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Treatment of severe COVID-19 patients with either low- or high-volume of convalescent plasma versus standard of care: A multicenter Bayesian randomized open-label clinical trial (COOP-COVID-19-MCTI)

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Summary

Background Administration of convalescent plasma may serve as an adjunct to supportive treatment to prevent COVID-19 progression and death. We aimed to evaluate the efficacy and safety of 2 volumes of intravenous convalescent plasma (CP) with high antibody titers for the treatment of severe cases of COVID-19.

Methods We conducted a Bayesian, randomized, open-label, multicenter, controlled clinical trial in 7 Brazilian hospitals. Adults admitted to hospital with positive RT-PCR for SARS-CoV₂, within 10 days of the symptom onset, were eligible. Patients were randomly assigned (1:1:1) to receive standard of care (SoC) alone, or in combination with 200 mL (150–300 mL) of CP (Low-volume), or 400 mL (300–600 mL) of CP (High-volume); infusion had to be performed within 24 h of randomization. Randomization was centralized, stratified by center. The primary outcome was the time until clinical improvement up to day 28, measured by the WHO ten-point scale, assessed in the intention-to-treat population. Interim and terminal analyses were performed in a Bayesian framework. Trial registered at ClinicalTrials.gov: NCT04415086.

Findings Between June 2, 2020, and November 18, 2020, 129 patients were enrolled and randomly assigned to SoC ($n = 42$), Low-volume ($n = 43$) or High-volume ($n = 44$) CP. Donors presented a median titer of neutralizing antibodies of 1:320 (interquartile range, 1:160 to 1:1088). No evidence of any benefit of convalescent plasma was observed, with Bayesian estimate of 28-day clinical improvement of 72.7% (95%CI, 58.8 to 84.7) in the SoC versus 64.1% (95%CI, 53.8 to 73.7) in the pooled experimental groups (mean difference of -8.7%, 95%CI, -24.6 to 8.2). There was one case of cutaneous mild allergic reaction related to plasma transfusion and one case of suspected transfusion-related acute lung injury but deemed not to be related to convalescent plasma infusion.

Interpretation In this prospective, randomized trial of adult hospitalized patients with severe COVID-19, convalescent plasma was not associated with clinical benefits.

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Research in context

Evidence before this study

We searched Pubmed database from March 1, 2020, to October 5, 2021, for randomized trials evaluating the administration of convalescent plasma for the treatment of patients with COVID-19 using the search terms (“COVID-19”, “SARS-CoV-2”, and “coronavirus”) and (“convalescent plasma”, or “hyperimmune plasma”), and we identified 14 randomized clinical trials. Two trials were labeled as “early administration” with patients presenting up to 7 days of symptoms, with one study presenting clinical benefit in patients older than 65 years and up to 72 h of symptoms, and another failed to demonstrate clinical improvement. In 12 trials, patients were hospitalized and in 10 studies, no clinical benefit was reported, and while only one study demonstrated better survival in patients who received convalescent plasma.

Added value of this study

This is the first trial to compare two different volumes of convalescent plasma, with high titers of neutralizing antibodies, and no clinical benefit was found, compared to standard of care therapy, in hospitalized patients with a median of 8 days of symptoms. There was also no significant impact on duration of mechanical ventilation, length of hospital stays, time to SARS-CoV-2 negativity in nasopharyngeal swab,

Implications of all the available evidence

In hospitalized patients with severe covid-19, the administration of convalescent plasma demonstrates no clinical therapeutic benefits.

Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused approximately 370 million confirmed cases, with over 5 million deaths worldwide.¹ The search for an effective and accessible antiviral treatment is ongoing. The rather old concept of using neutralizing antibodies infusion to treat COVID-19 patients was initially revived with the use of plasma from convalescent donors² and further explored with the administration of monoclonal antibodies.^{3,4} The use of convalescent plasma has been previously studied in infections caused by H1N1 influenza, H5N1 avian

influenza virus, SARS-CoV-1, and Ebola virus, with some case series and clinical trials suggesting that this strategy can be effective.^{5–9} However, these studies have important limitations, and well conducted clinical trials addressing this strategy are scarce.

In March 2020, the Food and Drug Administration (FDA) authorized convalescent plasma for emergency use in severe and potentially fatal COVID-19 patients.¹⁰ A study including 20,000 patients demonstrated that convalescent plasma transfusion was safe, with a low incidence of serious adverse events (point estimate of 0.06% to 0.18% of related serious adverse events). The use of monoclonal antibodies in the treatment of mild to moderate COVID-19 non-hospitalized patients who are at risk for progressing to severe disease or hospitalizations⁴ has been approved for emergency use by the FDA. Nevertheless, in many countries this treatment is not available, and convalescent plasma would be a more cost-effective and accessible alternative if efficacy was to be demonstrated. In April 2020, the Brazilian Health Ministry, via the National Sanitary Surveillance Agency (ANVISA, from the acronym in Portuguese) issued a national authorization for use of convalescent plasma in the treatment of COVID-19.¹¹

In Brazil, by November 8th, 2021, there were over 21 million confirmed COVID-19 cases, with over 600,000 deaths, with daily rising numbers.

Here, we report the findings of our randomized clinical trial, that aimed to assess the efficacy and safety of the administration of 200 mL or 400 mL of convalescent plasma compared to standard of care alone, in severe and potentially severe COVID-19 hospitalized patients.

Methods

Study design and participants

The COOP-COVID-19-MCTI trial was a multicenter, randomized, open-label, clinical trial. Patients were randomized to one of three groups: standard of care (SoC) alone, and two experimental groups: SoC plus SoC associated with convalescent plasma either at 200 mL (range 150–300 mL) (Low-volume) or at 400 mL (range 300–600 mL) (High-volume).

Accrual took place in seven participating research sites in Brazil. Patients aged 18 years or older, with RT-PCR-confirmed COVID-19 infection in any clinical sample, less than 10 days after onset of symptoms at screening, presence of COVID-19 pneumonia with a typical, indeterminate, or atypical compatible chest computerized tomography scan

and at least one of the following criteria, were enrolled: need for >3 L of O_2 in catheter/mask or $>25\%$ in the Venturi mask to maintain O_2 saturation $>92\%$; or presence of respiratory distress syndrome with $PaO_2/FiO_2 <300$ mmHg. Intubated patients were considered eligible within 48 h of orotracheal intubation. Patients were excluded if they had a history of serious adverse reactions to transfusion, participation in another COVID-19 treatment clinical trial using antiviral or immunobiological drugs, IgA deficiency, presence of a clinical condition that precluded infusion of 400 ml of plasma at clinical discretion, pregnant or breastfeeding women, a history of receiving immunoglobulin in the past 30 days, or a significant risk of death within the next 48 h at clinical discretion. The protocol was approved by the Brazilian Ethics in Research Committee (CONEP) and by each site's Institutional Review Board. Written informed consent was obtained from all participants or their legal representatives, and the trial was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines. The authors take full responsibility for the design and conduct of the trial and vouch for the accuracy and completeness of the data, as well as data analysis and adherence to the original protocol.

Randomisation and masking

Eligible patients were randomly allocated (1: 1: 1) to one of three randomized groups, one control group (SoC) and two experimental groups (Low-volume and High-volume). The randomization scheme used computer generated lists performed by the clinical research center, stratified by center, with blocks of various sizes and performed through a centralized internet service to ensure allocation concealment.

This was an open-label study in which both participants and investigators knew to which groups participants had been randomly assigned.

Procedures

Convalescent plasma donor selection: Donors aged 18 to 60 years, recovered from COVID-19 with a documented SARS-CoV-2 RNA detection by RT-PCR, and absence of COVID-19 symptoms for at least 15 days, were selected. In donors with less than 30 days since complete recovery, SARS-CoV-2 RNA testing prior to donation was performed. All plasma units were tested for SARS-CoV-2-specific neutralization, and those with titers $\geq 1:80$, were considered eligible. We excluded donors with previous pregnancies (unless blood anti-HLA antibodies were not detected) and those with a history of receiving blood components. Additional routine donor screening criteria (minimum body weight of 50 Kg; hemoglobin >12.0 g/dL; negative results in serological and molecular screening tests for transfusion-transmitted infections (HIV, hepatitis B, hepatitis C, Chagas disease, HTLV and syphilis) were applied.

Interventions: Standard of care treatment included oxygen supplementation, corticosteroids, anticoagulation, and/or antibiotics, according to the clinical judgement of attending physicians. Patients in experimental groups additionally received either (Low-volume or 1 unit) 200 ml (range, 150–300 ml) or (High-volume or 2 units) 400 ml (range, 300–600 ml) of compatible convalescent plasma, administered within 24 h after randomization. The plasma infusion lasted up to 1 h. In the High-volume group, the infusion could be split in two stages within 24 h. All participants of the experimental groups received 50 mg of intravenous diphenhydramine 30 min prior to plasma transfusion.

Assessments: Patients were assessed once daily by study investigators who captured clinical and laboratory data, including the 10-category disease progression scale from day 0 to day 28, hospital discharge, or death. After hospital discharge, participants were contacted by phone or in-person visits. Safety was monitored by the research staff on day 1 and 2. Serial oropharyngeal swab samples were obtained at baseline and on days 1, 3, 5, 7, 14, and 28 for SARS-CoV-2 RT-PCR testing (see Supplementary materials). Serial serum and plasma samples were obtained at baseline and days 1, 3, 5, 7, 14, and 28 for neutralizing antibody titers and specific SARS CoV-2 IgG, IgM, and IgA titers (see Supplementary materials). For neutralizing antibody titer measurements, we used the cytopathic effect-based virus neutralization test; and for IgG, IgM, and IgA measurements, we used the enzyme-linked immunosorbent assay (ELISA). Clinical and laboratory data were registered in an electronic database and validated by the trial coordinating staff.

Outcomes

The primary outcome was time to clinical improvement at day 28, defined as the number of days from randomization to the first decline of at least two categories on the World Health Organization's ordinal progression scale¹² (**Supplementary Table 1**) or hospital discharge, whichever came first.

Secondary outcomes were incidence of acute adverse events, as defined by the International Society of Blood Transfusion/International Haemovigilance Network¹³; ordinal scale of 10 categories assessment at D7, D14, and D28; length of hospital stay in survivors up to 28 days and time from randomization to death; time to a first negative SARS-CoV-2 RT-PCR in nasopharyngeal swab; SARS-CoV-2 specific IgG, IgM and IgA titers on days 0, 1, 3, 5, 7, 14 and 28; and detection of neutralizing antibodies on days 0, 1, 3, 5, 7, 14 and 28.

Statistical analysis

No sample size calculations were done due to the absence at the time of any pre-existing data on effect size for convalescent plasma in COVID-19 patients. A

total of 120 patients, that is, 40 in each randomized group, were scheduled to be enrolled, with the trial adopting a Bayesian framework as recommended when comparing multiple treatment strategies against one another.¹⁴ In this Bayesian framework, minimal sample sizes of 25–40 patients in each group allow providing accurate estimate as shown in early clinical trials.

All efficacy and safety analyses were based on the intent-to-treat principle, and conducted blindly to treatment assignment, except for the control group given the trial objectives. Summary statistics were used, with frequencies and percentages for categorical variables, or median and interquartile range (IQR) for continuous or discrete variables.

Bayesian paradigm allowed sequential analyses as data accumulated, with one interim analysis of the primary outcome performed once 30 patients were enrolled in each randomized group, in order to assess the futility, or the potential harm of trial continuation, planning to stop the trial when the clinical questions were considered sufficiently well answered for applying the results to the broader patient population. Noninformative Beta (1,1) were used as prior for the day 28-outcome in each randomized group, then actualized in posterior probabilities.¹⁵ For decision-making, probabilistic statements of difference in the probability of 28-day improvement over the SoC group, were derived, with Bayesian decision criteria derived from Harrell in the COVID-19 setting as detailed in the *Appendix*.¹⁶ Briefly, they aim at quantifying the futility or harm of the experimental over the control, pooling the two experimental arms, or for each arm, separately, and, if both relevant, compared to each other. The interim analysis performed on October 17, 2020, based on the first 90 enrolled patients, did not allow any decision regarding futility or harm of experimental groups, so that enrollment continued.

Terminal analysis further displayed the cumulative incidence of clinical improvement within the 18 days of randomization, where death free of success defined a competing risk event. Prespecified treatment by subset interactions, according to age (<, > 50), body mass index (<, > 30), time since symptoms onset (<, > 6 days), total specific SARS-CoV-2 antibody titers, and neutralizing antibodies titers (<, > 20), were assessed. The evolution of the WHO scale over time was described using multistate modeling,¹⁷ then compared by linear mixed models, as well as the detection of SARS-CoV-2, the IgG, IgM, and IgA titers, and that of neutralizing antibodies.

All analyses were performed on R (<https://www.R-project.org/>). R2jags package was used for Bayesian analyses.

A data safety monitoring board periodically reviewed and evaluated the accumulated study data for participant safety, study conduct, and efficacy, and made recommendations to the coordinating team concerning

continuation, modification, or termination of the trial. No issues of participant safety or data integrity were raised.

This trial was registered with ClinicalTrials.gov, NCT04415086.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From June 2, to November 18, 2020, a total of 164 individuals were screened for participation, of whom 35 patients had at least one exclusion criteria (**Figure 1**). A total of 129 patients (median age 61 years (IQR, 46–69), 41 (32%) female, 119 (92%) with comorbidities) were randomly allocated to control arm (SoC, $n = 42$), 200 ml plasma arm B (Low-volume, $n = 43$) or 400 ml plasma arm C (High-volume, $n = 44$). Three patients withdrew consent after randomization, 2 from the SoC group, and 1 from the Low-volume plasma group before plasma infusion. Of the 119 participants who underwent testing, 114 (96%) had a positive SARS-CoV-2 RT-PCR in a nasopharyngeal swab sample. The infused convalescent plasma units in Low-volume and High-volume contained a median of 1:320 (IQR, 1:256–1:800) and 1:320 (IQR, 1:160–1:088) neutralizing antibody titers, respectively.

Baseline characteristics of study participants are summarized in **Table 1**, similar across randomized groups. The comorbidities are detailed in **Supplementary Table S2**. Median time between onset of symptoms and enrollment was 8 days (IQR, 6 to 9). At the time of enrollment, 52 (40%) were on oxygen by mask or nasal prongs, 23 (18%) on non-invasive ventilation or high-flow oxygen, and 54 (42%) on mechanical ventilation. Almost one third of study participants (28/96, 29%) had undetectable neutralizing antibodies at baseline.

Within the first 28 days of randomization, 83 patients improved their WHO scale by at least 2 points, while four additional patients who did not, were discharged alive from the hospital, accounting 87 clinical improvements, including 31 in SoC, 26 in Low-volume and 30 in High-volume. **Figure 2** displays the estimated cumulative incidence of clinical improvement and the Bayesian posterior densities of 28-day probability of such an improvement in each randomized group. No evidence of any benefit of convalescent plasma was observed, with 28-day clinical improvement of 72.7% (95% credible interval, 58.8 to 84.7) in the SoC versus 64.1% (95% credible interval, 53.8 to 73.7) in the pooled experimental groups (mean difference of -8.7%, 95% credible interval, -24.6 to +8.2). Posterior estimates of decision criteria did not suggest any efficacy of

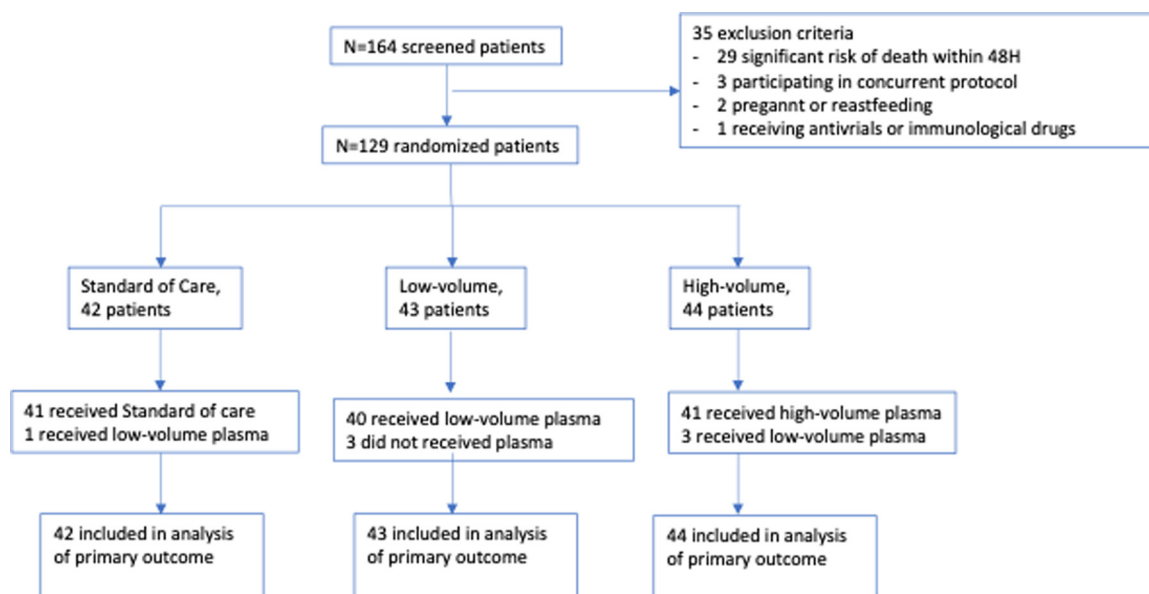


Figure 1. Flow chart of the study.

experimental groups; on the opposite, some evidence of inefficacy of the Low-volume group over the control was shown (*Supplementary Table S3*). Indeed, when restricting the comparison to the Low-volume group, 60% (95% credible interval, 45.6 to 73.7) of clinical improvement at day 28 were observed (mean difference, -12.7%, 95% credible interval, -31.7 to +6.7), while, with the High-volume group, the difference with SoC alone was reduced (-5.4%, 95% credible interval, -23.9 to +13.4), with an estimated 28-day probability of clinical improvement of 67.4% (95% credible interval, 53.4 to 79.9).

Table 2 lists secondary endpoints. The various lengths of time spent in the different states from the WHO ordinal scale are displayed in each randomized group in **Figure 3**. At day 28, of the 100 surviving patients, 29 were still in the hospital and 71 had been discharged. There was no evidence of any difference

across randomized groups in the cumulative incidence of hospital discharge (**Figure 4A**) or in terms of survival (**Figure 4B**). A total of 66 (69%) of 95 who were tested for nasopharyngeal SARS-CoV-2 RT-PCR during follow-up became negative within the first 28 days (25 in the SoC, 18 in the Low-volume, and 23 in the High-volume). Of the 76 patients for whom a baseline total anti-SARS-CoV-2 IgG antibody level was determined, levels were undetectable in 28 (36.8%). There was no evidence of any effects of group allocation in terms of time course of specific IgG, IgM and IgA titers for SARS-CoV-2 (*Supplementary Figure 2*).

Only 2 patients, both in High-volume group, developed one adverse event each. There was one non-severe allergic reaction that could be definitely imputed to the treatment (patient received antihistamines with complete resolution) and one severe transfusion-related

| | SoC group, 42 patients | Low-volume group, 43 patients | High-volume group, 44 patients |
|---|---------------------------|----------------------------------|-----------------------------------|
| Age, years | 62 (47.8–69.8) | 62.8 (50.6–70.2) | 55.0 (45.1–69.1) |
| Male gender, % | 33 (78.6) | 25 (58.1) | 30 (68.2) |
| BMI, Kg/m ² | 30.9 (27.0–33.8) | 28.8 (25.9–35.9) | 28.4 (25.4–33.3) |
| Comorbidities, % | 36 (85.7) | 43 (100) | 40 (90.9) |
| Time since symptom onset, days | 8 (6–9) | 7 (6–9) | 8 (7–9) |
| Positive RT-PCR SARS-CoV-2 nasopharyngeal swab, % | 39 (97.5) | 35 (92.1) | 39 (97.5) |
| Detectable neutralizing antibodies titers, % | 23 (74.2) | 22 (68.7) | 23 (69.7) |
| IgG positivity, % | 24 (80.0) | 18 (58.0) | 21 (66.0) |

Table 1: Baseline demographics and clinical characteristics of study participants according to randomization groups.

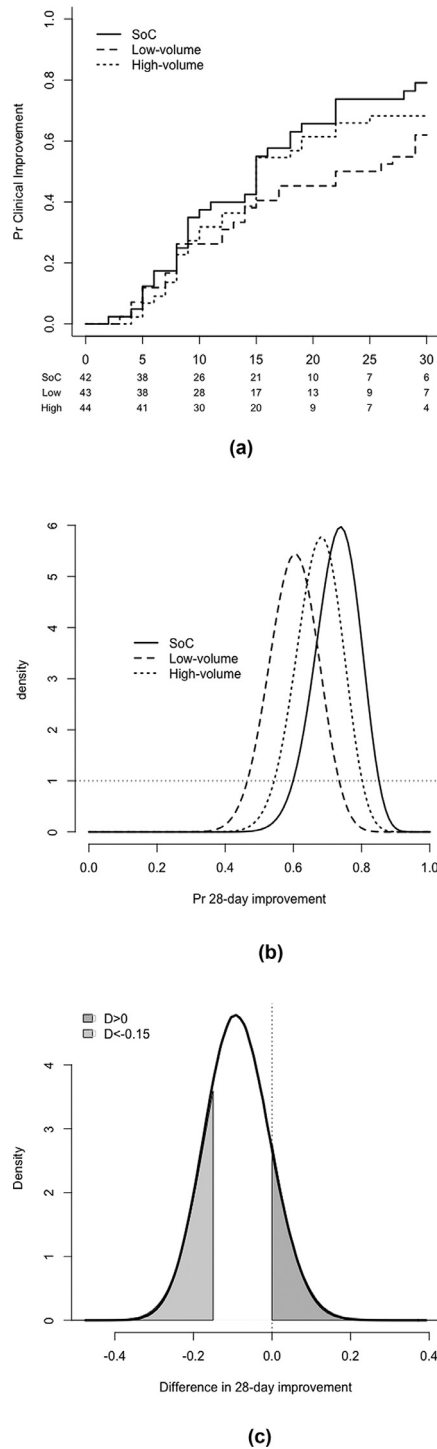


Figure 2. Estimated 28-day clinical improvement across randomized groups. (A) Overall cumulative incidence according to the randomization group, (B) Bayesian posterior density in each randomized group, (C) Bayesian posterior density of the difference in outcome probability in the experimental versus the control group.

acute lung injury unlikely related to plasma infusion. In the latter case, leukocyte antibodies directed against human leukocyte antigens were negative and pulmonary distress was attributed to COVID-19.

Complications of COVID-19 occurred in 15 patients: ten patients presented a secondary bacterial infection, including nine pneumonia and one catheter-related bloodstream infection. There were 13 episodes of thromboembolism overall, with five occurring after randomization (2 in SoC, 3 in High-volume groups). The different drugs administered to the patients during follow-up are summarized in *Supplementary Table S4*.

Subgroup analyses

Analysis of treatment effect, as measured by relative risk (RR) of success in the experimental arms against the SoC arm in subgroups defined by days since symptoms onset, patient baseline detection of neutralizing antibodies, age, and BMI is reported in [Figure 5](#).

Discussion

In this randomized, Bayesian, open-label, multicenter, clinical trial conducted in severe COVID-19 patients with up to 10 days of symptoms onset, no evidence of any clinical benefit of convalescent plasma use (either using low or high volume) was observed when compared to standard of care alone. Safety of convalescent plasma infusion was confirmed, as previously reported.¹⁸

Although observational studies suggested potential clinical effects on mortality,^{2,19,20} the findings of our study corroborate with previous randomized trials that failed to prove any improved clinical outcomes. Earlier in the pandemic, Li et al.²¹ analyzed 103 randomized patients with severe and life-threatening COVID-19 in a trial that was halted prematurely, although the timing of the plasma receipt was late (median time of symptoms of 27 and 30 days in the plasma and control groups, respectively). One trial was prematurely halted because 79% of patients presented titers of neutralizing antibodies > 1:20 at baseline.²² An Indian multicentric trial that included 484 participants also failed to demonstrate clinical benefit, with the limitation that 36% of the donors in that study had undetectable neutralizing antibodies, whereas in our study, roughly 70% of patients presented detectable neutralizing antibodies at baseline. A recent trial in Argentina in which the median time of symptoms to enrollment was 8 days (IQR, 5–10) and approximately 95% of the patients were not intubated, also failed to demonstrate clinical benefit.²³ Similarly, an Italian randomized trial in hospitalized patients presenting with up to 10 days of symptoms and high-titer neutralizing antibodies

| | SoC group 42 patients | Low-volume group 43 patients | High-volume group 44 patients | Risk/Mean Difference (95%CI) | |
|--------------------------------|--------------------------|---------------------------------|----------------------------------|-------------------------------|-------------------------------|
| | | | | Low-volume versus SoC | High-volume versus SoC |
| Length of hospital stay, days | 13.5 (10.7–21.2) | 16.0 (8–20) | 13 (9–20) | -0.5 (-4.2 to 5.3) | -2.0 (-2.3 to 6.3) |
| 28-day Overall survival, % | 83.7 (72.5 to 96.6) | 69.9 (56.9 to 85.7) | 79.0 (67.7 to 92.2) | -13.8% (-38.7 to 11.2) | -4.6% (-25.7 to 16.4) |
| Undetectable SARS-CoV-2 PCR | 6/24 (25.0) | 12/25 (48.0) | 10/27 (37.0) | 23.0 (-4.0 to 47.2) | 12.0 (-13.9 to -36.1) |
| Neutralizing antibodies titers | 1:160 (1:30–1:1920) | 1:120 (1:20–1:640) | 1:160 (1:20–1:640) | -1:330 (-1:2432 to 1:1772) | -1:256 (-1:2388 to 1:1875) |

Table 2: Outcomes according to randomization groups.

convalescent plasma did not reduce disease progression or death.²⁴ The RECOVERY trial, with the largest number of patients to date, also failed to demonstrate clinical benefit, although the median duration of symptoms was also quite late, of 9 days (IQR, 6–12 days).²⁵ The PLA-COVID trial (donor plasma with neutralizing titers \geq 1:80 and patients with a median of 10 days of symptoms),²⁶ and another recently published randomized trial in patients with 12 days of symptoms²⁷ failed to demonstrate clinical benefit as well. A German group demonstrated that a subgroup of patients that received a higher cumulative amount of neutralizing antibodies also presented clinical improvement and survival.²⁸ Although not having demonstrated clinical improvement, one trial has shown better survival in hospitalized patients.²⁹

Whether some subsets of COVID-19 patients may benefit from convalescent plasma or not, was also questioned. Subset analyses in our study including baseline neutralizing antibodies titers, age, and BMI did not provide evidence that convalescent plasma infusion impacted clinical outcome. The absence of interaction with age was also reported in the study by Korley et al.³⁰ whereas, a benefit of early convalescent plasma administration was suggested in patients older than 65 years presenting less than 72 h of symptoms,³¹ or in seronegative patients.³² Other trials with earlier administration of convalescent plasma in the first week of symptoms have also resulted in prevention of disease progression or mortality at 28 days,^{33,34} suggesting that patients are more likely to be seronegative. Only 29% of our cohort was comprised of patients with undetectable neutralizing antibodies, and there was a higher proportion of seropositive patients in the control group, this could favor plasma groups, and there was still no clinical benefit.

The lack of efficacy of convalescent plasma in our trial may have resulted from timing of plasma administration, selection of patients, and source of convalescent plasma. All included patients in this study were on supplemental oxygen, while 54% were on mechanical ventilation, therefore already in the inflammation phase of the course of the disease. For two centers that included 26% of the patients, convalescent plasma was sourced

approximately 700 miles away. Given that plasma near-sourced likely represents the local variants,³⁵ this might also have impacted the efficacy. A monoclonal antibody combination containing casirivimab and imdevimab³⁶ reduced 28-day mortality among patients who were seronegative at baseline, also in the RECOVERY trial. With the emergence of SARS-CoV-2 variants escaping the monoclonal antibodies targets, patients recovering from variant viruses will most likely develop convalescent plasma that is capable of neutralizing these variants,³⁷ which suggests a possible window of administration of convalescent plasma in selected patients.

The main strengths of this trial include the fact that all donated plasma units presented neutralizing antibody titers of at least 1:80, and with a Bayesian analysis of interim data at every 30 patients included we were able to reach an inefficacy conclusion with 129 patients. Inclusion criteria comprising participants with a higher demand of oxygen supplementation but limited to less than 48 h of mechanical ventilation resulted in a more homogeneous population. Importantly, this is the first trial to assess the benefits of two different volumes of plasma, as the volume to be administered is still a subject of debate.

Limitations of the study include the fact that each center may have had different standard of care treatment protocols, although the use of corticosteroids, proven effective as support therapy, was used by all centers.³⁸ This was likely reduced by stratification of randomization by site. Additional difficulties include the definition of transfusion-related acute lung injury as an adverse event in this specific population with severe pneumonia, while plasma transfusion took place when patients often had deteriorated respiratory function.

Conclusions

The administration of either low or high volume of convalescent plasma in patients with severe COVID-19 had no impact on clinical improvement with up to 10 days of symptoms onset. There was also no significant

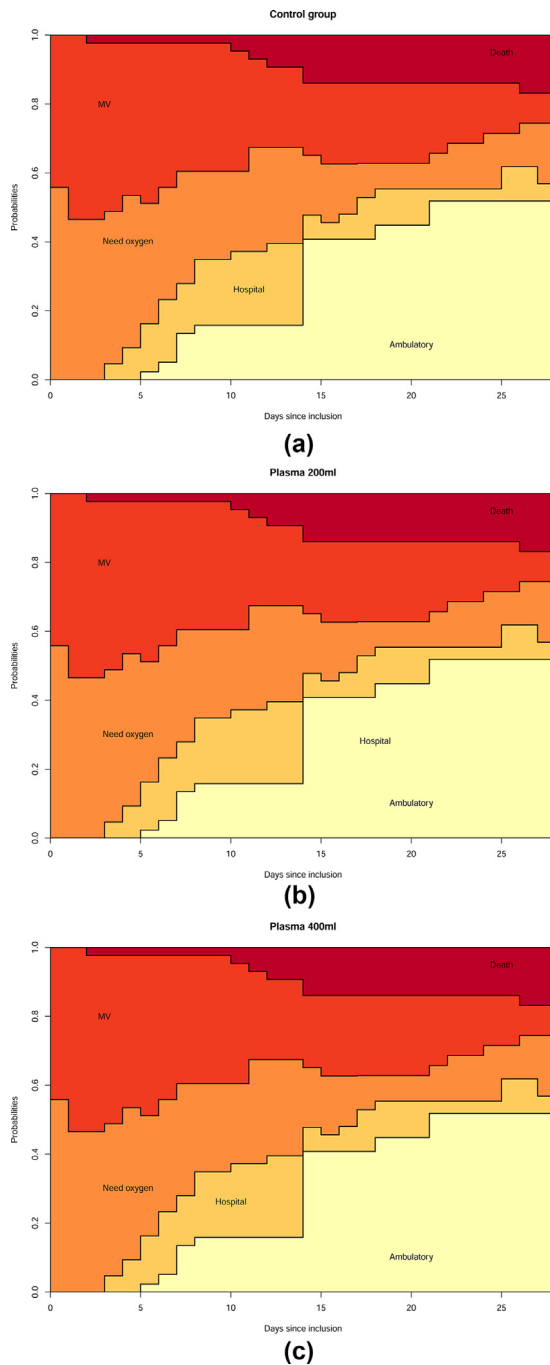
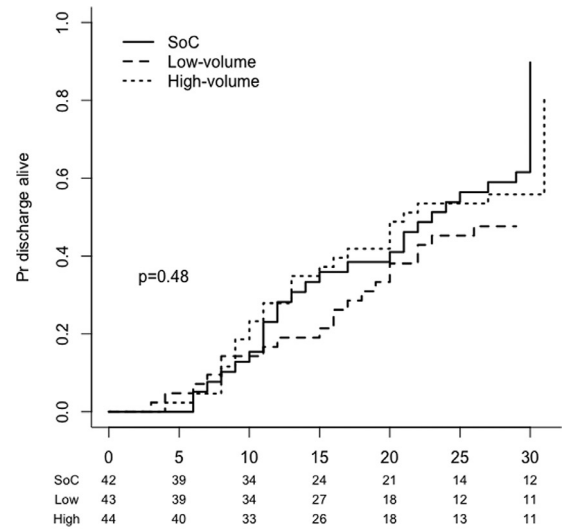
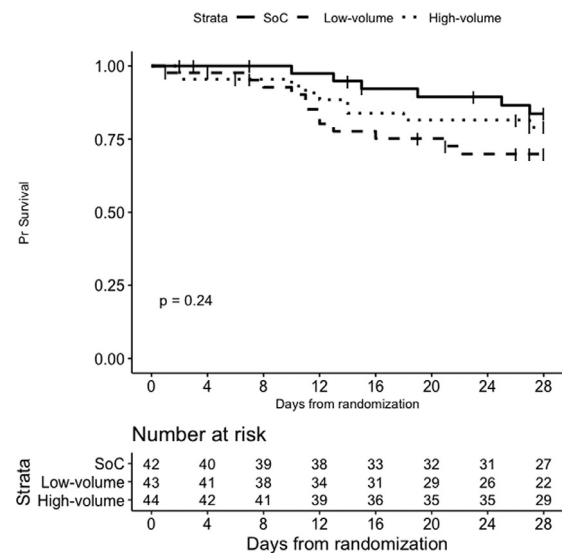


Figure 3. Multistate model representation of the mean times in the different WHO scale states in each randomized group. MV: mechanical ventilation.

impact on secondary outcomes (duration of mechanical ventilation, length of hospital stays, time to SARS-CoV-2 negativity in nasopharyngeal swab, time to antibodies titers). Nevertheless, convalescent plasma transfusion appears to be a safe procedure.



(a)



(b)

Figure 4. Cumulative incidence of hospital discharge (A) and overall survival (B) after randomization according to the randomization group.

Contributors

EGK, VR, RTC, BDB, SW, ECS, LVR, and JMK conceived the trial and EGK is the chief investigator. ATWS, NBC, DGA, and EGK coordinated the trial. EGK, VR, RTC, BDB, SW, ECS, AMJ, GCS, JMK, LVR, ATP, JAMB, DMV, BALF, BPAP, LFLR, MDBC, ARM, APHY, CBB, RF, RRG, VIAS, and ELD contributed to the protocol and design of the study. EGK, VR, RTC, BDB, SW, AMJ, GCS, JMK, LVR, ATP, JAMB, DMV, BALF, BPAP, LFLR, MDBC, ARM, APHY, CBB, RF,

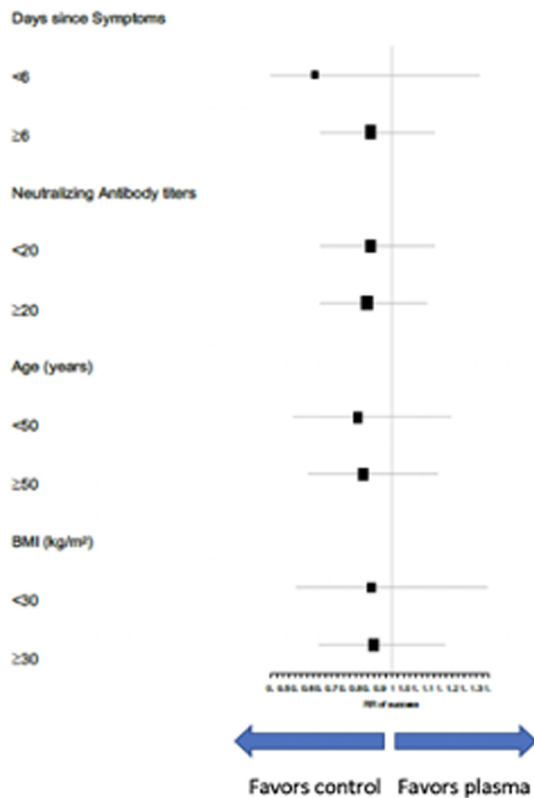


Figure 5. Search for treatment by subset interaction on the main outcome according to days since symptom onset, recipients' neutralizing antibody titers, age, and BMI.

TV, LSM, JCF, CSL, and FCB led the implementation of the study. SC did the statistical plan and analysis and SC, ATWS, VIAS, NBC, and DGA have verified the underlying data. RRG, ELD, CPS, RM, DBA, CSL, and EDC generated laboratory data. ATWS, VR, SC, VIAS, and EGK drafted the report. All other authors contributed to the implementation and data collection. All authors reviewed and approved the final report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data sharing statement

De-identified participant data set collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others upon request, for researchers whose proposed use of the data has been approved, for any purpose. Data will be available with publication. If needed, requests will require the ethics committee approval of the Coordinating Center at the University of Sao Paulo (Brazil).

The statistical analysis plan is available in the supplementary materials. Other additional protocol information related not informed in the manuscript will be available upon requests, as well as informed consent forms, if needed.

Declaration of interests

Authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.lana.2022.100216](https://doi.org/10.1016/j.lana.2022.100216).

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