Convalescent Plasma as Adjunct Therapy for COVID-19 (PlaSenTer) (NCT04873414) https://clinicaltrials.gov/ct2/show/NCT04873414	Indonesia National Institute of Health Research and Development,	Open-Label RCT	Phase II Phase III	364 participants	18 Years to 60 Years	December 31, 2021
Convalescent Plasma Therapy - Zurich Protocol (CPT-ZHP) (NCT04869072) https://clinicaltrials.gov/ct2/show/NCT04869072	Switzerland University of Zurich	Single group, open-label	Phase I	30 participants	Child, adult, older adult	March 30, 2021

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

Appendix 7: Report Version Details

Note that this appendix has been formatted for accessibility but has not been copy-edited.

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[38,41]
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[26] **Total number of included studies:** Three[26,38,41] **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[40] **Total number of included studies:** Four[26,38,40,41] **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[36] **Total number of included studies:** Five[26,36,38,40,41] **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]

Version Number	Date of Publication	Report Version Details
		Total number of included studies: Six[26,36,38,40,41,83] **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[27,37,39,42] **Total number of included studies:** Ten [26,27,36-42,83] **What is new:** New evidence was found and the overall conclusions have not changed. Findings from one randomized study and 3 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 6 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	February 23, 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[28,29,43-47] **Total number of included studies:** 16[26-29,36-47] **What is new:** New evidence was found and the overall conclusions have not changed. Findings from 2 randomized studies and 3 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.
Version 8.0	July 5, 2021	**Date of literature search update:** May 20, 2021 **Date of focused internet search:** May 10, 2021 **Number of new relevant studies included in this update:** 21[31-35,48-63] **Total number of included studies: 37**[26-29,31-35,37-63] **What is new:** New evidence was found, and the overall conclusions have not changed. Findings from 5 randomized studies and 16 non-randomized studies

Version Number	Date of Publication	Report Version Details
		were similar to those from the previously included studies. One new study that compared convalescent plasma to tocilizumab 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 the literature search (i.e., May 20, 2021). This is the final version of this report.