




Efficacy of early transfusion of convalescent plasma with high-titer SARS-CoV-2 neutralizing antibodies in hospitalized patients with COVID-19

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Abstract

Background: Despite most controlled trials have shown no measurable benefit of COVID-19 convalescent plasma (CCP) in patients with COVID-19, some studies suggest that early administration of CCP with high-titer anti-SARS-CoV-2 can be beneficial in selected patients. We investigated the efficacy of early administration of high-titer CCP to patients with COVID-19 who required hospitalization,

Study design and methods: Observational, propensity score (PS) matched case-control study of COVID-19 patients treated with CCP within 72 h of hospital admission and untreated controls from August 2020 to February 2021. All CCP donations had a Euroimmun anti-SARS-CoV-2 sample-to-cutoff ratio ≥ 3 . PS matching was based on prognostic factors and presented features with high-standardized differences between the treated and control groups. The primary endpoint was mortality within 30 days of diagnosis.

Results: A total of 1604 patients were analyzed, 261 of whom received CCP, most (82%) within 24 h after admission. Median age was 67 years (interquartile range: 56–79), and 953 (60%) were men. Presenting factors independently associated with higher 30-day mortality were increased age, cardiac disease, hypoxemic respiratory failure, renal failure, and plasma D-dimer >700 ng/ml. After PS matching, transfusion of CCP was associated with a significant reduction in the 30-day mortality rate (odds ratio [OR]; 0.94, 95% confidence interval [CI]: 0.91–0.98; $p = .001$) that extended to the 60th day after COVID-19 diagnosis (OR: 0.95; 95% CI: 0.92–0.99; $p = .01$).

Conclusion: Our results suggest that CCP can still be helpful in selected patients with COVID-19 and call for further studies before withdrawing CCP from the COVID-19 therapeutic armamentarium.

Abbreviations: CCP, COVID-19 convalescent plasma; CI, confidence interval; IQR, interquartile range; LOS, length of stay; OR, odds ratio; PS, propensity score; RT-PCR, reverse transcriptase-polymerase chain reaction; STD, standardized differences; TRALI, transfusion-related lung injury.

KEYWORDS

blood center operations, FFP transfusion, transfusion practices (adult)

1 | INTRODUCTION

Passive immunotherapy with COVID-19 convalescence plasma (CCP) has extensively been investigated from the early days of the pandemic. Recent systematic reviews and meta-analyses of randomized, controlled trials have concluded that transfusion of CCP is safe but lacks any measurable efficacy in treating COVID-19.¹⁻⁶

The issue, however, is far from being settled because of the heterogeneity among published studies concerning the characteristics of recruited patients and the severity of disease, the diversity of evaluated outcomes,^{1,3,5-9} the dose of CCP (200–1200 ml),^{1,8,10,11} time of CCP infusion over the disease's course (1–30 days after COVID-19 diagnosis), variable content of neutralizing SARS-CoV-2 antibodies in CCP,^{1,3,5,12} and degree of geographical and temporal matching between convalescent donors and recipient patients. In addition, many randomized, controlled trials were prematurely interrupted because of slow recruitment or anticipation of futility,^{1,2,9,13} thereby eroding the statistical power to detect minor but real treatment effects.

On the opposite side, some experimental and observational studies suggest that early administration of CCP with high-titer of SARS-CoV-2 neutralizing antibodies to mildly ill patients can reduce the rate of COVID-19 progression to severe disease,¹⁴⁻¹⁶ and it even might decrease mortality.^{7,8,12,17-19}

This study aimed to investigate the possible beneficial effect of the early administration of CCP with high-titer SARS-CoV-2 spike IgG antibodies to patients with COVID-19 who required hospital admission.

2 | PATIENTS AND METHODS

2.1 | Patients

Every patient admitted to the Hospital Clinic of Barcelona (Spain) diagnosed with COVID-19 from February 2020 is recorded in a prospectively managed database. We queried this database for patients who received CCP from August 2020 to February 2021 ($n = 319$) to select patients transfused within 72 h after admission ($n = 261$). We considered only the first hospital admission. Subsequent hospital admissions of patients

regularly transfused with CCP (i.e., immunosuppressed) were excluded from the analysis. Patients with COVID-19 not transfused with convalescent plasma and admitted during the same period were retrieved as controls ($n = 1343$).

Diagnosis of COVID-19 was based on bilateral pneumonia by clinical and radiological criteria and a positive reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2. All patients received a diagnosis within 24 h of being first seen at the Emergency Room.

Oral informed consent (to avoid paper handling) was obtained from all the patients. Written witnessed consent was documented in the medical record, and written permission by the patient was later obtained when feasible. The study was approved by the Research Ethics Committees of our center with regard to the transfusion arm (HCB/2021/0467), and the Vall d'Hebron Hospital Research Unit in relation to the plasma collection arm (PR(BS)207/2020). A waiver for approval from the Spanish Medicines Agency was obtained due to the classification of CCP as a blood product.

2.2 | Collection, processing, and transfusion of convalescent plasma

The CCP was collected from donors who had recovered from RT-PCR confirmed COVID-19 and tested positive for IgG antibodies against SARS-CoV-2. Only nontransfused men were eligible as donors to minimize the risk of transfusion-related lung injury (TRALI). Additional donor qualifications included adequate venous access through peripheral veins and the standard eligibility criteria for voluntary plasma donors. Plasma donations of 600 ml collected by apheresis were depleted of leukocytes by filtration, pathogen-reduced with methylene blue by the Macopharma method, divided into two equal units of 250 ml, and stored frozen below -30°C until utilization.

All patients received two consecutive 250 ml units of ABO compatible CCP from the same donor. A minority of patients ($n = 9$) who had a transfusion reaction to the first unit did not receive the second one. Patients were monitored for vital signs and clinical status before, during, and after transfusion in order to detect any transfusion-related adverse event.

2.3 | Determination of anti-SARS-CoV-2 antibodies in convalescent plasma

The CCP donations were tested for SARS-CoV-2 anti-spike IgG with a commercial CE-marked ELISA microplate coated with recombinant Spike S1 domain protein (Euroimmun Medizinische Labordiagnostika, Lübeck, Germany). The Euroimmun IgG has been shown to correlate well with neutralization activity in prior assays.²⁰ Only donations with a sample-to-cutoff ratio (S/Co) equal to or higher than 3 were selected for transfusion (The US FDA later recommended S/Co ratio for EUROIMMUN to qualify high-titer CCP).²¹ Collection and processing of CCP and testing for SARS-CoV-2 antibodies were performed at the regional blood bank of Catalonia (*Banc de Sang i Teixits*).

2.4 | Statistical methods

The primary study outcome was mortality within 30 days after COVID-19 diagnosis. Predefined secondary endpoints included admission to the intensive care unit (ICU) and need for invasive or noninvasive respiratory support by the 30th day, mortality within 60 days, and length of stay (LOS) of surviving patients.

We estimated the average treatment effect associated with convalescent plasma after matching cases and controls through a propensity score (PS) for receipt of CCP. Variables used to estimate the PS included those with an absolute standardized difference (STD) >1.20 between the treatment and control groups and variables independently associated with the primary endpoint (30-day mortality). Matching was performed with repositioning and forced to find at least one control for every case within a caliper of 0.1 (maximum allowed distance along the PS scale between matched pairs). According to this matching method, some cases may have more than one matched control, and some controls may have matched more than one case.²²

Continuous and ordered variables were summarized as the median and the interquartile range (IQR) and statistically compared by the Mann-Whitney *U* test. Categorical variables were represented by frequencies and proportions and compared by the chi-squared test. Differences between the treated and the control group before and after PS matching were measured in the scale of STD. We evaluated the association between baseline variables and 30-day mortality by calculating the odds ratio (OR) and 95% confidence interval (CI) through parsimonious multivariable logistic regression. Candidate variables for prognosis evaluation and their cutoff values were selected based on clinical meaning and published literature.²³ They included age, sex, time from symptoms

onset to hospital admission, comorbidities, hypoxemic respiratory failure at presentation (SatO₂ <93%), systolic and diastolic blood pressure, serum creatinine, serum ferritin, and plasma D-dimer.

For all the statistical analyses, we used the software Stata, version 14 (www.stata.com). PS matching was performed with the “teffects psmatching” module incorporated in Stata.

3 | RESULTS

3.1 | Patients and survival

A total of 1604 patients were analyzed, 261 of whom received CCP. Among patients in the plasma group, 213 (82%) were transfused within 24 h after admission, 34 (13%) between 24 and 48 h, and 14 (5%) between 48 and 72 h.

The median age for the whole series was 67 years (IQR: 56–79), and 953 (60%) were men. Table 1 summarizes the baseline characteristics for cases and controls. In the unmatched sample, recipients of convalescence plasma were slightly younger than control patients (median: 64 and 67 years, respectively, STD 0.126) and were more likely to suffer from comorbid kidney disease (16.8% and 11.7%, respectively, STD 0.184), and less likely to have chronic arterial hypertension (36.4% and 45.9%, STD –0.195). Patients in the convalescent plasma group were also less likely to be hypotensive at presentation (systolic blood pressure (SBP) <100 mm Hg; 8.6% and 13.3%, respectively, STD –0.149).

Corticosteroids were used in 74.3% of CCP recipients and 72.5% of control patients at some time during admission. Remdesivir and tocilizumab were used in 13.0% and 19.9% of patients in the CCP group and in 27.2% and 11.4% of the control group, respectively.

In total, 171 (10.6%) patients died within 30 days of COVID-19 diagnosis, and 25 additional patients died between the 30th and 60th day. Four hundred twenty-five (26.5%) patients required ICU admission, and 242 (15.1%) needed intensive respiratory support. Median LOS for survivors was 8 days (IQR: 5–8). The crude 30-day mortality rate was significantly lower in the CCP group than in the control group (6.9% vs. 11.5%, *p* = .03), and so was the mortality by the 60th day (8.0% vs. 13.1%, *p* = .02).

Presenting factors associated with higher 30-day mortality at the multivariable analysis were increased age, cardiac disease, hypoxemic respiratory failure (SatO₂ <93%), renal failure (serum creatinine >1.3 mg/ml), and plasma D-dimer >700 ng/ml (Table 2). After adjusting for the above prognostic factors, the transfusion of CCP was independently associated with lower 30-day mortality (OR: 0.41, 95% CI: 0.22–0.78; *p* = .007).

TABLE 1 Clinical features at diagnosis of COVID-19 in patients treated with convalescent plasma and nontreated, control patients

| | Patients treated with convalescent plasma (n = 261) | Control patients not treated with convalescent plasma (n = 1343) | Standardized difference |
|--|---|--|-------------------------|
| Age, years | 64 (54–79) | 67 (56–79) | –0.126 |
| Men–female | 163 (62.7%)/97 (37.3%) | 790 (59.2%)/545 (40.8%) | 0.074 |
| Days from symptoms to admission | 7 (4–8) | 7 (4–10) | –0.105 |
| Prior lung disease | 55 (21.1%) | 323 (24.0%) | –0.071 |
| Cardiac disease | 57 (21.8%) | 353 (26.3%) | –0.104 |
| Kidney disease | 44 (16.8%) | 157 (11.7%) | 0.148 |
| Diabetes | 57 (21.8%) | 262 (19.5%) | 0.058 |
| Chronic arterial hypertension | 95 (36.4%) | 617 (45.9%) | –0.195 |
| Immunosuppression ^a | 61 (23.4%) | 280 (20.8%) | 0.043 |
| Hypoxemic respiratory failure (SatO ₂ <93%) | 72 (31.2%) | 297 (27.3%) | 0.084 |
| Systolic blood pressure <100 mm Hg | 20 (8.6%) | 144 (13.3%) | –0.149 |
| Lymphocyte count <1.5 × 10 ⁹ /L | 232 (88.8%) | 1145 (85.3%) | 0.108 |
| Serum creatinine ≥1.3 mg/dl | 67 (25.7%) | 305 (22.7%) | 0.095 |
| Serum ferritin >500 ng/ml | 150 (59.1%) | 611 (53.4%) | 0.114 |
| D-dimer >700 ng/ml | 116 (44.4%) | 621 (51.8%) | –0.114 |

^aRecipients of solid organ transplantation and patients with solid tumors or hematological cancers on treatment.

TABLE 2 Presenting features at diagnosis of COVID-19 independently associated with increased 30-day mortality

| | Odds ratio (95% confidence interval) | p |
|------------------------|--------------------------------------|-------|
| Age, per year | 1.08 (1.06–1.10) | <.001 |
| Cardiac disease | 2.25 (1.45–3.49) | <.001 |
| SatO ₂ <93% | 2.62 (1.71–4.03) | <.001 |
| Creatinine >1.3 mg/dl | 2.59 (1.69–3.97) | <.001 |
| D-dimer >700 ng/ml | 2.14 (1.33–3.45) | .002 |

3.2 | Treatment effect after PS matching

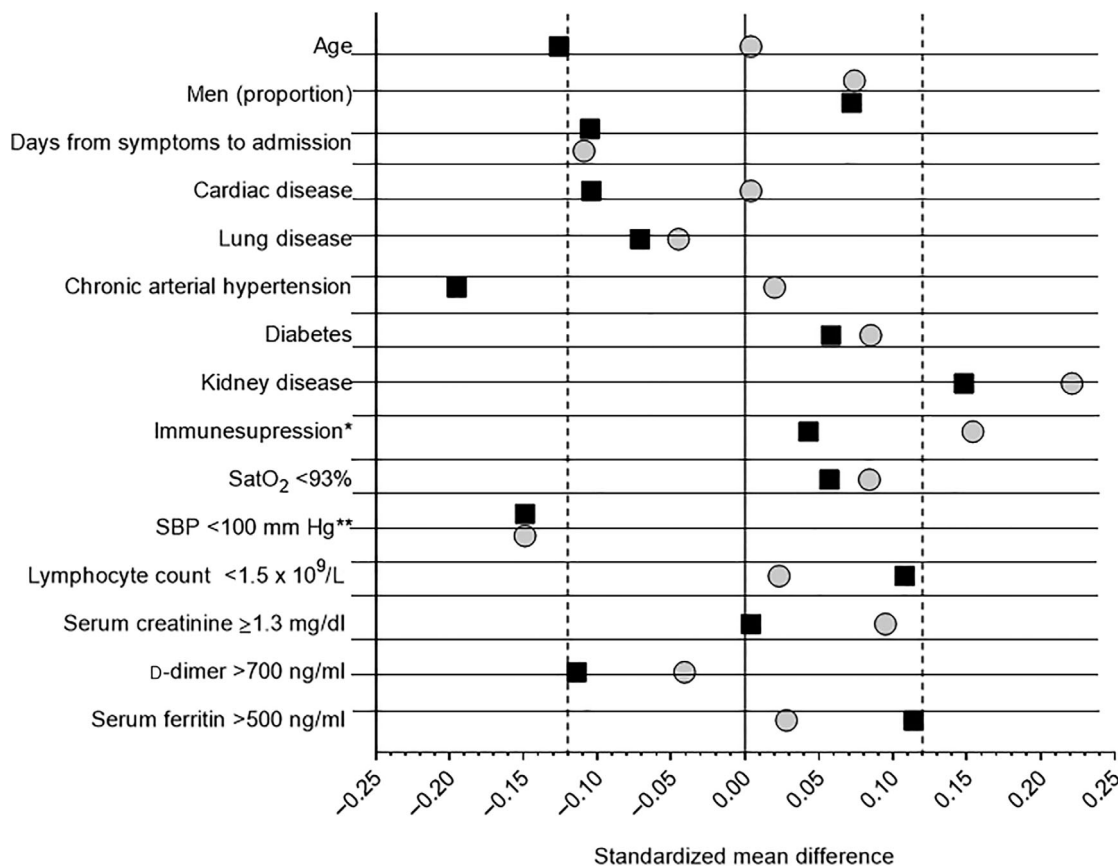
Variables used for calculating the PS included the history of kidney disease or chronic arterial hypertension, SBP <100 mm Hg at presentation, and the abovementioned prognostic factors (age, cardiac disease, creatinine >1.3 mg/dl, SatO₂ <93%, and D-dimer >700 ng/ml). As shown in Figure 1, the PS matching balanced the treatment and control groups for the presenting variables that could have influenced the physician's decision to use CCP. Only the history of kidney disease and current immunosuppression remained more incident in the CCP group. In contrast, SBP <100 mg Hg remained more frequent in the control group at the 0.12 absolute STD level. The PS matching also yielded a notable level of overlap

between the probabilities of having received or not CCP along the scale of PS values (Figure S1).

Table 3 summarizes the average treatment effect for the main and secondary outcomes after PS matching. Use of CCP was associated with a significant reduction in the 30-day mortality rate (OR: 0.94, 95% CI: 0.91–0.98; $p = .001$) that extended to the 60th day after COVID-19 diagnosis (OR: 0.95; 95% CI: 0.92–0.99; $p = .01$). There was no significant difference between cases and controls in the incidence of ICU admission, the requirement of intensive respiratory support, or the LOS of surviving patients.

3.3 | Treatment effect in immunosuppressed and nonimmunosuppressed patients

We further investigated whether the decreased mortality associated with CCP in the whole population might have been driven by the minority of patients purportedly immunosuppressed (transplant recipients, hemat oncology patients, and others on immunodepressant drugs). Use of CCP was associated with a significant reduction of the 30-day mortality in the immunosuppressed ($n = 61$; OR: 0.88, 95% CI: 0.70–0.89; $p = .018$) and the nonimmunosuppressed patients ($n = 200$; OR: 0.96, 95% CI: 0.93–0.99; $p = .012$).



* includes recipients of solid organ transplantation and patients with hematologic or solid organ neoplasms on treatment. ** SBP: systolic blood pressure.

FIGURE 1 Standardized mean difference in presenting features between cases and controls before (black squares) and after (gray circles) propensity score matching

TABLE 3 Primary and secondary outcomes associated with the use of convalescent plasma in the propensity score-matched sample

| Outcome | Odds ratio (95% confidence interval [CI]) | p |
|-------------------------------------|---|------|
| 30-day mortality | 0.94 (95% CI: 0.91 to 0.97) | .001 |
| 60-day mortality | 0.95 (95% CI: 0.93 to 0.99) | .01 |
| 30-day ICU admission | 1.05 (95% CI: 0.96 to 1.14) | .31 |
| 30-day respiratory support | 1.03 (95% CI: 0.97 to 1.09) | .30 |
| | Coefficient (95% CI) | |
| Length of stage or survivors (days) | 0.76 (95% CI: -1.38 to 2.9) | .49 |

3.4 | Neutralizing SARS-CoV-2 antibodies in convalescence plasma

The signal-to-cutoff ratio for SARS-CoV-2 spike IgG antibodies in CCP ranged from 3 to 13.5, with a median signal-to-cutoff ratio of 7.6 (IQR: 6.4–8.8). CCP units were

arbitrarily categorized in the higher and lower half of the signal-to-cutoff ratio distribution by taking the median as the cutoff. One hundred and twenty-seven patients received CCP with titers above the median and 134 with titers below the median.

There was no significant difference between patients who received CCP in the higher or the lower half titer distribution concerning the 30-day mortality (5.2% vs. 8.6%, respectively, $p = .27$) or the secondary outcomes.

3.5 | Adverse effects related to the transfusion of convalescent plasma

Nine minor and two severe reactions to CCP transfusion were reported. Seven urticarial reactions were resolved with antihistaminics, and two febrile reactions were managed with antithermic drugs. The two severe reactions consisted of episodes of dyspnea, one of them progressing to respiratory failure requiring endotracheal

intubation and mechanical respiratory support. In both cases, testing for HLA and neutrophil-specific antibodies in the donors yielded negative results.

4 | DISCUSSION

In the present study, transfusion of CCP with high-titer SARS-CoV-2 neutralizing antibodies early after hospital admission was associated with a moderate but statistically significant reduction in the 30- and 60-day mortality rates in patients with COVID-19. No effect was seen on the need for respiratory support or ICU admission within the first 30 days, nor on the LOS of surviving patients.

Our study's overall 30-day mortality rate (10.6%) was comparable to figures reported in most previous studies on CCP^{4,18,24} but notably inferior to those reported in others.^{2,5,9} In addition, factors independently associated with increased mortality in our patients were similar to those found in previous studies,^{7,15,18} including older age, cardiac disease, hypoxemic respiratory failure, renal failure, and high D-dimer values at COVID-19 presentation.

We used the above prognostic factors and initial variables unequally distributed between the treated and untreated cohorts to ensure an equal distribution of potential confounders simultaneously associated with prognosis and the physician's decision to employ CCP. The procedure successfully matched the treated and control cohorts for all relevant variables except for kidney disease and coexisting immunosuppression, which remained more prevalent in the treated group. Both variables reflected the preferential use of CCP when remdesivir was contraindicated because of renal failure and in patients in whom a low humoral response against the virus could be entertained. It is worth noting that renal failure and immunosuppression have previously been associated with poor outcomes in COVID-19,^{25,26} so they could have biased the outcomes against CCP. We lack any explanation for the higher prevalence of low SBP in the treated cohort. Still, this feature was neither associated with poorer outcomes in our series nor previously linked to prognosis in COVID-19. On the other hand, the resulting matched groups had a similar probability of having received or not the treatment, an essential but often forgotten condition for successful PS matching.²⁷

Our findings agree with the results from clinical studies testing the effectiveness of CCP with high-titer SARS-CoV-2 neutralizing antibodies when transfused early in the course of COVID-19.^{7,12,16–18} In the randomized, controlled trial conducted by Libster et al.,⁸ transfusion of 250 ml of CCP with high-titer SARS-CoV-2 spike antibodies within 72 h of the onset of symptoms yielded a 48% reduction in the relative risk of progressing to severe respiratory failure. Unfortunately, the trial was prematurely

interrupted because of slow recruitment, which may have precluded finding minor but relevant differences in survival.

There is a biological rationale to support the administration of high-titer CCP in the early stages of COVID-19. Viral burden has not yet peaked beyond the possibility of neutralization, the host is still mounting the humoral response, and the uncontrolled inflammatory reaction that defines severe disease has not yet started. This would be the window period for a high dose of exogenous neutralizing antibodies to effectively eradicate or block SARS-CoV-2,²⁸ as it has recently been shown by using monoclonal antibodies.²⁹ In contrast to prior studies with CCP,^{8,12,18} we did not find any association between the anti-SARS-CoV-2 titers in CCP and the clinical outcomes. It is worth noting that all our CCP donors had a high minimum level of neutralizing antibodies, which may have precluded observing a clinical benefit associated with higher titers. Indeed, it is plausible that excess antibodies, once the virus has already been neutralized, would not confer any additional benefit.

In order to exploit the possible window period of CCP efficacy soon after infection, two recent trials have tested the early administration of high-titer CCP outpatient. In the Shoham et al.³⁰ study, CCP did not reduce the infection rate in persons exposed to a high-risk contact. However, subsequent hospitalization and adverse events in the CCP arm were less frequent than in controls transfused with nonconvalescent plasma. On the other hand, in the clinical trial conducted by Alemany et al.,³¹ CCP administered soon after infection did not prevent hospitalization in the subsequent days. Still, the study was underpowered because of the early termination of the trial.

The RECOVERY trial,⁵ the largest randomized, controlled trial on CCP in COVID-19, has been decisive in negating the efficacy of this therapy in patients hospitalized because of COVID-19. After analyzing 11,558 patients randomly allocated to CCP with high-titer anti-spike IgG or standard treatment, no difference emerged in the 28-day survival rate or other meaningful clinical outcomes. However, mortality in the control and treatment groups of RECOVERY (24%) more than doubled the rates observed in our study and others,^{4,18,24} suggesting a more severe disease. It must also be noted the trend to lower mortality in patients receiving CP early after disease onset reported in RECOVERY.⁵

Based on the RECOVERY trial and other sources of evidence negating the efficacy of CCP, the FDA has recently limited the use of CCP to immunosuppressed patients with COVID-19.³² This decision let us investigate whether the minority of immunosuppressed patients might have driven the decreased 30-day mortality associated with CCP in our whole cohort. We found that CCP

was associated with a 30-day reduced mortality in both immunosuppressed and nonimmunosuppressed patients. Unfortunately, the patient immune status had to be inferred from the baseline disease and its treatment, since no measure of the immune response to the SARS-CoV-2 was available before the transfusion of CCP.

Adverse effects of CCP transfusion in our patients were rare and mostly mild, agreeing with previous reports,^{12,13,17,18,24,33} except for an episode of severe pulmonary reaction that merits further comment. Both TRALI and circulatory overload were ruled out and, though a definite diagnosis was lacking, the clinical picture in this patient was compatible with the antibody-dependent enhancement phenomenon.³⁴

We selected only CCP donors with a Euroimmun sample-to-cutoff ratio above 3.0. In fact, in 97% of our donors, the ratio was above the 3.5 threshold later used by the FDA to define high-titer CCP,²¹ and it was above the 6.0 figure required by RECOVERY investigators in 83% of our donors. In addition, our plasma donors and recipient patients inhabited the same geographical area, and both collections and transfusions were performed while most infections in our region were caused by the European SARS-CoV-2 variant (G614). A recent analysis has demonstrated that geographical matching between CCP donors and recipients translates into better outcomes.³⁵ Moreover, most CCP transfusions were completed less than 24 h after COVID-19 diagnosis (all within 72 h) for a total dose of 500 ml.

Donor CCP was submitted to pathogen-reduction to minimize the hypothetical risk of SARS-CoV-2 transmission and comply with the Spanish Government requirements for plasma transfusion. Prior studies have shown that photoinactivation with methylene blue does not significantly reduce the titers of SARS-CoV-2 antibodies.³⁶⁻³⁷ In fact, the methylene blue method has been reported to be less detrimental to anti-SARS-CoV-2 titers than other pathogen-reduction technologies currently applied to donated plasma.³⁶ However, we cannot certainly disregard some decrease in the *in vivo* neutralizing capacity due to pathogen-reduction.

Among the study weaknesses, we should mention the observational design, which precludes establishing a causal association despite PS matching. Moreover, the absolute treatment effect was small enough to rule out unmeasured confounding with certainty. Nevertheless, despite the above drawbacks, our results suggest that CCP can still be helpful in selected patients with COVID-19 and support the need for further studies before withdrawing CCP from the COVID-19 therapeutic armamentarium.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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