Convalescent Plasma for the Prevention and Treatment of COVID-19: A Systematic Review and Quantitative Analysis

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Table of Contents

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Abstract

Background: The coronavirus disease (COVID-19) pandemic caused by a novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread quickly worldwide. Currently, no vaccine or specific therapeutics are available to prevent and/or treat COVID-19. Convalescent plasma (CP) obtained from patients following resolution of COVID-19 infection and development of antibodies against the virus is an attractive option for either prophylactic or therapeutic treatment, since antibodies may have direct or indirect antiviral activities and immunotherapy has proven effective in principle, and in many clinical reports.

Objective: We sought to characterize the latest advances and evidence in the use of CP for COVID-19 through a systematic review and quantitatively analysis, identify knowledge gaps in this setting, and offer recommendations and directives for future research.

Methods: PubMed, Web of Science and Embase were continuously searched for studies assessing the use of CP for COVID-19 including clinical studies, commentaries, reviews, guidelines/protocols and in vitro testing of CP antibodies. Screening process and data extraction were performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Quality appraisal of all clinical studies was conducted using an universal tool independent on study designs. Meta-analysis of case-controlled and randomized controlled trials (RCTs) was conducted using a random-effects model.

Results: Substantial literature has been published covering various aspects of CP therapy for COVID-19. Of the references included in this review, a total of 243 eligible studies including 64 clinical studies, 79 commentary articles, 46 reviews, 19 guidance and protocols, 35 in vitro testing of CP antibodies, matched the criteria. Positive results have been mostly observed so far when utilising CP for the treatment of COVID-19. There are remarkable heterogeneities in the CP therapy with respect to patient demographics, donor antibody titers, time and dose of CP administration. The studies assessing the safety of CP treatment reported low incidence of adverse events. Most clinical studies in particular case reports and case series had poor quality. Only one RCT was of high quality. Randomized and non-randomized data were found in two and 11 studies, respectively and included for meta-analysis suggesting that CP could reduce mortality and increase viral clearance. Despite promising pilot studies, the benefits of CP treatment can only be clearly established through carefully designed RCTs.

Conclusions: There is developing support for CP therapy particularly for patients who are critically ill or mechanically ventilated and resistant to antivirals and supportive care. These studies provide important lessons that should inform the planning of well-designed RCTs to generate more robust knowledge for the efficacy of CP in COVID-19 patients. Future research is necessary to fill the knowledge gap regarding prevention and treatment of COVID-19 patients with CP while vaccines and other treatment are being developed.

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Convalescent Plasma for the Prevention and Treatment of COVID-19: A Systematic Review and Quantitative Analysis

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Abstract
Background: The coronavirus disease (COVID-19) pandemic caused by a novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread quickly worldwide. Currently, no vaccine or specific therapeutics are available to prevent and/or treat COVID-19. Convalescent plasma (CP) obtained from patients following resolution of COVID-19 infection and development of antibodies against the virus is an attractive option for either prophylactic or therapeutic treatment, since antibodies may have direct or indirect antiviral activities and immunotherapy has proven effective in principle, and in many clinical reports.
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Conclusions: There is developing support for CP therapy particularly for patients who are critically ill or mechanically ventilated and resistant to antivirals and supportive care. These studies provide important lessons that should inform the planning of well-designed RCTs to generate more robust knowledge for the efficacy of CP in COVID-19 patients. Future research is necessary to fill the knowledge gap regarding prevention and treatment of COVID-19 patients with CP while vaccines and other treatment are being developed.

KEYWORDS
COVID-19; SARS-CoV-2; antibodies; convalescent plasma

Introduction
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease (COVID-19), was declared a pandemic in early 2020 by the World Health Organization [1, 2]. This

is the third coronavirus to emerge in the past two decades, causing multinational outbreaks and carrying substantial morbidity and mortality [3]. Since its emergence in Wuhan, China in late 2019, there have been over 40 million confirmed COVID-19 cases world-wide with more than 1.1 million deaths and counting, at the time of writing this article [4]. Currently, there are no specific treatments or prophylaxis available for COVID-19 [5] which is characterized by a spectrum of symptoms – ranging from mild subclinical infection, with self-limiting respiratory tract illness (dry cough, fever, fatigue, difficulty breathing) to severe progressive manifestations (acute respiratory distress syndrome, multiorgan failure, death) in high-risk patients with known co-morbidities (advanced age, diabetes, obesity, cardiopulmonary disease) [6, 7]. Case-fatality rates range from 4–50%, with higher mortality observed in the most critically ill [8]. Estimates suggest the pandemic will continue for many months. As such, COVID-19 represents an overwhelming universal health crisis [9] and the burden of this disease continues to threaten lives and livelihoods across the world [10] As this highly transmissible virus continues to spread globally, international research efforts are being accelerated to identify effective preventive and therapeutic approaches to mitigate its impact [11, 12].

The magnitude and urgency of this public health emergency has prompted global scientific collaborations to seek rapid solutions via repurposing of previously approved antiviral drugs for high-risk patients, while fast-tracking development of vaccines and other novel therapeutics [13]. To that end, many clinical trials of potential COVID-19 therapies are now underway [14, 15] including testing combinations of existing broad-spectrum antivirals (such as remdesivir, ritonavir, lopinavir, chloroquine, hydroxychloroquine, interferon) [16, 17], therapeutic doses of corticosteroids (dexamethasone, hydrocortisone, methylprednisolone) [18, 19] and sub-therapeutic anticoagulant/antithrombotic regimens (low molecular weight heparin) [20] – none of which have demonstrated conclusive evidence of clinical efficacy in patients at this time.

In the absence of an approved vaccine or other definitive treatment against this new human pathogen, clinical management of hospitalized, severely ill patients remains mainly supportive care, including oxygen and mechanical ventilation, and is based largely on preclinical studies or previous experience with SARS-CoV [21]. Thus, an effective evidence-based therapeutic intervention is urgently needed to reduce the morbidity, mortality, and length of in-hospital stay for COVID-19 patients.

On the other hand, systematic reviews have been conducted for current medications that have been used for treatment of COVID-19. A comparative analysis of three treatment modalities for COVID-19, chloroquine and hydroxychloroquine, CP, and remdesivir found that each modality had both favorable and unfavorable characteristics, but none showed clear evidence of benefit for early outpatient disease or prophylaxis, while CP therapy appeared to show clinical advantages for inpatient use [17]. Moreover, meta-analysis of the safety and efficacy of various interventions including the three treatment as well as dexamethasone, lopinavir-ritonavir, showed that dexamethasone and remdesivir might be beneficial for COVID-19 patients, but the certainty of the evidence was low to very low, so more trials are needed [5].

Another quantitative analysis of 26 articles involving 3263 patients found that the clinical effect of immunomodulatory agents (especially tocilizumab and anakinra) was noticeable compared to other medications with a Risk Ratio (RR) of 0.22 (95% CI 0.09-0.53; I(2) = 40.9%) for mortality and 1.25 (95% CI 1.07-1.46; I(2) = 45.4%) for clinical improvement. Moreover, Antivirals (RR 1.13, 95% CI 1.01-1.26; I(2) = 47.0%) and CP therapy (RR 1.41, 95% CI 1.01-1.98; I(2) = 66.6%) had significant beneficial effects on clinical improvement [22].

Based on the preliminary data from clinical trials and considering the United States National Institute of Health (NIH) and Food and Drug Administration (FDA) recommendation, remdesivir and convalescent plasma are the most promising potential for COVID-19 treatment [23].

Furthermore, CP therapy has advantages over other proposed treatment: it requires low technology (and therefore it can be produced where required independent of pharmaceutical companies), it is low cost and has strong biological plausibility and the potential for rapid development and deployment (production is easily scalable as long as there are sufficient donors) [24-26].

Accordingly, on March 24, 2020, FDA approved the use of convalescent plasma (CP) therapy, as an emergency investigational new drug to treat patients with serious or immediately life threatening COVID-19 infections [27]. Subsequently, on August 23, 2020, the FDA issued an Emergency Use Authorization (EUA) for CP for treating COVID-19 [28]. According to the FDA regulation, the plasma must be collected from recovered patients who can donate blood, have had no symptoms for 14 days, and have had negative results on COVID-19 tests.

CP for treating COVID-19 is accessible via 3 regulatory pathways: investigational new drug (IND) regulatory pathway. Another is expanded access, also called "compassionate use,", emergency Investigational New Drug Application an investigational medical product, to treat patients [29]. Criteria for issuing an EUA for medical products include: the public health concern must be serious or life threatening; sufficient evidence must exist that the product "may be effective"; the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product; and no adequate, approved alternatives to the product are available [28]. Severe disease is a clinical situation in which the patient has dyspnea, tachypnea (respiratory rate ≥ 30 breaths/min), blood oxygen saturation ≤ 93% on room air, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 PaO_2/FiO_2 <300, and/or lung infiltrates >50% within 24 to 48 hours on chest x-ray. Life-threatening disease is defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure [30].

Passive immunotherapy with human convalescent blood products, in particular convalescent plasma (CP), is a promising strategy for the prevention and treatment of COVID-19 [31-33]. CP therapy involves transfusing whole or fractionated plasma, collected from patients that have recently recovered from SARS-CoV-2 infection, in order to confer passive humoral immunity in persons who are infected or at risk of infection [33, 34].

The biological basis for efficacy of CP entails the transfer of specific antiviral immunoglobulins (Igs; antibodies) and other bioactive substances in the plasma of patients in the convalescent phase of COVID-19 infection [35, 36]. In theory, administration of CP containing high levels of polyclonal neutralizing antibodies (comprised mainly of IgG, with smaller amounts of IgM, IgA) can confer immediate pathogen-specific protection by inhibiting viral infection in a susceptible person [37]. However, findings suggest considerable variation in antibody titers and the duration of protective anti-CoV-2 IgG-IgM immunity observed in recovered CP donors [38, 39]. A recent population-based study of humoral immune responses to SARS-CoV-2 demonstrated that >90% of people who recovered from COVID-19 were seropositive on virus-specific pan-Ig assays by day 25, and hospitalized patients seroconverted more frequently than non-hospitalized persons. Furthermore, anti-CoV-2 antibody titers remained stable in recovered patients for the next 2 months, suggesting a durable Ig response [40]. Aside from CP, pooled human immunoglobulins may also be prepared from plasma as a concentrated antibody-containing solution to be administered as intravenous, subcutaneous or intramuscular Ig. These pooled plasma-derived Ig products benefit from the polyclonal response of each individual donor and from the inter-individual variability in such responses [41]. In addition, purified, high-titer hyperimmune immunoglobulin (H-Ig) formulations can be obtained from vaccinated or convalescing donors, which have known levels of plasma-derived neutralizing antibodies that may prove valuable against COVID-19 [42-44].

Although not fully elucidated, the protective mechanisms of CP are based on direct and indirect antiviral activities, including antibody neutralization of viral infectivity [36, 41]. In the case of SARS-CoV-2 pathogenesis, the viral spike (S) glycoprotein is critical to the dissemination and pathogenesis of the virus [45]. The S protein mediates binding of SARS-CoV-2 to host cell angiotensin-converting enzyme 2 (ACE2) surface receptors, thereby, acting as the first step in cellular entry and infection. Several lines of evidence from studies of SARS-CoV / CoV-2 show that infected hosts produce neutralizing antibodies directed against the receptor binding domain (RBD) of the homotrimeric S protein and can block infection by preventing viral entry and subsequent replication [46]. Other beneficial immune effects of CP are thought to include, enhanced antibody-

dependent cellular cytotoxicity (ADCC), complement activation, and phagocytosis, along with restoration of the vascular endothelial glycocalyx [47, 48]. Moreover, a majority of convalescent patients display robust antiviral SARS-CoV-2-specific T-cell responses; with enhanced in vivo priming and expansion of CD8+ cytotoxic T cells, and a higher frequency of CD4+ memory T cells in those who recovered from severe COVID-19, which may provide long-term antiviral protection even if antibodies wane [49]. Therefore, T cells could help to control SARS-CoV-2 infection and serve as correlates of protective antiviral immunity [50].

Past experience suggests that CP therapy could be used as an empirical treatment modality to prevent further progression and/or promote early recovery in critically ill COVID-19 patients [51, 52]. CP has been used safely for decades in an attempt to treat infectious diseases where no specific treatment is available [43, 53]. In the late 19th and early 20th century, CP was given to treat a wide range of viral infections, including diphtheria, polio, measles, mumps, and Spanish influenza A (H1N1) [48, 54, 55]. Although no randomized trials were conducted, a retrospective meta-analysis of studies on the use of CP during the Spanish influenza flu pandemic showed a significant decrease in mortality in patients who received CP, versus those given plasma from unexposed donors [56]. After World War II, plasma became a highly valuable pharmaceutical component, which used it for diverse products to successfully treat everything from bleeding disorders to immune deficiencies to hypovolemic shock [57]. Since then, CP has been used in outbreaks of Ebola and other coronavirus diseases, including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) infection with varying efficacy [43]. CP was proven to be efficacious in patients with severe 2009 pandemic H1N1 flu, reducing respiratory tract viral load, serum cytokine responses, length of hospital stay and patient mortality [58].

Studies are currently underway to evaluate use of CP as treatment for patients with severe COVID-19 and to prevent infection (prophylaxis) in certain high-risk patients exposed to COVID-19. Currently, CP is being given to small numbers of hospitalized patients with severe or life-threatening COVID-19 illness [59]. Several case reports suggest treatment is helpful, but larger studies are still needed. Although there is a lot that is unknown, CP may work best for patients earlier in the disease course. Therapy using CP may also beneficial for prophylaxis against SARS-CoV-2 in high-risk individuals; there is considerable interest to leverage CP for front-line health care workers, first-responders, other caregivers and vulnerable individuals with underlying medical conditions [60, 61]. This strategy has been previously used in SARS-CoV and MERS-CoV outbreaks [62]. Although the evidence for CP therapy remains inconclusive, preliminary trials for CP suggest that there may be some benefits and there is growing consensus that CP is an important first-line immunotherapy for emerging viral infections when vaccines or other specific treatments are not available [63]. Currently, several countries and health institutions are collecting CP for either empirical treatment or clinical trials [60, 64]. However, research to date is at high risk of bias, and randomized control trials are desperately needed to determine the efficacy and safety of this therapeutic option.

There is a large number of ongoing trials and of reviews/perspectives/commentaries/guidelines published every day related to all aspects of COVID-19 CP ranging from donor selection, plasma collection, testing and storage to clinical use.

In this article, we sought to review all aspects of use of CP for COVID-19 from detection of the level and activity of CP antibodies to appraisal of the quality and meta-analysis of original clinical studies of CP therapy, in order to characterize the knowledge gap and provide recommendations for future directions.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [65].

Search Strategy

We searched relevant databases including PubMed and Web of Science databases from June 19, 2020, for published and unpublished trials with no limitations by starting date, with the terms

COVID-19 OR SARS-CoV-2 OR “coronavirus* 2019” AND convalescent plasma/ser*; we continued the search and updated the review during the manuscript preparation until October 22, 2020. Both plasma and serum or sera have been used in the literature. In this review, plasma is used representative for both terms.

Data Abstraction

Titles and abstracts were screened to determine relevance and if deemed appropriate the full article was reviewed. Additional publications were selected from the cross-references listed in the original papers and from the cited articles. Disagreements were resolved by consensus or with another review author.

Study Eligibility Criteria

Experimental (randomized controlled trials [RCTs], quasi-RCTs, non-RCTs), quasi-experimental (controlled before-after studies, interrupted time series), and observational (cohort, case-control) studies are eligible if they examined convalescent plasma/serum for prevention, diagnosis, or treatment for COVID-19.

Review articles were excluded unless they were focused on or directly related to convalescent plasma (e.g., passive immunotherapy) for COVID-19. Papers on antibody detection and immunity were also excluded unless specifically related to convalescent plasma.

Data Extraction and Study Appraisal

All literature search results were screened independently by two reviewers. The same strategy was used for data abstraction. The commentaries in support of the use of CP for COVID-19 was considered positive, those suggesting improvements in CP treatment were categorized as neutral, and precautions against CP were determined negative. The review type was determined according to a typology of reviews by Grant et al. 2009 [66]. The quality appraisal of included clinical studies was conducted using Effective Public Health Practice Project (EPHPP) Quality Assessment Tool [67]. Specifically, each clinical study was evaluated for the following components: sample selection, study design, identification and treatment of confounders, blinding of outcome assessors and participants, reliability and validity of data collection methods, and withdrawals and dropouts. The overall rate of each study was determined by assessing the six component ratings. Those with no weak ratings and at least four strong ratings were rated strong. Those with less than four strong ratings and one weak rating were considered moderate. Those with two or more weak ratings were rated weak.

Analyses

Studies were analysed separately according to their design (case report, case series, observational or randomized trials). Clinical and methodological heterogeneities across the studies were assessed by examining the details of the subjects, the baseline data, the interventions, and the outcomes, to determine whether the studies were sufficiently similar.

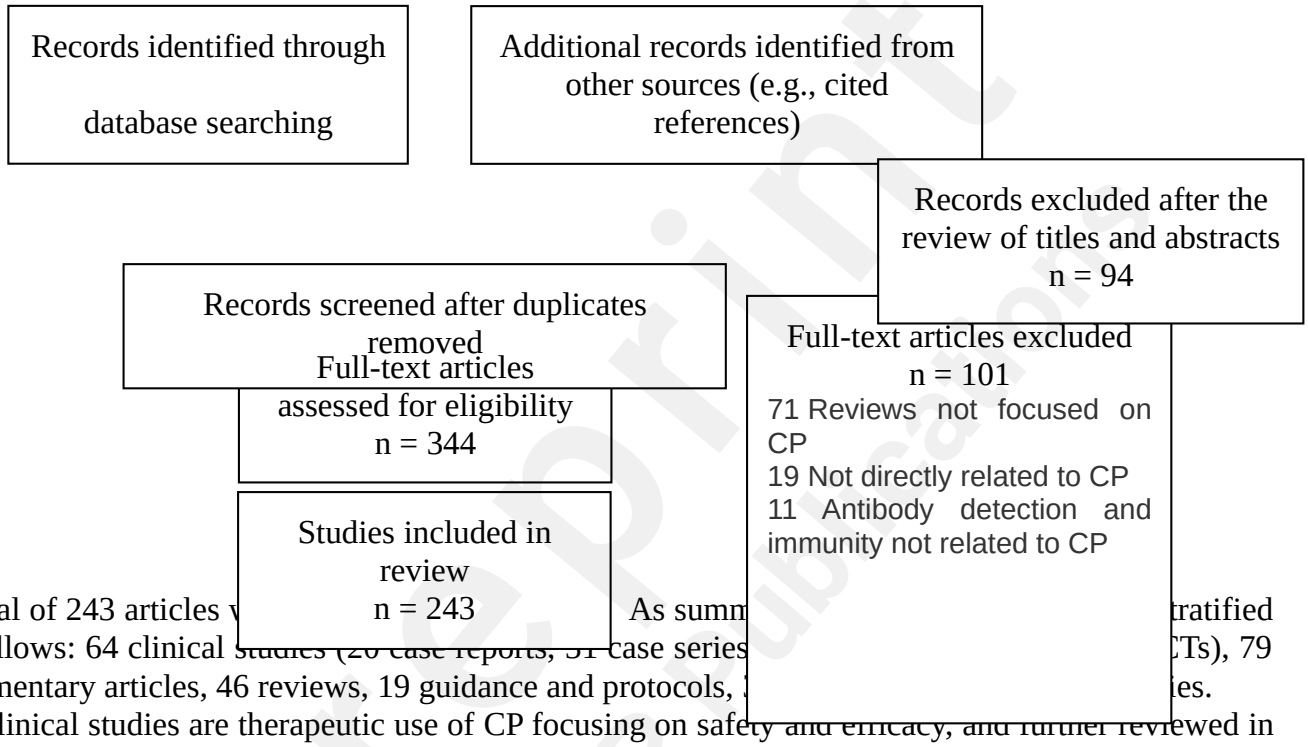
Case and randomized controlled studies were combined in meta-analyses using Review Manager (Version 5.4, The Cochrane Collaboration, 2020). Data were pooled using an inverse variance method and analyzed using a random-effects model as this approach accommodates clinical and statistical variations. Odds ratio (OR) and 95% confidence intervals (CI) were used as statistical measures for mortality, clinical improvement and viral clearance as a dichotomous outcome, respectively. Mean and standard deviation (SD) was the statistical measure used to describe length of hospital stay. In studies that reported data in medians and interquartile ranges (IQR), mean and SD were estimated using the sample size in each study arm, medians and the first and third IQRs as demonstrated in the method published by Wan et al. 2014 [68]. Heterogeneity was determined using the I^2 statistic and the chi-square test. High values of both tests ($I^2 > 40\%$, a significant chi-square value [p value < 0.05], respectively), demonstrate high levels of inconsistency and heterogeneity.

Results

As illustrated in Figure 1, we reviewed 438 titles and abstracts and identified 243 manuscripts relevant to 5 areas of focus/types: 1) original clinical studies, 2) commentary in the form of Letter to the Editor, Correspondence or Editorial, brief communication, opinions, perspectives and viewpoints,

3) review of the use of CP, 4) protocol/guidance for clinical trials or production of CP, and 5) in vitro testing of CP.

Figure 1. PRISMA flow diagram.



A total of 243 articles w As summ tratified as follows: 64 clinical studies (20 case reports, 31 case series CTs), 79 commentary articles, 46 reviews, 19 guidance and protocols, ies.

All clinical studies are therapeutic use of CP focusing on safety and efficacy, and further reviewed in the following section. The commentaries cover various aspects of CP ranging from critiques of clinical studies [69-74] and literature review [75, 76] to the stability of antibodies in CP [77, 78], even relevant news [79] and response letter [80], while a majority focus on the safety and efficacy of CP. Most commentaries were in favor of CP therapy for COVID-19 recognizing the need for more high-quality evidence from large and well-designed clinical trials to show its efficacy, and other issues (e.g., CP collection), still need to be addressed. Some commentaries proposed alternative or complementary CP-based approaches to COVID-19 that possesses fewer risks [81, 82], but may not be immediately available for clinical use. Only a few commentaries put more emphases on the potential risks over benefits of CP therapy [83-87].

In a particular correspondence, a metadata analysis of the efficacy of CP treatment based on nine clinical studies (most case series) suggests that CP reduced viral loads (Risk Ratio (RR) 0.13 [95% Confidence Interval (CI), 0.09 to 0.18], $p<0.001$) (n=75), C-reactive protein levels (Ratio of Mean (ROM) 0.11 [95% CI, 0.01 to 0.86], $p<0.05$) (n=42), and improved the clinical status of COVID-19 patients (ROM 0.53 [95% CI, 0.36 to 0.79], $p<0.01$) (n=149), when compared to baseline (date of CP transfusion) [88]. In addition, the effects of CP on C-reactive protein levels and clinical improvement were not associated with the patient's age, and the use of antivirals, antibiotics, and hydroxychloroquine.

Several commentary papers and reviews advocated for the rationale of developing fast access to CP collection and treatment of COVID-19 patients [29, 48, 64, 71, 89, 90].

Among the reviews, most were descriptive overviews of existing literature and recommendations for

clinical use and trial without any search strategies. Few were conducted following the PRISMA guidelines [44, 91, 92]. It is noteworthy that one systematic review and meta-analysis of the safety and efficacy of CP therapy for other severe respiratory viral infections to provide indirect evidence for CP therapy for COVID-19 [93] and another two systematic reviews and meta-analysis of completed and ongoing clinical studies on the safety and efficacy of CP or hyperimmune immunoglobulin transfusion in the treatment of COVID-19 [42, 94]. One review and meta-analysis included 20 studies [one RCT, three controlled non-randomised studies of interventions (NRSIs), 16 non-controlled NRSIs] with 5443 participants [42]. The meta-analysis of four controlled studies (one RCT and three controlled NRSIs) with 339 patients could not support any effects of CP treatment on all-cause mortality at hospital discharge, time to death, improvement of clinical symptoms at seven days. The review also investigated the safety of CP based on 14 studies (5201 participants with 5000 participants from one non-controlled NRSI) and found very low-certainty evidence for safety. The review was recently updated, which included 19 studies with 36,081 patients treated by CP and made the same conclusion [95]. The other review included seven studies, including two RCTs and five cohort studies, with a total of 5,444 patients [94]. The meta-analysis indicated that CP therapy reduced mortality, increased viral clearance and clinical improvement. It confirmed the safety of CP transfusion with very low incidence of serious adverse events. However, the risk of bias and quality assessment in both reviews indicated that the evidence for the efficacy and safety of CP therapy is of low quality, suggesting the need for a large well-designed RCT. In addition, a survey has been conducted for current registered clinical trials of CP therapy for COVID-19, including a description of their characteristics such as study design, patient populations, outcomes, eligibility criteria for CP donors, CP collection, antibody titre and CP dose [96].

Protocols, programs and standards have been developed to select donors, and collect, process, inactivate, characterize, store, distribute and apply CP to patients in need [97-100] as well as to conduct clinical trials [101-104]. Regional and national programs for COVID-19 CP have been established [105, 106] as well as a multi-criteria decision-making frame for both CP donor and receipt selection [107].

Some key findings and implications from the in vitro testing studies of CP antibodies should be considered: a variety of methods have been developed to measure CP antibody titers including gold standard neutralization assay using living SARS-Cov-2 [108, 109], Enzyme-Linked Immunosorbent Assay (ELISA) using the antigens derived from the virus, most in a microplate platform [110, 111], and a few in lateral flow [112], microsphere [113] and microarray platforms [114], and other methods, e.g., Polymerase Chain Reaction (PCR) tests [115, 116]; a number of studies showed a wide range of levels and neutralizing activities of anti-SARS-CoV-2 [113, 117, 118]. The neutralising antibody levels declined within the first three months following diagnosis, suggesting a short optimum time window for the collection of CP with high neutralising antibody titers [119]. A significant decrease was also observed in the antibody binding to the spike protein of SARS-CoV-2 and neutralizing capacity of plasma from convalescent donors at six and ten weeks after symptoms onset [108]. The short duration of neutralizing antibody titers within months may have important implications for immunity and ongoing efforts to deploy CP for prevention and therapy of COVID-19 [120]. There is a significant correlation to various extents between ELISA-measured IgG titer and neutralising antibody titre [118, 119, 121-130]. However, the ELISA-determined anti-SARS-CoV-2 IgG did not always inhibit the virus receptor binding [131]. Antibody binding to SARS-CoV-2 spike glycoprotein as measured by pseudovirus capture assay did not always translate into neutralization [108].

Highly sensitive and specific platforms for the detection of anti-SARS-CoV-2 antibodies are becoming increasingly important for evaluating potential SARS-CoV-2 CP donors and identifying individuals with seroconversion [132]. Various platforms demonstrate significant correlations with a SARS-CoV-2 plaque-reduction-neutralization assay, suggesting their use for screening of individuals who have recovered from SARS-CoV-2 infections. Notably, a novel multiplexed solid-phase

chemiluminescence immunoassay has been developed and commercially available from Meso Scale Discovery for simultaneous detection of IgG binding to four SARS-CoV-2 antigens [trimeric spike (S), spike receptor binding domain (RBD), spike N terminal domain and nucleocapsid antigen] and the quantification of antibody-induced angiotensin-converting enzyme 2 (ACE-2), ACE-2 binding inhibition (pseudo-neutralisation assay) [133].

In addition to neutralization and immune assays, biophysical and functional evaluation of CP showed that it may have diverse antiviral effects against SARS-CoV-2 beyond neutralization, namely ADCC, phagocytosis and complement activation [134]. Moreover, CP could act not only on the viral infection but also on the antithrombin deficiency to reduce thromboembolic events [135].

Table 1. Summary of literature

Article type	Number of articles	Group	Summary	References
Clinical studies	64		A 55-year-old previously healthy male with severe COVID-19 was successfully treated with CP after treatment with favipiravir and hydroxychloroquine, enoxaparin	Al Helali et al. 2020 [136]
			A 35-year-old critically ill obstetric patient with COVID-19 was successfully treated with remdesivir and convalescent plasma	Anderson et al. 2020 [137]
			A 38-year-old critically ill man infected by SARS-CoV-2 and suffered from cerebral hemorrhage was treated with 150 ml plasma of type A Rh positive COVID-19–convalescent patient	Bao et al. 2020 [138]
			A myelodysplastic COVID-19 patient with disseminated tuberculosis was treated with CP in combination with antiviral and anti-cytokine drugs	Cinar et al. 2020 [139]
			A 76-year-old woman with persisting COVID-19 following therapeutic lymphocyte depletion was treated with CP in combination of lopinavir/ritonavir, prednisone	Clark et al. 2020 [140]
			A six-year-old severe COVID-19 girl transfused with CP (inactivated using methylene blue) with anti SARS-CoV-2 IgG at a titer of 1:700 once in a 200 mL dose	Figlerowicz et al. 2020 [141]
			A 29-year-old woman at 24 2/7 weeks of gestation was treated with CP after antibiotic therapy (ceftriaxone and azithromycin) and prophylactic low-molecular-weight heparin	Grisolia et al. 2020 [142]
			A patient with severe COVID-19 on prolonged mechanical ventilation was successfully treated with CP	Hahn et al. 2020 [143]
			A 62-year-old man with history of moderate persistent asthma, sinus bradycardia, chronic obstructive pulmonary disease and newly diagnosed COVID-19 was successfully treated with CP	Hartman 2020 [144]
			A 68-year old man with COVID-19 who received 250 mL of ABO-incompatible CP for 2 consecutive days with mechanical ventilation	Im et al. 2020 [145]
			A 26-year-old woman with a twin pregnancy at 36 week and one	Jafari et al.

			day gestation with confirmed COVID-19 received one plasma transfusion obtained from cured COVID-19 patients in addition to favipiravir	2020 [146]
			A 70-year old kidney transplant female recipient with severe COVID-19 was treated with CP and moxifloxacin, piperacillin, methylprednisolone, tienam, fluconazole	Jiang et al. 2020 [147]
			A 61-year-old man with a history of autologous stem cell transplantation (ASCT) for lymphoma was treated with CP with an anti-SARS-CoV-2 IgG titer of 13.3	Karataş et al. 2020 [148]
			A 41-year-old male with acute myeloid leukemia (AML) and COVID-19 treated with remdesivir and CP	Khan et al. 2020 [149]
			A 100-year-old male diagnosed with COVID-19 and other health problems was successfully treated with CP (SARS-CoV-2 S-RBD-specific IgG titer of > 1:640)	Kong et al. 2020 [150]
			A 39-year-old male severe COVID-19 patient with x-linked agammaglobulinemia receiving monthly immunoglobulin replacement therapy was treated with 200-mL CP (antibodies against either the spike or nucleocapside viral proteins IgG with a titer ≥1/320) on day 23 after admission	Mira et al. 2020 [151]
			A 3.1-kg term 9-week-old female with congenital heart disease and COVID-19 refractory to remdesivir was treated successfully with CP	Rodriguez et al. 2020 [152]
			A 30- year-old woman (gravid 3, parity 2) at her 21 and 2/7 weeks gestation with ARDS caused by SARS-CoV-2 infection was treated with CP in addition to lopinavir/ritonavir and azithromycin and early methyl prednisolone therapy	Soleimani and Soleimani 2020 [153]
			A 65-year-old Chinese man with severe COVID-19 received CP transfusion twice and oral hydroxychloroquine administration for a week	Xu et al. 2020 [154]
			A 64-year-old critically ill female with hypertension and diabetes received CP (IgG titer>1:320) while receiving invasive mechanical ventilation	Zhang et al. 2020 [155]
		Case series	Two COVID-19 patients (a healthy 71-year-old man and a 67-year-	Ahn et al.

			old woman with a medical history of hypertension) presented severe pneumonia with ARDS showed a favorable outcome after use of CP in addition to systemic corticosteroid	2020 [156]
			Two male cases (46- and 56-year-old) with hypertension and severe COVID-19 were transfused with 200 mL of CP despite supportive care and antiviral therapy	Abdullah et al. 2020 [157]
			12 hospitalized COVID-19 patients (8 males and 4 females) with a median age of 52 years (range, 39–91 years) were transfused with CP to evaluate neutralizing antibody levels in CP or in recipients and clinical outcomes.	Bradfute et al. 2020 [127]
			Four critically ill children with COVID-19, 14–18 years were treated with 200–220 mL of CP in addition to SARS-CoV-2 directed therapies	Diorio et al. 2020 [158]
			16 critically ill COVID-19 patients appeared refractory to other therapies or supportive care, CP was thus pursued.	Enzmann et al. 2020 [159]
			26 severe COVID-19 patients received 200 mL CP in addition to supportive treatment, hydroxychloroquine, azithromycin and favipiravir	Erkurt et al. 2020 [160]
			Four immunosuppressed patients (two 42-year-old and one 62-year-old males, one 65-year-old female) with or at risk of progression to severe or life-threatening COVID-19 were transfused with CP collected as per FDA guidance	Fung et al. 2020 [61]
			40 consecutive patients with severe COVID-19 received a median of 2 units of CP as well as antiviral therapy	Gemici et al. 2020 [161]
			16 severe and 15 life-threatened COVID-19 patients received CP transfusion	Hartman et al. 2020 [30]
			38 hospitalized, severely or critically ill patients with confirmed COVID-19 were treated with CP to assess its safety and efficacy	Ibrahim et al. 2020 [162]
			Two critically ill patients with COVID-19 infection were treated with 3 × 200 mL CP in addition to antiviral agents and a full scale of supportive care.	Ilona et al. 2020 [163]

			Three patients with X-linked agammaglobulinemia hospitalized for COVID-19 failed supportive treatment but recovered after CP therapy	Jin et al. 2020 [164]
			5,000 hospitalized adults with severe or life threatening COVID-19, with 66% in the intensive care unit, were treated with ABO-compatible CP with safety as the primary outcome	Joyner et al. 2020 [165]
			20,000 hospitalized adults with severe or life-threatening COVID-19 were treated with approximately 200 to 500 mL of ABO-compatible CP with safety as the primary outcome	Joyner et al. 2020 [166]
			35,322 hospitalized patients with (or at risk of) severe or life threatening acute COVID-19 were treated with CP with seven and thirty-day mortality as main outcomes	Joyner et al. 2020 [167]
			Three critically ill male patients with COVID-19 were treated by CP in addition to standard care	Liu et al. 2020 [168]
			49 patients with moderate and severe COVID-19 were treated with CP in addition to various standard of care	Maor et al. 2020 [169]
			Three kidney transplant recipients with COVID-19 were treated with CP in addition to immunosuppressant/antiviral/antibiotic (one admitted to the general medicine service, two in ICU)	Naeem et al. 2020 [170]
			Ten male patients with severe COVID-19 and a median age of 53 years (range 27-72) received ABO-compatible CP and other therapies e.g., steroids hydroxychloroquine	Olivares-Gazca et al. 2020 [171]
			17 critically ill patients with COVID-19, including six with haematological malignancies, were treated with CP with marked clinical improvement in addition to other COVID-19 treatment and chemotherapy as required	Pal et al. 2020 [172]
			13 solid organ transplant (SOT) recipients with severe COVID-19 received CP with additional therapies (hydroxychloroquine alone or in combination with azithromycin, steroids, anticoagulation, and immunosuppression)	Rahman et al. 2020 [173]
			25 severe COVID-19 patients treated with CP anti-inflammatory and anti-viral treatments to evaluate safety and clinical status at day 14 post-transfusion	Salazar et al. 2020 [174]

			Five critically ill patients with COVID-19 treated with CP (IgG titer>1000, neutralization titer>40) between 10 and 22 days after admission in addition to various antiviral agents and steroids	Shen et al. 2020 [175]
			24 patients with cancer and severe or life-threatening COVID-19 treated with CP in addition to cancer-directed treatment and COVID-19 specific therapies (hydroxychloroquine, azithromycin, remdesivir, tocilizumab)	Tremblay et al. 2020 [176]
			Two COVID-19 patients with long-term positive viral infection for > 8 weeks treated with CP in addition to recombinant human interferon, arbidol, chloroquine phosphate, ritonavir-boosted danoprevir	Wei et al. 2020 [177]
			Five critically ill COVID-19 patients with a persistently positive nucleic acid test for SARS-CoV-2 received CP therapy	Wang et al. 2020 [178]
			27 patients with mild COVID-19 symptom, but prolonged positivity of SARS-CoV-2 for a median 44 (30–47) days between symptom onset and last positive test of SARS-CoV-2 RNA before CP therapy,	Wu et al. 2020 [179]
			Three severe patients received CP in addition to antiviral therapy, antibacterial therapy and traditional Chinese medicine	Xi et al. 2020 [180]
			Six critically ill patients with COVID-19 received the transfusion of ABO-compatible CP besides anti-viral drug arbidol, leading to improvement in patient's symptoms and ameliorating radiologic abnormalities	Ye et al. 2020 [181]
			Four critically ill patients with SARS-CoV-2 infection received CP in addition to supportive care (antiviral drugs, mechanical ventilation)	Zhang et al. 2020 [182]
			Eight patients (four males and four females) with critical or severe COVID-19 were administered one or two transfusions of CP	Zeng et al. 2020 [183]
		Observational (cohort, case-control) studies	115 CP treatment group and 74 control group to compare outcomes including all-cause mortality, total hospitalization days and patients' need for intubation between the two groups	Abolghasemi et al. 2020 [184]
			10 severe COVID-19 patients treated with CP as an addition to	Duan et al.

			maximal supportive care and antiviral agents in comparison with a control	2020 [185]
			20 patients with severe or critical COVID-19 were treated with one unit of ABO-compatible CP under an expanded access protocol, as compared with 20 matched controls	Hegerova et al. 2020 [186]
			39 hospitalized patients with severe to life-threatening COVID-19 received CP transfusion in comparison with a cohort of retrospectively matched controls	Liu et al. 2020 [187]
			46 moderate to severe COVID-19 patients treated with CP to assess safety and 7-day hospital mortality in comparison with a control cohort of 23 consecutive patients	Perotti et al. 2020 [188]
			31 out of 49 early-stage critically-ill COVID-19 patients received CP, while the rest 28 namely control group, did not receive, to compare clinical and laboratory outcomes	Rasheed et al. 2020 [189]
			64 patients received CP at a median of 7 days after symptom onset and were compared to a matched control group of 177 patients for all cause in-hospital mortality and rate of hospital discharge at day 28	Roger et al. 2020 [190]
			316 severe and/or life-threatening COVID-19 patients treated with CP versus 215 propensity score-matched patients to assess the efficacy of CP transfusion compared to standard of care	Salazar et al. 2020 [191]
			138 patients received ABO-compatible CP versus 1,430 patients in standard-treatment group to evaluate the effectiveness, safety, and indications of the CP transfusion therapy for severe or critical COVID-19 patients	Xia et al. 2020 [192]
			18 patients with severe and critical COVID-19 were divided to two groups with no significant differences in age, gender and basic clinical data except one with CP transfusion (n=6) and the other without CP transfusion (n=12)	Xiao et al. 2020 [193]
			Six critically ill patients with COVID-19 treated with CP to evaluate its efficacy in comparison with 15 patients in a control group	Zeng et al. 2020 [194]
		RCT	86 hospitalized patients randomized at 1:1 ratio for standard of care therapy with and without CP. The primary outcome was day-60	Gharbharan et al. 2020

			mortality.	[195]
			103 patients were enrolled and randomized to receive CP in addition to standard treatment (n=52) or standard treatment alone (n=51), the primary outcome of time to clinical improvement within 28 days	Li et al. 2020 [196]
Commentary (Correspondence, Editorial, Letter to the Editor, Opinions, Perspectives, Viewpoints)	79	Positive	Viewpoint of CP therapy as an effective, safe, and feasible therapeutic option for COVID-19 based on historical and current data for its treating coronaviruses including SARS-CoV-2, mechanism of action and possible drawbacks	Alghamdi and Abdel-Moneim et al. 2020 [197]
			Based on the evidence of CP efficiency in treating human coronaviruses, in favor of clinical use and evaluation as a method for treating COVID-19.	Alzoughool and Alanagreh, 2020 [198]
			Potential use of CP and stem cells for treating COVID-19 based on their unique immunomodulatory properties and emerging science and clinical trials	Borlongan et al. 2020 [199]
			Comparison of mortality rates between two groups of COVID-19 ICU patients: group 1 treated in a local hospital without CP and group 2 from three published studies involving CP showed that CP therapy reduced the death rate with an odds ratio value of 0.03223 (95% confidence interval 0,0018 – 0,5777).	Cantore and Valente 2020 [200]
			Comments on the first RCT of CP in COVID-19 that showed clinical improvement in severely ill patients compared to standard treatment, limited by the sample size due to lack of patient enrolment	Casadevall 2020 [69]
			Based on previous use of CP against coronaviruses and risks and benefits analysis, recommending emergency use of convalescent sera to treat individuals with early symptoms and prevent disease in those exposed and preparations as soon as possible.	Casadevall 2020 [48]
			Based on previous use of CP against coronaviruses, supporting studies of the safety and efficacy of CP transfusion in COVID-19 patients	Chen 2020 [32]
			Based on previous use, immediate availability of CP and five	Cheraghali

			clinical trials of CP therapy for COVID-19, with limitations in mind, supporting the efficacy of CP therapy for COVID-19 especially in patients with moderate to severe symptoms	2020 [201]
			Suggestions of a potential role for antithrombin in the treatment of COVID-19 with CP	Gazzaruso et al. 2020 [135]
			The importance of published experience and the pending establishment of efficacy to support the use of CP as standard treatment instead of experimental therapy for COVID-19	Farhat et al. 2020 [202]
			A variety of aspects to be considered for the optimal use of CP donations for COVID-19 including manufacturing turn-around time, safety, efficacy. cost and the logistics of storage, distribution and administration	Focosi et al. 2020 [203]
			Based on data from previous use of CP against coronaviruses and COVID-19 CP case series, supporting CP transfusion in COVID-19 patients, particularly at an early stage of the disease	Franchini 2020 [204]
			Suggestions for production of CP including donor selection (completely recovered by at least 14 days, titers ≥1:160), serologic tests for the titer of anti–SARS-CoV-2 neutralizing antibodies (neutralization test preferred to ELISA), CP collection (plasmapheresis procedures)	Franchini et al. 2020 [205]
			Comments on CP donation protocol and ongoing multicentre interventional single-arm trial for CP transfusion in critically ill COVID-19 patients	Franchini et al. 2020 [70]
			Key points in an operational protocol for donation of anti-COVID-19 CP in Italy	Franchini et al. 2020 [206]
			Summary of six observational studies (a total of 33 patients), requirements for CP collection (e.g., titers>1:320), storage (e.g., 1°C and 6°C for up to 40 days) and transfusion (e.g., ABO compatibility), recommendation of CP therapy for patients severely ill with COVID-19 upon hospitalisation	Islam et al. 2020 [207]
			Recommendations for therapeutic plasma exchange with CP to be	Kesici et al.

			performed earlier and in patients with severe COVID-19	2020 [208]
			A brief summary of initial experience establishing a CP program involving donor recruitment, CP testing and transfusion (dose and ABO compatibility), assessment of the effectiveness of CP therapy	Knudson and Jackson 2020 [209]
			Summary of previous studies and existing/ undergoing clinical trials of CP therapy in support of its emergency use for COVID-19	Kumar et al. 2020 [210]
			History and current evidence supporting the use of CP for COVID-19 treatment based on the results from a number of clinical studies	McAllister et al. 2020 [211]
			Historical use of CP for infectious diseases, current and future perspectives of CP therapy for COVID-19	Montelongo-Jauregui et al. 2020 [55]
			Opinions of CP and hyperimmune globulin therapy for COVID-19: potential benefits and risks	Morabito and Gangadharan 2020 [33]
			Comments on the review by Valk et al. 2020 and implications for the use of CP in South Africa	Nnaji et al. 2020
			Perspectives of the National Institutes of Health on COVID-19 treatment with CP based on scientific rationale, historical precedents and current scientific evidence	Pau et al. 2020 [212]
			Discussion about CP donor availability and use of serosurveys to identify CP donors and targeted populations at high risk of exposure to COVID-19	Perez-Cameo and Marin-Lahoz 2020 [24]
			Metadata analysis of the efficacy of CP treatment based on 9 clinical studies suggesting that CP reduced viral loads, C-reactive protein levels and improved the clinical status of COVID-19 patients, when compared to baseline	Rabelo-da-Ponte et al. 2020 [88]
			Comments on the limitations of a clinical study by Shen et al. and recommendations for collection and use of CP and future clinical	Roback and Guarner

			investigations of its therapeutic efficacy	2020 [71]
			Existing evidence, design of clinical studies, assessment of the titre of antiviral antibodies using a series of recently-developed assays, two ongoing RCTs	Roberts et al. 2020 [213]
			Perspectives of current and past clinical studies of CP therapy, supply and demand, timing and dosing, and future immunotherapy for COVID-19	Rubin 2020 [29]
			Recommendations based on current evidence for the compassionate use of CP in patients with severe COVID-19 in developing countries with adaptations to their conditions and a thorough risk-benefit evaluation for each patient, and more research in the field.	Sabando Velez et al. 2020 [214]
			Past experience with CP therapy during previous SARS and Ebola outbreaks, current evidence and ongoing trials for CP therapy for COVID-19, recommendations for neutralizing antibody titers, treatment population, and low risks, more use of CP for the treatment of severely ill patients and earlier use in the course of illness and/or for prophylaxis	Sahu et al. 2020 [215]
			Suggested CP use as a stopgap option amidst pandemic while the efforts by authorities were needed to protect high risk individuals and consider its urgent preparation and the emergent use	Sheikh and Baig 2020 [216]
			World-wide efforts on deploy CP and hyperimmune globulin for COVID-19 treatment	Sheridan 2020 [26]
			Recommendations of localized herd immunity and CP to impede the spread of and fight against COVID-19	Syal 2020 [217]
			Brief note of CP therapy for COVID-19 and other coronavirus infections, and a possible trial in India	Teixeira da Silva 2020 [218]
			Positive results of CP therapy for other virus infections and COVID-19, upcoming clinical trials for different populations, requirement of CP donation	The Lancet Haematology 2020 [219]
			No impairment of psoralen and ultraviolet light pathogen inactivation on the stability and neutralising capacity of SARS-CoV-2-specific antibodies in CP	Tonn et al. 2020 [78]

			Positive views of the role of CP in infectious diseases in particular the collection, production and usage of CP in Hong Kong	Wong and Lee 2020 [220]
			Combination of CP therapy with other treatment mechanisms, precautions for its side effects, requirements for institutional support	Yoo 2020 [221]
			Several issues raised: optimal timing of administering CP, availability of CP with SARS-CoV-2 neutralizing antibody titer ≥1:160, adverse reactions related to CP transfusion while recommending CP therapy as an alternative option in emergent situation of COVID-19	Zhao and He 2020 [222]
			Highlights of some experiences in CP collection and infusion to treat COVID-19 patients in China	Zhu et al. 2020 [223]
		Neutral	Both PROs and CONs, a tried and tested approach to a short-term solution	Adriana et al. 2020 [224]
			Viewpoint of using a combination of monoclonal antibodies derived from convalescent human B cell hybridomas against multiple immunogenic targets of SARS-CoV-2 spike protein	Begum and Ray 2020 [225]
			Comments on the paper by Hegerova et al. and other clinical studies on the use of CP to treat COVID-19 in terms of their limitations due to concomitant therapies, various dosage and tittering, majority of patients with severe or life-threatening COVID-19	Bloch 2020 [72]
			Response letter regarding the comments on the safety and efficacy of CP therapy for COVID-19 based on the information available at the time of submission, highlighting the need for RCTs	Brown 2020 [80]
			Implications of short duration of neutralizing antibody titers for immunity and ongoing efforts to deploy CP for prevention and therapy of COVID-19	Casadevall et al. 2020 [120]
			Implications of the kinetics of viral load and the antibody responses of 23 hospitalized patients with mild and severe COVID-19 for the use of CP therapy	Casadevall et al. 2020 [226]
			Potential risks and ethical considerations as an immunologically	Cunningham

			based strategy, a tried and tested approach and perhaps helpful in the short term	et al. 2020 [227]
			Risk–benefit analysis based on theoretical reasons and limited data available on the safety and efficacy of CP therapy for COVID-19	Dhanasekaran et al. 2020 [228]
			Potential harm by CP to patients and overall worldwide health care response to COVID-19, suggesting an urgent need for high-quality randomized trials	Dzik 2020 [229]
			Criticism of US FDA's authorisation for the emergency use of CP for COVID-19 and urgency for high quality evidence from large RCTs	Estcourt and Roberts 2020 [230]
			Recommendations on the development of hyperimmune immunoglobulin from CP without compromising the supply of CP for COVID-19 through the establishment of global networks and harmonisation between the major regulatory agencies	Farrugia 2020 [231]
			Current clinical studies may underestimate risk of antibody-dependent enhancement due to lack of representation of patients in the early phase of infection and confounding from multiple concurrent therapies and small patient numbers	Fleming and Raabe 2020 [232]
			Preference of blood group O donors for CP in COVID-19 for additional benefit over anti-SARS-CoV 2 neutralizing antibodies due to high anti-A isoagglutinin titer	Focosi 2020 [233]
			Built on the literature, questions raised regarding neutralizing antibodies, donors, testing and qualification of CP, timeframe for transfusing CP to recipients, quality of evidence and ethics of clinical trials while considering CP therapy as a rescue treatment in the absence of obvious form of treatment and soon-coming vaccine	Garraud 2020 [234]
			Issues on CP donor recruitment: availability, antibody tests, CP collection and use	Gniadek and Donnersberger 2020 [235]
			Comments on seven reported clinical studies of the efficacy of CP therapy for COVID-19, with respect to the anti-SARS-CoV-2	Han and Zhou 2020

			antibody level and disease severity of patients before the treatment, and the lack of a control group, and recommendation for a RCT	[73]
			Built on literature of CP therapy for other viruses and a case series of COVID-19, a number of questions proposed to be answered	Langhi et al. 2020 [236]
			Potential sources for obtaining safer therapeutic plasma or autologous antibodies to treat COVID-19	Lanza and Seghatchian 2020 [81]
			Comments on the US FDA approval for emergency use of CP and current evidence for its efficacy to treat COVID-19	Mahase 2020 [237]
			Misleading claim of 35% reduced deaths by CP and insufficient evidence for any efficacy of CP therapy for COVID-19	Mahase 2020 [79]
			Introduction to CP, its benefits and risks, how to donate	Malani et al. 2020 [238]
			Criticism on the review article of Brown and McCullough, regarding the inconsistent information in the text and Table for three cited clinical studies, cautions about the efficacy and safety of CP	Pawitan 2020 [239]
			Proposed use of virus neutralizing antibody from CP in the form of an isopathic preparation for treatment of COVID-19	Prajapati 2020 [82]
			Historical use of CP therapy for other infectious diseases and limited clinical trials for COVID-19, several problems to be addressed	Saverino 2020 [240]
			Involvement of Antimicrobial Stewardship Programs in CP pre-authorization process to enhance the optimal use of CP	Stevens et al. 2020 [241]
			Selection of CP donors for COVID-19 with the highest levels of detectable neutralising antibody	Tedder and Semple 2020 [242]
			Evidence to support and cautions against CP therapy for COVID-19 based on past and current clinical studies, challenges around the collection of CP, and theoretical risks of CP transfusion	van den Berg et al. 2020 [243]
			Commentary on the influence of CP characteristics in particular levels of SARS-CoV-2 specific IgG antibodies on CP-associated outcomes	Verkerke et al. 2020 [244]

			Historical and current experiences with CP therapy for infectious diseases including COVID-19, mechanism of action of CP, challenges for clinical studies of safety and efficacy of CP therapy	Xi 2020 [245]
			Some questions raised for two clinical studies by Duan et al. and Shen et al. in terms of requirement for virus inactivation, optimal time to collect CP from a donor, transfusion volume and neutralizing antibody titer, previous severity of the CP donors	Zeng et al. 2020 [74]
			Built on the literature, questions raised regarding neutralizing antibodies, donors, testing and qualification of CP, timeframe for transfusing CP to recipients, quality of evidence and ethics of clinical trials while considering CP therapy as a rescue treatment in the absence of obvious form of treatment and soon-coming vaccine	Garraud 2020 [234]
			Potential of equine polyclonal antibodies as a sound alternative to CP for COVID-19	Zylberman et al. 2020 [246]
		Negative	Potential treatment of severe COVID-19 with HLA-E-restricted unconventional CD8 T cells superior to SARS-CoV-2 specific and HLA-matched cytotoxic T cells, both could be rapidly and cost-effectively prepared in large numbers from convalescent COVID-19 patients	Caccamo 2020 [83]
			Concerns about the adverse effect and blood-borne pathogen transmission from CP therapy low- and middle-income nations because of their lack of healthcare infrastructure and regulations for collecting and administering blood products	Ferreira and Mostajo-Radji 2020 [86]
			Risk of contamination and hypersensitivity to proteins in CP and exaggerated benefits	Joob and Wiwanitkit 2020 [84]
			Safety issues associated with CP use, in particular thrombotic events with high risk of pulmonary embolism, and longer timeframe (>4 h) to evaluate the incidence of adverse events	Sanfilippo et al. 2020 [87]
			Cautiousness with CP for COVID-19 treatment due to potential pro-coagulant effects worsening underlying hypercoagulability and perfusion in vital organs	Sanfilippo et al. 2020 [247]

			Pathogen contamination and no protective immunity in CP, and other classic therapeutic options with likely lower risk for COVID-19 such as hydroxychloroquine	Wiwanitkit 2020 [85]
Review	46	Rapid review	Use of CP for SARS, MERS, EBOV, H1N1, COVID-19 and summary of ongoing clinical trials	Barone and DeSimone 2020 [248]
			Introduction and challenges of CP therapy, and summary of ongoing clinical trials of CP therapy for COVID-19	Majbour and El-Agnaf 2020 [249]
		State-of-the-art review	Clinical use of convalescent plasma for infectious diseases including 3 case series for COVID-19 (total 19 patients) and pathogen reduction of CP recommendations for establishing a convalescent plasma program, enhancement considerations for convalescent plasma, and considerations around pathogen reduction treatment of convalescent plasma	Brown and McCullough 2020 [89]
			Historical use of CP and current approaches for donor selection and CP collection, pooling technologies, pathogen inactivation systems, and banking of CP, results of published clinical studies of CP therapy, and list of ongoing registered clinical trials.	Focosi et al. 2020 [250]
		Scoping review	Clinical trials of CP for SARS, Influenza A/B, Ebola virus, COVID-19 and timing of CP treatment	Cao and Shi 2020 [47]
			Assessment of the feasibility to conduct a rapid and timely meta-analysis based on the review of the registered clinical trials of CP for COVID-19 identified on ClinicalTrials.gov and the WHO registry of COVID-19 studies (www.who.int/ictrp/en/)	Zheng et al. 2020 [251]
		Review of the evidence	Examination of the risk of antibody-dependent enhancement from CP-derived polyclonal hyperimmune globulin therapy and its mitigation based on literature search in English on PubMed from 1965 till March 2020	de Alwis et al. 2020 [252]
			Existing clinical studies of passive immunization in particular CP therapy for COVID-19 and SARS-CoV-2 immunology	Fischer et al. 2020 [253]
			The mechanism of action and potential side effects of CP, evidence supporting its use from previous infectious diseases epidemic and	Mucha and Quraishy

			current COVID-19 pandemic, and donor selection criteria	2020 [254]
		Systematic review and meta-analysis	An update on the review by Piechotta et al. 2020 [42] with more completed and ongoing studies identified on 19 August 2020	Chai et al. 2020 [95]
			Safety and efficacy of CP therapy for other severe respiratory viral infections to provide indirect evidence for CP therapy for COVID-19	Devasenapathy et al. 2020 [93]
			Systematic search in WHO COVID-19 Global Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, CDC COVID-19 Research Article Database and trial registries on 4 June 2020 to identify completed and ongoing studies of the safety and efficacy of CP or hyperimmune immunoglobulin transfusion in the treatment of COVID-19	Piechotta et al. 2020 [42]
			Systematic search in major electronic databases (PubMed, Medline, Google Scholar and MedRxiv) to identify available evidence on the CP for treatment of COVID-19 up to 10 July 2020 in accordance with the PRISMA guideline	Sarkar et al. 2020 [94]
			Systematic search in major electronic databases (PubMed, Web of Science, Embase, and the Cochrane Library) to identify available evidence on the CP for treatment of different types of infectious including COVID-19 up to March 30, 2020 in accordance with the PRISMA guideline	Sun et al. 2020 [255]
		Overview	Pathophysiology of COVID-19 and summary of three clinical studies of CP treatment and discussion of low-dose radiation therapy for COVID-19 and combination therapy involving both	Abdollahi et al. 2020 [256]
			Passive immunotherapy, requirements for hyperimmune plasma donor and product, directions and methods of clinical use	Annamaria et al. 2020 [257]
			Explanation for how and why the CP can serve as a plausible therapeutic modality and current clinical trials for its use for COVID-19 treatment.	Anudeep et al.2020 [258]
			Evidence of benefit, regulatory considerations, logistical workflow (donor eligibility, donor recruitment, collections and transfusion), and proposed clinical trials	Bloch et al. 2020 [60]

			Brief of CP therapy, monoclonal antibody therapy, and SARS-CoV-2 RBD mutations and infectivity	Kumar et al. 2020 [259]
			Perspectives of immunity (cross-reactivity, vaccination) and immune therapy (intravenous immunoglobulin, CP, monoclonal antibodies) in COVID-19	Gasparyan et al. 2020 [260]
			Historical evidence for CP in previous infectious outbreaks including MERS and SARS-Cov-1 and implication for CP as an explicit option for containment of COVID-19 disease.	Iftikhar et al. 2020 [261]
			Mechanism of action, historical evidence for CP in previous infectious outbreaks, safety of CP therapy, and factors affecting the efficacy of CP therapy for COVID-19	Li et al. 2020 [262]
			Following topics covered: the immune responses of COVID-19 patients, passive immunity therapy using immunoglobulin or CP including two clinical studies for COVID-19, potential adverse effects of CP, procedure for CP use	Lindholm et al. 2020 [263]
			Survey of current clinical trials of CP to treat COVID-19 infection and description of their characteristics including study design, patients population, outcomes, eligibility criteria for CP donors, CP collection, antibody titre and CP dose	Murphy et al.2020 [96]
			Background, immunological basis and clinical indications of CP treatment for COVID-19, some examples and future perspectives of clinical applications of CP therapy	Sayinalp et al. 2020 [264]
			Overview of RCTs of CP and hyperimmune intravenous globulin for treatment for severe influenza A and B and reported clinical studies on the use of CP in OCIVD-19 (two case reports, one case-control, one observational study and one RCT) and key considerations for passive immunization studies for COVID-19	Subbarao et al. 2020 [265]
		Mixed studies review	Literature search using Elsevier, PubMed, Taylor & Francis, Springer, Nature and Google search engines, and consultation with experts, highlights of clinical studies of CP therapy for SARS–CoV-2 and other viruses infections, protocol of CP therapy for COVID-19 and any potential risks	Pawar et al. 2020 [76]

		Systematic review	Systematic search in electronic databases (PubMed, Embase, Google Scholar, Cochrane Library, and Medline) to identify clinical studies related to CP and COVID-19 up to June 2020 in accordance with the PRISMA guideline for a systematic review	Bakhtawar et al. 2020 [91]
			Analyses of three clinical studies in China involving 19 patients who received CP transfusion and recommendations for collection, testing and clinical use of COVID-19 CP identified by searching PubMed, Embase and Medline databases from December 8, 2019 (first breakout) to May 5, 2020	Chen and Xia 2020 [266]
			Systematic search in major electronic databases (PubMed, Embase, and Medline) to identify available evidence on the CP for treatment of COVID-19 up to 19 April 2020 in accordance with the PRISMA guideline	Rajendran et al. 2020 [92]
			Systematic search in WHO COVID-19 Global Research Database, MEDLINE, Embase, Cochrane COVID-19 study register, Centers for Disease Control and Prevention COVID-19 research article database and trials registries to identify ongoing studies and results of completed studies on 23 April 2020 for case-series, cohort, prospectively planned, and RCTs for CP therapy	Valk et al. 2020 [44]
			A PubMed search was conducted on 13 July 2020 to summarize the literature and identify future research regarding CP therapy for coronaviruses (SARS-CoV, MERS-CoV and, in particular, SARS-CoV-2) as well as currently registered RCTs for CP in COVID-19 from the World Health Organization International Clinical Trials Registry and clinicaltrials.gov	Wooding and Bach 2020 [62]
		Critical review	Summary of the results from RCTs published to date and analysis their flaws and biases to provide suggestions for next round of RCTs, with regard to CP specification, therapeutic dose, timing, control arm, disease stage, and outcome measures	Daniele and Albert 2020 [267]
			Various aspects and limitations of CP therapy for COVID-19 based on current literature	Nagoba et al. 2020 [268]
			Available evidence about CP in COVID-19 and other epidemics,	Psaltopoulo

			mechanisms of action, registered trials on CP therapy for COVID-19, guidance from authorities for donor selection including neutralizing antibody titers, CP recipients and blood establishments.	u et al. 2020 [269]
			CP to treat virus diseases and SARS-CoV-infected patients without significant adverse events, antibody-mediated immunopathology and response in coronavirus diseases, CP collection and study design to evaluate the safety and efficacy of COVID-19 CP	Tiberghien et al. 2020 [64]
		Literature review	Historical precedents and recent clinical studies of CP for infectious diseases and COVID-19, mechanism of action, safety, patient and donor eligibility, antibody titer measurement, and system development for CP therapy	Choi 2020 [59]
			Introduction of SARS-CoV-2, brief of diagnosis and treatment of COVID-19, potential benefits and risks, mechanism of CP therapy, summary of eight completed clinical studies and challenges of CP therapy in patients with COVID-19	Khulood et al. 2020 [267]
			Review of the clinical utility of convalescent blood products, primarily CP and immunoglobulins, and available evidence in the previous coronavirus epidemics and COVID-19 pandemic	Long et al. 2020 [270]
			Review of the mechanism, completed and ongoing clinical studies, challenges and future direction for CP therapy in the treatment of COVID-19	Ouyang et al. 2020 [271]
			Concept of passive antibody therapy including CP therapy, strategy, mechanisms, risks, current evidence and ongoing clinical trials of CP therapy for COVID-19	Piyush et al. 2020 [272]
			Clinical studies of CP in patients with respiratory infection by coronavirus (SARS, MERS, and SARS-CoV-2), associated adverse events, acquisition and plasma composition, antiviral mechanisms, and immunomodulation	Rojas et al. 2020 [36]
			Basic principles of passive immunization, with particular reference to CP, CP therapy during past epidemics and current pandemics, analysis of the possible side effects, summary of clinical studies and various aspects regarding CP therapy for COVID-19	Selvi 2020 [267]
			Current status of various antibody-based immunotherapeutics such	Sharun et al.

			as CP, monoclonal and neutralizing antibodies, and intravenous immunoglobulins against COVID-19 with highlights of their advantages, disadvantages, and clinical utility	2020 [273]
			Clinical studies of CP used during previous viral outbreaks and pandemics, and potential use of CP during the present COVID-19 pandemic (three case series) with a risk benefit analysis, pros and cons of CP against COVID-19	Sullivan and Roback 2020 [274]
			Historical examples and recent clinical studies of CP for infectious diseases and COVID-19, mechanism of action, regulations of CP collection, CP dose, patient selection, CP for prophylaxis, risks of CP administration	Yigenoglu et al. 2020 [275]
Protocol/ Guidance	19	Preparation/ production of CP	Requirements for CP donors, and the standards for preparation, qualification, storage, distribution and control of use of the product	Accorsi et al. 2020 [97]
		A study protocol for a non-randomized trial	A national collaborative multicenter phase II cohort study in Saudi Arabia for assessing feasibility, safety, and potential efficacy of CP in treating COVID-19 patients with severe disease in comparison with a propensity score matched control	Albalawi et al. 2020 [101]
		Clinical study and application of CP	Gaps in knowledge were identified as follows: study design, patient eligibility, dose, frequency and timing of administration, parameters to assess response to the treatment and long-term outcome, adverse events, and CP application in less resourced countries as well as in paediatrics and neonates	Al-Riyami et al. 2020 [98]
		Conceptual framework	An intelligence-integrated concept to identify the most appropriate CP for corresponding prioritised patients with COVID-19 to help doctors hasten treatments	Albahri 2020 [107]
		expert	Donor selection, recruitment, blood collections, processing and distribution pre-donation qualification of CCP donors (including antibody testing) and operational considerations pertaining to collection, storage and distribution of CCP	Bloch et al. 2020 [99]

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		COVID-19 CP program	Registration of hospitals and investigators with a national IND protocol, collaboration with a regional blood donor center, targeted recruitment of CP, IT support for CP ordering, distribution, and transfusion, prioritization of patients to receive CP, and evaluation of CP products including antibody characteristics and patient response to therapy	Blackall et al. 2020 [105]
			Donor identification and recruitment, quantification, scheduling, CP collection by apheresis, testing, processing, labeling, inventory management and distribution	Budhai et al. 2020 [106]
		Study protocol for RCTs	A structured summary of a study protocol of a phase II RCT to assess the safety, efficacy and dose response of CP transfusion in severe COVID-19 patients	Chowdhury et al. 2020 [276]
			A prospective, single-center, phase 2, RCT to evaluate the efficacy and safety of CP in hospitalized adults with severe SARS-CoV-2 infection	Eckhardt et al. 2020 [277]
			An open label phase II RCT with or without infusion of CP to assess the clinical outcome in high-risk patients with confirmed severe COVID-19	Janssen et al. 2020 [104]
		Perspective document of the Working Party on Global Blood	Key factors for eligibility criteria of CP donors; pre-screening and pre-donation testing of CP donors; criteria for CP collection; post-donation treatment of CP; and recommendations for CP transfusion	Epstein and Burnouf 2020 [278]

		Safety of the International Society of Blood Transfusion		
		Commentary	The same quality and safety standards for collection and use of CP in low- and middle-income countries as in the high-income countries	Epstein et al. 2020 [279]
		Guidance for treating early to moderate COVID-19 patients with CP	The guidance includes patient and donor selection criteria, plasma harvesting, plasma product specifications, dosage and precautions for CP collection and transfusion process and is to be adopted by Sudan's health authority	Hassan et al. 2020 [100]
		Initiative for provision of CP	Collaboration and resource management for CP collection, inventory development, clinical use and donor recruitment in Arkansas with constrained resources	Ipe et al. 2020 [280]
		A pilot program of CP collection	Criteria for CP donor screening and selection, collection procedures via plasmapheresis, CP testing for SARS-CoV-2 nucleic acid and S-RBD-specific IgG antibody	Li et al. 2020 [281]
		Strategy and experience	Criteria for CP donor recruitment, collection and preparation of CP, laboratory examination of CP, guidance for clinical use, and three clinical cases of COVID-19 treatment with CP	Pei et al. 2020 [282]
		An one arm proof-of-concept clinical trial protocol	Efficacy of the administration of CP therapy for critically ill patients with COVID-19 in terms of their survival	Perotti et al. 2020 [103]
		An apheresis research project proposal	Suggestions for CP collection process, donor safety, clinical use, quality management, targeted patients	Seghatchian aand Lanza 2020 [283]
		Authority guide by Turkish Ministry of Health	Principles and criteria for collection, preparation and clinical use of CP, and a treatment follow-up process	Yilmaz et al. 2020 [284]

In vitro testing of convalescent plasma	35	ELISA with recombinant antigen (e.g., spike protein sequences) as substrate	An ELISA that could detect different antibody types in serum and plasma, and correlate with neutralizing activity to identify highly reactive human donors for CP therapy	Amanat et al. 2020 [110]
			A high-throughput competitive assay that could simultaneously determine an individual's seropositivity against the SARS-CoV-2 Spike protein and estimate the neutralizing capacity of anti-Spike antibodies to block interaction with the human ACE2 required for viral entry, and be used to identify candidate sera for therapeutic use	Byrnes 2020 [111]
		ELISA plate-bound recombinant ACE2 and SARS-CoV-2 RBD	or antibodies and compounds capable of inhibiting the binding Plasma from COVID-19 convalescent patients approximately 10 weeks after confirmation of COVID-19 by RT-PCR with relatively mild symptoms and no need for hospitalization contained significant amount of SARS-CoV-2-specific IgG, but did not always inhibit the virus receptor binding	Gattinger et al. 2020 [131]
		Pseudovirus capture assay and virus neutralization (VN) assay	The capacity of CP to bind to SARS-CoV-2 spike protein correlated with neutralizing activity (Spearman correlation coefficients $\rho > 0.86$), but did not always translate into neutralization	Ding et al. 2020 [108]

		VN assay using SARS-CoV-2 strain and monkey Vero-E6 cells	In vitro evaluation of potency of CP and potential anti-SARS-CoV-2 drug candidates for COVID-19 treatment	Ianevski et al. 2020 [109]
		VN assays based on different viruses	The neutralizing activity of CP and human monoclonal antibodies measured using pseudotyped and chimeric viruses correlated quantitatively with that measured using an authentic SARS-CoV-2 neutralization assay ($\rho \geq 0.86$)	Schmidt et al. 2020 [285]
		A lateral flow assay (LFA) testing platform	CP collected from adults who met all criteria for donating blood, had confirmed COVID19 by positive SARS-CoV-2 PCR test, had complete resolution of symptoms at least 14 days prior to donation, showed qualitatively diverse (strong, weak and negative) IgG and IgM profiles, with 87.3% and 50.8% being positive for IgG and IgM, respectively	Ragnesola et al. 2020 [112]
		Microarray	A microarray containing a panel of antigens from SARS-CoV-2 spike protein and nucleoprotein in addition to other human coronaviruses	de Assis et al. 2020 [114]
		PCR based tests	SARS-CoV-2 neutralizing antibodies were detectable as early as 10 days after onset of symptoms and continue to rise, plateauing after 18 days and were not altered by amotosalen and UVA radiation to inactivate potentially contaminating infectious pathogens in CP	Danh et al. 2020 [115]
			Detectable viral RNA in older COVID-19 patients screened for CP donation even 12 to 24 days after symptom resolution	Hartman et al. 2020 [116]
		VN assays based on pseudotyped and live SARS-CoV-2 virus, and ELISA based on S-RBD and ACE2	ELISA results had an overall agreement with authentic VN titers with a coefficient of determination of 0.6) and a high correlation with pseudotyped VN titers (R^2 = 0.76) in a cohort of 58 potential donors for CP therapy	Abe et al. 2020 [130]

		VN assays based on pseudotyped SARS-CoV-2 virus, and S-RBD-specific IgG, IgM, and IgA ELISA	The levels of S-RBD-specific IgG and IgA slightly decreased between 6 and 10 weeks after the onset of COVID-19 symptoms in contrast with a rapid decreased level of S-RBD-specific IgM. Similarly, the neutralization capacity of CP was significantly decreased a few weeks after the symptom onset. The loss of neutralizing activity over time correlated with the loss of anti-RBD IgM, IgA, and IgG antibodies, higher for IgM than for IgG and IgA	Beaudoin-Bussières et al. 2020 [286]
		VN assay and commercial anti-SARS-CoV-2 IgG ELISA	In 130 CP donors, higher levels of anti-spike avidity were associated with older age, male sex, and hospitalization. Neutralizing antibody titers correlated with anti-spike and anti-NP IgG avidity, respectively (ρ=0.386 and 0.211)	Benner et al. 2020 [126]
		VN assay using authentic SARS-CoV-2 and commercial anti-SARS-CoV-2 IgG ELISA	Amongst 250 donors studied a median of 67 days since symptom onset, 97% were seropositive on one or more assays. Sixty percent of donors had neutralizing antibody titers ≥1:80. Higher neutralizing antibody titer correlated with older age, male sex, fever during acute illness, and disease severity represented by hospitalization. The antibody titer declined in 37 of 41 paired specimens collected a median of 98 days (range, 77-120) apart. ELISA results corresponded well with the antibody titers	Boonyaratanakornkit et al. 2020 [287]
		VN assay using a SARS-CoV-2 strain and commercial ELISA and CLIA using virus antigens	There were positive correlations of varying strength (ρ= 0.37-0.52) between antigen binding and VN assays in a cohort of 47 CP donors with a history of nonsevere COVID-19. The neutralization activity was the highest in the donors age 48-75 years compared to the younger age groups 19-37 and 38-47, but was not affected by sex fever and symptom duration	Gniadek et al. 2020 [128]
		VN assay and commercial ELISA and CLIA	There were significant positive correlations between VN assay values and ELISA or CLIA values (ρ=0.81-0.40). Some commercial assays may be useful to identify CP donors with high neutralizing antibodies	Patel et al. 2020 [129]
		SARS-CoV-2	In the study sample of 436 donations, more individuals with	Harvala et

		infected cell lysate and spike protein ELISA and VN assay	previously laboratory-diagnosed SARS-CoV-2 infection developed measurable antibody responses and neutralising antibodies than those with a self-diagnosed infection. Neutralising antibody levels declined within the first 3 months following diagnosis, which suggests the collection of CP with high neutralising antibody may be optimum within a short time window. Finally, commercial ELISA can perform effectively as surrogate assays for predicting neutralising antibody titres	al. 2020 [119]
		Anti–NP SARS-CoV-2 IgM, IgG, and IgA ELISA and cytopathic effect–based VN test	Neutralizing antibody titers of ≥160 were found in 63.6% of 271 eligible CP donors recovered from mild/moderate COVID-19 (absence of symptoms for ≥14 days). Correlation between IgG signal/cut-off of ≥5.0 and neutralizing antibody of ≥160 was 82.4%. The neutralizing antibody titer was associated with donor's weight, days between disease onset and plasma collection, and IgG/IgM levels	Wendel et al. 2020 [288]
		VN assays based on pseudotyped and authentic SARS-CoV-2 strains, and anti-SARS-CoV-2 NP IgG ELISA	The highest neutralizing antibody titers were observed among ICU patients, followed by general hospitalized patients, and CP donors (>55% of CP samples (21/38) exhibited a titer <1:160). The pseudotype VN titer correlated with the ELISA result ((r=0.4192), but had no correlation with age	Zeng et al. 2020 [289]
		Commercial CLIA for anti-SARS-CoV-2 IgM and IgG, and PCR test	82% CP donors had positive IgG antibodies, 40% donors tested positive by PCR even symptom-free for ≥2 weeks. There was a decline in the IgG level over a short duration of 10 days. CP recipients with detectable plasma viral load had lower IgG levels; there was no relationship between plasma viral load, blood type or death.	Dulipsingh et al. 2020 [290]
		Commercial CLIA for detecting RBD-specific	RBD-specific serum IgG, IgM and IgA COVID-19 convalescent patients continued to decline from 28 to 99 days after hospital discharge	Ma et al. 2020 [291]

		IgG, IgM and IgA levels		
		VN assay using mNeonGreen SARS-CoV-2 and Vero-E6 cells	A high-throughput fluorescence-based assay comparable to plaque reduction neutralizing assay, the gold standard of test for SARS-CoV-2 neutralizing activity, useful to identify donors with high-titers for CP for COVID-19 therapy	Muruato et al. 2020 [292]
		Biophysical antibody profiling	CP antibodies can elicit Fc-dependent functions beyond viral neutralization such as complement activation, phagocytosis and antibody-dependent cellular cytotoxicity against SARS-CoV-2	Natarajan et al. 2020 [134]
		Pseudotyped VN assay, anti-SARS-CoV-2 IgG/IgM ELISA, fluorescent bead-based immunoassay	Hospitalized patients had up to 3000-fold higher antibody and neutralization titers compared to CP donors. VN titers correlated with IgG, IgM and IgA levels and increased with the subject age. There were no gender differences in the VN titer and IgG level.	Dogan et al. 2020 [123]
		Anti-SARS-CoV-2 IgG ELISA and VN assay	A range of neutralization titers from 8 to 1765 were seen in 100 CP units with a tendency of higher-titer plasma units from donors with increased disease severity, of advanced age, and of male sex. The neutralization titer correlated with ELISA results (R^2=0.2830)	Jungbauer et al. 2020 [124]
		ELISA for NP-specific IgM/ IgG, and S-RBD-specific IgG, and VN assay	The S-RBD-specific IgG antibody reaches higher levels after 4 weeks from the onset of COVID-19 symptoms in potential CP donors with no symptoms for >2 weeks. N-specific IgM and IgG, and S-RBD-specific IgG levels had a negative and positive correlation with time from the onset of symptoms to the plasma donation (Pearson correlation r=−0.3591, 0.2635 and 0.4540, respectively). There is a positive correlation between the SARS-CoV-2 VN titer and the S-RBD-specific IgG titer (r=0.6222). A VN titer of 1:80 is approximately equivalent to a S-RBD-specific IgG titer of 1:1280. The antibody levels were not correlated to age, sex, or blood type.	Li et al. 2020 [125]

		Anti-SARS-CoV-2 IgG/IgM ELISA and neutralizing antibody assay	ELISA plates coated overnight with recombinant NP and S-RBD (100 ng/well) for detection of immunoglobin antibodies, pNL43Luci and GPpCAGGS co-transfected into 293T cells for the neutralizing activities of CP. There was a significant correlation between neutralizing antibody titers and AUC of anti-S-RBD IgG, but not of anti-NP IgG	Ni et al. 2020 [293]
		Anti-SARS-CoV-2 IgG/IgM ELISA and pseudotyped and authentic virus neutralization assay	Most CP obtained from individuals who recover from COVID-19 do not contain high levels of neutralizing activity with 33% undetectable	Robbiani et al. 2020 [294]
		Anti-SARS-CoV-2 IgG ELISA and virus neutralization (VN) assay	There was a strong positive correlation between both CP anti-S-RBD and anti-S- ectodomain IgG titers, and VN titer with more than 80% VN title ≥160 corresponding to IgG titer ≥1:1350	Salazar et al. 2020 [122]
		A fluorescence immunoassay (CEFIA) and a microsphere immunoassay (MIA)	CP showed a wide range of antibody levels. Agreement between the two immunoassays was 90.4%-94.5%	Yang et al. 2020 [113]
		A modified cytopathogenic assay based on cell culture of Vero cells in the presence of plasma samples and SARS-CoV-	There were individual differences in the antibody level (neutralizing antibody titers <1:16 to >1:1024) and its changes over 12 to 60 days since onset of symptoms among 8 representative convalescent patients	Wang et al. 2020 [117]

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		ELISAs based on the NP of SARS-CoV-2	IgG antibody titers of CP from six donors ranged from 1:40 to >320	Zhang et al. 2020 [155]
		Commercial LFA and ELISA targeting SARS-CoV-2 antigens	A combination of antigenic targets (NP, spike protein, S-RBD) may be required to improve the accuracy of IgG detection in CP donors	DomBourian et al. 2020 [295]
		VN assay, ELISA, CLIA, and LFA from different manufacturers	Neutralizing antibody titers of CP ranged from 1: <7.7 to 1:1765.0 with mean titer of 1:231 and a standard deviation of 331.9. The best correlations to the VN titer were obtained with the Euroimmun IgG ELISA assay (ρ=0.759) and the Wantai ELISA assay (ρ=0.729).	Weidner et al. 2020 [118]
		Commercial immunoassays based on SARS-CoV-2 SP and NP antigens	Anti-SARS-CoV-2 spike protein IgG antibody strength correlated with age and hospitalization for COVID-19, suggesting individuals who suffered severe COVID-19 disease symptoms may represent better CP donors. Total anti-SARS-CoV-2 nucleocapsid protein antibody strength correlated with time from symptom resolution to sample collection and symptom duration.	Ikegami et al. 2020 [296]

ACE2=Angiotensin Converting Enzyme 2, ARDS=Acute Respiratory Distress Syndrome, AUC=Area under the Curve, CDC=Centers for Disease Control and Prevention, ELISA=Enzyme-Linked Immunosorbent Assay, CCP=COVID-19 Convalescent Plasma, CLIA=Chemiluminescent Immunoassay, HLA=Human Leucocyte Antigen, ICU=Intensive Care Unit, LFA=Lateral Flow Assay, MERS=Middle Eastern Respiratory Syndrome, NP=Nucleocapsid Protein, PCR=Polymerase Chain Reaction, RBD=Receptor Binding Domain, RCT=Randomized Controlled Trial, SARS=Severe Acute Respiratory Syndrome, SP=Spike Protein, S-RBD=Spike protein Receptor-Binding Domain, TRALI=Transfusion-Related Acute Lung Injury, UVA=Ultraviolet A, VN=Virus Neutralization

Findings of Clinical Studies

As summarized in Table 2, there are considerable heterogeneities amongst the clinical studies in terms of the populations, the amount of CP received, and a variety of comparators. The CP therapy studies differ in the following aspects: patient demographics (e.g., age, gender, comorbidities), donors' selection (i.e., age, gender, diagnosis of SARS-Cov-2 infection and of recovery, anti SARS-CoV-2 antibody titer required for plasma donation), plasma collection and biologic qualification (number, volume and frequency of donations, infectious disease markers and pathogen inactivation), treatment and disease characteristics (dose and timing of administration, stage of the disease at which to start CP treatment).

Patient demographics

A total of 36379 patients with most patients (35,322) from a single study [167] have been treated with CP in all clinical studies included in this review. There is a patient heterogeneity across the clinical studies in terms of age ranging from infant [152] and 6 [141] to 100 years old [150], gender, different underlying diseases in particular hypertension and diabetes [184, 192, 194, 297]. Some case studies investigated CP therapy for COVID-19 in immune compromised/deficient patients [61, 151, 164, 170, 173, 195].

A few studies reported the antibody titers of patients before CP transfusion, which varied from undetectable IgG RBD antibody levels (<1:50 serum dilution) to extremely high level >1:25600 [158]. Studies suggested that patients with low antibody levels may benefit more from CP therapy [158, 195].

Donor selection and CP antibody titer

Most individuals with previously laboratory-diagnosed SARS-CoV-2 infection developed measurable antibody responses and also developed neutralising antibodies. There is evidence for a significant decline in neutralising antibody levels over time [119].

Studies suggest that the efficacy of CP depends on the antibody levels of the donor plasma and CP with high antibody levels could confer immediate immunity to recipients [192]. One key factor associated with CP therapy is the neutralizing antibody titer and when the infused plasma has a high antibody titer it may be of greatest benefit [158, 167, 169, 183]. Hence, it may be a prerequisite to find eligible donors who have high levels of neutralizing antibody.

Prior smaller studies have reported on a variety of titer cut-offs [175, 185]. The FDA has recommended that CP with a virus neutralizing antibody titer of ≥1:160 be used for therapeutic transfusion [298]. Studies have reported the levels of CP antibody titer ranging from no minimum neutralizing-antibody titer level [166] to >1:640 [185], and an even wider range of RBD-specific IgG titer from <1:160 to >1:6000 within the same study [158].

There was substantial heterogeneity in the antibody response among potential CP donors, but sex, age and hospitalization emerged as factors that can be used to identify individuals with a high likelihood of having strong antiviral antibody levels [299]. In vitro testing of CP showed a tendency of higher neutralizing antibody titers from donors with increased disease severity, of advanced age, and of male sex, however the clinical relevance of this difference needs to be investigated [123, 124, 126, 179, 287, 296]. Moreover, pooling CP samples from many donors may prove more effective for increasing and standardizing anti-SARS-CoV-2 neutralizing antibody titers [245].

In addition, CP collection efforts should be organized around the temporal dynamics of the immune response to viral clearance and a rise in neutralizing antibody titer, with a recommended window for plasma collection beginning at 4 weeks after the resolution of symptoms and

narrowing rapidly by 12 weeks [120].

Timing and dose

One key factor associated with CP efficacy is the optimal treatment time point [185]. The phase of the disease at which this treatment modality may be most beneficial is still a matter of some debate, with early versus intermediate-late stages of the cytokine storm reaction being associated with acute respiratory distress syndrome (ARDS) or other severe disease complications [300].

There was no therapeutic effect from CP treatment on severely or critically ill patients with COVID-19 more than 2 weeks after the onset of disease as reported by Liu et al. 2020 [187]. However, CP therapy has been limited to severe or critically ill COVID-19 patients. The majority of the patients were severe or critical ill because of COVID-19 with only a few mild cases [150, 160, 179].

Similar to most viral illnesses, viremia in COVID-19 peaks in the first week of infection and the primary immune response develops by days 10–14, which is followed by virus clearance. Therefore, transfusion of CP at the early stage of disease theoretically should be more effective [184, 191, 194]. CP appears to be of greater clinical benefit when administered early in the course of disease than delaying transfusion under the development of severe disease [30, 178], in principle, the course of disease does not exceed 3 weeks [138].

Studies have found that regardless of COVID-19 severity at time of transfusion, patients received CP earlier in their course of disease showed lower mortality, more rapid viral clearance, and shorter hospital stays [162, 183].

Based on the current findings, CP treatment should be given to patients with COVD-19 at the right phase or severity of illness and at the right time point. It is known that most patients with mild COVD-19 can recover without treatment, and CP may be an improper therapy for those patients. For patients with end-stage COVD-19, treatment with CP may be unable to avert a poor outcome, as demonstrated by the current findings [178, 194, 297]. Therefore, CP treatment may be more beneficial if used in potentially critically ill patients with COVD-19 at an early stage of disease. Thus, early recognition of COVD-19 patients who are likely to become critically ill is critical for the timely treatment with CP [194].

This is in line with one of the first published RCTs of CP, in which Li and colleagues found that clinical improvement was limited to those without life-threatening disease, with 91% improvement in the plasma group compared to 68% in the control arm [297]. A large multi-center study involving 35,322 patients found significant reductions in 7- and 30-day mortality with early use of CP containing high levels of SARS-CoV-2 specific IgG antibodies in a subset of patients [167].

Transfusion volume ranged from 2x50 mL [180] to 8x300 mL [182]. Total antibody dose could be calculated as the transfused volume of CP multiplied by SARS-CoV-2 neutralizing antibody titer. CP dose has also been recognized as a key characteristic that may influence CP-associated outcomes [244]. One study showed that patients transfused with 400 mL of CP had a tendency to turn faster to viral clearance than those who received 200 mL of CP [183].

Safety

All studies that assessed adverse events have reported no or minimal adverse events [93, 172]. Of major interest is one of the first large trials published so far—concerning the safety of 5000 recipients—that has identified only limited and non-unexpected transfusion complications [165]. The case series study focused on the safety of CP transfusion in COVID-19 reported that out of 5000 patients, there were 7 transfusion-associated circulatory overload (TACO), 11 transfusion-related lung injury (TRALI) and 3 severe allergic reactions. However, the reported low

incidence of serious adverse effects might be due to an extremely short time-frame of observation (4 h) [87]. The latest update of the study involving 20000 hospitalized adults with severe or life-threatening COVID-19 further demonstrated low adverse events because of the treatment with 36 TACO, 21 TRALI, 21 severe allergic reactions, and 38 transfusion-related thromboembolic events [166]. Consistently, other studies reported no to minimal adverse events. Half of the case reports that assessed the safety of CP did not indicate any adverse events or complications related to its use. One case series study reported five serious adverse events in 4 out of 46 patients [188]. The controlled studies reported 15 adverse events out of 695 patients. Overall, among a total of 20749 patients reported with safety data, the incidence of adverse events related to CP transfusion was less than 0.8% comparable or even lower than the incidence of adverse events related to plasma transfusions in other clinical settings [301].

There has been no evidence so far of antibody mediated enhancement of disease in COVID-19 patients treated with CP despite the concern that this might be a possibility in the presence of reactive but non-neutralising antibodies against SARS-CoV-2 [230].

Although it is not yet clear whether the SARS-CoV-2 virus is transmitted by blood [302] donor selection criteria in compliance with existing policies and routine procedures should be met and pathogens reduction by solvent/detergent-based treatments or light-based methods (especially for non-covered or detected in screening tests) should be performed in each donated plasma product as a standard for any plasma production [220, 270]. Ultraviolet light and riboflavin used in the pathogen reduction process could effectively reduce SARS-CoV-2 in plasma and blood products without decreasing the quality of the blood products [303]. Further studies have shown that the pathogen reduction processes did not alter neutralizing antibodies [78, 115].

Outcomes

These were measured by SARS-CoV-2 negative PCR tests, improvements of clinical symptoms assessed by respiratory distress and fever, computed tomography, time to death, length of hospital stay and mortality at discharge.

All case reports showed either viral load decrease/clearance or different extents of improvements of clinical symptoms with no mortality. Preliminary evidence from case reports and case series is favorable as significant clinical, biochemical improvement and hospital discharge have been reported.

COVID-19 severity and underlying diseases affected the outcome of CP treatment. A patient with lymphoma who underwent autologous stem cell transplantation (ASCT) showed persistent SARS- CoV-2 viral shedding for 74 days, even with the administration of CP [148]. On the other hand, one study reported that two patients with long-term positive viral infection for > 8 weeks showed substantial improvement after treatment with CP and ritonavir-boosted danoprevir [177]. Similarly, another study showed that CP therapy could rapidly reduce viral loads in more than half of 27 patients with prolonged positivity of SARS-CoV-2 for a median of 44 days after symptom onset [179]. It should be noted that most of these patients had mild COVID-19 symptoms.

Studies demonstrated that CP could effectively improve the respiratory symptoms of severe patients and help them wean from oxygen support. However, extremely critical and life-threatening patients could not benefit from CP [30, 192, 194, 297].

The case series reported a mortality rate of 24.4% in 35,666 patients mainly from one study with 35,322 patients [167]. The case controlled and randomized controlled studies included a total of 2289 patients in the control group and 695 patients in the CP group, and reported a total of 219 (9.6%) and 63 (9.1%) deaths in each group, respectively. The number of patients and the

mortality rates varied remarkably among these studies from 6 [194] to 1430 patients [192] and from 0 [185] to 93.3% [194], respectively. The mortality at discharge [184] or at 28 day post-transfusion [191, 297] have been reported as a primary outcome. Some studies showed improved survival for the CP group compared to its control [185, 187, 192], more clinical improvements [185, 187], and viral clearance [185, 194].

The efficacy of CP on mortality, length of hospital stay, clinical improvement and viral clearance was further analyzed by meta-analysis of controlled studies as presented below.

Table 2. Summary of original clinical studies of CP therapy for COVID-19

Study	Study design	Population	Details of CP	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Al Helali et al. 2020 [136]	Case report	A 55-year-old previously healthy male with severe COVID-19	Not reported	About 300-mL CP was transfused over 1 h in addition to other therapeutics: favipiravir, hydroxychloroquine, enoxaparin, paracetamol, diphenhydramine	A significant radiological and clinical improvement in a few days after CP transfusion and negative PCR test for COVID-19 in <48 h and discharged 12 days post transfusion	No significant adverse effects
Anderson et al. 2020 [137]		A 35-year-old pregnancy critically ill female with COVID-19 and past medical history for type 2 diabetes mellitus, asthma, and class III obesity	Not reported	One unit of CP on the day of admission at ICU and supportive care and therapeutic agents	Discharged on day 14 with no further issues afterward and continuing antenatal care with both primary obstetric office and maternal fetal medicine specialists.	Not reported
Bao et al. 2020 [138]		A 38-year-old critically ill man infected by SARS-CoV-2 and suffered from cerebral hemorrhage	Not reported	150-200 ml CP of type A Rh positive was given twice 9 days after hospital admission in addition to antiviral and	Both SARS-CoV-2 nucleic acid tests were negative (24 h interval) two days after the	Not reported

				antibacterial treatment	transfusion and the patient's symptoms gradually stabilized	
Cinar et al. 2020 [139]		A 55-year-old male patient with severe COVID-19 and active myeloid malignancy, disseminated tuberculosis and kidney failure	Collected using Trima Accel® Automated Blood Collection System from a donor who had previously recovered from COVID-19 disease and met universal donation criteria, anti-SARS-CoV-2 IgG titer 6.6	200 mL of CP on fifth day of the symptom-onset and another 200 mL of CP at ICU, in combination with antiviral and anti-cytokine drugs	SARS-CoV-2 was negative, discharged from the hospital with full recovery	No adverse reaction or complication
Clark et al. 2020 [140]		A 76-year-old immunocompromised woman with persisting COVID-19 following therapeutic lymphocyte depletion	Not reported	CP transfused at day 50 after symptom onset over 2 days (200 mL/day) in addition to treatment with lopinavir/ ritonavir, and prednisone	Rapid improvement in health condition, allowing definitively withdrawing oxygen, apyrexia ensued, and negative SARS-CoV-2 test, discharged on day 69	No adverse events
Figlerowicz et al. 2020 [141]		A six-year-old severe COVID-19 girl	CP inactivated using methylene blue with anti SARS-CoV-2 IgG	CP transfused once in a 200-mL dose at five weeks from the beginning	SARS-CoV-2 was negative for the next 3 weeks after CP therapy.	No adverse events

			at a titer of 1:700	of the disease and treatment with antiviral drugs and immune modulators, antibiotics and antifungal drugs	The hematologic parameters did not improve after SARS-CoV-2 elimination	
Grisolia et al. 2020 [142]		A 29-year-old woman at 24 2/7 weeks of gestation	Not reported	The patient was transfused with 300 mL of CP on day 7 from onset of symptoms, and another 300 mL of CP on day 12, and also treated with antibiotics, low-molecular-weight heparin, hydroxychloroquine, methylprednisolone	The patient's clinical condition rapidly improved as shown by normalization of laboratory tests, body temperature, O_2 saturation and vital signs within three days of the second CP transfusion, discharged 13 days after admission	No adverse effects
Hahn et al. 2020 [143]		A previously healthy man in his 70s with severe COVID-19 admitted to ICU	Obtained from two blood donors with one being diagnosed with high-level anti-SARS-CoV-2 IgG antibody	A total of 900 ml of CP was transfused at a slow infusion rate on day 31 after admission, and treatment with a respirator, muscle relaxants, antibiotics	The patient became afebrile and was tested negative for SARS-CoV-2 the following day after CP therapy, gradually improved and was weaned from the ventilator and	Not reported

					discharged alive from the ICU on day 63	
Hartman 2020 [144]		A 62-year-old man with history of moderate persistent asthma, sinus bradycardia, chronic obstructive pulmonary disease and newly diagnosed COVID-19	Not reported	The patient received 217 mL of CP with no other interventions at the time estimated seven days after onset of symptoms (cough and shortness of breath)	The patient showed rapid improvement in symptoms and electrocardiogram findings, and was discharged 36 hours after the transfusion	Not reported
Im et al. 2020 [145]		A 68-year old man with severe COVID-19	A donor with ABO blood group A (Rh-positive) incompatible with the patient ABO blood group B (Rh-positive)	250 mL of CP at 16 days after symptom onset for 2 consecutive days with mechanical ventilation and ECMO, steroid, heparinization, and antibiotic treatment	The patient showed clear improvement in respiratory distress and fever symptoms for 3 days after the CP transfusion, discharged without any detectable virus and other complication	No evident acute adverse effect
Jafari et al. 2020 [146]		A 26-year-old woman with a twin pregnancy at 36 week and one day gestation with confirmed COVID-19	Not reported	One unit of CP was transfused on the sixth day after hospital admission in addition to favipiravir,	The patient showed dramatic clinical and radiologic improvements and discharged	Not reported

				oxytocine	two weeks after admission with no infection on the newborns	
Jiang et al. 2020 [147]		A 70-year old kidney transplant female recipient with immunosuppression, severe COVID-19 and a history of chronic bronchitis, hypertension, and hyperlipidemia	Collected by apheresis from a donor who had recovered from SARS-CoV-2 infection for >14 days, with an ELISA antibody titer > 1:1000	200 mL CP was administered at day 4 and 11 after admission, respectively in addition to treatment with moxifloxacin, piperacillin, methylprednisolone, tienam, fluconazole	The patient's body temperature became normal and chest CT was significantly better than at admission, and the patient was discharged on day 30	Not reported
Karataş et al. 2020 [148]		A 61-year-old man with a history of autologous stem cell transplantation (ASCT) for lymphoma with persistent positive tests for SARS-CoV-2 RT-PCR and fever	Obtained using Trima Accel® Automated Blood Collection System from a donor satisfying universal donation criteria and recovered from COVID-19 disease. ELISA IgG titer 13.3	CP transfusion on the 40th day of the infection (dose not specified)	After the CP transfusion, his fever resolved after 3 days. He was discharged from the hospital on the 78th day of hospitalization, viral shedding remained positive as demonstrated by RT-PCR	Not reported
Kong et al. 2020 [150]		A 100-year-old mild COVID-19 male with a 30-year record of hypertension, abdominal aortic	collected via plasmapheresis from a donor who had recovered from COVID-19	The patient received CP twice 200 ml on the seventh day of hospitalization and 100 ml on the	Patient's viral load decreased significantly, by a factor of ~18, 24 h after the first	Not reported

		aneurysm, cerebral infarction, prostate hyperplasia, and complete loss of cognitive function for the preceding 3 years	for more than two weeks and had a SARSCoV-2 S-RBD-specific IgG titer of > 1:640	eleventh day of hospitalization	transfusion of convalescent plasma and then became undetectable after the second, discharged on day 13 of hospitalization	
Mira et al. 2020 [151]		A 39-year-old male patient with severe COVID-19 and XLA, receiving monthly immunoglobulin replacement therapy	IgG antibodies against either the spike or nucleocapside viral proteins with a titer greater than or equal to 1:320	200 mL, single dose, on day 23 after admission	After 24 h of infusion, fever ceased without subsequent reappearance and with progressive improvement of asthenia. After 48 h of infusion, no detectable virus in qPCR from nasopharyngeal exudate	Not reported
Soleimani and Soleimani 2020 [153]		A 30- year-old woman (gravid 3, parity 2) at her 21 and 2/7 weeks gestation with ARDS caused by SARS-CoV-2 infection	Not reported	CP was administered in addition to lopinavir/ritonavir and azithromycin and early methyl prednisolone therapy	A mild clinical improvement and decrease in inflammatory markers, normal growth of the fetus	Not reported
Xu et al. 2020 [154]		A 65-year-old man with severe COVID-19	Collected from two convalescent patients, no details provided	CP was given at a 400-mL dose on day 1 and 2 after admission, and	On day 11 after CP transfusion, temperature returned to	No apparent side-effects

				hydroxychloroquine was orally administrated for a week	normal and mechanical ventilation was withdrawn, the RNA test remained positive in throat swab, and CT revealed severe pulmonary lesions	
Zhang et al. 2020 [155]		A 64-year-old critically ill female with hypertension and diabetes	Collected by apheresis from a 37-year-old male with blood type O at 36 days after symptom onset and 17 days after discharge. CP IgG titer>1:320 by ELISA	200 mL CP on day 17 of hospitalization while receiving invasive mechanical ventilation	The patient did not require mechanical ventilation 11 days after plasma transfusion, and was transferred from ICU to a general ward	No adverse event
Ahn et al. 2020 [156]	Case series	A previously healthy 71-year-old man and a 67-year-old woman with a medical history of hypertension, both diagnosed with severe COVID-19	Obtained with Spectra Optia apheresis system from a male donor in his 20s who had recovered from COVID-19 for 21 and 18 days, respectively and met the blood donor eligibility criteria for plasma donation. ELISA	A total 500 mL of CP was divided into two doses and given over for 1 hour for each dose at 12 hours interval after 22 days from the onset of symptoms in Case 1, and 7 days in Case 2, respectively	SARS-CoV-2 became negative in both cases, Case 1 underwent a tracheostomy and currently, was successfully weaned from the mechanical ventilator. Case 2 was successfully extubated and discharged from	No adverse reaction occurred after the administration of CP

			optical density ratio for Anti-SARS-CoV-2 IgG was 0.586 and 0.532 (cut-off value 0.22)		the hospital on day 24.	
Abdullah et al. 2020 [157]		A 46-year-old male and a 56-year-old male, both with hypertension and severe COVID-19	Collected from a recovered moderate COVID-19 patient after performing necessary investigations for donor plasma (hemoglobin level and viral screen), but not antibody tests	deteriorated despite supportive care and antiviral therapy, 200 mL of CP at day 3 of hospitalization (day 7 after symptom onset) in Case 1, day 10 of hospitalization (day 13 after symptom onset) in Case 2	improve clinically 4 days and 70 h after CP, discharged from the hospital 16 and 21 days after admission with three consecutive negative RT-PCR tests each with at least 24 h apart.	Not reported
Bradfute et al. 2020 [127]		12 hospitalized COVID-19 patients (8 males and 4 females) with a median age of 52 years (range, 39–91), 9 obese patients, 10 patients in the ICU, and 2 on the general ward	Collected by apheresis from donors ≥28 days after positive PCR test, with complete recovery from COVID-19 and a median of neutralizing antibody titer of 1:40 (range, undetectable to 1:160)	Patients received one unit (200 mL) CP at a median of 8.5 days (range, 6–16 days) after the onset of symptoms and a median 3.5 days (1–10 days) after hospitalization.	Temporal increases in neutralizing antibody titers and IgG/IgM levels, gradual decreases in viral loads, with two deaths within 14 days after CP transfusion	No serious adverse events
Diorio et al. 2020 [158]		Four critically ill children with COVID-	Collected from donors proven	200–220 mL of CP at 7-14 days after	One died, two showed no	No emergent adverse

		19, 14-18 years, female, varied antibody titer levels pretransfusion	positive for SARS-CoV-2 by a laboratory test; and either ≥14 days from symptom resolution with a repeat negative test for SARS-CoV-2 or ≥28 days from symptom resolution without the repeat test. RBD-specific IgG titer <1:160 to >1:6000	symptom onset	clinical improvement, one recovered	events related to CP infusion
Enzmann et al. 2020 [159]		16 critically ill COVID-19 patients with most (12 patients) underlying cardiovascular disease	Not reported	Not reported	In-hospital mortality rate was 31% and median length of hospital stay was 19 (8-36 days)	No apparent adverse effects
Erkurt et al. 2020 [160]		26 (8 females and 18 males) severe COVID-19 patients (67.4 ± 15.5 years old)	Collected via apheresis ≥14 days after complete recovery from the eligible blood donors who had mild or moderate COVID-19 with positive antibodies	200 mL of CP was administered at 13.87 ± 6.5 days after admission in addition to supportive treatment, hydroxychloroquine, azithromycin and favipiravir	The patients who did not need mechanical ventilation improved with CP treatment while 6 of 17 patients on mechanical ventilation were dead	No severe adverse reactions
Fung et al.		Four immune-	Collected per FDA	Approximately 200	All patients were	No adverse

2020 [61]		suppressed patients (two 42-year-old and one 62-year-old males, one 65-year-old female) with or at risk of progression to severe or life-threatening COVID-19	guidance from donors with confirmed COVID-19 and resolution of symptoms within 14-28 days and a negative PCR test or >28 days without a PCR test. ELISA anti-SARS-CoV-2 spike protein IgG titer>1:400	mL of CP was transfused at 4-27 days following symptom onset	clinically improved, with two discharged home and fully recovered, and two discharged to skilled nursing facilities	reactions
Gemici et al. 2020 [161]		40 consecutive patients (median age 57.5 and 72.5% male) with severe COVID-19	Collected from eligible blood donors recovered from COVID-19 with negative laboratory results and symptom free for ≥14 days	Patients received a median of 2 (1–3) units of CP at median time of 5 days from the diagnosis in addition to antiviral therapy	90% patients who received CP outside ICU totally recovered at a median of 9 days after the transfusion and a half of the patients treated in ICU were free of mechanical ventilation	No TRALI or severe allergic reactions
Hartman et al. 2020 [30]		16 (7 female) severe and 15 (3 female) life-threatened patients	collected from a local donor recruitment and referral program	Dose and timing not reported	Respiratory support requirements began to on or about day 7 following CP transfusion,	Not reported

					especially in the severe patients	
Ibrahim et al. 2020 [162]		38 hospitalized, severely (16) or critically ill patients (22) with confirmed COVID-19 (63±12 years old, 18 female), 31.5% had three or more comorbidities, with 68% hypertension and 47% diabetes	Collected by apheresis from adults who were confirmed positive and had recovered from SARS-CoV-2 with negative PCT test for the virus and had total anti-SARS-CoV-2 titer >1:320	ABO-compatible CP was given in two consecutive 200-mL infusions 18.7±9.0 days following symptoms' onset. Another unit of CP was given to those with undetectable anti-SARS-CoV-2 antibodies	24 (63%) recovered and were discharged from the hospital, and 14 (37%) died. The survival patients received CP earlier in their course of disease (mean 15.3±6.9 days) and hospital stay (8.4±6.8 days) compared to those who died with mean durations of 24.5±9.6 days and 16.6±9.5 days, respectively	No adverse effects except for a transient transfusion reaction (fever and hematuria) within 2 h of CP infusion in one patient
Ilona et al. 2020 [163]		Two critically ill Hungarian patients (59- and 72-year-old male) with COVID-19 and hypertension and cardiovascular disease	Collected by plasmapheresis from recovered COVID-19 patients who had been asymptomatic for at least 2 weeks negative PCR tests and IgG-type antibody detectable by	3 × 200 mL of CP with the first dose administered on the fourth day of the patient's ICU mechanical ventilation	Both showed improved oxygenation and inflammatory decreased markers, were weaned from mechanical ventilation within 2 weeks	No severe adverse effects

			ELISA			
Jin et al. 2020 [164]		Three patients (10, 24 and 40 year-old males) with X-linked agammaglobulinemia hospitalized for COVID-19	CP containing anti-spike protein titer ≥1:320	Two units of 200 mL ABO-compatible CP were given on days 16, 22 or 44 of illness when there was minimal improvement on other therapies	Various clinical and laboratory improvements including increases in antibody titers, discharged within days after CP transfusion	Not reported
Joyner et al. 2020 [165]		5,000 hospitalized adults (median age of 62) with 81% being severe or life threatening COVID-19 and 66% admitted to ICU	ABO-compatible CP	CP dose of 200 – 500 mL	The incidence of SAEs was less than 1% and mortality rate at the seventh day after CP transfusion was 14.9%	Of 36 SAEs, 7 and 11 incidents of TACO and TRALI were judged as related to CP transfusion
Joyner et al. 2020 [166]		20,000 hospitalized adults (age 20-80) with severe or life threatening COVID-19	ABO-compatible CP with no minimum neutralizing-antibody titer level donated by recently recovered COVID-19 survivors	CP dose of 200 – 500 mL	141 SAEs classified as transfusion reactions were reported (<1% of all transfusions); 38 thromboembolic or thrombotic events and cardiac events were related to the transfusion. The mortality rate at the seventh day	Of 141 SAEs, 36 reports of TACO, 21 reports of TRALI, and 21 reports of severe allergic transfusion reaction

					after transfusion was 13.0%	
Joyner et al. 2020 [167]		35,322 hospitalized patients with (or at risk of) severe or life-threatening acute COVID-19 and a diverse representation of gender, age, weight status, race, and ethnicity	Collected from recently-recovered COVID-19 survivors without symptoms for ≥14 days and the antibody levels in the units collected were unknown at the time	All patients were treated with at least one unit (~200 mL) of CP with the option to administer additional doses if clinically justified, as well as adjunctive COVID-19 medications	A gradient of seven and thirty-day mortality associated with higher IgG levels in CP and early CP transfusion within three days of COVID-19 diagnosis	Ref. Joyner et al. 2020 [166]
Liu et al. 2020 [187]		Three critically ill male patients with COVID-19 (42, 56, 58 years old, two healthy, one with hypertension)	Collected from COVID-19 survivors who had fully recovered and tested negative for the virus and a total anti SARS-CoV-2 IgG titer of 160	Patients were transfused with 200-225 mL CP between 20 and 30 days after disease onset at the critical illness stage in addition to standard care	No therapeutic effect of CP was observed in any of the patients	Not reported
Maor et al. 2020 [169]		49 patients (median age 64.0 years, IQR 50.5–76.0, 35 males) with moderate and severe COVID-19 and comorbidities (diabetes and hypertension) in one third of the patients	Collected by apheresis procedure from recovered COVID-19 patients eligible for plasma donation and >14 days since the last negative PCR test. Neutralizing antibody titer 1:20 to 1:2560	The first dose of 200 mL CP was transfused at median 10.0 days (IQR 4.0–14.0) after PCR diagnosis, followed by a second unit of 200 mL 24 h later, in addition to various standard of care	At day 14 after the first CP dose, 24 patients improved, 9 died, and 13 were ventilated. More patients improved when treated with CP containing higher antibody levels or earlier	No serious adverse events except that one developed a rash that responded to antihistamine therapy

Naeem et al. 2020 [170]		Three kidney transplant recipients with COVID-19 treated with CP (one 65-year-old female admitted to the general medicine service, 35- and 36-year-old female and male in ICU)	Collected from donors at local and regional blood centers	One or two units of CP were given on day 2, 4, or 7 after hospital admission, in addition to immunosuppressant/ antiviral/antibiotic	All showed clinical improvement and discharged 9, 16, 25 days after hospital admission with no evident infectious complications	One experienced acute chest pain and dyspnea, but improved over the following 12-24 h
Olivares-Gazca et al. 2020 [171]		Ten male severe COVID-19 patients with a median age of 53 years (range 27-72) and comorbidities (diabetes, hypertension)	Obtained by apheresis from five donors (two females) with a median age of 35 years (range 24-52) and two negative PCT tests in a 24-h interval 10 days after the resolution of COVID-19 symptoms	Each patient received 200 mL of ABO-compatible CP and other therapies e.g., steroids hydroxychloroquine	Improvement in overall respiratory function and clinical condition over a period of eight days with six discharged and two died	No side effects
Pal et al. 2020 [172]		17 critically ill patients (mean age 56, range 24-81 years old, 10 males) with COVID-19, and most patients had multiple medical comorbidities including six with haematological malignancies	Collected from donors 18 to 56 days following full recovery from COVID-19 with anti-SARS-COV-2 Spike protein IgG titres 1:400-1:6400 as measured by ELISA	A single unit of 200 mL CP was given at an average time of 12 days (range 4-41) from illness three patients received two units roughly 8 days apart in addition to other COVID-19 treatment and	All patients showed a decline in oxygen needs and ventilatory support with most effects seen in patients when CP was administered early in their disease course.	No adverse events except a fever during transfusion in one patient, resulting in infusion of only 100 mL

				chemotherapy as required		
Rahman et al. 2020 [173]		13 solid organ transplant (SOT) recipients (median age 51 range of 20-75 years old, 8 males) with severe COVID-19 and comorbidities (e.g., hypertension and diabetes)	Collected from eligible blood donors with anti-SARS-COV-2 spike protein antibody titers ≥1:320 as measured by ELISA	All patients received two ABO-compatible units of CP, for a total of 500 mL at median time 8 days from symptom onset and additional therapies (hydroxychloroquine alone or in combination with azithromycin, steroids, anticoagulation, and immunosuppression)	Eight patients had de-escalating oxygenation support by day 7 post-CP. Nine patients were discharged, one still hospitalized, and three patients died ~3 months after the CP transfusion	No apparent transfusion-related adverse reactions
Salazar et al. 2020 [174]		25 patients (median age of 51) with severe and/or life-threatening COVID-19 and one or more underlying chronic conditions	Obtained from donors eligible according to standard blood donor criteria, confirmed SARS-CoV-2 infection and symptom free for 14 days, tested negative for SARS-CoV-2 by RT-PCR. ELISA IgG titer ranged from 0 to 1350	One 300-mL dose of CP at the median time of 10 days from symptom onset and concomitant anti-inflammatory and antiviral treatments, and one patient received a second dose six days after the initial transfusion	By day 14 of CP transfusion, 19 (76%) patients had clinical improvement and 11 were discharged	No adverse events within 24 h after transfusion. One patient developed a morbilliform rash 1 day after transfusion that lasted for several days.
Shen et al. 2020 [175]		Five critically ill patients (age range,	Obtained from 5 patients who	ABO-compatible CP was administered at a	Improvement in their clinical	Not reported

		36-65 years; 2 female) with laboratory-confirmed COVID-19 and rapid progression and continuously high viral load despite antiviral treatment	recovered from COVID-19 Anti SARS-CoV-2 IgG titer >1:1000 as determined by ELISA and a neutralization titer >40 titer	dose of 200-250 twice (400 mL in total) between 10 and 22 days after admission.	status as indicated by declined viral load, body temperature reduction, improved Pa_{O2} / F_{iO2}, and chest imaging	
Tremblay et al. 2020 [176]		24 patients with cancer and severe or life-threatening COVID-19 (median age 69, range 31-88, 14 males), some having other comorbidities (e.g., hypertension in 15 patients)	Collected via plasmapheresis, spike protein-directed ELISA antibody titers ≥ 1:320	Two units (250 mL) of ABO-compatible CP were transfused at 3 (IQR 2-7) days from admission in addition to cancer-directed treatment and COVID-19 specific therapies (hydroxychloroquine, azithromycin, remdesivir, tocilizumab)	Marked variability in both the timing and degree of improvement or worsening of oxygen requirement, 13 discharged, 10 deaths	Three patients experienced febrile non-hemolytic transfusion reactions
Wang et al. 2020 [178]		Five critically ill COVID-19 patients (median age 56, IQR, 50-62 years) admitted to ICU with a persistent (>30 days) positive nucleic acid test for SARS-CoV-2 and underlying chronic comorbidities, including hypertension	Collected from the recently cured patients whose antibody titers were above 1:640.	200 mL of cross-matching CP was transfused over 15 min initiated at median 37 (IQR 34-44) days from the onset of symptoms. In total, three patients received 400 mL and the other two received 1200 mL,	Within six days after CP therapy, all patients became negative for two consecutive nucleic acid tests Additionally, 4–9 days following the CP, three patients showed	No adverse reactions

		and diabetes		all received antibiotics, antiviral and anti-inflammatory agents	resolution of pulmonary lesion. Two recovered and three died	
Wei et al. 2020 [177]		Two COVID-19 patients (50 and 81 year-old males, the latter with type 2 diabetes mellitus, hypertension, and aortic dissection) with long-term positive viral infection	Not reported	One or two 200-mL doses of CP were administered >8 weeks after symptom onset, other therapeutics: interferon, arbidol, chloroquine phosphate, ritonavir-boosted danoprevir	Substantial improvement as confirmed by CT scan and discharged after three consecutive negative nucleic acid tests	Not reported
Wu et al. 2020 [179]		27 adult patients, with prolonged infection for a median 44 (IQR, 30–47) days between symptom onset and last positive test of SARS-CoV-2 before CP therapy (median age 64 (IQR, 57–72) years and 55.5% males), some with chronic diseases	Collected from donors without transfusion-related infectious diseases, recovered from COVID-19, > 3 weeks after symptom onset and > 10 days after discharge. Neutralizing antibody titer> 1:160	The patients were treated with a median of 400 (IQR, 200-600) mL CP at median 45 (35–49) days after symptom onset and other therapeutics: anti-virals, antibiotics, corticoid, immunoglobulin	The patients showed pulmonary imaging improvement (within 5–8 days) and viral clearance (18 patients) 15 days after the CP transfusion, and three died within 60 days	No transfusion-related adverse reactions
Xi et al. 2020 [180]		Three severe COVID-19 patients with comorbidities (hypertension, liver injury and Hepatitis B)	Collected from 2 recovered patients with the level of IgG very high (>30 AU/mL) and IgG	50 mL twice with 2 day interval and other treatments with non-invasive mechanical	The CT images, blood gas analysis and symptoms improved after	No adverse event

			titer > 1:80	ventilation and antiviral, antibacterial drugs and traditional Chinese medicine	CP therapy. All recovered after 16-18 days of hospitalization	
Ye et al. 2020 [181]		Six laboratory-confirmed critically ill COVID-19 patients (age 58±16.4, three male)	Collected from patients at least 3 weeks following disease onset consecutive two negative RT-PCR tests, seropositive for anti-SARS-CoV-2 IgG and IgM	One to three doses of ABO-compatible CP (200 mL/dose) at 6-31 days after admission. Each transfusion was administered over a 30-minute period	A resolution of ground-glass opacities and consolidation in five out of 6 patients and an elimination of the virus in two in the following days of CP therapy	No adverse events
Zhang et al. 2020 [182]		Four critically ill patients infected with SARS-CoV-2 (age: 31-73 years old, two male)	Prepared from recovered patients without details	One to eight doses of CP (200-2400 mL in total) 11-41 days after admission in addition to antiviral therapy	The time from transfusion to negative RT-PCR test results ranged from 3 to 22 days. Three discharged from hospital, one remained in ICU up to the time of report writing	No adverse events
Zeng et al. 2020 [183]		Eight patients (four males, median age 65)) with severe or critical COVID-19, five patients had coexisting chronic	Collected from seven donors (median age of 37) who had mild or moderate COVID-19 with no	ABO-compatible and cross-matched CP were administered at one (three patients) or two doses of 100–200 mL of CP within	Six of eight patients showed an improvement in oxygen support status within 5 days from CP	No adverse events

		diseases	comorbidities and were at the median day of 11 from discharge. Neutralizing antibody titer 1:255–1:1576	24 h between 9 and 34 days following the onset of symptoms	treatment, partial resolution of pulmonary lesions and decreased viral load	
Abolghasemi et al. 2020 [184]	Observational (cohort, case-control) studies	115 CP treatment group with an average age of 54.4 and 74 control group marched by age, gender, underlying diseases (hypertension and diabetes) and COVID-19 severity	selected from clinically and laboratory-confirmed recovered patients of COVID-19 who were between 18–60 years old and had no remaining symptoms of COVID-19 infection at least 14. ELISA antibody titer cut off index >1.1	One unit of 500 mL was infused in less than 3 days of hospital admission (≤7 days since illness onset), followed by another unit if the patient did not show any improvement after 24 h	More discharged patients (98.2 % vs. 78.7 %), shorter hospital stay (9.54 vs. 12.88 days), less requirement for intubation (7% vs. 20%) in the CP group than the control group	No adverse effect
Duan et al. 2020 [185]		10 severe COVID-19 patients (six males and four females) with a median age of 52.5 in comparison with a historic control group of 10 patients matched by age, gender, and severity of the diseases	Collected by apheresis using a Baxter CS 300 cell separator from 10 donor patients who recovered from COVID-19 at 3 weeks after illness and 4 days after discharge, two consecutively	One dose (200 mL) of CP at the median time of 16.d days from onset of illness in combination with antiviral, antibiotic or antifungal treatment, glucocorticoid therapy	Improved clinical symptoms and paraclinical criteria within 3 day after CP, varying degrees of absorption of lung lesions for all patients within 7 day, as compared to three	No SAEs or safety events, one patient showed an evanescent facial red spot.

			negative results of sputum SARS-CoV-2 by RT-PCR assay (1-day sampling interval) neutralization activity of >1:640		deaths, six cases in stabilized status, and one case in improvement in the control group ($p < 0.001$)	
Hegerova et al. 2020 [186]		20 patients (median age 60 years (range, 29-95) with severe or critical COVID-19 treated with CP under an expanded access protocol, as compared with 20 matched controls with regard to age, number of comorbidities, and severity of illness	Collected from 29- to 79-year old patients recovered from COVID-19 (symptom free) for >28 days without hospitalization, most showing anti–SARS-CoV-2 IgG	One unit of ABO-compatible CP was administered early at the median time of two days (IQR, 1-4.3) from hospitalization and additional therapies (e.g., azithromycin, hydroxychloroquine)	Improved laboratory and respiratory parameters in patients following CP infusion, similar to those in controls, but lower mortality (two vs. six deaths)	No adverse events
Liu et al. 2020 [187]		39 hospitalized patients (age 55 ± 13, male 25) with severe to life-threatening COVID-19 received CP transfusion in comparison with a cohort of retrospectively matched controls (n=156)	Collected by plasmapheresis from donors with anti-spike antibody titers ≥1:320 as measured by ELISA	Two units (250 mL each unit) of ABO-type matched was infused over 1 to 2 hours at the median time of 4 days after admission in addition to a variety of inpatient pharmacotherapies.	More likely improvements in supplemental oxygen requirements by post-transfusion day 14, improved survival, compared to control patients especially for non-intubated patients	No significant transfusion-related morbidity or mortality
Perotti et al.		46 moderate to severe	Collected using	24 patients received	Three patients out	Five serious

2020 [188]		COVID-19 patients (63±12 years old) with 19 (41%) having two or more comorbidities in comparison with a control cohort of 23 consecutive patients	Trima Accel blood collection device from eligible COVID-19 recovered subjects with 2 consecutive negative tests for SARS-CoV-2, followed by pathogen reduction, Neutralization titers≥1:80	one unit of plasma, 21 received two units and one patient received 3 units after having symptoms for two weeks with most having been treated with antibiotics, hydroxychloroquine and anticoagulants	of 46 (6.5%) died within 7 days (at 1, 4 and 6 days), lower than 30% in the control, and showed improved respiratory function (PaO_2 /FiO_2), chest radiogram, laboratory parameters (CRP, Ferritin, LDH, viral load), and weaning from mechanical Ventilation	adverse events occurred in 4 patients
Rasheed et al. 2020 [189]		49 early-stage (no more than three days in ICU) critically-ill COVID-19 patients randomized to receive CP or not (21 and 28 patients matched in terms of age, sex, comorbidities)	Collected from healthy donors younger than 50 years recovered from moderate COVID-19 and having IgG index ≥1.25 as measured by ELISA	400 mL of CP were transfused over 2 hours in addition to standard of care in the control group	CP treated patients showed reduced duration of infection in about 4 days and less death rate (1/21 versus 8/28) and high levels of SARS-CoV-2 IgG and IgM three days after CP transfusion compared to the control group	No adverse events except that one developed mild skin redness and itching lasted for 1 hour after CP resolved by anti-histamine injection

Roger et al. 2020 [190]		64 patients with symptom onset ≤ 10 days prior to admission and supplemental oxygen (but not invasive ventilation) within 48 h of hospitalization versus a matched control group of 177 patients for all cause in-hospital mortality and rate of hospital discharge at day 28	SARS-CoV-2 antibody content in CP was assessed retrospectively with 13% of the units below the cut-off for a positive antibody index	Three of 64 patients received one and the remainder received two units of CP at a median of 7 days (IQR 5 – 9) after symptom onset	No significant difference in the risk of in-hospital mortality overall rate of hospital discharge between the two groups except for a significantly increased hospital discharge rate among patients ≥65 years old	Two patients had TRALI reactions associated with the first unit of CP and one had TACO approximately 3 h after transfusion of the second units of CP
Salazar et al. 2020 [191]		136 severe and/or life-threatening COVID-19 patients treated with CP versus 215 propensity score-matched patients to assess the efficacy of CP transfusion compared to standard of care	Collected from the donors who had been asymptomatic for more than 14 days and negative SARS-CoV-2 RT-PCR test at the time of plasmapheresis. Anti-spike IgG antibody titers ≥ 1:1350 as measured by ELISA	Majority of patients received one and some patients reviewed two units of CP due to worsening COVID-19 conditions	Patients treated by CP with IgG titer≥ 1:1350 within 72 h of hospital admission had decreased mortality within 28 days	Reported in Joyner et al. 2020 [165]
Xia et al. 2020 [192]		1,568 severe or critical COVID-19 patients, most with comorbidities, among whom 1,430 patients	Not reported	200-1200 mL of CP were transfused at a median of 45 days of symptom onset (1 week to ≥8 weeks	Compared to that in the standard-treatment group reduced mortality rate (2.2 vs.	No significant differences in cardiac, liver, and renal functions

		(median age of 63, 50% male) only received standard treatment and 138 patients (median age of 65, 56% male) also received ABO-compatible CP		from symptom onset to CP therapy)	4.1%), lower admission to ICU (2.4% vs. 5.1%) improved respiratory symptoms of severe patients as evaluated by SCSS.	before and after CP therapy, except for the decrease in total bilirubin and three patients with minor allergic reactions (pruritus or erythema) during the transfusion
Xiao et al. 2020 [193]		18 patients with severe and critical COVID-19 divided into two groups with no significant differences in age, gender and basic clinical data: one with CP transfusion (n=6) and the other without CP transfusion (n=12)	Collected from donors between age 18-55 fully recovered from COVID-19 without symptoms for two weeks and ≥four weeks from symptom onset. Anti-SARS-CoV-2 IgG titers>1:160	200~500 mL (4~5 mL/kg body weight) of CP were transfused	No difference between the two groups of patients in terms of ventilator and ECMO weaning time, time for viral clearance, and hospitalization	
Zeng et al. 2020 [194]		21 critically ill patients with COVID-19 and respiratory failure: six patients (median age of 61.5, 5 male) in the CP group versus 15 patients (media age of 73, 11 male) in a	200–400 mL obtained from each young adult individual who had recovered from COVID-19 for 1–2 weeks and was negative at SARS-	A median volume of 300 mL CP was transfused at a median of 21.5 days after viral shedding was first detected	All CP treated patients tested negative for SARS-CoV-2 RNA within 3 days after infusion vs. 26.7% in the	No immediate or noticeable adverse effects

		control group with no significant differences in demographic and clinical features	CoV-2 RNA and immunoglobulin (Ig) M testing and positive at IgG testing before donation		control group , but five patients eventually died with a longer survival period, suggesting treatment should be initiated earlier.	
Gharbharan et al. 2020 [195]	RCT	86 hospitalized patients (median age of 63, 72% male) randomized at 1:1 for standard of care therapy with and without CP	Collected from donors confirmed with a RT-PCR SARS-CoV-2 infection and be asymptomatic for at least 14 days. Neutralizing antibodies titer ≥1:80 determined by a SARS-COV-2 plaque reduction neutralization test	One unit of 300 mL ABO=compatible CP was transfused on the day of inclusion followed with second plasma unit after five days for patients with persistent positive RT-PCR tests	There was no difference in day-60 mortality, hospital stay (p=0.68) or day-15 disease severity (p=0.58) between CP treated patients and patients on standard of care. The study was discontinued due to high neutralizing antibody titers at hospital admission in the majority of study population	No plasma related serious adverse events were observed
Li et al. 2020 [196]		103 patients (median age, 70 years; 60 [58.3%] male) with severe and life-	Collected based on routine plasma collection procedures via	ABO-compatible CP was transfused at approximately 4 to 13 mL/kg of	More clinical improvement occurred within 28 days in the CP	Two patients in the CP group experienced

		threatening COVID-19 randomized to receive CP in addition to standard treatment (n = 52) or standard treatment (antiviral medications, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications) alone (control) (n = 51)	plasmapheresis from 18-55 year-old adults suitable for blood donation, initially diagnosed with COVID-19 but with 2 negative PCR results from nasopharyngeal swabs (at least 24 h apart) prior to hospital discharge, discharged for ≥2 weeks from the hospital, and no persisting COVID-19 symptoms. CP S-RBD–specific IgG titer≥1:640 correlating to serum neutralisation titre of 1:80	recipient body weight and at approximately 10 mL for the first 15 minutes, which was then increased to approximately 100 mL per hour with close monitoring.	group than in the control group among those with severe disease (91.3% vs. 68.2% (p=0.03), not those with life-threatening disease (20.7% vs. 24.1%, p=0.83). A higher negative conversion rate of viral PCR at 72 hours in the CP group than in the control group (87.2% vs. 37.5%, p < 0.001).	adverse events within hours after transfusion that improved with supportive care.

CPR=C-Reactive Protein, CT=Computed tomography, ECMO=Extracorporeal membranous oxygenation, ICU=Intensive care unit, ELISA=Enzyme-linked immunosorbent assay, F_{iO2}=Fraction of inspired oxygen, IQR=Interquartile Range, LDH=Lactate Dehydrogenase, P_{aO2}=Partial pressure of oxygen, RCT=Randomized controlled trial, RT-PCR=Real time polymerase chain reaction, SAEs=Serious adverse events, SCSS=Six-Category Scale Score, TACO=Transfusion associated circulatory overload, TRALI=Transfusion-related acute lung injury, XLA=X-linked agammagloblulinemia

Quality Assessment of Clinical Studies

As indicated in Table 3, 24 clinical studies showed overall weak quality, six had moderate and one presented with strong quality. Patients often had underlying medical conditions (hypertension, diabetes). Case reports and series with limited number of patients were considered weak for selection of participants (high risk of selection bias). Some studies included only males with a total of three patients [187] or only pediatric patients with fewer than four children [141, 158], and therefore, were judged to be weak for sample selection. Studies that targeted a specific group (e.g., old population (median age > 60 years old) were rated moderate selection bias [192, 194-196]. While studies that selected patients with a broad range of ages, balanced gender and comorbidities [184, 191] were ranked as strong.

With respect to the study design, case reports and series were considered to be weak; case-controlled studies and RCTs were determined to be moderate and strong, respectively. The confounders for case reports and series studies were ranked weak given the uncontrolled nature of these studies involving other therapeutic treatments and supportive care, the use of other treatment regimens, including antiviral medications along with CP transfusion. Two different analytical methods were used to control for confounding in one case series study [167] subsequently determined to be of moderate risks for confounders. This component was ranked to be strong for RCTs and moderate for case-controlled studies except for one by Duan et al. 2020 [185] given the uncertain characteristics of participants selected into the intervention group and the use of an historical control group.

As CP treatment was not blinded to either outcome assessors or study patients in most studies the blinding component was judged to be weak except for the RCT by Li et al. 2020 [196] where the evaluation of clinical outcomes was performed by an investigator who was blind to the treatment.

If there was no detailed CP therapy in terms of CP collection, neutralizing antibody or anti SARS-CoV-2 IgG titers, timing and dose of the treatment, and valid measures of clinical outcomes the data collection methods of the study were deemed to be weak. Some case reports did not provide any information for CP donators and antibody titers as well as adverse events [137, 138].

There were no dropouts in the case reports and case series. One case series study where all patients were followed up for only 7 days [188] was ranked as moderate. In the RCT reported by Gharbharan et al. 2020 [195], all 86 patients had been followed for at least 15 days after inclusion, and 75 and 32 patients for at least 30 and 60 days, respectively.

Both RCTs were terminated prematurely due to the concerns over the potential benefit of CP in the study population with high neutralizing antibody titers (≥1:160) at baseline [195], and the lack of patients with COVID-19 to reach the planned recruitment target of 200 patients [196], resulting in underpowered study sample size.

Table 3. Quality assessment components and their rankings for clinical studies

	Patient selection	Study design	Confounders	Blinding	Data collection methods	Withdraws/dropouts	Overall
Al Helali et al. 2020 [136]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Anderson et al. 2020 [137]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Bao et al. 2020	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Cinar et al. 2020 [139]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Clark et al. 2020 [140]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Figlerowicz et al. 2020 [141]	Weak	Weak	Weak	Moderate	Moderate	Strong	Weak
Grisolia et al. 2020 [142]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Hahn et al. 2020 [143]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Hartman 2020 [144]	Weak	Weak	Moderate	Weak	Weak	Moderate	Weak
Im et al. 2020 [145]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Jafari et al. 2020 [146]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Jiang et al. 2020 [147]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Karataş et al. 2020 [148]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Kong et al.	Weak	Weak	Weak	Moderate	Moderate	Strong	Weak

2020 [150]							
Mira et al. 2020 [151]	Weak	Weak	Moderate	Weak	Moderate	Strong	Weak
Soleimani and Soleimani 2020 [153]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Xu et al. 2020 [154]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Zhang et al. 2020 [155]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Ahn et al. 2020 [156]	Weak	Weak	Weak	Weak	Strong	Strong	Weak
Abdullah et al. 2020 [157]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Bradfute et al. 2020 [127]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Diorio et al. 2020 [158]	Weak	Weak	Weak	Weak	Strong	Strong	Weak
Enzmann et al. 2020 [159]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Erkurt et al. 2020 [160]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Fung et al. 2020 [61]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Gemici et al. 2020 [161]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Hartman et al. 2020 [30]	Moderate	Weak	Weak	Weak	Weak	Strong	Weak
Ibrahim et al.	Moderate	Weak	Weak	Weak	Strong	Strong	Weak

2020 [162]							
Ilona et al. 2020 [163]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Jin et al. 2020 [164]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Joyner et al. 2020 [165]	Strong	Weak	Weak	Weak	Weak	Strong	Weak
Joyner et al. 2020 [166]	Strong	Weak	Weak	Weak	Moderate	Strong	Weak
Joyner et al. 2020 [167]	Strong	Weak	Moderate	Weak	Strong	Strong	Weak
Liu et al. 2020 [168]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Maor et al. 2020 [169]	Moderate	Weak	Weak	Weak	Strong	Strong	Weak
Naeem et al. 2020 [170]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Olivares-Gazca et al. 2020 [171]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Pal et al. 2020 [172]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Rahman et al. 2020 [173]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Salazar et al. 2020 [174]	Weak	Weak	Weak	Weak	Strong	Strong	Weak
Shen et al. 2020 [175]	Moderate	Weak	Weak	Weak	Strong	Strong	Weak
Tremblay et al. 2020 [190]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Wang et al. 2020 [178]	Weak	Weak	Weak	Weak	Strong	Strong	Weak

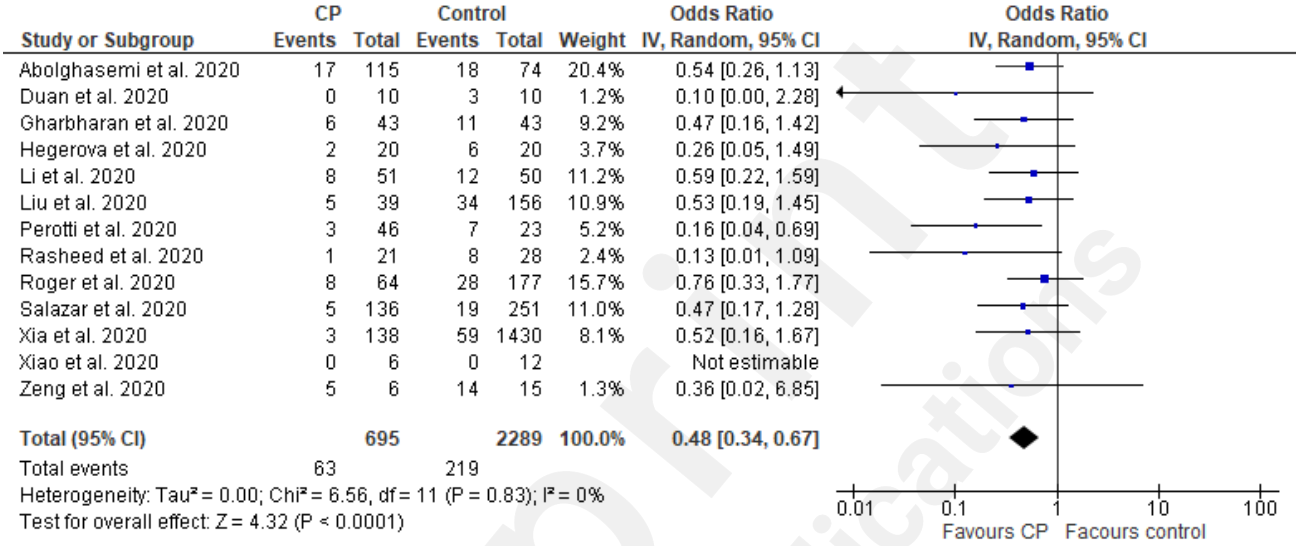
Wei et al. 2020 [177]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Wu et al. 2020 [179]	Moderate	Weak	Weak	Weak	Strong	Strong	Weak
Xi et al. 2020 [180]	Weak	Weak	Weak	Weak	Weak	Moderate	Weak
Ye et al. 2020 [181]	Moderate	Weak	Weak	Weak	Strong	Strong	Weak
Zhang et al. 2020 [182]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Zeng et al. 2020 [183]	Weak	Weak	Weak	Weak	Strong	Strong	Weak
Abolghasemi 2020 [184]	Strong	Moderate	Moderate	Weak	Strong	Strong	Moderate
Duan et al. 2020 [185]	Moderate	Moderate	Weak	Weak	Strong	Strong	Weak
Hegerova et al. 2020 [186]	Moderate	Moderate	Weak	Weak	Strong	Strong	Weak
Liu et al. 2020 [187]	Moderate	Moderate	Moderate	Moderate	Strong	Strong	Moderate
Perotti et al. 2020 [188]	Moderate	Moderate	Moderate	Weak	Strong	Moderate	Moderate
Rasheed et al. 2020 [189]	Moderate	Strong	Strong	Weak	Moderate	Strong	Moderate
Roger et al. [190]	Moderate	Moderate	Moderate	Weak	Strong	Strong	Moderate
Salazar et al. 2020 [191]	Strong	Moderate	Moderate	Weak	Strong	Strong	Moderate
Xia et al. 2020 [192]	Moderate	Moderate	Moderate	Weak	Moderate	Strong	Moderate

Xiao et al. 2020 [193]	Weak	Moderate	Moderate	Weak	Moderate	Strong	Weak
Zeng et al. 2020 [194]	Moderate	Moderate	Moderate	Weak	Moderate	Strong	Moderate
Gharbharan et al. 2020 [195]	Moderate	Strong	Strong	Weak	Strong	Strong	Moderate
Li et al. 2020 [297]	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong

Meta-analyses

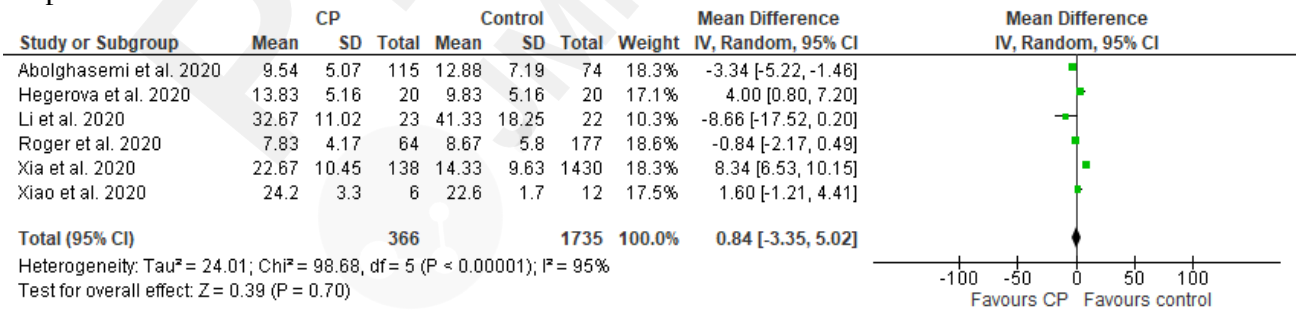
Figures 2-5 summarize the statistical analyses of pooled results from the controlled clinical studies addressing the efficacy of CP treatment for COVID-19. We found 13 controlled articles (two RCTs and 11 cohort studies) assessing mortality with a total of 695 and 2289 patients in the CP and control groups, respectively. CP reduced the mortality by half in COVID-19 (OR =0.48, 95% CI 0.34 to 0.67, I^2=0) as demonstrated in the Forrest plot (Figure 2).

Figure 2. Efficacy of convalescent plasma (CP) treatment on mortality in COVID-19 patients.



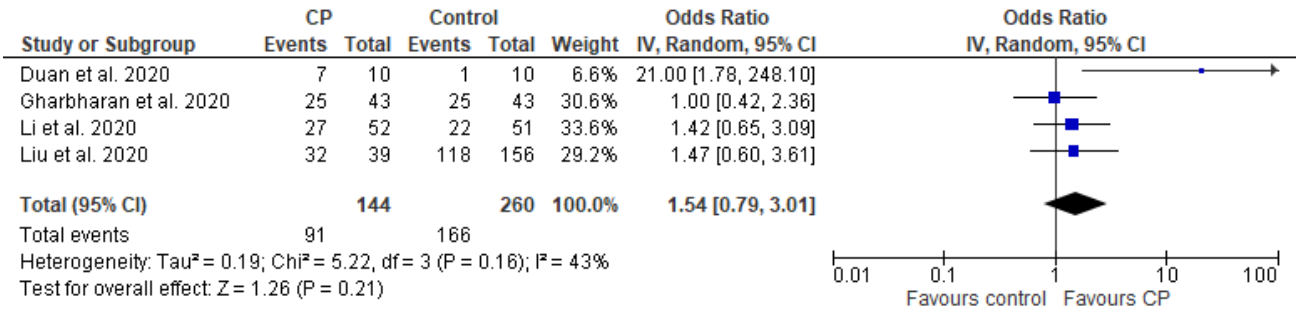
However, fewer studies were available to assess the effects of CP treatment on the length of hospital stay, clinical improvement and viral clearance. We identified only three studies (one RCT and two cohort studies) reporting the length of hospital stay with a total of 366 and 1735 patients in the CP and control groups, respectively (Figure 3). These studies had significant heterogeneity (p<0.001, I^2=95%) and when combined did not show any effects of CP treatment on the length of hospital stay (mean difference (MD)=0.84, 95% CI -3.35 to 5.02 days).

Figure 3. Efficacy of convalescent plasma (CP) treatment on length of hospital stay in COVID-19 patients.



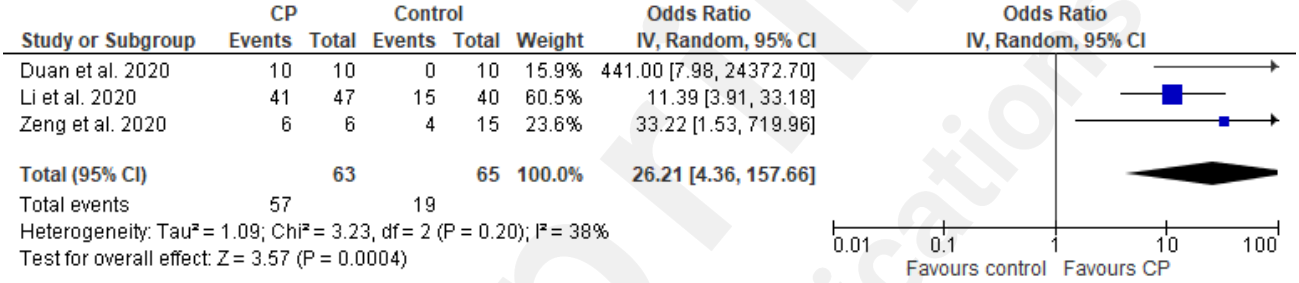
Similarly, four studies (two RCTs and two cohort studies) assessed the clinical improvement with the number of patients in both CP and control groups. As depicted in Figure 4, a larger portion of the patients in the CP group showed improved clinical status compared to that in the control, but the difference is not statistically significant (OR=1.54, 95% CI 0.79 to 3.01, I^2=43%).

Figure 4. Efficacy of convalescent plasma (CP) treatment on clinical improvement in COVID-19 patients.



Based on the three studies (one RCT and two cohort studies) with a total of 63 and 65 patients in the CP and control groups, respectively, we found that the use of CP increased the viral clearance significantly (OR=26.21, 95% CI 4.36 to 157.66, I^2=43%) as shown in Figure 5.

Figure 5. Efficacy of convalescent plasma (CP) treatment on viral clearance in COVID-19 patients.



Except for the high heterogeneity among the studies on assessing the length of hospital stay (I^2=0.98, p<0.001), the heterogeneity among the studies assessing the clinical improvement and viral clearance is mild (I^2=43%, p=0.16 and I^2=38%, p=0.20). Furthermore, since the included studies of the efficacy of CP treatment on mortality are homogenous (I^2=0, p=0.99), the overall effect on the mortality from the meta-analysis seems to be conclusive.

Discussion

Main Findings

This systematic review summarizes a variety of evidence on the use of CP for treatment of COVID-19. Though the focus of this review was to identify and assess the quality of clinical studies reporting CP treatment for COVID-19, the broad search strategy identified a large number of studies related to various aspects of CP use, highlighting tremendous research in this field. The data on this topic is being rapidly generated and reported. Most are commentary and review articles, and protocol/guidance descriptions, on the theme of CP treatments for COVID-19. The main findings according to each group of articles dealing with COVID-19 CP are: (1) clinical studies - overall, there are significant variations among the studies regarding the study design and population, the timing of initiation of CP transfusion, dosage and neutralizing antibody titer, and concomitant therapy. The quality of the current evidence on the use of CP for COVID-19 was low. However, there is a widespread belief that CP should be used given no other efficacious treatment is currently available; (2) Commentary articles - this category mainly consists of commentary and letter to the Editor in addition to a few editorials and perspectives that collectively support the use of CP for COVID-19 and suggested further clinical trials; (3) Review - the volume and the pace of the clinical trials launched to evaluate the safety and efficacy of CP against COVID-19 reflects the need for high-quality evidence for the therapy to be practiced by clinicians; (4) Protocol/guideline - this category of literature showed the importance for establishment of CP production and storage, transfusion program in a public

health care network as well as decision-making framework; and the requirements applicable to plasma donors and the standards for preparation, qualification, storage, distribution and control of use of the product; (5) In vitro testing of CP - a variety of tests have been developed to measure the levels of CP antibodies. Generally, two methods have been most used to determine antibody titers of CP: ELISA for IgG, IgM and neutralization assay for neutralizing antibodies. ELISA-based antibody titers can correlate well with neutralizing titers. Certain ELISA testing may be an alternative for more demanding neutralization assay based on live viral infected cells. It can provide quantitative measurements of antibody titers in hours and be performed at biosafety level 2 laboratory given the recombinant nature of the selected antigens (and therefore can be carried out more widely than the neutralization assay for measuring virus neutralizing activity of CP, which involves a lengthy process (several days) and needs to be performed within a biosafety level 3 laboratory). Other assay tools such as a cell-free neutralization PCR assay that can yield results within 2-3 h may be also readily deployable in standard laboratories with biosafety level 2 capability [115].

Our meta-analysis of controlled studies showed significant reduction in mortality by CP therapy in comparison to controls. Similar meta-analysis of the efficacy of CP therapy on different types of infectious disease found 44% reduction in the mortality in COVID-19 patients (OR=0.44, 95% CI 0.25 to 0.77, I^2=0) [94], and 25% reduction in other severe acute respiratory infections (OR, 0.25; 95% CI, 0.14–0.45; I^2=0%) [43], and 32% reduction in SARS coronavirus infection, severe influenza, and Ebola infection (OR = 0.32; 95% CI 0.19–0.52; I2 = 54%) [255]. In contrast, the meta-analysis from four RCTs on CP treatment for influenza infection (n=572) showed no convincing effects on deaths (RR=0.94, 95% CI 0.49 to 1.81) [93].

Another recent systematic review of one RCT and three controlled non-randomised studies of CP therapy in COVID-19 patients reported about a potential reduction in mortality, time to death, improvement of clinical symptoms, but was unable to provide any opinion regarding the efficacy of CP treatment for COVID-19 due to paucity in quantitative synthesis [42].

Our meta-analysis showed no effect of CP on the length of hospital stay (mean difference (MD)= 0.84, 95% CI -3.35 to 5.02 days), which is consistent with another meta-analysis of three RCTs for the effect of CP on the length of hospitalization (MD=–1.62, 95% CI –3.82 to 0.58 days), in other severe respiratory viral infections, as reported by Devasenapathy et al. 2020 [93]. Other systematic reviewers reported mixed results of both reduced length of hospital stay and no effects on the length of hospitalization in SARS coronavirus infection, severe influenza, and Ebola infection [255], suggesting that the effectiveness of CP in reducing hospital length of stay might be dependent on early administration of the therapy, and its use as prophylaxis is more likely to be beneficial than treating severe disease [43]. However, the optimal timing and dosage of CP therapy remains to be defined.

The insignificant effect of CP on the improvements of clinical conditions COVID-19 symptoms is comparable to another systematic review and meta-analysis of five studies with a total of 259 COVID-19 patients, showing more clinically improved patients treated with CP than no CP treatment, but not statistically significant (OR=2.06, 95% CI 0.8 to 4.9, I^2=44%;) [94]. In contrast, the meta-analysis of nine controlled and uncontrolled studies showed improved clinical

status of COVID-19 patients, when compared to baseline (ROM=0.53, 95% CI 0.36 to 0.79, p<0.01, n=149) [88].

The significant increase in the viral clearance is also consistent with the other meta-analysis of two studies with a total of 144 patients, suggesting that the use of CP helps in viral clearance (OR=11.29, 95% CI 4.9 to 25.9, I^2=0%) significantly [94] as well with the meta-analysis of nine controlled and uncontrolled studies showing reduced viral loads (RR=0.13, 95% CI 0.09 to 0.18, p<0.001, n = 75) [88].

Overall, clinical studies and systematic reviews have confirmed that CP caused few or no serious adverse events with low-quality evidence.

Various tools have been developed for quality assessment involving slightly different components and ranking criteria [304]. We used the EPHPP tool as it can be used for all types of clinical studies. This is a generic tool used to evaluate a variety of intervention study designs such as RCTs, before-and-after and case–control studies [67]. A study has shown differences in quality assessment for RCTs between the EPHPP and the Cochrane Collaboration Risk of Bias tool [305].

In consistent with other reviews, our quality appraisal showed that the present studies on the efficacy of CP are generally of low quality, although there are certain agreements and discrepancies between our assessment and others on the overall quality of case and randomized controlled studies on the use of CP for COVID-19 as different assessment tools have been used. Only one high-quality (low risk of bias in the underlying study results) RCT by Li et al. 2020 [196] was identified in our assessment using the EPHPP tool, which is in agreement with the assessment in the systematic review by Sarkar et al. 2020 [94], but was rated to be unclear in another systematic review by Piechotta et al. 2020 [42] even both reviews used the same Cochrane risk-of-bias tool (RoB 2.0) for the RCT.

The overall quality of the case-controlled studies in our assessment lies in between the risk of bias assessed by other two systematic reviews conducted by Piechotta et al. 2020 [42] and Sarkar et al. 2020 [94]. Specifically, the study by Duan et al. 2020 was considered weak in our quality assessment, but was critical as assessed by Piechotta et al. 2020 [42] and moderate risk of bias by Sarkar et al. 2020 [94] in their respective reviews. The case-controlled study reported by Liu et al. 2020 [187] was of moderate quality in our assessment, but was critical and low risk of bias as assessed by Piechotta et al. 2020 [42] and Sarkar et al. 2020 [94], respectively using the same Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I). The case-controlled study reported by Zeng et al. 2020 [194] was moderate in our assessment in agreement with that in the systematic review by Sarkar et al. 2020 [94], but was rated to be critical risk of bias in the systematic review by Piechotta et al. 2020 [42].

In addition to controlled and randomized studies, EPHPP could be used to assess the quality of case reports and series studies [67]. The overall quality of all case reports and series were weak based on our assessment.

Most literature assessing the use of CP in COVID-19 focuses on the treatment in severe and life-threatening patients. A key recommendation is early use before patients become critically ill, prevention use, but no reports were found. Furthermore, the success of this intervention likely increases with the CP antibody titer. It is, therefore, important to select convalescent donors with the highest antibody titers. A known antibody titer that correlates with protection would also be extremely beneficial for vaccine development [306].

Large-scale controlled studies that include a myriad of COVID-19 patients along the continuum of disease severity will help to understand if CP treatment earlier in the course of disease can prevent clinical deterioration and improve survival rates. Surrogate inflammatory and cardiovascular markers that correlate with meaningful clinical outcomes such as ICU admission and mortality rates may also help in deciding the most appropriate timing of CP transfusion [88].
The historical and current data on the use of CP suggest it is safe in coronavirus infection, and benefits of its use in those at high risk or with early disease, particularly in elderly and vulnerable persons outweigh the risks.
In light of the promising evidence from existing clinical data, there is a clear need for randomized controlled trials on large patient numbers to evaluate the efficacy of the CP therapy. Apart from sample size and the non-comparative, non-randomized study design, numerous limitations hamper the interpretation of the aforementioned studies, such as the superimposition of effects mediated by other antiviral treatments, antibiotics, and glucocorticoids administered concomitantly with CP. As a whole, these studies indicate that patients receiving transfusions earlier than 14 days post infection may benefit from CP treatment [269, 270].

Strengths and Limitations

There are two systematic reviews and meta-analysis to appraise the literature on the CP therapy for COVID-19 patients. However, this review covers the latest literature as of the date of our manuscript submission, and provides insights about various aspects for the subject on the use of CP for COVID-19 that needs further investigation. The primary limitation of this review is that most data identified are non-randomized, and therefore, confounding is highly inevitable. Furthermore, study populations, interventions and measured outcomes have important clinical and methodological heterogeneity, which reflects an overall low to moderate quality of evidence identified by the appropriate quality assessment tool.
We selected the EPHPP tool which allows for the quality assessment of all clinical studies including case reports and series instead of specific tools for non-randomized and randomized trials as recommended by the Cochrane Collaboration.

Future Directions

We summarized various aspects of the evidence on the use of CP in COVID-19 patients. However, important gaps in knowledge remain. Notably, the following areas require further investigation:
Well-designed prospective observational studies, preferentially RCTs, with well-defined characteristics for both CP donors and recipients are warranted to answer questions concerning the effects on mortality or other important clinical outcomes, such as improvement in symptoms and respiratory status. Placebo or control should include standard-of-care and/or normal fresh frozen plasma. The plasma exchange has shown therapeutic effects for severe COVID-19 acute respiratory distress syndrome with multiple organ failure [307].
In practice, COVID-19 CP can be used for either prophylaxis of infection or treatment of disease. In a prophylactic mode, the benefit of CP administration is that it can prevent infection and

subsequent disease in those who are at high risk for disease, such as vulnerable individuals with underlying medical conditions, health care providers, and those with exposure to confirmed cases of COVID-19. Passive antibody administration to prevent infectious diseases is already used in clinical practice [308], but only studied in an *in vivo* animal model for COVID-19 [309].
Studies suggest that CP cannot alter the clinical course of illness in patients who are already critically ill and that it would be more effective if given to patients who are not yet severely ill but are at risk for worsening of clinical disease. Selecting such patients requires a biomarker or predictor of disease severity.
In vitro testing showed variable/diverse neutralizing antibody titers among individual donors, suggesting that an adequate pooling strategy of plasma units from different donors could reduce the variability of neutralizing antibody titers of CP and compensate deviations of individual antibody titers [118]. Clinical studies of safety and efficacy of pooled CP should be conducted.

On the other hand, anti SARS-CoV-2 therapeutic synthetic monoclonal and polyclonal antibodies or antibodies extracted from CP showed more potency in in vitro neutralization assays than the average of CP [37, 246, 310]. Monoclonal antibodies with high levels of neutralizing antiviral activity are urgently needed during this COVID-19 pandemic to be more specific and virus targeted for both therapy and prevention [273]. A combination of monoclonal antibodies derived from convalescent human B cell hybridomas against multiple immunogenic targets of SARS-CoV-2 spike protein might be a better therapeutic option than single target monoclonal antibodies [225].
The COVID-19 pandemic has dramatically reduced the national ability to provide blood products for medical care in an emergency [311], which further highlights the need to secure a stockpile of blood products with long shelf-lives (e.g., freeze-dried plasma) to be self-sufficient in a national crisis. Current CP protocols specify that once thawed, CP may be stored for up to 5 days at 4°C, similar to that for fresh frozen plasma. A recent study has demonstrated long-term stability of anti-SARS-CoV-2 spike antibodies in donor CP for 42 days when stored under refrigerated conditions [77]. There will be a need to stockpile freeze-dried CP for future waves of the pandemic for several years. Additionally, global concern over the potential for "second" or "third" waves of infection to occur before effective vaccines or drug therapies are available has many looking at other biological sources for large-scale production of neutralizing SARS-CoV-2 antibodies.
In collaboration with Canadian Blood Services, our group is currently investigating *in vitro* hemostasis, inflammatory mediators and COVID-19 antibody activities in freeze-dried CP. Specifically, we aim to demonstrate that COVID-19 convalescent freeze-dried plasma (C-FDP), maintains *in-vitro* anti-SARS-CoV-2 neutralizing antibody titers and activity, using specialized serological assays to detect antiviral immunoglobulins specific for the nucleocapsid protein from SARS-CoV Rp3. As this is a pooled plasma product of 10 donors, we also hypothesize that C-FDP will have higher anti-SARS-CoV-2 neutralizing Ab titers and activity than single donor CP. As well, this product may be administered in hypertonic solution, for those patients who cannot tolerate large volume CP transfusions, such as 500 mL The proposed studies will also demonstrate the capacity of C-FDP to modulate the cellular and humoral immune and inflammatory responses ex vivo.
In addition to further study of passive immunotherapy, it is important to gain more knowledge about the detailed pathogenesis of SARS-CoV-2, its interplay with the immune system, and viral-mediated responses which are crucial to identify efficient preventive and therapeutic approaches.

A systemic approach and further research seem essential to develop overarching treatment guidelines for COVID-19 [312].

Conclusions

There is still limited evidence but massively accumulating interest in the CP treatment for COVID-19. The theoretical reasons for the likely efficacy of passive immunization, the urgent need felt by clinicians around the world for effective treatment options for COVID-19 and the promising results offered mainly by retrospective clinical studies must be balanced against the lack of efficacy in the RCTs of CP and hyperimmune globulin therapy in severe influenza and COVID-19.

CP may be of greatest benefit for patients who are early in their illness and have not yet generated endogenous antibodies, and when the infused CP has a high antibody titer. Recurring observations suggested that treatment with CP within four to five days of symptom onset might be more effective than later treatment.

Our systematic review and analysis emphasize the low quality of clinical studies. These studies would provide important lessons that should inform the planning of adequately powered and properly designed RCTs to evaluate the promise of CP therapy in COVID-19 patients.

Future research is necessary to fill the obvious knowledge gaps regarding treatment of COVID-19 patients with CP. In brief, we offered recommendations around the need for a large scale properly designed RCT, the potential prophylactic use of CP, selection criteria for both CP donors and recipients, development of antibodies with higher potency than CP, and freeze-dried CP as a long-term strategy against the pandemic.

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Conflicts of Interest

The authors have no conflicts to declare.

Abbreviations

ACE2=Angiotensin Converting Enzyme 2, ARDS=Acute Respiratory Distress Syndrome, AUC=Area under the Curve, CDC=Centers for Disease Control and Prevention, CLIA=Chemiluminescent Immunoassay, CP=Convalescent Plasma, CPR=C-Reactive Protein, CT=Computed tomography, ECMO=Extracorporeal membranous oxygenation, ELISA=Enzyme-Linked Immunosorbent Assay, FiO_2=Fraction of inspired Oxygen, HLA=Human Leucocyte Antigen, ICU=Intensive Care Unit, IQR=Interquartile Range, LDH=Lactate Dehydrogenase, LFA=Lateral Flow Assay, MERS=Middle Eastern Respiratory Syndrome, NP=Nucleocapsid Protein, PaO_2=Partial pressure of Oxygen, PCR=Polymerase Chain Reaction, RBD=Receptor Binding Domain, RCT=Randomized Controlled Trial, RT-PCR=Real Time Polymerase Chain Reaction, SARS=Severe Acute Respiratory Syndrome, SAEs=Serious Adverse Events, SCSS=Six-Category Scale Score, SP=Spike Protein, S-RBD=Spike protein Receptor-Binding Domain, TACO=Transfusion Associated Circulatory Overload, TRALI=Transfusion-Related Acute Lung Injury, UVA=Ultraviolet A, VN=Virus Neutralization, XLA=X-linked agammagloblulinemia

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