The Emerging Role of Convalescent Plasma in the Treatment of COVID-19

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Abstract

Various agents are currently under evaluation as potential treatments in the fight against coronavirus disease 2019 (COVID-19). Plasma from patients that have overcome COVID-19 infection, referred to as convalescent plasma, is a treatment option with considerable background in viral diseases such as Spanish influenza, H1N1, Ebola, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS). Although convalescent plasma has historically proven beneficial in the treatment of some viral diseases, its use is still explorative in the context of COVID-19. To date, preliminary evidence from case series is favorable and ongoing randomized controlled trials of clinical, biochemical improvement and hospital discharge have been reported. A detailed overview of randomized as well non-randomized trials of treatment with convalescent plasma, which have been registered worldwide, is provided in this review. Based on these studies, data from thousands of patients is anticipated in the near future. Convalescent plasma seems to be a safe option, but potential risks such as transfusion-related acute lung injury and antibody-dependent enhancement are discussed. Authorities including the Food and Drug Administration (FDA), and scientific associations such as the International Society of Blood Transfusion (ISBT) and the European Blood Alliance (EBA), have provided guidance into the selection criteria for donors and recipients. A debatable, pivotal issue pertains to the optimal timing of convalescent plasma transfusion. This treatment should be administered as early as possible to maximize efficacy, but at the same time be reserved for severe cases. Emerging risk stratification algorithms integrating clinical and biochemical markers to trace the cases at risk of significant deterioration can prove valuable in this direction.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia was first noted in Wuhan (China) in December 2019 and the disease induced by the virus has been termed coronavirus infectious disease 2019 (COVID-19). To date, various treatment regimens are being evaluated as potential tools in COVID-19 in addition to the standard supportive care including oxygen supply, intensive care admission, or even extracorporeal membrane oxygenation for critically ill patients. Among agents, antiviral drugs such as remdesivir, lopinavir/ritonavir, the antimalarial agent hydroxychloroquine in combination with azithromycin, and monoclonal antibodies, such as the anti-interleukin-6 receptor tocilizumab, are currently under evaluation for treatment of COVID-19.

Plasma from patients that have overcome COVID-19 infection, namely convalescent plasma, is a treatment with considerable historical background in other diseases, but still explorative in the context of SARS-CoV-2. In a pandemic, convalescent plasma could provide an easily accessible source of antiviral antibodies. Indeed, fresh frozen plasma (FFP) is an established treatment in various epidemics. The present article summarizes available evidence about convalescent plasma in COVID-19, registered trials, and guidance from authorities, providing a critical overview of published studies and perspectives.

Historical evidence for convalescent plasma in other epidemics

In recent history, convalescent plasma has been successfully used in viral outbreaks and epidemics. In as early as the 1918–1925 Spanish influenza pandemic, studies evaluated convalescent blood products to treat pneumonia due to Spanish influenza in
Convalescent plasma in COVID-19 disease: emerging evidence from published studies

Table 1 presents the results of published studies that have evaluated transfusion of convalescent plasma in COVID-19 patients.20–26 Shen et al.20 first presented the experience on critically ill patients in Shenzhen (China). All patients received a single dose of 400mL convalescent plasma from donors with neutralizing antibody titer ranging between 1:80 and 1:480. After the transfusion, the titers of anti-SARS-CoV-2 IgG and IgM in recipients increased in a time-dependent manner. Three patients were discharged, whereas the remaining 2 remained hospitalized until the end of the study, with improvement in body temperature and clinical and biochemical indices. Notably, convalescent plasma was administered relatively late during the disease in all patients, namely between days 19 and 22 of hospitalization, except for 1 patient who received the treatment on day 10.20 All patients at the time of convalescent plasma administration had detectable IgM and IgG antibodies and neutralizing antibodies titer ranging from 1:40 to 1:160. All titers of antibodies increased in a time-dependent manner after transfusion.

Zhang et al.21 adopted a richer regimen of convalescent plasma transfusions in their series of four COVID-19 patients in Guangdong (China), with total volumes administered ranging between 200 and 2400mL. All patients in severe condition received convalescent plasma after day 12 of hospitalization. Very positive outcomes were reported, as three of 4 patients were discharged from the hospital, whereas the remaining one was finally PCR negative for the virus and was transferred to an unfenced intensive care unit. Two cases produced anti-SARS-CoV-2 IgG approximately 14 days after transfusion.21

The largest series published up to date is the one by Duan et al.22 encompassing 10 COVID-19 patients in China, administering convalescent plasma with neutralizing antibody titers above 1:640. Among them, those who received the transfusion relatively early during the disease (days 10 and 11 from initiation of symptoms) showed a rapid increase in lymphocyte counts, decrease in serum CRP levels, and a notable remission of lung lesions in CT. The neutralizing antibody titers of 5 patients increased rapidly up to 1:640, whereas 4 patients remained at the same high level (1:640) after transfusion. Overall, the results were excellent, as no deaths were noted, 3 patients were discharged, and the remaining 7 were ready for discharge; this is in contrast to a historical control group presented by the study authors, where a death rate of 30% was noted. No serious adverse effects were documented following transfusion of convalescent plasma; only a minor effect was reported by a patient, namely an evanescent facial palsy.22

The study by Ye et al.23 in Wuhan (China) encompassed 6 patients and examined the transfusion of convalescent plasma in a spectrum of clinical scenarios, including persistent SARS-CoV-2 detection, consolidation or extensive lesions in chest CT, comorbidity with Sjögren syndrome and post-discharge positivity to SARS-CoV-2; improvement and promising results were noted in all cases. Similarly, Zhang et al.24 reported improvement in a patient from Nanjing (China) receiving convalescent plasma. Ahn et al.25 provided the first report on 2 cases from Korea, where the administration of convalescent plasma was linked to beneficial effects, namely successful weaning from mechanical ventilator in one patient and hospital discharge in the other patient. On the other hand, the study by Zeng et al.26 from Zhengzhou (China), published in late April, 2020, highlighted the limitations of the new treatment; administration of convalescent plasma in critical, end-stage respiratory failure, at a late stage during the course of the disease (median: 21.5 days after first detection) was associated with suppression of viral shedding but ultimately death in 5 out of 6 examined cases.26

In line with the published case series concerning the optimal timing of convalescent plasma administration, a recent review by
Table 1

Studies and Main Findings of Published Studies Examining Convalescent Plasma in COVID-19 Patients.

| First author (year) | Patient | Clinical condition at transfusion | Other treatments | Transfusion features | Outcome |
|---------------------|---------|----------------------------------|------------------|---------------------|---------|
| Ahn (2020) – patient 1 | M, 71 | Severe ARDS | Lopinavir/ritonavir, hydroxychloroquine and empirical antibiotics, methylprednisolone | Hoop day 9 5000 mL divided into two doses and administered to the patient at 12 hours interval. Anti-SARS-CoV-2 IgG antibody measured by ELISA (OD ratio for IgG = 0.586 vs. a cut-off value 0.22) | No adverse reaction; fever subsided; oxygen demand decreased; condition much improved with decreased CRP and IL-6 to normal range. Further resolution of lung infiltrates on chest X-ray; SARS-CoV-2 was negative after day 26. Patient successfully weaned from mechanical ventilator. |
| Ahn (2020) – patient 2 | F, 67 | Severe ARDS | Lopinavir/ritonavir, hydroxychloroquine and empirical antibiotics, methylprednisolone | Symptom day 6 (500 mL divided into two doses and administered to the patient at 12 hours interval). Anti-SARS-CoV-2 IgG antibody measured by ELISA (OD ratio for IgG = 0.532) | No adverse reaction. Leukocytosis and lymphopenia immediately recovered; three days later bilateral infiltration on chest X-ray much improved. CRP and IL-6 also recovered to normal. SARS-CoV-2 was negative after day 20. Patient successfully extubated and discharged from hospital on day 24. |
| Duan (2020) – patient 1 | M, 46 | Severe | Arbidol, ribavirin, cefoperazone | Symptom day 11 (200 mL) | Pooled reporting |
| Duan (2020) – patient 2 | F, 34 | Severe, clustering infection | Arbidol, cefoperazone | Symptom day 11 (200 mL) | An exanevergent red spot as a non-serious adverse effect; pooled reporting |
| Duan (2020) – patient 3 | M, 42 | Severe, clustering infection | Arbidol, moxifloxacin, methylprednisolone | Symptom day 19 (200 mL) | Pooled reporting |
| Duan (2020) – patient 4 | F, 55 | Severe | Ribavirin, lоперидол, имипемил-слилатон, метилпреднизолон | Symptom day 19 (200 mL) | Pooled reporting |
| Duan (2020) – patient 5 | M, 57 | Severe | Arbidol, remdesivir, IFN-α, moxifloxacin, cefoperazone/tazobactam, methylprednisolone | Symptom day 14 (200 mL) | Pooled reporting |
| Duan (2020) – patient 6 | F, 78 | Severe, clustering infection | Arbidol, cefoperazone, levofloxacin, methylprednisolone | Symptom day 17 (200 mL) | Pooled reporting |
| Duan (2020) – patient 7 | M, 56 | Severe | Arbidol, cefoperazone/ tazobactam, fluconazole, methylprednisolone | Symptom day 16 (200 mL) | Pooled reporting |
| Duan (2020) – patient 8 | M, 67 | Severe | Arbidol, ribavirin, arbidol, darunavir | Symptom day 20 (200 mL) | Pooled reporting |
| Duan (2020) – patient 10 | M, 50 | Severe | Arbidol, IFN-α, cefoperazone, caspofungin, methylprednisolone | Symptom day 20 (200 mL) | Pooled reporting |
| Shen (2020) – patient 1 | M, 70s | Critical - Bacterial pneumonia; severe ARDS; MODS | Methylprednisolone, Lop/rit, IFNα-1b, favipiravir | Hoop day 22, 400 mL, 1:240 neutralizing | Remained hospitalized and intubated till case report (day 37 of hospitalization); Improvement in body temperature, SOFA score, viral load, CRP, procortin and IL-6 |
| Shen (2020) – patient 2 | M, 60s | Critical - Bacterial pneumonia; fungal pneumonia; severe ARDS; myocardial damage | Methylprednisolone, Lop/rit, arbidol, darunavir | Hoop day 10, 400 mL, 1:80 neutralizing | Remained hospitalized and intubated till case report (day 37 of hospitalization); Improvement in body temperature, SOFA score, viral load, CRP, procortin and IL-6 |
| Shen (2020) – patient 3 | F, 50s | Critical – Severe ARDS | Methylprednisolone, Lop/rit, IFNα-1b, favipiravir | Hoop day 20, 400 mL, 1:120 neutralizing | Discharged home, after clinical and biochemical marker improvement |
| Shen (2020) – patient 4 | F, 30s | Critical – Severe ARDS | Methylprednisolone, IFNα-1b, favipiravir | Hoop day 19, 400 mL, 1:240 neutralizing | Discharged home, after clinical and biochemical marker improvement |
| Shen (2020) – patient 5 | M, 60s | Critical – Severe ARDS | Methylprednisolone, Lop/rit, IFNα-1b | Hoop day 20, 400 mL, 1:480 neutralizing | Discharged home, after clinical and biochemical marker improvement |
| Ye (2020) – patient 1 | M, 69 | Persistent positive results for SARS-CoV-2 | Levofoxacin at disease onset | Symptom days 33, 36 and 39 (3 cycles) | Resolution of GGOs in chest CT 4 days after transfusion; negative tests for SARS-CoV-2 10 days after transfusion; discharged from hospital |
| Ye (2020) – patient 2 | F, 75 | Consolidation lesions in chest CT | Not reported | Symptom days 33 and 37 (2 cycles) | Symptom and radiologic improvement (consolidation turned to scattered GGOs) and two-fold increase in anti-SARS-CoV-2 IgM and IgG titers; negative SARS-CoV-2 tests |
| Ye (2020) – patient 3 | M, 56 | Respiratory distress | Not reported | Symptom days 33, 34 and 37 (3 cycles) | Symptom improvement, serum anti-SARS-CoV-2 IgM and IgG titers increased and resolution of lesions in chest CT; patient discharged from hospital |
| Ye (2020) – patient 4 | F, 63 | GGOs in chest CT, comorbidity with Sjögren syndrome | Levofoxacin at disease onset, arbidol | Symptom day 40 (1 cycle) | Density of GGOs reduced, negative SARS-CoV-2 test, discharged from hospital |

(continued)
Table 1 (continued).

| First author (year) | Patient gender, age | Clinical condition at transfusion | Other treatments | Transfusion features | Outcome |
|---------------------|---------------------|----------------------------------|------------------|---------------------|---------|
| Ye (2020) – patient 5 | F, 28               | Post-discharge SARS-CoV-2- positive COVID-19 patient | Not reported     | Symptom day 33 (1 cycle) | After transfusion, several consecutive SARS-CoV-2 tests negative, discharged from hospital |
| Ye (2020) – patient 6 | M, 57               | GGOs in chest CT, having turned negative in the SARS-CoV-2 test but with respiratory distress | Not reported     | Symptom day 60 (1 cycle) | Symptom relief and GGO resolution, discharged from hospital |
| Zeng (2020) | Five males, one female; median age: 61.5, IQR: 31.5–77.8 | Critical, end-stage respiratory failure in ICU, high flow nasal cannula oxygen therapy, mechanical ventilation (5/6), ECMO (4/6), CRRT (3/6) | Antibiotics, antiviral therapy (4/9), traditional Chinese medicine (3/6), intravenous immunoglobulin (5/6), glucocorticoids (4/9) | Median of 21.5 days after first detection of viral shedding; median volume of plasma infused: 300 mL | No adverse effects; all patients tested negative for SARS-CoV-2 RNA by 3 days after transfusion, but 5 died eventually |
| Zhang B (2020) – patient 1 | F, 69               | Intubated in ICU, ARDS, septic shock, pneumomothagia | Arbidol, lop/rit, IFNa-1b, human albumin, zadavin and immunoglobulin, antibacterial and antifungal drugs | Three transfusions: Hosp day 18 (200 mL), Hosp day 29 (400 mL), Hosp day 30 (300 mL) | Exubrated on hosp day 32, PCR (-) on hosp day 40 and discharged on hosp day 44 |
| Zhang B (2020) – patient 2 | M, 55               | ARDS, in non-invasive mechanical ventilation and high-flow nasal cannula | Arbidol, lop/rit, ifnalpha, ribavirin, IFNa-1b | Hosp day 12 (200 mL) | PCR (-) on hosp day 16, discharged on hosp day 19 |
| Zhang B (2020) – patient 3 | M, 73               | ARDS, CRRT multiple organ failure, septic shock, veno-venous ECMO | Lop/rit, ribavirin, imipeniem, vancomycin | A total of 2400 mL in 8 transfusions from hosp day 15 to hosp day 41 | PCR (-) on hosp day 44, transferred to uninfected ICU on hosp day 51 |
| Zhang B (2020) – patient 4 | F, 31               | Cesarean section (but newborn dead of endotumoral asphyxia) on day 1 due to ARDS, multiple organ dysfunction syndrome and septic shock, CRRT on day 2, veno-venous ECMO on day 6 | Lop/rit, ribavirin, imipeniem, vancomycin | Hosp day 19 (300 mL) | CRRT and ECMO removed on hosp day 27, PCR (-) and exubration on hosp day 40, discharged on hosp day 46 |
| Zhang L (2020) – one patient | F, 64               | ICU, invasive mechanical ventilation | Not reported | Hosp day 17 (200 mL), anti-SARS-CoV-2 lgM levels OD ratio = 1.22 and lgG levels OD ratio = 6.59 | No adverse event; no change in blood examinations and lymphopenia; however, the patient did not require mechanical ventilation 11 days after plasma transfusion and was transferred to a general ward. |

*Postulated reporting. In the study by Duan et al, patients 1, 2, and 9 (transfusion before day 14 of symptoms) showed a rapid increase of lymphocyte counts and a decrease of CRP, with remarkable absorption of lung lesions in CT. The neutralizing antibody titers of five patients increased rapidly up to 1:640, whereas four patients remained at the same high level (1:640) after transfusion. No deaths were noted among 10 examined patients; three patients were discharged and the remaining seven were ready for discharge. ARDS = acute respiratory distress syndrome; CRP = C-reactive protein; CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; ELSA = enzyme-linked immunosorbent assay; GGOs = ground glass opacities; Hosp = hospitalization; IFN = interferon; IL = interleukin; IQR = interquartile range; Lop/rit = lopinavir/ritonavir; OD = optical density; SOPA = Sequential Organ Failure Assessment.

Tiberghien et al has presented a strategy of administration for high-risk patients (older than age 70) dependent on oxygen with a baseline oxygen saturation <94%). According to preliminary remarks by the aforementioned research team, early treatment with convalescent plasma (not later than day 5) is preferred before seroconversion for SARS-CoV-2, which may occur on days 6 to 12. A regimen proposed by Tiberghien et al is the slow transfusion of two plasma units, under careful monitoring, for patients whose weight is within the 50 to 80 kg range. The volume is adjusted according to weight, whereas a second infusion of 2 additional units 1 or 2 days later can also be considered. The need for early administration is in line with observations in other diseases, such as pneumococcal pneumonia, where no benefit is noted if the antibody is administered after day 3 of the disease.

In light of the promising evidence from case series presented above, there is a clear need for randomized controlled trials on large patient numbers to evaluate the efficacy of the process. 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 convalescent plasma. As a whole, these studies indicate that patients receiving transfusions earlier than 14 days post infection may benefit from convalescent plasma treatment.

**Mechanism of actions**

Convalescent plasma may offer various beneficial actions in COVID-19 disease (Fig. 1). First and foremost, the apparent mechanism pertains to the fact that antibodies from convalescent plasma can suppress viremia. Similar to the strategies implemented in the SARS epidemic, theoretically the administration of convalescent plasma at the early stage of the disease would be more effective. Viremia peak is noted in the first week of infection in the majority of viral illnesses and a primary immune response of the host is usually developed by days 10 to 14 of infection (beginning somewhat earlier according to other researchers), signaling the clearance of the viruses. Other potential mechanisms include antibody-dependent cellular cytotoxicity, complement activation and phagocytosis (ADCP). Moreover, the presence of non-neutralizing antibodies binding to the pathogens may also be helpful. In any case, the administered antibody modifies inflammatory response and this can be optimally achieved during the early response, even at the
asymptomatic stage.33 It has also been suggested that apart from the direct anti-viral properties, plasma components can provide other beneficial actions, such as restoring coagulation factors.34

So far, information on immune response to SARS-CoV-2 is rather limited. According to studies in process, a detailed analysis of 9 cases with mild upper respiratory tract symptoms revealed that seroconversion occurred 6 to 12 days after onset of symptoms, while antibodies were not detectable between day 3 and 6, and all patients showed neutralizing antibodies after 2 weeks. Seroconversion coincided with a slow but steady decline of sputum viral load.35 In another study, the majority of PCR-confirmed SARS-CoV-2-infected persons seroconverted by 2 weeks after disease onset.36 A study on 173 COVID-19 patients showed that the presence of antibodies was less than 40% within the first week since onset, increasing to 94.3% for IgM and 79.8% for IgG since day 15 after onset, and higher titer of total antibodies correlated with worsened clinical classification.37 To further assess the time for seroconversion and its correlation with disease severity and antibody titers, additional longitudinal studies evaluating large numbers of serum samples from COVID-19 patients with a broad spectrum of clinical symptoms are needed.

Registered trials on convalescent plasma in COVID-19 disease

Tracing the progression of research on the potential utilization of convalescent plasma in COVID-19, 11 studies were identified in the clinicaltrials.gov register and their main features are summarized in Table 2. Of these 11 studies, 6 were single-arm, 4 were randomized comparative studies, and 1 pertained to the expanded access status for convalescent plasma (NCT04338360). Various countries have been implicated in these studies, including the USA, China, Colombia, Iran, Italy, Mexico, and the Netherlands. If completed, these studies would examine a minimum total of 1106 patients. At present, 5 studies are either recruiting, enrolling by invitation, or active and providing expanded access; six studies are not yet recruiting.

A cardinal point pertains to the timing of convalescent plasma administration in the study protocols, but the majority of studies did not provide this information. However, some studies necessitated an interval of 3 to 7 days from the beginning of illness (NCT04333251) or, less strictly, acute respiratory distress syndrome (ARDS) lasting less than 10 days (NCT04321421). Variable degrees of severity have been adopted as inclusion criteria; some studies focus on severe cases, whereas there were also studies focusing on less severe cases, as intubation (NCT04327349) or critical illness (NCT04332380) was an exclusion criterion. The total amount of convalescent plasma ranges from 1 to 3 units.

A particularly interesting study protocol (NCT04323800) involves the use of convalescent plasma as a prophylaxis for COVID-19. According to this protocol, convalescent plasma administration will be tested within 120 hours after high-risk contact exposure with a person with confirmed COVID-19. Individuals at high risk for a severe COVID-19 illness will be recruited, including elderly subjects and patients suffering from chronic conditions. This strategy of prophylaxis has been successfully implemented in the prevention of other viral diseases via passive immunity, such as the case of administration of hepatitis B immune globulin, human rabies immune globulin, and polyclonal hyperimmune globulin for respiratory syncytial virus (RSV), or more recently palivizumab, a humanized murine monoclonal antibody for high-risk infants.29,38 In addition to these studies, reports in the media have been appearing about other countries, such as Canada, starting to test convalescent plasma in COVID-19.39

Concerning immunoglobulin therapy in COVID-19, 2 studies were identified (Table 2, lower panels). The first one (NCT04261426) focuses on early administration of the immunoglobulin in severe cases, adopting an eligibility interval between the onset of symptoms and randomization that should not surpass 7 days. The second (NCT04261426) is a small exploratory study on 10 patients with the aim to evaluate this experimental treatment in severe COVID-19 pneumonia cases in China.

The examination of studies registered in the Chinese Clinical Trial Registry (Table 3) revealed a different pattern. In the registry, 10 studies on convalescent plasma were identified; among them, the majority (6 trials) were randomized comparative (vs conventional treatment with/without ordinary plasma), three were non-randomized comparative, and only was a single-
| Principal Investigator, Affiliation | Registration date (identifiers) | Current status (as per April 16, 2020) | Actual study start date - estimated study completion date | Participating centers | Sample size | Study design | Eligibility criteria for donors | Inclusion criteria for recipients | Exclusion criteria for recipients | Details about intervention | Outcomes |
|----------------------------------|-------------------------------|----------------------------------------|--------------------------------------------------------|-----------------------|--------------|--------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------|
| Shanghai Public Health Clinical Center | March 09, 2020 (NCT04326928) | Recruiting | February 1 to December 31, 2020 | 15 | Single Group | Not stated | COVID-19 written informed consent | Lack of detailed medical history | No details provided | Primary: Virological clearance rate of P1 in throat smear, sputum, or lower respiratory tract specimens (day 7 from plasma transfusion), secondary: death, critical illness, recovery |
| Dr Cesare Perotti, Foundation IRCCS San Matteo Hospital, Italy | March 25, 2020 (NCT04327142) | Active, not recruiting | March 17 to May 31, 2020 | 4 hospitals in Italy | 49 | Single-Group Assignment; no masking | Male, age ≥18 years; evaluated for transmissible disease; Adjunctive therapies: for hepatitis A virus, hepatitis B virus, and Parvovirus B-19 | Each plasma bag will be divided into two units | Each plasma bag obtained from plasmapheresis will be divided in two units and frozen, 500-600 mL of plasma will be obtained from each donor, 250-300 mL to treat each patient at most 3 times over 5 days | Primary: death from any cause (within 7 days) Secondary: time to evaluation (within 7 days), length of intensive care unit stay (within 7 days), time to CRP weaning (within 7 days), vital load (nonprotein-bound sputum and BAL) - day 1, 3, and 5, immune response (neutralizing antibody titre at day 1, 3, and 5) |
| Dr Shmuel Shoham, Johns Hopkins University, USA | March 27, 2020 (NCT04323800) | Not yet recruiting | May 1, 2020 - January 2023 | Johns Hopkins University | 150 (75 intermittent; 75 controls) | Randomized triple masking (Participant, Care Provider, Investigator), Higher Anti-SARS-CoV-2 plasma versus control (HANS-COVID-2 non-immune plasma) | Vitamin who recovered from COVID-19 disease, titre of neutralizing antibody > 1:64 | Each plasma bag will be divided into two units and frozen, 500-600 mL of plasma will be obtained from each donor, 250-300 mL to treat each patient at most 3 times over 5 days | Primary: death from any cause (within 7 days) Secondary: time to evaluation (within 7 days), length of intensive care unit stay (within 7 days), time to CRP weaning (within 7 days), vital load (nonprotein-bound sputum and BAL) - day 1, 3, and 5, immune response (neutralizing antibody titre at day 1, 3, and 5) |

(continued)
Table 2 (continued).

| Principal Investigator, Affiliation | Registration date | Current status (as per) | Study design | Eligibility criteria for donors | Inclusion criteria for recipients | Exclusion criteria for recipients | Details about intervention | outcome |
|------------------------------------|-------------------|-------------------------|-------------|--------------------------------|----------------------------------|----------------------------------|---------------------------|---------|
| Dr. Amir Shamshirian, Imam Khomeini Hospital, Mazandaran University of Medical Sciences, Iran | March 31, 2020 (NCT04327349) | Enrolling by Invitation | March 29 – September 30, 2020 | 30 | Single Group: Assignment; no masking | Complete recovery from severe COVID-19 disease and hospital discharge; 2. Consent to donate blood; 3. Age 30 to 60 years; 4. Normal CRP test results; 5. negative COVID-19 RT-PCR test. Exclusion criteria for donors: blood donor新区 infection / infectious diseases, uncontrolled diseases, high blood pressure, diabetes, smoking, use of blood products for donation. | History of hypersensitivity to blood products. 2. History of HIV, Hepatitis, or Hepatitis C infection. 3. Heart failure or any other factor that prevents the transmission of 500 ml plasma. 4. Entering the infarction stage. | No details provided. |
| Dr. Juan M. Arias-Cabreira, Universidad del Rosario, Colombia | April 02, 2020 (NCT04332380) | Not yet recruiting | April 1 to December 31, 2020 | 10 | Single Group: Assignment; no masking | Aged between 18 and 60 years, male or female; 2. Hospitalized participants with diagnosis of COVID-19 by RT-PCR. 3. Written informed consent. | No details provided. | Not stated. |
| Dr. Juan M. Arias-Cabreira, Universidad del Rosario, Colombia | April 03, 2020 (NCT04332830) | Not yet recruiting | April 1 to December 31, 2020 | 80 | Randomized, no masking | Convalescent plasma plus hydroxychloroquine vs hydroxychloroquine plus azithromycin. | Same as NCT04332380. | Same as NCT04332380. |
| Dr. Jose Fe Castilleja-Leal, Hospital San José, Tecnologico de Monterrey, Mexico | April 03, 2020 (NCT04333355) | Not yet recruiting | April 15, 2020 – April 30, 2021 | 80 | Single Group: Assignment; no masking | Consent individuals with proven COVID-19 and symptoms free for a period of not less than 10 days. Donors will be screened for infectious diseases including SARS-CoV-2. | Same as NCT04332380. | 500 ml of convalescent plasma, distributed in two 250 mL transfusions on the first and second protocol day. |
| Principal investigator, Affiliation                  | Registration date (identifier) | Current status as per April 10, 2020 | Actual study start date - estimated study completion date | Participating centers | Sample size | Study design | Eligibility criteria for donors | Inclusion criteria for recipients | Exclusion criteria for recipients | Details about intervention | Outcomes |
|----------------------------------------------------|--------------------------------|-------------------------------------|----------------------------------------------------------|----------------------|-------------|--------------|---------------------------|-------------------------------|-----------------------------|-------------------------|-----------|
| PI not stated, Baylor Research Institute, USA      | April 03, 2020 (NCT04333251)  | Not yet recruiting                   | April 1, 2020 – December 31, 2022                       | Baylor Research Institute, USA                            | 115          | Randomized; no masking (convalescent plasma vs. usual supportive care) | Refractory to treatment with hydroxychloroquine or chloroquine / hydroxy / chloroquine (defined as 48 hours with no improvement, 5. Signed informed consent | 1. Receipt of pooled immunoglobulin in past 30 days; 2. Contraindication to transfusion of blood products | Recipients will receive 1–2 units of ABO matched donor plasma | Primary: Reduction in oxygen and ventilation support during an average of 4 weeks; Secondary: not specified |
| Dr Michael Joyner, Mayo Clinic, USA                | April 08, 2020 (NCT04338360)  | Expanded Access Status : Available   | Expanded Access                                           | University of Chicago                                      | 10           | Single Group; no masking | 1. Age greater or equal to 18; 2. Able to donate blood per standard guidelines; 3. Prior confirmed diagnosis of COVID-19; 4. Complete resolution of symptoms: at least 24 days prior to donation; 5. Female donor who have never been pregnant; 6. Previous pregnancy for HLA antibodies, or male donor; 7. Resolution | 1. Laboratory confirmed COVID-19; 2. Severe illness (defined as, HR≥ 300 mm, Brain oxygen saturation ≤ 90%, PaO2/FIO2 < 300, lung infiltrates > 50% within 24–48 hours or life-threatening respiratory failure, shock, multiple organ dysfunction or failure). COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease; 5. Signed informed consent | Infusion of one unit of anti-SARS-CoV-2 convalescent plasma ~300 mL over 4 hours | Primary: Feasibility of performing study pathway number of donors and recipients type of respiratory support Secondary: (85) Cardiac arrest; Transfer to ICU (10) mortality; (53) length of stay; Hospital mortality; Hospital length of stay; Ventilation-free days; Overall survival |
| Dr Maria Lucia Madariaga, University of Chicago    | April 09, 2020 (NCT04340050)  | Not yet recruiting                   | April 30, 2020 – December 31, 2021                      | University of Chicago                                      | 10           | Single Group; no masking | 1. Age greater or equal to 18; 2. Able to donate blood per standard guidelines; 3. Prior confirmed diagnosis of COVID-19; 4. Complete resolution of symptoms: at least 24 days prior to donation; 5. Female donor who have never been pregnant; 6. Previous pregnancy for HLA antibodies, or male donor; 7. Resolution | 1. Laboratory confirmed COVID-19; 2. Severe illness (defined as, HR≥ 300 mm, Brain oxygen saturation ≤ 90%, PaO2/FIO2 < 300, lung infiltrates > 50% within 24–48 hours or life-threatening respiratory failure, shock, multiple organ dysfunction or failure). COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease; 5. Signed informed consent | Infusion of one unit of anti-SARS-CoV-2 convalescent plasma ~300 mL over 4 hours | Primary: Feasibility of performing study pathway number of donors and recipients type of respiratory support Secondary: (85) Cardiac arrest; Transfer to ICU (10) mortality; (53) length of stay; Hospital mortality; Hospital length of stay; Ventilation-free days; Overall survival |
Table 2 (continued).

| Principal investigator, Affiliation | Registration date | Current status (as per April 10, 2020) | Actual study start date | Planned end date | Actual end date | Participating centers | Sample size | Study design | Eligibility criteria for donors | Inclusion criteria for recipients | Exclusion criteria for recipients | Details about intervention | Outcomes |
|-----------------------------------|-------------------|----------------------------------------|-------------------------|------------------|----------------|----------------------|-------------|-------------|-------------------------------|---------------------------------|-------------------------------|-----------------------------|-----------|
| Bart Rijnders, Erasmus Medical Center | April 10, 2020 (NCT04343218) | Recruiting | April 1 – July 1, 2020 | Two hospitals in the Netherlands | 428 | Randomized, participant masking (Concurrent plasma versus standard care) | 1. History of COVID-19 infection documented by PCR; 2. Known ABO-Rh(D) blood group; 3. Negative screening for Hepatitis; 4. Asymptomatic for at least 24 hours; 5. Symptomatic COVID-19 infection (fever >38°C for at least 48 hours) | Only those who have not received plasma within the last 60 days | Primary: Overall mortality in patients admitted to the ICU within 24 hours; Secondary: Hospital days; Weaning from invasive ventilation | Informed consent 2. Written informed consent 3. Age > 18 years 4. Less than 2 years of age at discharge 5. Written informed consent | Informed consent 1. History of COVID-19 infection documented by PCR; 2. Written informed consent | Primary Overall mortality (until 60 days) Secondary: Hospital days; Weaning from invasive ventilation; Overall mortality in patients admitted to the ICU within 24 hours; Mortality in patients with a duration of symptoms less or more than the median; ICU days in patients admitted to the ICU within 24 hours; SARS-CoV2 shedding from airways (day 1, 3, 5, 7, 10, 14, at discharge) |
| Dr Li Taisheng, Peking Union Medical College Hospital | February 7, 2020 (NCT04264858) | Not yet recruiting | February 10 – June 30, 2020 | 2 hospitals in China | 80 | Randomized, re-masking (Preglomerular immunoglobulin versus standard care) | 1. Age ≥ 18 years; 2. RT-PCR confirmed COVID-19 infection in throat swab and/or sputum and/or lower respiratory tract samples; 3. Interval between onset of symptoms and randomization is within 7 days; 4. Any of the following criteria for severe or critical illness; 5. Written informed consent | Informed consent 1. Age ≥ 18 years; 2. Written informed consent 3. Participation in other studies | Primary Clinical improvement based on the 7-point scale (day 28 from randomization, Lower Limb Limp, Influenza A virus, Influenza B virus, Fungal pneumonia, Fungal pneumonia, Noninfectious causes) 2. Mortality in patients who meet the criteria for severe or critical illness 3. Other evidence that can explain pneumonia 4. Adverse Drug Events (through day 28) | Informed consent 1. Written informed consent 2. Age ≥ 18 years; 3. History of chronic obstructive pulmonary disease 4. Written informed consent | Primary: Time to Clinical improvement (up to 28 days) Secondary: Hospital days; Weaning from invasive ventilation; Clinical status assessed by the ordinal scale Differences in mortality in patients admitted to the ICU within 24 hours; Mortality in patients with a duration of symptoms less or more than the median; ICU days in patients admitted to the ICU within 24 hours; SARS-CoV2 shedding from airways (day 1, 3, 5, 7, 10, 14, at discharge) |
| Dr Xiang Cheng, Wuhan Union Hospital, China | February 11, 2020 (NCT04346896) | Not yet recruiting | March 17, 2020 – May 31, 2020 | Union Hospital, Tongji Medical College, Huazhong University of Science and Technology | 10 | Randomized of cured patients vs. control gamma-globulin | 1. Written informed consent; 2. Age ≥ 18 years; 3. Acute severe COVID-19 pneumonia; 4. Written informed consent | Informed consent 1. Written informed consent 2. Age ≥ 18 years; 3. Acute severe COVID-19 pneumonia; 4. Written informed consent | Primary: Time to Clinical improvement (up to 28 days) Secondary: Hospital days; Weaning from invasive ventilation; Clinical status assessed by the ordinal scale Differences in mortality in patients admitted to the ICU within 24 hours; Mortality in patients with a duration of symptoms less or more than the median; ICU days in patients admitted to the ICU within 24 hours; SARS-CoV2 shedding from airways (day 1, 3, 5, 7, 10, 14, at discharge) | Informed consent | Primary: Time to Clinical improvement (up to 28 days) Secondary: Hospital days; Weaning from invasive ventilation; Clinical status assessed by the ordinal scale Differences in mortality in patients admitted to the ICU within 24 hours; Mortality in patients with a duration of symptoms less or more than the median; ICU days in patients admitted to the ICU within 24 hours; SARS-CoV2 shedding from airways (day 1, 3, 5, 7, 10, 14, at discharge) |
Table 2 (continued).

| Study identifier | Principal investigator (NCT04264858) | Current status (as per date- estimated study start April 10, 2020) | Inclusion criteria for recipients | Exclusion criteria for recipients | Details about intervention |
|------------------|--------------------------------------|---------------------------------------------------------------|----------------------------------|-------------------------------|---------------------------|
| Afili et al. (ChiCTR0000030702, ChiCTR2000030929) | | | | | Not suitable for donors according to the document were set at a level greater than 1:320, although it was recognized that lower antibody titers should be greater than 1:160, whereas a titer of 1:80 could be deemed acceptable if alternative matching units are not available. | |

No details have been provided regarding the selection of donors. Regarding immunoglobulin therapy for COVID-19, the identified study in the Chinese Clinical Trial Registry (ChiCTR20000308410) seemed to correspond to the previously presented study in clinicaltrials.gov by the same principal investigator (NCT04264858).

Current situation – American and European framework for donors

On March 24, 2020, the Food and Drug Administration (FDA) took an important step facilitating access to COVID-19 convalescent plasma to be used in COVID-19 patients at a serious or immediately life-threatening stage of the disease, allowing the process of single patient emergency Investigational New Drug Applications (referred to as eINDs) under Title 21 of the Code of Federal Regulations (CFR) 312.310. Under this process, convalescent plasma can be used for the treatment of an individual patient by a licensed physician upon the authorization of the FDA.

According to the FDA, eligible donors could be recovered COVID-19 patients who had been proven positive either by a diagnostic test such as nasopharyngeal swab at the time of illness, or antibody-positive patients on whom a diagnostic test had not been performed during their illness. The level of neutralizing antibody titers should be greater than 1:160, whereas a titer of 1:80 could be deemed acceptable if alternative matching units are not available. Symptoms should have resolved completely at least 28 days prior to donation; alternatively, a symptom-free interval of at least 14 days prior to donation and negative results in one or more nasopharyngeal swabs or in blood-based molecular diagnostic tests are necessitated. Male donors are eligible; special attention is paid to female donors who should be negative for human leukocyte antigen (HLA) antibodies in case of previous pregnancy. General donor eligibility requirements along with the additional criteria for plasmapheresis should be also met, including infection status control. The FDA has also provided guidance on blood establishment standards, labeling, and recordkeeping.

Regarding donors, the International Society of Blood Transfusion (ISBT) Working Party set an interval of 14 days or more after full recovery and necessitated a non-reactivity of the sample for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, and locally transmitted infections. As a means to avoid the incidence of transfusion-related acute lung injury (TRALI)—a serious condition emerging within 6 hours from transfusion—donors should preferably be either males or females who have never been pregnant, including abortions. On April 4, 2020, the European Commission issued the guidance document on the collection and transfusion of convalescent COVID-19 plasma, adopting similar criteria regarding donor eligibility. Notably, the titers of neutralizing antibodies for donors according to the document were set at a level greater than 1:320, although it was recognized that lower thresholds could also be effective.
| Study leader and affiliation | Registration date (registration number) | Participating centers | Sample size | Study design | Inclusion criteria | Exclusion criteria | Details about intervention | Outcomes |
|-----------------------------|----------------------------------------|----------------------|-------------|--------------|------------------|-------------------|--------------------------|----------|
| Dr Cao Bin, China-Japan Friendship Hospital | February 12, 2020 (ChiCTR2000029757) | 12 hospitals in China | 200 (100 intervention; 100 control) | Randomized with experimental group (convalescent treatment combined with convalescent plasma) vs. control (convalescent treatment group), not blinded | 1. Informed consent, 2. Age ≥ 18, 3. COVID-19 diagnosed by PCR, 4. Nutritional acid positive within 72 hours before blood transfusion, 5. Pneumonia confirmed by imaging, 6. Clinical symptoms severe RR ≥ 30, oxygen saturation < 93%, in resting state, PaO2/FiO2 < 300 or critical (respiratory failure and mechanical ventilation, shock, other organ failure needing IOC), 7. Accept randomization, 8. Hospitalized before the end of the clinical study, 9. Willing to participate in directions and follow-up, 10. No participation in clinical trials | | | |
| Dr Xiaowei Xu, First Affiliated Hospital of Zhejiang University School of Medicine | February 15, 2020 (ChiCTR2000029850) | First Affiliated Hospital of Zhejiang University School of Medicine | 20 (10 intervention; 10 control) | Non-randomized research, no statement about blinding. Standardized comprehensive treatment combined with convalescent plasma treatment vs. standardized comprehensive treatment | 1. Laboratory confirmed diagnosis of COVID-19 infection by RT-PCR, 2. Aged > 18 years; 3. Written informed consent; 4. Clinical deterioration requiring IOC | | | | |
| Dr Zhang Dingyu, Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital) | February 19, 2020 (ChiCTR2000030010) | Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital) | 100 (50 intervention; 50 control) | Patients stratified according to the respiratory support conditions and randomized to the intervention (anti-SARS-CoV-2 virus inactivated plasma) and the control group (ordinary plasma) at a ratio of 1:1. Blinding not stated. | 1. Aged 18 to 70 years old, inpatients, male or female; 2. Severe COVID-19, meeting any of the following: Respiratory distress, RR ≥ 30/min; oxygen saturation < 93% in the resting state; PaO2/ FiO2 < 300; 3. Signed informed consent. | | | | |

(continued)
### Table 3 (continued)

| Study leader and affiliation | Registration date (registration number) | Participating centers | Sample size | Study design | Inclusion criteria | Exclusion criteria | Details about intervention | Outcomes |
|-----------------------------|-----------------------------------------|-----------------------|-------------|--------------|-------------------|-------------------|--------------------------|----------|
| Dr Xuebing Yan, Affiliated Hospital of Xuzhou Medical University | Feb 21, 2020 (ChiCTR2000030039) | 3 hospitals in China | 10 | Single-arm case series with anti-2019-nCoV virus inactivated plasma | 1. Age 18 to 80 years old, male or female; 2. Confirmed diagnosis, whose clinical classification is common or severe case; 3. Effective contraception measures within 3 months after this trial; 4. Confirmation by doctors; 5. Written informed consent. | 1. Previous or current allergic history to human plasma protein products or recipients; 2. Severe COVID-19; 3. Pneumonia due to other causes; 4. History of DVT, pulmonary embolism or arterial embolism within 1 year before; 5. Severe heart disease, including myocardial infarction and chronic heart failure (NYHA grades III and IV); 6. Severe liver and kidney diseases; 7. Positive HBsAg, or nucleic acid test; 8. Hypoxemia; 9. Unfever; 10. No evidence of severe or critical illness. | No details provided | Primary: Cure rate, Mortality rate, Length of stay, Secondary: Length of stay |
| Dr Bende Liu, First People’s Hospital of Jiangxia District, Wuhan (Union Jiangnan Hospital) | February 21, 2020 (ChiCTR2000030046) | 3 hospitals in China | 10 | Non-randomized, no blinding | 1. COVID-19 confirmed diagnosis; 2. Clinical classification is normal, severe or critical; 3. Subject aged ≥18 years did; 4. Signed informed consent. | 1. Highly allergic constitution or history of severe allergy, especially plasma allergy; 2. Other reasons according to doctors not to include the patient. | Conventional therapy with infusion of convalescent plasma: 200-500 mL, two infusions are recommended | Secondary: Laboratory examinations, Length of admission, Mortality rate, Incidence of adverse events in blood transfusion |
| Dr Le Aiping, The First Affiliated Hospital of Nanchang University | February 24, 2020 (ChiCTR2000030179) | The First Affiliated Hospital of Nanchang University | 100 (50 intervention; 50 control) | Randomized, binding not stated (Routine treatment plus plasma treatment versus Routine treatment) | 1) Written informed consent; 2) Aged 18 to 65 years; 3) Real-time fluorescent RT-PCR of respiratory specimens or blood specimens positive; 4) Severe and critical illness; 5) Hypersensitivity to plasma products; severe translation reactions in the past. | 1) No safety; 2) Margin constitution; allergic to plasma or drugs; 3) Old age with severe underlying diseases that affect survival; 4) Severe respiratory failure; heart failure, and multiple organ failure; 5) Incompatible with clinical trials. | No details provided | Primary: Cure rate, Mortality rate, Secondary: Length of stay |
| Dr Guojun Zhang, The First Affiliated Hospital of Zhengzhou University | March 08, 2020 (ChiCTR2000030627) | The First Affiliated Hospital of Zhengzhou University | 30 (15 intervention; 15 control) | Randomized, binding not stated (Convalescent plasma therapy plus routine treatment versus routine treatment) | 1) Written informed consent; 2) Aged ≥18 years old; 3) COVID-19 patients diagnosed by PCR; 4) Nucleic acid positive within 24 hours. | 1) Lack of cooperation; 2) Pregnant or lactating women; 3) Immunoglobulin allergy; 4) IgA deficiency; 5) The clinical symptoms are mild (no pneumonia on imaging) or reach the standard of severe, (RR ≥ 3). | No details provided | Primary: Temperature, Virus neutralizing agent detection, Secondary: Laboratory examination, Length of admission, Mortality rate, Incidence of adverse events in blood transfusion |
| Dr Cao Bin, China-Japan Friendship Hospital | March 10, 2020 (ChiCTR2000030702, retrospective registration) | 4 hospitals in China | 50 (25 intervention; 25 control) | Randomized with experimental group (convalescent treatment plus convalescent) | 1) Written informed consent; 2) Aged ≥18 years old; 3) COVID-19 patients diagnosed by PCR; 4) Nucleic acid positive within 24 hours. | 1) Lack of cooperation; 2) Pregnant or lactating women; 3) Immunoglobulin allergy; 4) IgA deficiency; 5) The clinical symptoms are mild (no pneumonia on imaging) or reach the standard of severe. | No details provided | Primary: Time to clinical recovery after randomization, Secondary: 28-day mortality, Hospitalization time, Incidence of breathing oximeters, Time for conscious cough compensation |

*Note: Details about intervention and outcomes are not fully provided in the table.*
### Table 3 (continued)

| Study leader and affiliation | Registration date (registration number) | Participating centers | Sample size | Study design | Inclusion criteria | Exclusion criteria | Details about intervention | Outcomes |
|-----------------------------|----------------------------------------|-----------------------|-------------|--------------|-------------------|---------------------|---------------------------|----------|
| Dr Binghong Zhang, Renmin Hospital of Wuhan University | March 17, 2020 (ChiCTR2000030929) | Renmin Hospital of Wuhan University | 60 (30 intervention; 30 control) | Randomized, double-blind study (Anti-SARS-CoV-2 virus inactivated plasma vs. Ordinary plasma) | before blood transfusion: 1. Aged 18 to 70 years old, inpatients, male or female; 2. Patients with severe confirmed COVID-19; Adult patients with severe COVID-19 shall meet any of the following: respiratory distress, RR≥30/minute; oxygen saturation <93% in resting state; Leishman more than 50% in lung radiology; PaO₂/FiO₂ <300 mmHg; 3. Written informed consent. | is ≤39% in resting state; PaO₂/FiO₂ ≤300; or critical (respiratory failure and need mechanical ventilation; shock; organ failure needing ICU); 6. Diseases that may increase the risk of thrombosis; 7. High titer of anti-novel coronavirus antibody RBD IgG (higher than 1). 8. Received any experimental treatment for COVID-19 within 30 days before screening; 9. Life-threatening conditions, near death state or expected survival time <24 hours, severe septic shock or DIC, etc.; 10. Severe congestive heart failure, or other relative contraindications for transfusion. | no further details provided. | Relief during infection (cough present when enrolled), Time to remission of conscious disturbance during infection (existed disturbance upon enrollment), 28-day assisted oxygen therapy or non-invasive mechanical ventilation rate, Incidence of ICU surveillance required during infection, Incidence of clinical support measures increased during infection, Proportion of viral nucleic acid negative, Cumulative incidence of severe adverse events (SAE), Cumulative incidence of adverse events (AE), grades 3 and 4. Incidence of adverse plasma transfusion reactions |
| Dr Weiqin Li, Eastern Theater General Hospital | April 02, 2020 (ChiCTR2000031501) | Huazhenshan hospital, Wuhan | 20 (10 intervention; 10 control) | Pragmatic, prospective, non-randomized trial; no blinding (Routine treatment plus Infusion of convalescent plasma versus Routine treatment) | 1. Severe or critical patients with confirmed COVID-19 pneumonia; 2. 18-85 years old; 3. Obtained informed consent. | 1) Respiratory failure with mechanical ventilation; 2) Shock; 3) Combined failure of other organs requiring ICU; 4. Allergic to blood products or plasma components and auxiliary; 5. Multiple organ failure, estimated survival time <3 days; 4. HIV positive before enrolment; 5. Women pregnant or breastfeeding or with a birth plan; 6. Participants in other clinical trials within 1 month before; 7) Poor adherence or other conditions (such as poor physical condition). | No details provided. | Primary: Improvement of clinical symptoms (defined as a reduction of 2 points on the 6-point scale of the patient’s admission status or discharge from the hospital). Secondary: Improving time of main clinical symptoms (coughing, fever, dyspnea, etc.), ICU hospitalization days, 14 and 28-day all-cause mortality. |
### Table 3 (continued)

| Study leader and affiliation | Registration date (registration number) | Participating centers | Sample size | Study design | Inclusion criteria | Exclusion criteria | Details about intervention | Outcomes |
|-----------------------------|----------------------------------------|-----------------------|-------------|--------------|-----------------|-------------------|---------------------------|----------|
| Dr. Xiang Cheng, Union hospital of Tongji Medical College, Huazhong University of Science and Technology | March 15, 2020 (ChiCTR2000030841) | Union hospital of Tongji Medical College, Huazhong University of Science and Technology | 10 (5 intervention; 5 control) | Non-randomized research, no blinding (Immunoglobulin of cured patients versus control gamma globulin) | COPD with end-stage chronic diseases, including NYHA heart failure above grade II, chronic kidney disease with GFR < 40 ml/min or requiring family oxygen therapy. | 0.3, 7, 14; COP (day 3, 7, 14); IL-6 (day 3, 7, 14); New onset of organ failure; New ICU admission rate; Length of hospital stay; Length of ICU stay; Incidence of secondary bacterial infection; Incidence of secondary fungal infection; Incidence of critical illness; Day 90 mortality; Day 90 readmission for COVID-19 pneumonia. | 1. Written informed consent; 2. Aged ≥ 18 years; 3. Acute confirmed, severe 2019-nCoV pneumonia: Severe, at least one of: RR ≥ 30/min; oxygen saturation < 93% in resting state; PaO2/FiO2 < 300 mmHg; respiratory failure and mechanical ventilation required; shock; ICU required in combination with other organ failure. | 1. Viral pneumonia with other viruses besides 2019-nCoV; 2. Patients not suitable for immunoglobulin therapy; 3. Participation in other studies; 4. Other circumstances of patient not being suitable for the clinical trial. | No details provided | Primary: Time to Clinical Improvement; Secondary: Clinical status assessed by the ordinal scale; Differences in oxygen intake methods; Duration of supplemental oxygenation; Duration (days) of mechanical ventilation; Mean PaO2/FiO2; Lesions of the pulmonary segment numbers involved in pulmonary CT; Time to 2019-nCoV RT-PCR negativity in respiratory tract specimens, Dynamic changes of 2019-nCoV antibody titer in blood, Length of hospital stay, All-cause mortality. |
Convalescent plasma recipients and blood establishments

According to the FDA, eligible recipients of convalescent plasma should be COVID-19 positive patients with severe disease (dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation 93% or less, partial pressure of arterial oxygen to fraction of inspired oxygen ratio less than 300, and/or lung infiltrates > 50% within 24 to 48 hours) or a life-threatening disease (respiratory failure, septic shock, multiple organ dysfunction) who have given informed consent for the procedure. Nevertheless, as evidenced by the registered trials (Tables 2 and 3), a wide variety of selection criteria have been envisaged. Following the FDA’s National Expanded Access Treatment Protocol, 2115 sites have registered to participate to convalescent plasma administration by April 27, 2020, enrolled a total of 5,968 patients, with 2576 receiving convalescent plasma.

Convalescent plasma administration seems to be a safe procedure free from serious adverse effects. Meticulous selection of donors can minimize the risk of TRALL. Another potentially concerning phenomenon pertains to antibody-dependent enhancement (ADE) of coronavirus entry. This has been reported in viral diseases and refers to an enhancement of disease in the presence of certain antibodies. Keeping in mind the high titers of neutralizing antibodies that convalescent plasma includes against the same virus (SARS-CoV-2), as well as the previously documented safe experience in SARS and MERS, the occurrence of ADE does not seem to represent a major problem; however, surveillance is warranted.

In accordance to the Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19 infection, convalescent plasma is recommended in the framework of a clinical trial. Similarly, the International Society of Blood Transfusion (ISBT) Working Party on Global Blood Safety has underlined that the clinical use of convalescent plasma should be performed as an experimental therapy, ideally in the context of an organized research trial.

Plasma should be collected in certified blood establishments through legally approved blood collection or plasmapheresis equipment by trained professionals; 200 to 600 mL of plasma can be collected and in most cases, the interval between potential subsequent new donations should be longer than 7 days. Regarding collection workflow, the existing blood transfusion infrastructure can be useful. However, along with increased numbers of survivors, the increasing pool of potential donors may entail logistical challenges, spanning the assessment of donor eligibility, coordination of donor recruitment and collections, as well as transfusion.

Facing the COVID-19 pandemic, the European Blood Alliance (EBA), together with the European Commission’s Directorate-General for Informatics (DIGIT) and Directorate-General for Health and Food Safety (DG SANTE), has been developing an open database hosted on a platform by the European Commission with the aim to collect, monitor, and share all information on convalescent plasma. Blood establishments will organize collection, enter donor data in the database to supply plasma to hospitals, and research projects and the industry; afterwards, the patient outcomes of transfusion can serve as the basis of aggregated data, reports, and pragmatic assessment of convalescent plasma effectiveness. According to the guidance document by the European Commission, the data should include gender, age, comorbidities, time point of transfusion, number, volume and antibody titer of the unit, other therapies administered, clinical symptoms (prior to transfusion, 5 days later and at discharge for survivors), serious adverse events, and length of hospitalization.

Critical appraisal, perspectives, and conclusions

As of April 2020, more than 350,000 people have recovered from COVID-19 worldwide. These individuals may offer a valuable pool of a life-saving treatment for future patients during the pandemic. Asymptomatic, antibody positive carriers may also prove helpful as donors of the disease. For instance, there is anecdotal evidence that in Northern Italy among 60 volunteer blood donors in the town of Castiglione d’Adda, Lombardy, 67% were antibody positive although asymptomatic; nevertheless, their specific antibody titers were not declared in detail.

If proven in larger cohorts, these results may be promising in terms of identifying a large number of eligible convalescent plasma donors. Thorough research into the evaluation of humoral response and neutralizing antibodies in the context of COVID-19 seems an important step in designing strategies pertaining to convalescent plasma.

Until now the number of COVID-19 patients with known outcomes of convalescent plasma administration is particularly limited, stemming from 6 case series. The follow-up of cases reaching hospitalizations of 51 days and 60 days after onset of symptoms highlights the need for adequate observation, but also underlines the time needed from the early, sizable Chinese cohorts (reportedly reaching 245 COVID-19 patients, with improvement in 91 of them) to provide robust results in relevant scientific publications.

A pivotal and controversial point is the time of convalescent plasma administration in COVID-19; that should be as early as possible to maximize efficacy, but at the same time oriented to severe cases. To this direction, the examination of risk markers and integrating clinical (gender, age, comorbidities) and biochemical aspects in a comprehensive risk stratification can provide a valuable tool for decision making, promptly tracing those patients with forthcoming poor prognosis who would most need early intervention with convalescent plasma. Emerging markers with such potential are lymphopenia, elevated procalcitonin, ferritin, D-dimer, and C-reactive protein.

Along with the evaluation of convalescent plasma from blood donors, the plasma industry could take future steps, manufacturing concentrated hyperimmune globulin preparations that contain standardized antibody doses and could provide a further reach in terms of health setting administering therapy. As a whole, the promising results of convalescent plasma transfusion could change the course of COVID-19. The formulation, namely convalescent plasma or hyperimmune globulin, as well as the optimal time frame, remain to be identified in the future.

References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1294–1302.
2. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Crit Care. 2020;24:91.
3. Cao YC, Deng QX, Dai SX. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: an evaluation of the evidence. Travel Med Infect Dis. 2020;101647.
4. Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-Ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382:1787–1799.
22. Duan K, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;105:949.

26. Zeng GL, Yu ZJ, Gou JJ, et al. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. J Infect Dis. 2020 Apr 29. [Epub ahead of print].

28. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest. 2020;130:1545–1548.

30. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in COVID-19. Eur J Clin Microbiol Infect Dis. 2020;39:44–46.

31. Chen L, Xiong J, Bao L, et al. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;20:398–400.

32. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020 Apr 7. [Epub ahead of print].

33. Casadevall A, Pirofski LA. Antibody-mediated regulation of cellular immunity and the inflammatory response. Trends Immunol. 2003;24:474–478.

34. Roback JD, Guerner J. Convalescent Plasma to Treat COVID-19: Possibilities and Challenges. JAMA. 2020 March 27. [Epub ahead of print].

35. Woelfel R, Corman M, Guggemoos W, et al. Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster. 2020;https://doi.org/10.1101/2020.03.05.20030502. Accessed April 12, 2020.

36. Okba NMA, Muller MA, Li W, et al. Severe acute respiratory syndrome coronavirus 2–specific antibody responses in coronavirus disease 2019 patients. Emerg Infect Dis. 2020 April 8. [Epub ahead of print].

37. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. 2020 March 28. [Epub ahead of print].

38. Luke TC, Casadevall A, Watowich SJ, et al. Hark back: passive immunotherapy for influenza and other serious infections. Crit Care Med. 2010;38(4 Suppl):e66–e73.

39. The Globe and Mail. Canada begins clinical trial of experimental COVID-19 treatment using plasma from recovered individuals. 2020;https://www.theglobemail.com/canada/article-canada-begins-clinical-trial-of-experimental-covid-19-treatment-using-plasma/19380130. Accessed April 10, 2020.

40. Food and Drug Administration. Revised Information for Investigational COVID-19 Convalescent Plasma. 2020;https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemptiation/ide-process-cber/revised-information-investigational-covid-19-convalescent-plasma. Accessed April 08, 2020.

41. Epstein J, Burnouf T. Points to consider in the preparation and transfusion of COVID-19 convalescent plasma. 2020;https://jfpalab/or/wp content/uploads/2020/03/Points_to_consider_in_the_preparation_of_COVID_convalescent_plasma__.200331.ISBT_WP_GBS_Final-1.pdf. Accessed April 10, 2020.

42. European Commission. An EU programme of COVID-19 convalescent plasma collection and transfusion. Guidance on collection, testing, processing, storage, distribution and monitored use. 2020;https://ec.europa.eu/health/sites/health/files/blood_tissues_organisms/docs/guidance_CE_plasma_covid19_en.pdf. Accessed April 10, 2020.

43. Rubin R. Testing an old therapy against a new disease: convalescent plasma for COVID-19. JAMA. 2020 April 30. [Epub ahead of print].

44. Yan W, Shang J, Sun S, et al. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. J Virol. 2020;94:e0215–e0219.

45. Bhiraj B, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection. 2020;https://www.idsociety.org/practiceguideline/covid-19-guideline-treatment-and-management/. Accessed April 12, 2020.

46. European Blood Alliance. COVID-19 and blood establishments. Update April 08, 2020. 2020;https://euronan cavernibloodalliance.eu/covid19-and-blood-establishment/. Accessed April 10, 2020.

47. Johns Hopkins University of Medicine. Coronavirus Resource Center. 2020;https://coronavirus.jhu.edu/map.html. Accessed April 10, 2020.

48. Medicine OU-TCIE-B, COVID-19: What proportion are asymptomatic? 2020;https://www.cebm.net/2020/04/covid-19-what-proportion-are-asymptomatic/. Accessed April 08, 2020.

49. Serra M, Coronavirus, Castiglione d’Adda è un caso di studio: “Il 70% dei donatori di sangue è positivo” [article in Italian]. 2020;https://www lastampa.it/topnews/primo-piano/2020/04/02/news/coronavirus-casti glione-d-adda-e-un-caso-di-studio-il-70-dei-donatori-di-sangue-epo sitivo-j.38866841/1. Accessed April 08, 2020.

50. Felber BK, Pavliaks GN. HIV vaccine: better to start together? Lancet HIV. 2019;6:e724–e725.

51. Xinhuannet. China puts 245 COVID-19 patients on convalescent plasma therapy. 2020;http://www.xinhuanet.com/english/2020/02/ 29/c_1389291777.htm. Accessed April 08, 2020.

52. Terpos E, Ntanasis-Stathopoulos I, Kastritis E, et al. Haematological findings and complications of COVID-19. Am J Hematol. 2020 April 13. [Epub ahead of print].