Use of convalescent plasma therapy in hospitalised adult patients with non-critical COVID-19: a focus on the elderly from Hungary

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Abstract Convalescent plasma therapy might be a feasible option for treatment of novel infections. During the early phases of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, several promising results were published with convalescent plasma therapy, followed by more disappointing findings of randomised controlled trials. In our single-centre, open-label, prospective, cohort study, we assessed the findings of 180 patients treated with convalescent plasma during the first four waves of the pandemic in Hungary. The primary outcome was all-cause mortality; secondary outcomes were clinical improvement and need for intensive care unit admission by day 28. Subgroup analysis comparing elderly and non-elderly (less than 65 years of age) was performed. Twenty (11.4%) patients died by day 28, at significantly higher rates in the elderly subgroup (3 vs. 17, \( p < 0.01 \)). One hundred twenty-eight (72.7%) patients showed clinical improvement, and 15 (8.5%) were transferred to the intensive care unit until day 28. Non-elderly patients showed clinical improvement by day 28 in significantly higher rates (improvement 74 vs. 54, no improvement 15 vs. 11, worsening or death 4 vs. 18 patients, \( p < 0.01 \)). In conclusion, we found similar clinical outcome results as randomised controlled trials, and the impact of risk factors for unfavourable clinical outcomes among patients in the elderly population.

Keywords SARS-CoV-2 · COVID-19 · Coronavirus disease · Convalescent plasma therapy · Elderly

Introduction

At the beginning of 2020, a new pandemic started across the globe, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), affecting millions of people and causing deaths in immense numbers worldwide. Since then, health care systems have experienced a serious pressure, facing the novel respiratory illness called coronavirus disease 2019 (COVID-19). Naturally, the pandemic encouraged the scientific society to search for effective treatment strategies as soon as possible.

SARS-CoV-2 is a positive-sense, single-stranded RNA virus belonging to the family Coronaviridae. Most COVID-19 cases are asymptomatic or have a
mild respiratory disease course, but, in some patients, it manifests as severe pneumonia, even requiring intensive care unit admission and mechanical ventilation, or leading to death [1]. In the early phase of an epidemic caused by a novel infectious agent, passive immunotherapy can be a feasible treatment option. Passive immunotherapy with convalescent plasma dates back to the late nineteenth century, when it was first used as an effective therapy for diphtheria. Since then, it has been applied in several disease outbreaks, such as the 1918 Spanish flu pandemic, the global spread of 2005 H5N1 avian influenza [2, 3], the 2009 H1N1 influenza pandemic [4], the 2003 SARS [5, 6] and 2013 Middle East respiratory syndrome coronavirus (MERS) epidemics [7], and the 2014 West African Ebola outbreaks [8, 9], with promising clinical outcomes [10, 11]. Most of these studies concluded that immunotherapy with convalescent plasma may be effective early in the disease course, explained by the early viral phase of the diseases and the delayed immune responses. Besides the passive immunisation mechanism, convalescent plasma therapy may have an immunomodulatory effect as well [12], including direct virus neutralisation, control of an overreacting immune response (i.e. cytokine storm, helper T-lymphocyte functions, complement activation) and immunomodulation of a hypercoagulable state. Lastly, convalescent plasma can be obtained from survivors in a relatively easy manner even in low-income countries, providing the opportunity to treat acutely infected patients with specific antibodies.

At the early phases of the SARS-CoV-2 pandemic, experiences with plasma therapy were only available from previous disease outbreaks. Our aim was to assess the clinical use of convalescent plasma therapy in non-critical hospitalised adult COVID-19 patients, with a specialised focus on the elderly populations at our centre.

Methods

Study design and setting

A single-centre, open-label, prospective, observational study was carried out among a cohort of hospitalised adult COVID-19 patients receiving convalescent plasma therapy between 1 April 2020–31 December 2021 at the South Pest Central Hospital, National Institute of Haematology and Infectious Diseases (Budapest, Hungary), the national referral centre with more than 150 dedicated beds for COVID-19 patients during the pandemic. All patients gave informed consent for anonymised data collection and processing. The study was in accordance with the Helsinki Declaration and national ethical standards. The study protocol, as part of the CONTRAST (COmparing Novel TReatment Strategies Against SARS-CoV-Two) clinical trial, has been approved by Institutional Review Board of South Pest Central Hospital, National Institute of Haematology and Infectious Diseases (EB-14/2020) and the Scientific and Research Ethics Committee of the Hungarian National Medical Scientific Council (ETT-TUKEB IV/3937–1/2020/EKU).

Patient eligibility and participant selection

All symptomatic adult patients with respiratory SARS-CoV-2 PCR positivity hospitalised at our centre during the first four waves of the COVID-19 pandemic in Hungary were eligible for inclusion. Patient enrollment was performed consecutively during daily on-site and real-time visits by attending physicians. All patients receiving COVID-19 convalescent plasma (CCP) therapy for COVID-19 were included in the final cohort; patients receiving other medications for COVID-19 were not excluded. Anonymised data of included patients were collected from electronic medical charts and paper-based documentation into a standardised case report form.

Definitions

Mild COVID-19 at baseline was defined as categories 1 to 3 on the World Health Organisation (WHO) Clinical Progression Scale (CPS), moderate disease as categories 4 and 5, severe disease as category 6 [https://www.who.int/docs/default-source/documents/emergencies/minimalcoreoutcomemeasure.pdf]. Since in the original WHO-CPS description the application of the different oxygen supplements are not detailed, we used the flow rate of 12 l pro minute for the distinction between mask or nasal prongs supplementation in category 5 and non-invasive ventilation or high-flow oxygen administration in category 6, as another study suggested [13].
Risk factors for progression to severe or critical COVID-19 disease were defined as >60 year of age, resident of a long-term care facility, underlying severe or chronic comorbidities (essential hypertension, obesity, diabetes mellitus, chronic cardiovascular, cerebrovascular, kidney disease, chronic obstructive pulmonary disease, chronic immunosuppression including active haematological and oncological malignancies, congenital immunodeficiencies, asplenia, uncontrolled HIV infection, solid organ or haematopoietic stem-cell transplant recipient, chemotherapy or other immunosuppressant therapy in the previous 6 months, systemic corticosteroid therapy ≥ 20 mg/die prednisolone equivalent dose for ≥ 2 weeks, systemic autoimmune diseases, hepatic cirrhosis and chronic alcohol abuse.

Date of symptom onset was defined as the day of the first recognition of any COVID-19 attributable symptom, reported by the patient or caregiver. When the patient remained asymptomatic or where no relevant data was available, the date of symptom onset was marked as the day of the first positive respiratory SARS-CoV-2 PCR or first day of recognition of any COVID-19 attributable symptom by a health care professional. The day of symptom onset and the day of receiving the first unit of convalescent plasma were considered as day 0 during specified statistical analyses.

Administration of COVID-19 convalescent plasma and follow-up of COVID-19 patients

Indications for COVID-19 convalescent plasma (CCP) therapy were severe COVID-19 disease showing no clinical improvement to other treatments within 72 h of therapy initiation, and mild to moderate COVID-19 with high risk for progression to severe or critical disease. Contraindications for CCP were documented total serum IgA or haptoglobin deficiency, documented severe allergic reaction related to the use of blood products, development of fluid overload and lack of informed consent. Each patient received at least one unit of ABO and Rh blood group compatible CCP over a period of ≥ 1 h. Patients were monitored closely for adverse events until 12 h after the CCP was administered.

The clinical status of the patients was monitored daily by the attending physicians until hospital discharge, intensive care unit admittance or death. Chest imaging (computer tomography or chest X-ray if computer tomography was not feasible) was performed in 24 h from admission, and repeated every 7 days or when clinical deterioration was observed. Supplemental oxygen was administered via low-flow nasal cannula, high-flow nasal cannula or Venturi facemask. Clinical status and oxygen supplementation rate were evaluated on days 0, 3, 5, 7, 10, 14 and 28 from the initiation of CCP therapy. Data regarding length of hospital stay, length of intensive care unit (ICU) stay, need for ICU admittance and time to ICU admittance were collected until hospital discharge or death. Post-discharge follow-up until a total of 28 days since index hospital admission was done by clinical outpatient visits, telephone calls or the National eHealth Infrastructure.

Study outcomes and statistical analysis

The primary outcome was all-cause in-hospital mortality. Secondary outcomes were clinical improvement in relation to the WHO-CPS scale and need for intensive care unit admission. Clinical improvement was defined as at least 2 points reduction in the WHO-CPS score. Patients with less than 2 points reduction or without changes in their scores were identified as showing no improvement. Worsening clinical status was defined as elevation of the WHO-CPS score. Patients lost from follow-up were not included in the clinical outcome analyses. Outcomes were assessed on day 28. Subgrouping was performed according to age groups, where elderly patients were defined as patients at least or older than 65 years of age. Continuous variables were expressed as median ± interquartile range (IQR), with minimum–maximum ranges. Normality was tested by the Shapiro–Wilk test. Categorical variables were expressed as absolute numbers (n) with relative percentages (%). Statistical comparisons were done with Mann–Whitney U-test or Fisher’s exact test, depending on variable type. For all statistical tests, a 2-tailed p-value of <0.05 determined statistical significance. To assess clinical improvement as a time-dependent outcome during the follow-up period, Kaplan–Meier probability curves of the subgroups were and statistically compared by the log rank test. Data collection was done with Microsoft Office Excel 2016; tests were calculated using IBM SPSS Statistics 23. For reporting, we adhere
to the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) Statement.

**Results**

From 3598 patients screened, 180 (5.0%) received CCP therapy during the study period and were included in the final cohort. Baseline demographic and clinical characteristics are detailed in Table 1. Four patients of the non-elderly group lost from follow-up. In the cohort, the median age was 63 ± 25 (18–96) years, with a male predominance (66.1%). The elderly group consisted of 83 patients, the non-elderly group of 97 patients. Main comorbidities were essential hypertension (51.1%), active haematological malignancy (43.3%) and chronic systemic corticosteroid or immunosuppressive treatment (38.9%); 7 chronic comorbidities were prevalent among elderly patients in a statistically significant manner. Fifty patients (27.8%) had mild, 57 (31.7%) had moderate and 73 (40.6%) had severe COVID-19, and while moderate-to-severe forms were more frequently diagnosed among elderly patients (25.8% and 39.2% vs. 38.6% and 42.2%, *p* = 0.04), the presence of pulmonary infiltrates consistent with COVID-19 on chest X-ray or CT was balanced between subgroups (84.5% vs. 78.3%, *p* = 0.28). The median to CCP from admission was 2 ± 4 (0–44) days, while the median CCP units administered was 2 ± 2 (1–8). Among other therapies against COVID-19 applied, only the use of remdesivir differed between subgroups (95.9% vs. 77.1%, *p* < 0.01).

Clinical outcomes are shown in Table 2. In-hospital all-cause mortality at 28 days was 11.4%, with a statistically significant difference between subgroups (3.2% vs. 20.5%, *p* < 0.01). Fifteen (8.5%) patients had to be transferred to the intensive care unit at 28 days, but rates were similar between elderly and non-elderly. Although the length of hospital stay was significantly longer among elderly patients, the length of ICU stay was similar between subgroups (14 ± 27 days vs. 5 ± 16 days, *p* = 0.1). In total, one hundred twenty-eight (72.7%) patients showed clinical improvement by day 28, with more favourable outcomes among non-elderly subgroup (79.6%, 16.1% and 4.3% vs. 65.1%, 13.3% and 21.7%, *p* < 0.01). In Fig. 1, probability distributions for clinical improvement in the non-elderly and elderly subgroups showed a statistical significant difference at 28 days (log rank *p* < 0.01).

**Discussion**

Main findings and limitations

Our main findings do not differ in merit from the data published in the literature so far. Our primary endpoint, in-hospital all-cause 28-day mortality (11.4%), was found to be similar to the 3.9 to 23% 28-day mortality rates of the CCP arms of RCTs studying similar numbers of hospitalised, moderate-to-severely ill COVID-19 patients [14–21]. The need for ICU admission (8.5%) was similar in our cohort compared to the findings of the two RCTs detailing rates of ICU admission and studying similar amounts of severely ill patients (8.3–15%) [15, 21]. However, in our cohort, among elderly versus patients of ≤65 years, a trend towards statistically similar rates of ICU admittance and lengths of ICU stay was noted. In this view, perhaps a residual benefit might be apprehended by delaying or possibly preventing transmission to the ICU in some elderly patients, preferably if convalescent plasma therapy is initiated early during the disease course.

Furthermore, considering statistically significant baseline differences between subgroups, namely that elderly patients had more comorbidities, presented with more severe disease and received remdesivir therapy in a lower rate, clinical outcomes might rather be related to these risk factors of unfavourable disease course, than to the ineffectiveness of CCP therapy.

Our study has several limitations. Due to its non-randomised structure and small sample size, our results must be interpreted with caution, despite the parallel findings with RCTs. The significant baseline characteristic differences and rates of remdesivir usage probably determined the results of our subgroup analysis results as well. As a placebo-controlled subgroup was not defined, an estimation of absolute risk reduction was not feasible. Lastly, some residual bias might have influenced our study data. Further investigation and determination whether defined patient subgroups would benefit from CCP therapy would be necessary.
| Parameter                                                                 | Total (n = 180) | Non-elderly (n = 97) | Elderly (n = 83) | p value |
|--------------------------------------------------------------------------|----------------|----------------------|----------------|---------|
| Age (years, median ± IQR, min–max)                                       | 63 ± 25 (16–96) | 51 ± 15 (18–64)      | 77 ± 12 (65–96) | < 0.01  |
| Male gender (n, %)                                                       | 119 (66.1)     | 72 (74.2)            | 47 (56.6)      | 0.01    |
| Comorbidities (n, %):                                                    |                |                      |                |         |
| - Essential hypertension                                                 | 92 (51.1)      | 33 (34.0)            | 59 (71.1)      | < 0.01  |
| - Chronic heart disease                                                  | 37 (20.6)      | 9 (9.3)              | 28 (33.7)      | < 0.01  |
| - Chronic vascular disease (excluding chronic neurovascular disease)     | 45 (25.0)      | 8 (8.3)              | 37 (44.6)      | < 0.01  |
| - Chronic neurovascular disease                                          | 30 (16.7)      | 2 (2.1)              | 28 (33.7)      | < 0.01  |
| - Chronic pulmonary disease                                              | 17 (9.4)       | 5 (5.3)              | 12 (14.5)      | < 0.01  |
| - Chronic liver disease                                                  | 9 (5.0)        | 6 (6.2)              | 3 (3.6)        | 0.43    |
| - Chronic kidney disease                                                 | 35 (19.4)      | 9 (9.3)              | 26 (31.3)      | < 0.01  |
| - Diabetes mellitus                                                      | 41 (22.8)      | 10 (10.3)            | 31 (37.6)      | < 0.01  |
| - Active oncological malignancy                                          | 5 (2.8)        | 1 (1.0)              | 4 (4.8)        | 0.12    |
| - Active haematological malignancy                                       | 78 (43.3)      | 48 (49.5)            | 30 (36.1)      | 0.07    |
| - Chronic systemic corticosteroid or immunosuppressive treatment         | 70 (38.9)      | 42 (43.3)            | 28 (33.7)      | 0.19    |
| - Systemic autoimmune disease                                            | 9 (5.0)        | 6 (6.2)              | 3 (3.6)        | 0.43    |
| - Pregnancy                                                              | 2 (1.1)        | 2 (2.1)              | 0 (0)          | n.a     |
| Number of comorbidities per patient (median ± IQR, min–max)              | 2 ± 3 (0–7)    | 2 ± 2 (0–7)          | 4 ± 3 (0–7)    | < 0.01  |
| COVID-19 severity at baseline (n, %):                                    |                |                      |                |         |
| - Mild disease (WHO-CPS 0–4)                                             | 50 (27.8)      | 34 (35.1)            | 16 (19.3)      | 0.04    |
| - Moderate disease (WHO-CPS 5)                                           | 57 (31.7)      | 25 (25.8)            | 32 (38.6)      |         |
| - Severe disease (WHO-CPS 6)                                             | 73 (40.6)      | 38 (39.2)            | 35 (42.2)      |         |
| Presence of pulmonary infiltrates consistent with COVID-19 on chest X-ray or CT at baseline (n, %) | 147 (81.7) | 82 (84.5) | 65 (78.3) | 0.28 |
| COVID-19 vaccination status at baseline (n, %):                          |                |                      |                |         |
| - Unvaccinated                                                           | 128 (71.1)     | 70 (72.2)            | 58 (69.9)      | 0.42    |
| - Incomplete primary series                                              | 4 (2.2)        | 3 (3.1)              | 1 (1.2)        |         |
| - Primary series only                                                     | 36 (20)        | 20 (20.6)            | 16 (19.3)      |         |
| - Booster vaccinated                                                     | 12 (6.7)       | 4 (4.1)              | 8 (9.6)        |         |
| Antiviral therapies for COVID-19 during hospitalisation (n, %):          |                |                      |                |         |
| - Hydroxychloroquine                                                     | 0 (0)          | 0 (0)                | 0 (0)          | n.a     |
| - Lopinavir/ritonavir                                                    | 0 (0)          | 0 (0)                | 0 (0)          | n.a     |
| - Favipiravir                                                            | 34 (18.9)      | 19 (19.6)            | 15 (18.1)      | 0.89    |
| - Remdesivir                                                             | 157 (87.2)     | 93 (95.9)            | 64 (77.1)      | < 0.01  |
| Immunomodulatory therapies for COVID-19 during hospitalisation (n, %):   |                |                      |                |         |
| - Dexamethasone                                                          | 159 (88.3)     | 88 (90.7)            | 71 (85.5)      | 0.28    |
| - Tocilizumab                                                            | 8 (4.4)        | 7 (7.2)              | 1 (1.2)        | 0.05    |
| - Baricitinib                                                            | 52 (28.9)      | 33 (34.0)            | 19 (22.9)      | 0.10    |
| - Ruxolitinib                                                            | 4 (2.2)        | 2 (2.1)              | 2 (2.4)        | 0.87    |
| - Intravenous immunoglobulin                                             | 21 (11.7)      | 15 (15.5)            | 6 (7.2)        | 0.08    |
| Monoclonal antibody therapies for COVID-19 during hospitalisation (n, %):|                |                      |                |         |
| - Bamlanivimab                                                           | 3 (1.7)        | 1 (1.0)              | 2 (2.4)        | 0.47    |
| - Casirivimab/imdevimab                                                  | 6 (3.3)        | 4 (4.1)              | 2 (2.4)        | 0.52    |
| Experimental therapies for COVID-19 during hospitalisation* (n, %):      |                |                      |                |         |
| - SARS-CoV-2-specific T cell therapy                                     | 2 (1.1)        | 2 (2.1)              | 0 (0)          | n.a     |
| Time to CCP from symptom onset (days, median ± IQR, min–max)             | 8 ± 8 (0–58)   | 9 ± 9 (0–58)         | 7 ± 7 (0–36)   | 0.27    |

*In the context of an ongoing clinical trial

CCP, COVID-19 convalescent plasma; ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay; n.a., not applicable; WHO-CPS, World Health Organisation Clinical Progression Scale
Previous studies from the literature

Several promising case reports and observational studies have been published, appreciating CCP therapy throughout the world, mainly during the first waves of the pandemic. Nevertheless, later published randomised controlled trials (RCT) could not universally reproduce these encouraging findings. Until the drafting of the current manuscript, 31 RCTs were published in the literature investigating the clinical effectiveness of CCP therapy in non-critically ill COVID-19 patients. The details, primary endpoints and results of these RCTs are summarised in Table 3.

Eighteen (58.1%) of these trials were open label, and 5 of them were performed in an outpatient setting. Almost half of the studies, 14 (45.2%) enrolled at least 200 patients. Twenty-six (83.9%) enrolled patients with severe disease; 8 enrolled (25.8%) critically ill COVID-19 patients among others. Twelve RCTs were terminated earlier than planned, mainly due to decrease in numbers of enrollable patients or detecting potent neutralising antibody titres of patients comparable to the CCP products.

Twenty-three RCTs marked varieties of clinical status, progression or improvement as primary endpoint, but only one of them, carried out by Bar et al.

| Outcome* | Total (n=180) | Non-elderly (n=97) | Elderly (n=83) | p value |
|----------|---------------|---------------------|---------------|---------|
| All-cause in-hospital mortality (n, %) | 20 (11.4) | 3 (3.2) | 17 (20.5) | <0.01 |
| Need for ICU admission (n, %) | 15 (8.5) | 7 (7.5) | 8 (9.6) | 0.55 |
| Clinical improvement according to WHO-CPS (n, %): | | | | |
| - Improvement | 128 (72.7) | 74 (79.6) | 54 (65.1) | <0.01 |
| - No improvement | 26 (14.8) | 15 (16.1) | 11 (13.3) | |
| - Worsening or death | 22 (12.5) | 4 (4.3) | 18 (21.7) | |
| Length of hospital stay (days, median ± IQR, min–max) | 15 ± 14 (3–110) | 14 ± 11 (3–110) | 17 ± 16 (3–68) | 0.03 |
| Length of ICU stay (days, median ± IQR, min–max) | 9 ± 22 (3–81) | 14 ± 27 (7–81) | 5 ± 16 (3–36) | 0.1 |

*Patients lost to follow-up were not included in the final analysis

ICU, intensive care unit; IQR, interquartile range; WHO-CPS, World Health Organisation Clinical Progression Scale

Fig. 1 Kaplan–Meier curves for clinical improvement probability of adult COVID-19 in-patients receiving COVID-19 convalescent plasma therapy cumulated for 28 days, grouped by age (elderly subgroup defined as older than 65 years of age at study baseline)
| First author, journal and year of publication | Area       | Trial design | Patient no. (CCP vs. SOC/placebo) | Age | Study setting | COVID-19 WHO severity | Transfusion timing from symptom onset (days) | Units and CCP titre transfused | Concomitant medications | Primary endpoints | Primary endpoint results |
|---------------------------------------------|------------|--------------|----------------------------------|-----|---------------|------------------------|-----------------------------------------------|--------------------------------|-------------------------|-------------------|------------------------|
| Li et al. JAMA, 2020 [23]                   | Wuhan, China | OL MC        | 23 vs. 22                        | 70 ± 16<sup>a</sup> | Hospitalised            | Severe, critical         | 30 ± 19<sup>a</sup>                           | NA units high titre            | LPV/r, OST, ARB, RBV, CS, hIVIG, INF | Time to clinical improvement at 28 days | No significant difference, signal of possible clinical benefit for CCP among patients with severe COVID-19<sup>1</sup> |
| Agarwal et al. BMJ, 2020 (PLACID trial) [14] | India      | OL MC        | 235 vs. 229                      | 52 ± 19<sup>a</sup> | Hospitalised            | Moderate, severe         | 8 ± 5<sup>a</sup>                            | 2 × 1 units variable titre   | HCQ, REM, LPV/r, OST, CS, TOZ, hIVIG | Progression to severe disease or death at 28 days | No significant difference |
| Simonovich et al. N Engl J Med, 2020 (PlasmAr trial) [15] | Argentina | DB MC PC     | 228 vs. 105                      | 62 ± 20<sup>a</sup> | Hospitalised            | Severe                  | 8 ± 5<sup>a</sup>                            | 1 × 2 units high titre        | CS, LPV/r, TOZ, IVM, HCQ | Clinical status at 30 days | No significant difference |
| Libster et al. N Engl J Med, 2021 [25]     | Argentina  | DB PC        | 80 vs. 80                        | 77.2 ± 8.6<sup>b</sup> | Outpatient hospitalised | Mild                    | <3                                            | 1 × 1 unit high titre          | -                       | Development of severe respiratory disease at 15 days | CCP significantly reduced progression risk to severe disease by 48%, CCP group showed longer time to development of severe disease<sup>1</sup> |
| First author, journal and year of publication | Area | Trial design | Patient no. (CCP vs. SOC/placebo) | Age | Study setting | COVID-19 WHO severity | Transfusion timing from symptom onset (days) | Units and CCP titre transfused | Concomitant medications | Primary endpoints | Primary endpoint results |
|-----------------------------------------------|------|--------------|----------------------------------|-----|--------------|----------------------|---------------------------------------------|---------------------------------|------------------------|-------------------|-------------------|
| Balcells et al. PLoS Med, 2021 [29]          | Chile | OL SC        | 28 early vs. 30 deferred CCP     | 65.8 ± 65b | Hospitalised  | Severe               | 6 ± 3a                                      | 2×1 units high titre                | HCQ, CS, TOZ, LPV/r   | Composite of hospitalisation >14 days, IMV or inhospital death | No significant difference |
| Pouladza-deh et al. Intern Emerg Med, 2021 [27] | Iran | SB SC        | 30 vs. 30                        | 53.5 ± 10.3b (CCP arm) | Hospitalised  | Severe               | <7                                          | 1–2×1 unit variable titre | CHQ, LPV/r          | Improvement of cytokine storm levels | Mean levels of lymphocytes and IL-10 significantly increased, levels of IL-6, TNF-α, and IFN-γ decreased in the CCP group |
| AIQahtani et al. Sci Rep, 2021 [30]           | Bahrain | OL MC       | 20 vs. 20                         | 52.6 ± 14.9b (CCP arm) | Hospitalised  | Severe               | NA                                         | 2×1 units variable titre | HCQ, LPV/r, RBV, IFN, TOZ, CS | Requirement of NIV or IMV, duration of ventilation | No significant difference |
| RECOVER-ERY Coll. Group JAMA, 2021 [28]       | UK   | OL MC        | 5795 vs. 5763                     | 63.5 ± 14.7b | Hospitalised  | Moderate, severe, critical | 9 ± 6a                                     | 2×1 units high titre | HCQ, LPV/r, CHQ, REM, TOZ, SAR | All-cause mortality at 28 days | No significant difference |
| Gharbharan et al. Nat Commun, 2021 (Con-COVID trial) [31] | Netherlands | OL MC   | 43 vs. 43                         | 63 ± 18a | Hospitalised  | Severe               | 10 ± 9a                                   | 1×1 unit high titre | HCQ, LPV/r, REM | All-cause mortality at 60 days | No significant difference |

**Table 3 (continued)**
| First author, journal and year of publication | Area | Trial design | Patient no. (CCP vs. SOC/placebo) | Age | Study setting | COVID-19 WHO severity | Transfusion timing from symptom onset (days) | Units and CCP titre transfused | Concomitant medications | Primary endpoints | Primary endpoint results |
|----------------------------------------------|------|--------------|-----------------------------------|-----|---------------|----------------------|------------------------------------------|--------------------------------|------------------------|-------------------|-------------------------|
| O'Donnell et al. J Clin Invest, 2021 [24]    | USA, Brazil | DB MC | 150 vs. 73 | 61<sup>a</sup> | Hospitalised | Severe, critical | 9<sup>a</sup> | 1 × 1 unit high titre | HCQ, REM, CS | Clinical status at 28 days | No significant difference, trends toward improved clinical status among patients who received CCP ≤ 7 days of symptom onset, CCP with higher titres of neutralising antibody and concomitant CS |
| Bennett-Guerrero et al. Crit Care Med, 2021 [32] | USA | DB SC | 59 vs. 15 | 67 ± 15.8<sup>b</sup> (CCP arm) | Hospitalised | Severe, critical | 9 ± 12<sup>a</sup> (CCP arm) | 1 × 2 units high titre | HCQ, CS, REM, TOZ, SAR | Ventilator-free days at 28 days | No significant difference<sup>3</sup> |
| Kirenga et al. BMJ Open Resp Res, 2021 [16] | Uganda | OL SC | 69 vs. 67 | 50 ± 23.5<sup>a</sup> | Hospitalised | Mild, severe | 7 ± 4<sup>a</sup> | 1 × 1 unit variable titre | CS | Time to viral clearance | No significant difference |
| Korley et al. N Eng J Med, 2021 (C3PO trial) [33] | USA | SB MC PC | 257 vs. 254 | 54 ± 21<sup>a</sup> | Outpatient | Mild | 4 ± 3<sup>a</sup> | 1 × 1 unit high titre | - | Disease progression at 15 days | No significant difference<sup>4</sup> |
| First author, journal and year of publication | Area | Patient no. (CCP vs. SOC/placebo) | Age | Study setting | COVID-19 WHO severity | Transfusion timing from symptom onset (days) | Units and CCP titre transfused | Concomitant medications | Primary endpoints | Primary endpoint results |
|---------------------------------------------|------|----------------------------------|-----|---------------|-----------------------|---------------------------------------------|--------------------------------|-----------------------|----------------|-------------------------|
| Bégin et al. Nat Med, 2021 (CON-COR-1 trial) [17] | Canada, USA, Brazil | OL MC 625 vs. 313 69 ± 21a | Hospitalised | Severe | 8 ± 5a | 2 × 1 units high titre | CS | Intubation or death at 30 days | No significant difference |
| Avendano-Sola et al. J Clin Invest, 2021 (ConP-las-19 trial) [19] | Spain | OL MC 179 vs. 171 62 ± 22a | Hospitalised | Severe | 6 ± 3a | 1 × 1 unit variable titre | REM, TOZ, CS | Proportion of patients in WHO ordinal categories of 5–7 at 14 days | No significant difference |
| Körper et al. J Clin Invest, 2021 (CAPSID trial) [34] | Germany | OL MC 53 vs. 52 60 ± 13a | Hospitalised | Severe, critical | 7 ± 7a (CCP arm) | 3 × 1 units variable titre | REM, TOZ, CS | Composite of survival and no IMV, ICU or tachypnea at 21 days | No significant difference |
| Menichetti et al. JAMA Netw Open, 2021 (TSU-NAMI trial) [19] | Italy | OL MC 241 vs. 246 64 ± 20a | Hospitalised | Moderate, severe | 7.7 ± 4a | 1–3 units high titre | REM, CS | Composite of worsening respiratory failure or death at 30 days | No significant difference |
| Holm et al. BMC Res Notes, 2021 [35] | Sweden | OL MC 17 vs. 14 80 ± 26 (CCP) | Hospitalised | Severe | 7 ± 4a (CCP, arm) | 3 × 1 units variable titre | CS, REM | Days with oxygen support at 28 days | No significant difference |
| First author, journal and year of publication | Area | Trial design | Patient no. (CCP vs. SOC/placebo) | Age | Study setting | COVID-19 WHO severity | Transfusion timing from symptom onset (days) | Units and CCP titre transfused | Concomitant medications | Primary endpoints | Primary endpoint results |
|-----------------------------------------------|------|--------------|-----------------------------------|-----|---------------|------------------------|---------------------------------------------|-------------------------------|-------------------------|---------------------|--------------------------|
| Bar et al. J Clin Invest, 2021 (PencnCCP2 trial) [22] | USA | OL MC | 41 vs. 39 | 63 ± 22a | Hospitalised | Severe | 6 ± 5a | 1 × 2 units variable titre | HCQ, CS, REM | Comparison of clinical severity scores | Significant difference favouring CCP |
| Baldeón et al. Transfus Med, 2022 [20] | Ecuador | DB MC PC | 63 vs. 95 | 56.3 ± 12.7b (CCP) | Hospitalised | Severe | 10.6 ± 4.9b (CCP arm) | 1 × 1 unit variable titre | CS | Survival rate at 28 days | No significant difference |
| Ray et al. Nat Commun, 2022 [36] | India | OL SC | 40 vs. 40 | NA | Hospitalised | Severe | 4.2 ± 2.2b (CCP arm) | 2 × 1 units variable titre | HCQ, CS, REM, IVM | All-cause mortality at 30 days, identification of immunological correlates of response | No significant difference |
| De Santis et al. Emerg Infect Dis, 2022 [37] | Brazil | OL MC | 36 vs. 71 | 60 ± 56a | Hospitalised | Severe, critical | 8 ± 3a | 3 × 1 units high titre | N/A | death rate at 30 and 60 days | no significant difference |
| Ortigoza et al. JAMA Intern Med, 2022 (CONTAIN COVID-19 trial) [38] | USA | DB MC PC | 468 vs. 465 | 63 ± 21a | Hospitalised | Severe | 7 ± 5a | 1 × 1 unit variable titre | HCQ, REM, CS | Clinical status at 14 days | No significant difference |
| First author, journal and year of publication | Area | Trial design | Patient no. (CCP vs. SOC/placebo) | Age | Study setting | COVID-19 WHO severity | Transfusion timing from symptom onset (days) | Units and CCP titre transfused | Concomitant medications | Primary endpoints | Primary endpoint results |
|-----------------------------------------------|------|--------------|----------------------------------|-----|---------------|-----------------------|-----------------------------------------------|---------------------------------|--------------------------|-------------------|-----------------------------|
| Alemany et al. Lancet Respir Med, 2022 (CONV-ERT trial) [39] | Spain | DB MC PC | 188 vs. 188 | 56 ± 10<sup>a</sup> | Outpatient | Mild, moderate | 4.4 ± 1.4<sup>b</sup> | 1 × 1 unit high titre | N/A | Incidence of hospitalisation at 28 days, change in viral load in nasal swabs at 7 days | No significant difference |
| Devos et al. Eur Respir J, 2022 (DAWnp-plasma trial) [21] | Belgium | OL MC | 326 vs. 163 | 62 ± 14<sup>b</sup> | Hospitalised | Severe | 6 ± 6<sup>a</sup> | 2 × 2 units high titre | CHQ, HCQ, REM, TOZ, LPV/r, CS | Proportion of patients alive without IMV at 15 days | No significant difference |
| Sekine et al. Eur Resp J, 2022 (PLA-COVID trial) [40] | Brazil | OL SC | 80 vs. 80 | 60.5 ± 20<sup>a</sup> | Hospitalised | Severe, critical | 10 ± 4<sup>a</sup> | 2 × 1 units variable titre | CS | Proportion of patients with clinical improvement at 28 days | No significant difference |
| van den Berg et al Sci Rep, 2022 (PROTECT-Patient trial) [41] | South Africa | DB MC PC | 52 vs. 51 | 56 ± 17<sup>a</sup> | Hospitalised | Severe | 9 ± 5<sup>a</sup> | 1 × 1 unit variable titre | CS | Successful treatment at 28 days | No significant difference<sup>5</sup> |
| Bajpai et al. BMJ Open, 2022 [42] | India | OL MC | 200 vs. 200 | 55.5 ± 1.17<sup>b</sup> | Hospitalised | Severe, critical | NA | 2 × 1 unit variable titre | REM, CS | Time to clinical improvement at 28 days | No significant difference |
Table 3 (continued)

| First author, journal and year of publication | Area | Trial design | Patient no. (CCP vs. SOC/placebo) | Age | Study setting | COVID-19 WHO severity | Transfusion timing from symptom onset (days) | Units and CCP titre transfused | Concomitant medications | Primary endpoints | Primary endpoint results |
|---------------------------------------------|------|--------------|-----------------------------------|-----|---------------|------------------------|---------------------------------------------|---------------------------------|------------------------|---------------------|------------------------|
| Sullivan et al. N Engl J Med, 2022 [26]     | USA  | DB MC        | 592 vs. 589 42 ± 22.5<sup>a</sup> | Outpatient | Mild     | 6 ± 3<sup>a</sup> | 1 × 1 unit high titre | -                 | COVID-19-related hospitalisations at 28 days | CCP decreased the incidence of hospitalisation (RRR 54%) |
| Rojas et al. BMC Infect Dis, 2022 [43]     | Colombia | SB MC | 45 vs. 46 55.5 ± 24.8<sup>a</sup> (CCP) | Hospitalised | Severe | 10 ± 3<sup>a</sup> | 2 × 1 unit variable titre | CS            | Reduction of viral load, increase in titres of IgG and IgA | No significant difference, CCP was associated with an early transient increase in IgG levels at day 4 |
| Gharbharan et al. Clin Microbiol Infect, 2022 (CoV-Early trial) [44] | Netherlands | DB MC PC | 207 vs 209 med 60 ± 10<sup>a</sup> |
| | | | | | | | | | | | Clinical improvement at 28 days<sup>6</sup> | No significant difference |

<sup>a</sup>Median ± interquartile range
<sup>b</sup>Mean ± standard deviation
<sup>1</sup>Early study termination due to decreasing number of enrolled patients
<sup>2</sup>Early study termination due to patients having potent neutralising antibody titres
<sup>3</sup>Early study termination due to emergency-use authorisation (EUA)
<sup>4</sup>Early study termination due to interim analysis indication
<sup>5</sup>Early study termination due to novel evidence published
<sup>6</sup>Recruitment discontinued due to elevating vaccination uptake rates

ARB, arbidol; CCP, COVID-19 convalescent plasma; CHQ, chloroquine; COVID-19, coronavirus disease 2019; CS, corticosteroid; DB, double blind; HCQ, hydroxychloroquine; hIVIG, human intravenous immunoglobulin; ICU, intensive care unit; IFN-γ, interferon gamma; IgA, immunoglobulin A; IgG, immunoglobulin G; IL-10, interleukin-10; IL-6, interleukin-6; IMV, invasive mechanical ventilation; INF, interferon; IVM, ivermectin; LPV/r, lopinavir/ritonavir; MC, multicentre; NIV, non-invasive ventilation; OL, open label; OST, oseltamivir; PC, placebo controlled; RBV, ribavirin; REM, remdesivir; RRR, relative risk reduction; SAR, sarilumab; SB, single blind; SOC, standard of care; TNF-α, tumour necrosis factor alpha; TOZ, tocilizumab; WHO, World Health Organisation
in the USA, showed significant difference favouring CCP therapy among hospitalised patients [22]. One found signal of possible clinical benefit among patients with severe COVID-19 [23], and one other observed trends toward improvement in clinical status by day 28 among hospitalised patients receiving CCP within 7 days of symptom onset and with higher titres of neutralising antibodies and concomitant corticosteroid usage [24]. Among the RCTs evaluating CCP therapy with clinical primary endpoints in the outpatient setting, the one carried out by Libster et al., administering CCP less than 72 h after symptom onset in long-term care facilities in Argentina, found a statistically significant difference: CCP reduced the risk of progression to severe respiratory disease by 48%, and the CCP group showed longer time to the development to severe respiratory disease [25]. Sullivan et al. found that CCP decreased the incidence of hospitalisation when administered in a relatively younger outpatient population with mild disease in the USA; the relative risk reduction was 54% [26].

Nine RCTs included mortality in the primary endpoints, and none of them found significant difference in mortality rates among hospitalised COVID-19 patients. One study evaluated the cytokine storm indices after CCP therapy, with results that the mean levels of lymphocytes and IL-10 significantly increased, the levels of IL-6, TNF-α and IFN-γ decreased in the CCP group [27]. None of the RCTs enrolling more than 200 hospitalised patients showed significant differences in the primary endpoints. The largest RCT, as part of the RECOVERY trial, examined more than 11,000 patients with various disease severity, receiving CCP, but found no statistically significant difference between the CCP and usual care groups concerning mortality, length of hospital stay or progression to need for mechanical ventilation [28].

In summary, CCP therapy seems to have limited effect on clinical status and mortality based on the RCTs available in the literature. Favorable outcomes were seen mainly in outpatient settings, when CCP was applied very early in disease courses and in mild cases. Thus, RCTs published so far might have limitations as well. Many of them studied patients with heterogeneous disease severity, applied CCP units with various neutralisation antibody titres, determined different study endpoints and differed in the timing of CCP administration as well. Despite the heterogeneity, a meta-analysis of eligible RCTs found no correlation of CCP therapy with better clinical outcomes [45]. It could be hypothesised that CCP therapy might possess a clinically relevant effect in some COVID-19 patient subgroups. Elderly patients may benefit from CCP therapy, as they are expected to mount a slower antibody response due to immunosenescence. Also, patients with advanced B-cell defects or other immunocompromised conditions lacking efficient antibody producing ability may benefit from passive immunisation [46–50]. Furthermore, the Association for the Advancement of Blood and Biotherapies recently published a clinical practice guideline for the appropriate use of CCP that suggests CCP transfusion in addition to the usual standard of care for selected patient groups, based on low-to-moderate-certainty pieces of evidence [51].

**Conclusion**

In our single-centre, open-label, prospective, observational study enrolling 180 patients, we found that among elderly patients hospitalised for non-critical COVID-19, the use of convalescent plasma therapy did not seem to possess an additional positive effect on most clinically relevant outcomes. Further investigation is needed to determine potential patient subgroups which might benefit from adequately timed CCP therapy.

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**Declarations**

**Conflict of interest**  The authors declare no competing interests. The Copyright Transfer Statement was completed by the corresponding author on behalf of all co-authors.

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