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A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19

Max R. O'Donnell, Beatriz Grinsztejn, Matthew J. Cummings, Jessica E. Justman, Matthew R. Lamb, Christina M. Eckhardt, Neena M. Philip, Ying Kuen Cheung, Vinay Gupta, Esau João, Jose H. Pilotto, Maria Pia Diniz, Sandra Wagner Cardoso, Darryl Abrams, Kartik N. Rajagopalan, Sarah E. Borden, Allison Wolf, Leon Claude Sidi, Alexandre Vizzoni, Valdilea G. Veloso, Zachary C. Bitan, Dawn E. Scotto, Benjamin J. Meyer, Samuel D. Jacobson, Alex Kantor, Nischay Mishra, Lokendra V. Chauhan, Elizabeth F. Stone, Flavia Dei Zotti, Francesca La Carpia, Krystalyn E. Hudson, Stephen A. Ferrara, Joseph Schwartz, Brie A. Stotler, Wen-Hsuan W. Lin, Sandeep N. Wontakal, Beth Shaz, Thomas Briese, Eldad A. Hod, Steven L. Spitalnik, Andrew Eisenberger, Walter I. Lipkin

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Research In-Press Preview

BACKGROUND. Although convalescent plasma has been widely used to treat severe coronavirus disease 2019 (COVID-19), data from randomized controlled trials that support its efficacy are limited.

METHODS. We conducted a randomized, double-blind, placebo-controlled trial among adults hospitalized with severe and critical COVID-19 at five sites in New York City (USA) and Rio de Janeiro (Brazil). Patients were randomized in a 2:1 ratio to receive a single transfusion of either convalescent plasma or placebo (normal control plasma). The primary outcome was clinical status at 28 days following randomization, measured using an ordinal scale and analyzed using a proportional odds model in the intention-to-treat population.

RESULTS. Of 223 participants enrolled, 150 were randomized to receive convalescent plasma and 73 to normal control plasma. At 28 days, no significant improvement in clinical status was observed in participants randomized to convalescent plasma (OR 1.50, 95% confidence interval (CI) 0.83-2.68, p=0.180). However, 28-day mortality was significantly lower in participants randomized to convalescent plasma versus control plasma (19/150 [12.6%] versus 18/73 [24.6%], OR 0.44, 95% CI 0.22-0.91, p=0.034). The median titer of anti-SARS-CoV-2 neutralizing antibody in infused convalescent plasma units was 1:160 (IQR 1:80-1:320). In a subset of nasopharyngeal swab samples from Brazil that underwent genomic sequencing, no evidence of neutralization-escape mutants was detected.

CONCLUSIONS. In adults hospitalized with severe COVID-19, use of convalescent […]

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Authors:

Max R. O'Donnell,[1,2,3] Beatriz Grinsztejn,[4] Matthew J. Cummings,[1,3] Jessica Justman,[2,5,6] Matthew R. Lamb,[2,5] Christina M. Eckhardt,[1] Neena M. Philip,[5] Ying Kuen Cheung,[7] Vinay Gupta,[8] Esau João,[9] Jose Henrique Pilotto,[10] Maria Pia Diniz,[4] Sandra Wagner Cardoso,[4] Darryl Abrams,[1] Kartik Rajagopalan,[1] Sarah Borden,[1] Allison Wolf,[1] Leon Claude Sidi,[9] Alexandre Vizzoni,[4] Valdilea G. Veloso,[4] Zachary C. Bitan,[11] Dawn E. Scotto,[1] Benjamin J. Meyer,[12] Samuel D. Jacobson,[12] Alex Kantor,[1] Nischay Mishra,[3] Lokendra V. Chauhan,[3] Elizabeth Stone,[11] Flavia Dei Zotti,[11] Francesca La Carpia,[11] Krystalyn E. Hudson,[11] Stephen A. Ferrara,[11] Joseph Schwartz,[11] Brie Stotler,[11] Wen-Hsuan Lin,[11] Sandeep Wontakal,[11] Beth Shaz,[13] Thomas Briese,[3] Eldad A. Hod,[11] Steven L. Spitalnik,[11] Andrew Eisenberger,[14] W. Ian Lipkin[2,3,11]

Affiliations:

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA; 622 West 168th Street, New York, NY, 10032, USA.

[2]Department of Epidemiology, Columbia University Mailman School of Public Health, New York, NY, USA; 722 West 168th Street, New York, NY, 10032, USA.

[3]Center for Infection and Immunity, Columbia University Mailman School of Public Health, New York, NY, USA; 722 West 168th Street, New York, NY, 10032, USA.

[4]Instituto Nacional de Infectologia Evandro Chagas, Av. Brasil, 4365 - Manguinhos, Rio de Janeiro , 21040-360, Brazil

[5]ICAP, Columbia University Mailman School of Public Health, New York, NY, USA; 722 West 168th Street, New York, NY, 10032, USA.

[6]Division of Infectious Diseases, Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA; 622 West 168th Street, New York, NY, 10032, USA.

[7]Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY, USA; 722 West 168th Street, New York, NY, 10032, USA.

[8]Institute for Health Metrics and Evaluation, University of Washington, Box 351615, 3980 15th Ave NE, Seattle, WA, 98195, USA

[9]Hospital Federal dos Servidores do Estado, R. Sacadura Cabral, 178 - Saúde, Rio de Janeiro, 20221-161, Brazil

[10]Hospital Geral de Nova Iguaçu, Av. Henrique Duque Estrada Meyer, 953 - Posse, Nova Iguaçu and Laboratório de Aids e Imunologia Molecular, Instituto Oswaldo Cruz – Fiocruz, Rio de Janeiro, 21040-360, Brazil

[11]Department of Pathology and Cell Biology, Columbia University Irving Medical Center, 622 West 168th Street, New York, NY, 10032, USA.

[12]Vagelos College of Physicians and Surgeons, Columbia University, New York, NY; 630 West 168th Street, New York, NY, 10032, USA.

[13]New York Blood Center, 310 E 67th Street, New York, NY 10065, New York, NY, USA.

[14]Division of Hematology and Oncology, Department of Medicine, Columbia University Irving Medical Center, 622 West 168th Street, New York, NY, 10032, USA.

Corresponding Author: Max R. O'Donnell, MD, MPH, Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Irving Medical Center, 622 West 168th St, PH 8E-101, New York, NY, 10032, USA. Email: mo2130@columbia.edu; Telephone: +12123055794; Fax: +12123058464

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Conflicts of Interest: MRO'D and MJC participated as investigators for clinical trials evaluating the efficacy and safety of remdesivir in hospitalized patients with COVID-19, sponsored by Gilead Sciences. All compensation for this work was paid to Columbia University. VG is employed by Amazon Care. The remaining authors declare no interests relevant to the submitted work.

Abstract

Background: Although convalescent plasma has been widely used to treat severe coronavirus disease 2019 (COVID-19), data from randomized controlled trials that support its efficacy are limited.

Methods: We conducted a randomized, double-blind, placebo-controlled trial among adults hospitalized with severe and critical COVID-19 at five sites in New York City (USA) and Rio de Janeiro (Brazil). Patients were randomized 2:1 to receive a single transfusion of either convalescent plasma or placebo (normal control plasma). The primary outcome was clinical status at 28 days following randomization, measured using an ordinal scale and analyzed using a proportional odds model in the intention-to-treat population.

Results: Of 223 participants enrolled, 150 were randomized to receive convalescent plasma and 73 to normal control plasma. At 28 days, no significant improvement in the clinical scale was observed in participants randomized to convalescent plasma (OR 1.50, 95% confidence interval (CI) 0.83-2.68, p=0.180). However, 28-day mortality was significantly lower in participants randomized to convalescent plasma versus control plasma (19/150 [12.6%] versus 18/73 [24.6%], OR 0.44, 95% CI 0.22-0.91, p=0.034). The median titer of anti-SARS-CoV-2 neutralizing antibody in infused convalescent plasma units was 1:160 (IQR 1:80-1:320). In a subset of nasopharyngeal swab samples from Brazil that underwent genomic sequencing, no evidence of neutralization-escape mutants was detected.

Conclusion: In adults hospitalized with severe COVID-19, use of convalescent plasma was not associated with significant improvement in day 28 clinical status. However, convalescent plasma was associated with significantly improved survival. A possible explanation is that survivors remained hospitalized at their baseline clinical status.

Trial Registration: ClinicalTrials.gov, NCT04359810

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Introduction

As of April 19th, 2021, over 141 million cases of coronavirus disease 2019 (COVID-19) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) had been reported worldwide (1). Available data suggest that approximately 10-25% of patients with SARS-CoV-2 infection develop severe COVID-19 characterized primarily by pneumonia and in a subset, acute respiratory distress syndrome (ARDS) (2-4) and among severe cases, mortality occurs in 39-49% (2,4).

Following the emergence of SARS-CoV-2, convalescent plasma was proposed as a rapidly scalable therapeutic to prevent or mitigate severe illness through virus neutralization or antibody-dependent immunomodulation (5). During recent epidemics of emerging respiratory viruses such as SARS-CoV, H5N1 and 2009 H1N1 influenza, observational and non-randomized studies reported improved clinical outcomes and minimal adverse effects associated with use of convalescent plasma in severely ill patients (6). In patients with severe COVID-19, observational studies have suggested possible clinical efficacy and safety using convalescent plasma, primarily among patients not receiving invasive mechanical ventilation (IMV) and those with shorter durations of illness (7-10). Despite these signals, data from randomized controlled trials supporting use of convalescent plasma in hospitalized patients with COVID-19 are limited. Open-label trials, including the large Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, reported no significant improvements in clinical outcomes among patients hospitalized with severe COVID-19 (11-13). A double-blind, placebo-controlled trial in Argentina also reported no improvement in clinical outcomes with use of convalescent plasma among adults hospitalized with severe COVID-19, including among subgroups stratified by illness duration and clinical severity (14).

In the United States and Brazil, approximately 31 and 14 million cases of Covid-19 have been reported as of April 19th, 2021, respectively (1). Given the lack of effective medical therapies against SARS-CoV-2, we conducted a randomized, double-blind, controlled phase 2 clinical trial to evaluate the clinical efficacy and safety of convalescent plasma among adults hospitalized with severe and critical COVID-19 in New York City and Rio de Janeiro.

Results

Participants

Between April 21st and November 27th, 2020, a total of 630 patients were evaluated for inclusion criteria across the five study sites. Two-hundred-twenty-three were enrolled, randomized and included in the intention to treat (ITT) analysis (**Figure 1**). Four participants were randomized but did not receive their assigned treatment: three participants (two randomized to convalescent plasma and one to control plasma) had improvements in oxygen saturation to >94% prior to transfusion, and one participant randomized to convalescent plasma developed a maculopapular rash prior to receipt of plasma for which subsequent transfusion was deferred. Thus, 219 patients were included in the per-protocol and safety analysis: 147 participants transfused convalescent plasma, and 72 participants transfused control plasma (**Figure 1**). Data on neutralizing antibody titers were available for 89% (130/150) of convalescent plasma units. Of these, the median titer was 1:160 (IQR 1:80-1:320).

Of the 223 participants enrolled, 73 were enrolled in New York City and 150 in Rio de Janeiro (**Table 1**). The median age of participants was 61 years and 66% (147/223) were male. The median duration of symptoms prior to randomization was 9 days. Nearly all participants required respiratory support at baseline: 57% (126/223) of participants required supplemental oxygen, 25% (55/223) required high-flow oxygen therapy or non-invasive mechanical ventilation, and 13% (28/223) required IMV or ECMO. Some imbalances were present between

treatment groups; participants enrolled in the convalescent plasma group were younger, with fewer men and a slightly longer symptom duration. During the trial period, 81% (181/223) of participants received corticosteroids and 6% (13/223) received remdesivir, the latter exclusively in New York City.

Primary outcome assessment of clinical status at 28 days was completed for 215 (96%) of 223 randomized patients. Eight participants with indeterminate clinical status at day 28 were discharged alive but were unable to be contacted at day 28. Of these eight participants, three had ≥14 days of follow-up and five had <14 days of follow-up.

Primary outcome

Using a one-sided Mann-Whitney test of the alternative hypothesis favoring the convalescent plasma arm, the primary outcome analysis of the ITT population was consistent with a "go" decision (p=0.09). Although participants randomized to receive convalescent plasma had 1.5 times the odds of a one-point improvement in clinical status at day 28, this difference was not statistically significant (OR 1.5, 95% confidence interval [CI] 0.83-2.68, p=0.18) (**Table 2**). After adjustment for age, sex, and illness duration, the odds of improvement were similar (**Table 2**). Results were also similar in unadjusted and adjusted analyses of the per-protocol population and in two sensitivity analyses, one in which the 8 participants without a definitive day 28 outcome were considered deceased, and another in which the last available clinical status was carried forward for patients with ≥14 days of follow-up and patients with <14 days of follow-up were considered deceased (**Tables S1-S3 in supplement**).

28-day Mortality

In the ITT population, mortality at 28 days was significantly lower among participants randomized to convalescent versus control plasma (19/150 [12.6%] versus 18/73 [24.6%], OR

0.44, 95% CI 0.22-0.91, p=0.034) when the last available clinical status was carried forward for the 8 patients without definitive day 28 outcome status (**Table 2, Figure 2**). These results were consistent in adjusted analyses and in sensitivity analyses to account for the 8 patients without definitive day 28 outcome (**Tables 2 and S4-S5 in supplement**). All recorded deaths occurred during hospitalization. No significant between-group differences were observed in the other secondary outcomes (**Table 2 and Figure 3**).

Subgroup Analyses

In pre-specified analyses of the primary outcome based on respiratory support and symptom duration at baseline, no significant between-group differences were observed in the primary outcome (**Figure 4 and Tables S6-S7 in supplement**). However, we observed trends towards improved clinical status among patients who received convalescent plasma ≤7 days after symptom onset and those who received convalescent plasma with higher-titers of neutralizing antibody and concomitant corticosteroids (**Figures 4 and S1-S2 and Tables S6-S7 in supplement**). The median time to corticosteroids was 1 day prior to transfusion in the convalescent plasma and control plasma intervention groups (IQR -2 to 0 days for both). In stratified analyses of 28-day mortality, unadjusted point-estimates consistently favored the convalescent plasma group **(Figure S3).**

SARS-CoV-2 genomic sequencing

RNA template was sufficient to recover near complete (>99%) genomic sequence from 40 nasopharyngeal samples from Brazil. Twenty-nine (73%) represented common clades circulating worldwide and had no spike protein mutations. None of the samples contained the mutations characteristic of B.1.1.28 P1. Four had mutations found in B.1.1.28 (E484K) but did not have the N501Y, K417N/T mutations found in P1. One sample had 3 of 4 mutations

characteristic of B.1.1.28 (AM-II), including V1176K in S, that is not known to impair neutralization. In short, we found no evidence of neutralization-escape mutants.

Safety Analysis

Serious adverse events occurred in 39 of 147 (26.5%) patients who received convalescent plasma and 26 of 72 (36.1%) patients who received control plasma (**Tables S8-S11 in supplement**). Adverse events considered as definitely or probably associated with plasma transfusion were reported in 4 of 147 (2.7%) patients who received convalescent plasma and 3 of 72 (4.2%) patients who received control plasma. In patients who received convalescent plasma, these events included worsening anemia, urticaria, skin rash, and transfusion-associated circulatory overload.

Discussion

In this randomized, blinded, and controlled phase 2 trial conducted in New York City and Rio de Janeiro, treatment with convalescent plasma as compared to control plasma did not result in significant clinical improvement at 28 days, based on an ordinal scale of clinical status, among adults hospitalized with severe and critical COVID-19. However, mortality at 28 days was significantly lower among patients randomized to convalescent plasma. This effect was observed across analyses adjusted for imbalances in baseline variables with prognostic relevance and in sensitivity analyses performed to account for indeterminate 28-day vital status in 8 patients.

Although limited, available data suggest that treatment efficacy for convalescent plasma may be dependent on illness duration and severity and titers of neutralizing anti-SARS-CoV-2 antibody in transfused plasma. In a recent clinical trial from Argentina, transfusion of high-titer convalescent plasma within 72 hours of symptom onset prevented progression to severe

illness among elderly adults with mild COVID-19 (15). In contrast, no overall improvements in clinical status were observed in recent trials of convalescent plasma among inpatients with severe COVID-19 in China, Argentina, and the United Kingdom (11-13). However, subgroup analyses in two of these trials suggested a possible benefit among patients with less severe and shorter durations of illness (11,12). These signals are consistent with results of a retrospective study of over 3,000 U.S. adults who received convalescent plasma for treatment of severe COVID-19 (10). In this analysis, high-titer convalescent plasma was associated with improved mortality among inpatients who were not receiving IMV at the time of transfusion. Considering power limitations of our trial, we similarly observed trends towards improvement in the primary outcome among patients in the convalescent plasma group who were transfused within 7 days of symptom onset and those who received convalescent plasma with higher-titers of neutralizing anti-SARS-CoV-2 antibody.

In the context of emerging SARS-CoV-2 variants, some of which may be associated with greater transmissibility and more severe illness (16), convalescent plasma may offer distinct therapeutic advantages. Since convalescent plasma, which contains polyclonal antibodies, may be donated and transfused locally, its use may be more adaptable to rapidly changing local viral ecology than other interventions. In contrast, monoclonal antibody therapies may need to be repeatedly engineered and combined to optimize potency among emergent SARS-CoV-2 variants (17,18). Further, since collection and distribution of convalescent plasma units can be performed using existing blood donation protocols and infrastructure, convalescent plasma may be more scalable for use in low- and middle-income countries.

Mortality at 28-days was significantly lower among patients randomized to receive convalescent plasma. This important secondary finding contrasts with our primary outcome which shows no significant difference in clinical scale through day 28. One possible

explanation for this apparent contradiction may be that, although patients had higher odds for survival in the convalescent plasma, they remained hospitalized at their baseline clinical status (e.g. mechanically ventilated) and therefore did not achieve an improvement in 28-day clinical score (4). Although this secondary outcome was pre-specified, our study was not powered to detect a difference in 28-day mortality and analyses of our secondary outcomes were not adjusted for multiplicity. This finding should be interpreted with caution as it differs from results of larger inpatient trials adequately powered to detect differences in mortality, such as RECOVERY (13).

We observed no significant difference in adverse events between treatment groups and very few events were considered related to plasma infusion. Although use of control plasma may have potentially contributed to hypercoagulability (19), the incidence of thrombotic events in our study population was similar to that reported in observational studies of patients with severe COVID-19 (20).

Our trial has several strengths. First, the randomized, blinded, controlled design of our trial was implemented with high adherence to the study protocol. Second, we enrolled severe and critical COVID-19 patients in racially and ethnically diverse urban settings in two countries. Third, our strategy for qualification and collection of convalescent plasma was pragmatic, increasing generalizability of our findings to settings where quantification of neutralization activity is unavailable. However, we quantified neutralizing antibody titers in approximately 90% of convalescent plasma samples post hoc. Fourth, our use of control plasma was a strength since both study agents had the same appearance, enhancing the blinded nature of the trial, and both had a similar effect on volume expansion. As convalescent plasma may have other immunomodulatory factors apart from anti-SARS-CoV-2 antibodies, such as immunoglobulins,

hemostatic proteins and cytokines, use of normal plasma as a comparator allowed us to evaluate the effect of convalescent antibodies while controlling for these other factors.

Our trial has several limitations. Although convalescent plasma was collected from donors with anti-SARS-CoV-2 total IgG antibody titer of ≥1:400, neutralizing antibody titers in some convalescent plasma units were low, and we do not have data on antibody titers in patient samples pre- and post-transfusion. Second, although all control plasma units were collected prior to the first known cases of COVID-19 in Rio de Janeiro and New York City, one out of 19 units tested neutralized SARS-CoV-2 at low titer. Although this could represent a false-positive, it is possible that other control plasma units could have contained anti-coronavirus antibodies. Third, the median duration of symptoms at baseline was 9 days; earlier administration of high-titer convalescent plasma may have a higher potential for benefit (15). Fourth, supportive care was not standardized across study sites. However, we observed no significant differences in outcomes in stratified by country.

In conclusion, although use of convalescent plasma was not associated with improved clinical status at 28 days, mortality at this time point was significantly reduced. This result should be interpreted with caution until full results from larger inpatient trials adequately powered to detect differences in mortality are available.

Methods

Study Design

This was an investigator-initiated, randomized, double-blind, controlled trial to evaluate the efficacy and safety of convalescent plasma among adults hospitalized with severe COVID-19. The trial was conducted at five sites in New York City (USA) and Rio de Janeiro (Brazil) and was coordinated by Columbia University. Study sites included two hospitals affiliated with New

York-Presbyterian Hospital/Columbia University Irving Medical Center (CUIMC) in northern Manhattan (Milstein and Allen Hospitals) and three sites in Rio de Janeiro (Instituto Nacional de Infectologia Evandro Chagas, Hospital Federal dos Servidores do Estado, and Hospital Geral de Nova Iguaçu). Participants were enrolled at CUIMC beginning April 21st, 2020, and at the three clinical sites in Rio de Janeiro beginning August 15th, 2020. The trial protocol was previously published and is available as supplementary material (21).

Participants

Eligible participants were hospitalized patients aged ≥18 years with evidence of SARS-CoV-2 infection by polymerase chain reaction (PCR) of nasopharyngeal, oropharyngeal swab or tracheal aspirate sample within 14 days of randomization, with infiltrates on chest imaging and oxygen saturation ≤ 94% on room air or requirement for supplemental oxygen (including non-invasive positive pressure ventilation or high flow supplemental oxygen), IMV, or extracorporeal membrane oxygenation (ECMO) at the time of screening. Exclusion criteria included: participation in another clinical trial of anti-viral agent(s) for COVID-19; receipt of any anti-viral agent with possible activity against SARS-CoV-2 within 24 hours of randomization; duration of IMV or ECMO ≥ 5 days at time of screening; severe multi-organ failure; and a history of prior reactions to transfusion blood products. Following the U.S. Food and Drug Administration Emergency Use Authorization on May 1st, 2020 (22), concomitant use of remdesivir was permitted. The use of other treatments, including corticosteroids, was at the discretion of treating clinicians, and supportive care was provided according to standards at each site.

Procedures

Convalescent plasma used at all study sites was collected by the New York Blood Center from patients who had recovered from laboratory-confirmed COVID-19, provided informed consent, had a minimum anti-SARS-CoV-2 total IgG antibody titer of ≥1:400 by quantitative enzyme

linked immunosorbent assay against the spike protein (23), were at least 14 days asymptomatic following resolution of COVID-19, and had a negative PCR test for SARS-CoV-2 from a nasopharyngeal swab. Control plasma consisted of oldest available plasma at each study site without prior testing for anti-SARS-CoV-2 antibodies; all control plasma was collected prior to January 1st, 2020 in Rio de Janeiro and February 20th, 2020 in New York City. For all participants who received their treatment assignment, a single unit of plasma (~200-250 milliliters) was transfused over approximately 2 hours. Titers of neutralizing anti-SARS-CoV-2 antibody were measured in convalescent plasma units post hoc. Neutralization titer was determined with a SARS-CoV-2 viral neutralization assay which measured inhibition of virus growth after exposure to serial plasma dilutions using quantitative real-time reverse transcription-PCR (qRT-PCR). Further details are described in the protocol (21) and supplement. Given concern for emerging viral variants, we performed genomic sequencing of SARS-CoV-2 on nasopharyngeal swab samples from a subset of patients enrolled in Brazil. Sequences were mapped to the SARS-CoV-2 reference genome (sequence NC_045512) in NCBI. Additional methodological details are included in the supplement.

Randomization and Blinding

Enrolled participants were randomized in a 2:1 ratio to receive either convalescent plasma or control plasma using a web-based randomization platform; treatment assignments were generated using randomly permuted blocks of different sizes. Randomization was stratified by site but not by severity of illness. Participants were transfused within 48 hours of randomization. The clinical teams directly managing patients and the trial clinicians who adjudicated clinical status and determined 28-day outcomes were blinded to treatment allocation. The hospital blood bank at each site and the clinical research teams who completed

case record forms and performed other study specific procedures were not blinded; this was done to prevent errors in treatment allocation.

Outcomes

The primary outcome was clinical status at day 28 following randomization, measured using an ordinal scale based on that recommended by the World Health Organization (24): 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring high-flow oxygen therapy or noninvasive mechanical ventilation; 6, hospitalized, requiring ECMO, IMV, or both; 7, death. Since distinguishing between clinical status 1 and 2 on the ordinal scale was difficult in participants discharged from hospital, these two scores were combined, and a six-point ordinal scale was used for all analyses of the primary outcome. Pre-specified secondary outcomes included time-to-clinical improvement (defined as improvement in at least one point from baseline on the ordinal scale or alive at discharge from hospital, whichever came first), in-hospital mortality, 28-day mortality, time-to-discontinuation of supplemental oxygen, time-to-hospital discharge, and serious and grade 3 and 4 adverse events.

The initial primary outcome was time-to-clinical-improvement. However, it became clear that this primary outcome would not reflect instances when patients' clinical status subsequently worsened after improvement. Thus, the primary outcome of the study was amended to clinical status at day 28, and time-to-clinical-improvement became a secondary outcome. This change was made on August 8th, 2020 (at which point 31% [70/223] of the trial population was enrolled) without any knowledge of outcome data, and the protocol was updated accordingly with approval of the data safety and monitoring board (21).

Clinical status and adverse events were assessed daily during hospitalization through review of medical records and/or in-person visits. For participants discharged prior to day 28, clinical status and adverse events were determined via telephone and/or in-person visits. In patients who were discharged from hospital alive and not reachable for day 28 assessment, the last available clinical status was carried forward for the primary analysis, and sensitivity analyses were performed to account for potential bias due to loss-to-follow-up.

Statistics

The trial was analyzed by comparing patients randomized to convalescent plasma versus control plasma, with patients randomized to control plasma serving as the reference group. The primary outcome was analyzed using a one-sided Mann-Whitney test for an alternative hypothesis favoring the convalescent plasma arm (a “go” decision in this phase 2 trial). To assess the magnitude of clinical effects, an odds ratio (OR) for improved clinical status on the modified ordinal scale was estimated under the proportional odds model. An OR >1.0 indicated improved clinical status among patients randomized to convalescent plasma versus control plasma. Post hoc subgroup analyses for odds of clinical improvement and mortality were performed according to study country, age, sex, concomitant treatment with corticosteroids, and by titers of neutralizing anti-SARS-CoV-2 antibody in infused convalescent plasma units as reported in the supplement.

Pre-specified subgroups in analyses of the primary outcome were defined according to level of respiratory support at randomization (no supplemental oxygen, supplemental oxygen [including high-flow oxygen therapy and noninvasive ventilation], IMV or ECMO) and symptom duration at randomization (≤7 days, > 7 days) (21). Post hoc subgroup analyses were performed according to study country, age, sex, concomitant treatment with corticosteroids, and by titers of neutralizing anti-SARS-CoV-2 antibody in infused convalescent plasma units.

For the initial primary outcome of time-to-clinical-improvement, the intended sample size was 129 participants. However, after the primary outcome was amended, the sample size was re-calculated based on blinded pooled data of day 28 outcomes from an interim analysis by the data safety and monitoring board (July 2nd, 2020) and an OR of 1.7 under a proportional odds assumption. With a 2:1 randomization ratio and a total sample size of 219 participants (146 in the convalescent plasma arm versus 73 in the control arm), we determined that a one-sided Mann-Whitney test at a level of 15% would have 82% power to detect an OR 1.7. At the time the primary outcome was amended, a recent trial of remdesivir reported an OR 1.50 with 95% confidence interval (CI) of 1.18–1.91, which overlapped with our assumed OR (25).

Between group differences are reported using point estimates (OR or hazard ratio [HR]), with 95% confidence intervals and p-values. The p-value for the Mann-Whitney test in the primary outcome analysis ("go vs. "no-go" decision) is one-sided. All other p-values including those associated with point estimates are 2-sided and without adjustment for multiple comparisons. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Study Approval

The trial was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and the Brazilian National Ethics Committee Resolution 466/12. Written informed consent was obtained from all participants or from their legally authorized representative. The study protocol, definition of outcomes, and other relevant materials have been published previously (21). The trial protocol was approved by institutional review boards at CUIMC and at each site in Rio de Janeiro (21) and is registered at ClinicalTrials.gov (Identifier: NCT04359810).

Author Contributions

MRO'D and WIL conceived the study and led protocol development. MRO'D, MJC, JJ, NMP, AE, KC, and WIL contributed to study design. MRO'D, BG, MJC, CME, NMP, MRL, YKC, EJ, JHP, MPD, SWC, DA, KR, LCS, AV, VGV, DS, BJM, SDJ, and WIL contributed to data acquisition, analysis, and/or interpretation. NM, LC, TB, and WIL performed and interpreted neutralization assay experiments. EH, ZCB, SLS, ES, FDZ, FLC, KEH, SAF, JS, BS, WHL, SW, and BS contributed to convalescent plasma collection, qualification, and release. SB, AK, AW, and NMP coordinated study activities. MRL and KC performed statistical analyses. MRO'D, MJC, MRL, YKC, VG, and WIL wrote the manuscript. All authors contributed to critical revision of the manuscript.

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Tables

Table 1: Baseline patient characteristics

Variable	Convalescent plasma N = 150	Normal control plasma N = 73
Sex, n (%)		
Male	96 (64)	51 (70)
Female	54 (36)	22 (30)
Age in years, median (IQR)	60 (48-71)	63 (49-72)
Age group, n (%)		
<60 years	74 (49)	28 (38)
60-69 years	35 (23)	24 (33)
70-79 years	28 (19)	16 (22)
≥80 years	13 (9)	5 (7)
Geographic location		
United States	49 (33)	24 (33)
Brazil	101 (67)	49 (67)
Body mass index[a]		
BMI, median (IQR)	30.1 (26.6-34.7)	29.4 (26.2-33.0)
BMI $\geq$ 30 kg/m^2	76 (51)	33 (45)
Baseline conditions, n (%)		
Hypertension	53 (35)	22 (30)
Diabetes mellitus	55 (37)	27 (37)
Chronic cardiac disease	56 (37)	28 (38)
Chronic kidney disease	13 (9)	8 (11)
Chronic pulmonary disease	15 (10)	5 (7)
Chronic liver disease	3 (2)	1 (1)
HIV	4 (3)	0 (0)
Hyperlipidemia	27 (18)	9 (12)
Duration of COVID-19 symptoms prior to randomization, days, median (IQR)[b]	10 (7-13)	9 (7-11)
Symptoms reported, n (%)		
Shortness of breath	125 (83)	58 (79)
Fever	66 (44)	27 (37)
Cough	114 (76)	49 (67)
Clinical status at randomization based on ordinal scale[c]		
3: Hospitalized, not requiring supplemental oxygen	5 (3)	5 (7)
4-5: Hospitalized, requiring supplemental oxygen, HFO, NIV	125 (83)	57 (78)
6: Hospitalized, requiring IMV, ECMO, or both	17 (11)	11 (15)
Concomitant medications received during study period		
Corticosteroids	121 (81)	60 (82)
Remdesivir	8 (5)	5 (7)
Hydroxychloroquine	8 (5)	5 (7)
Antibacterial agent	111 (74)	60 (82)

Abbreviations: BMI: body mass index, IQR: interquartile range, HFO: high-flow oxygen therapy, NIV: non-invasive mechanical ventilation, IMV: invasive mechanical ventilation, ECMO: extracorporeal membrane oxygenation

Legend: [a]Unknown for 4 patients (2 in each treatment group), [b]Unknown for 6 patients (3 in each treatment group), [c]Baseline outcome assessment unknown for 3 patients (all in convalescent plasma group).

Table 2: Clinical efficacy outcomes among patients randomized to convalescent plasma versus control plasma (intention-to-treat population)

Outcomes	Convalescent Plasma N=150	Control Plasma N=73	OR or sHR (95% CI)	P-value	Adjusted[a] OR or sHR (95% CI)	P-value
Primary outcome, clinical status at 28-days, n (%)			OR 1.50 (0.83-2.68)	0.180	OR 1.38 (0.73-2.61)	0.318
1 and 2: Not hospitalized	108 (72.0)	48 (65.8)				
3: Hospitalized, not requiring supplemental oxygen	3 (2.0)	2 (2.7)				
4: Hospitalized, requiring supplemental oxygen	7 (4.7)	1 (1.4)				
5: Hospitalized, requiring high-flow oxygen therapy or noninvasive mechanical ventilation	1 (0.7)	0 (0.0)				
6: Hospitalized, requiring IMV, ECMO, or both	12 (8.0)	4 (5.5)				
7: Dead	19 (12.6)	18 (24.6)				
Secondary outcomes						
Time-to-clinical improvement, median,[b] days (IQR)	5 (4-6)	7 (5-8)	sHR 1.21 (0.89-1.65)	0.231	sHR 1.20 (0.87-1.64)	0.261
In-hospital mortality,[c] n (%)	19 (12.6)	18 (24.6)	OR 0.44 (0.22-0.91)	0.034	OR 0.47 (0.21-1.06)	0.068
28-day mortality,[c] n (%)	19 (12.6)	18 (24.6)	OR 0.44 (0.22-0.91)	0.034	OR 0.47 (0.21-1.06)	0.068
Time-to-discontinuation of supplemental oxygen,[d] median, days (IQR)	6 (3-16)	7 (3-11)	sHR 1.12 (0.80-1.56)	0.508	sHR 1.12 (0.80-1.56)	0.514
Time-to-hospital-discharge, median, days (IQR)	9 (6-28)	8 (6-22)	sHR 1.05 (0.77-1.43)	0.756	sHR 1.02 (0.75-1.38)	0.913

Abbreviations: CI: confidence interval, ECMO: extracorporeal membrane oxygenation, sHR: subhazard ratio, IMV: invasive mechanical ventilation, IQR: interquartile range, OR: odds ratio.
Legend: [a]Adjusted for age (continuous variable), sex, and duration of symptoms at baseline (duration of symptoms unknown for 6 patients); [b]Baseline outcome assessment unknown for 3 patients (all in treatment group); [c]No patients were known to have died following discharge from hospital; [d]13 patients excluded from unadjusted analysis (10 participants enrolled but did not require supplemental oxygen, 3 patients without a baseline assessment; 16 patients excluded from adjusted analysis).

Figures

Figure 1: Trial flow diagram

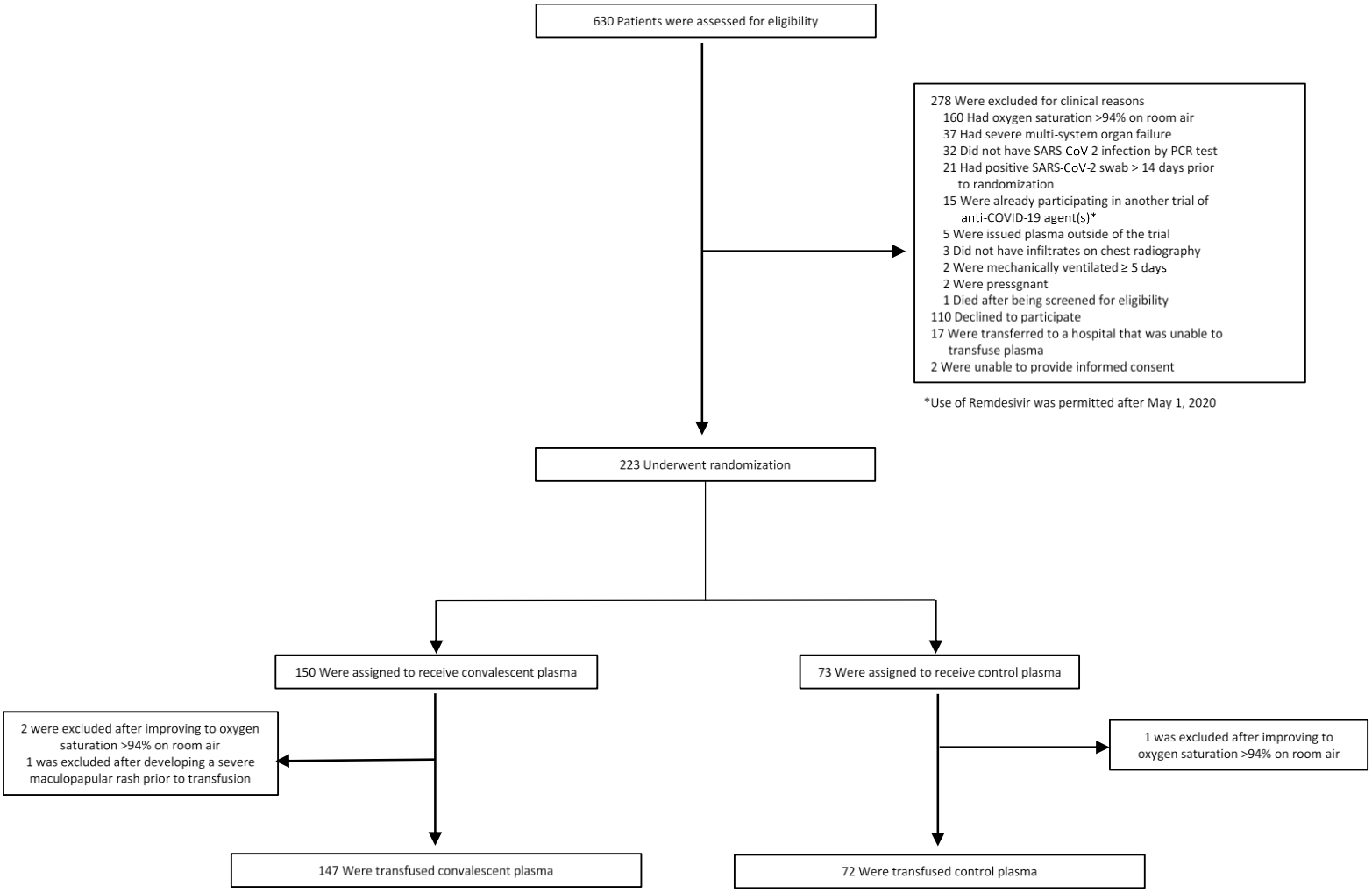
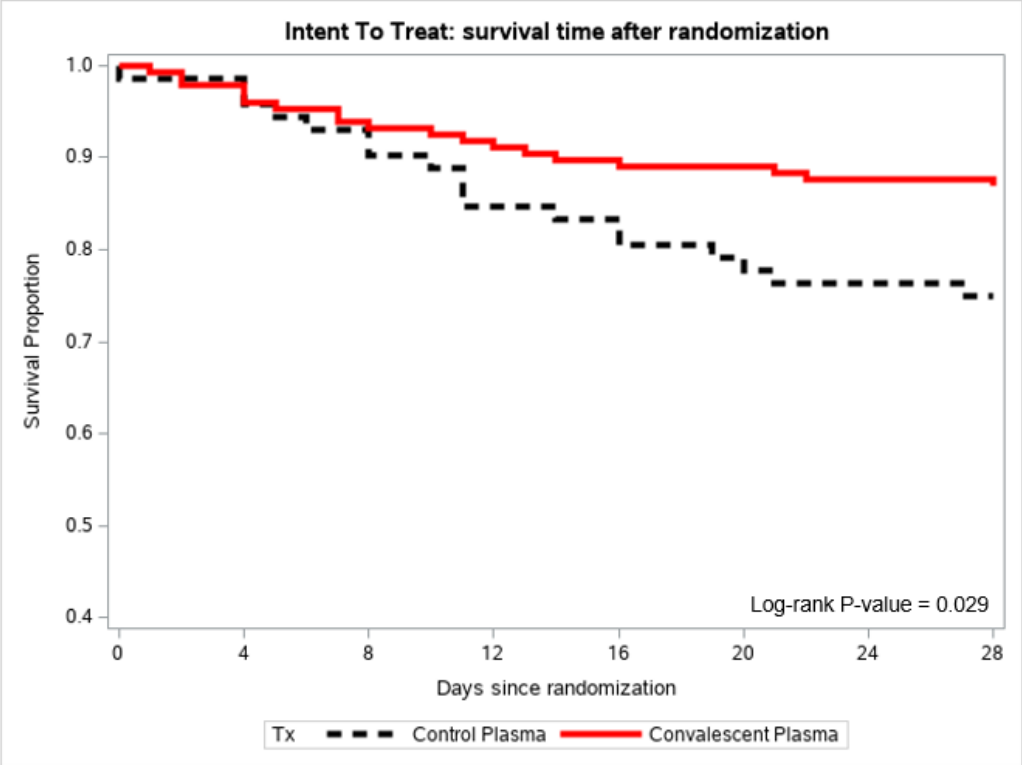
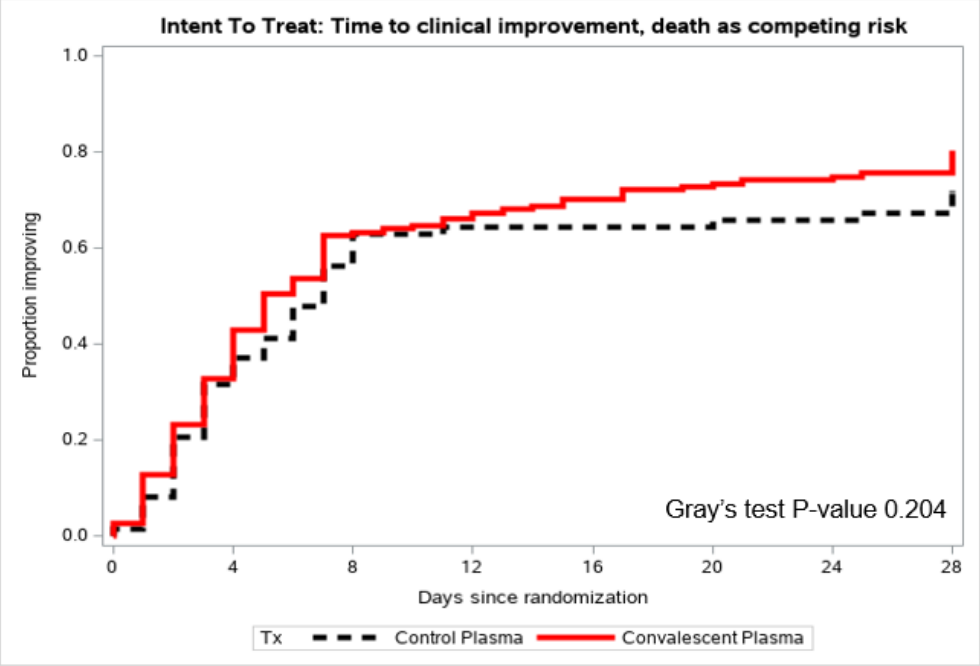


Figure 2: Kaplan-Meier estimates of mortality, stratified by treatment group.



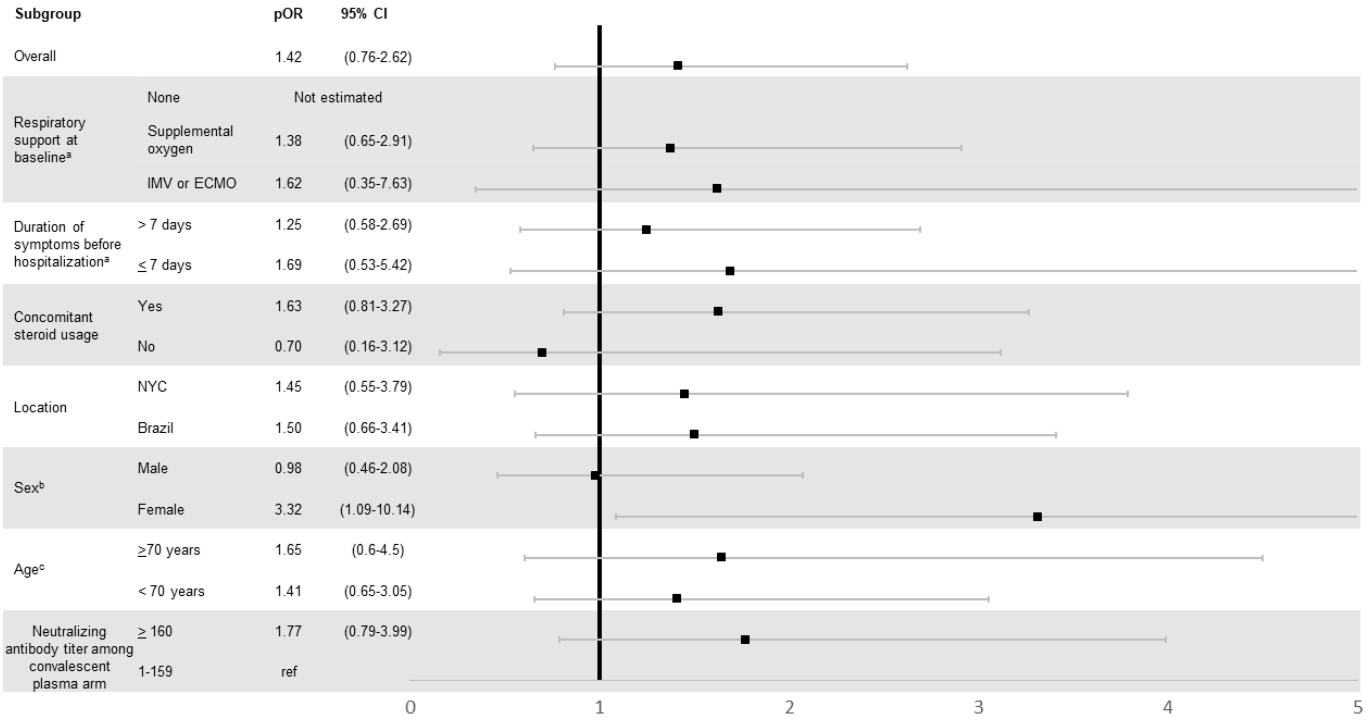
Time since randomization (days)		0	4	8	12	16	20	24	28
Control plasma	At risk	73	71	67	61	60	57	55	50
	Died	1	3	7	11	14	16	17	18
Convalescent Plasma	At risk	150	144	137	134	131	130	128	122
	Died	0	6	10	13	16	16	18	19

Figure 3: Time-to-clinical improvement with death considered a competing risk, stratified by treatment group.



Time since randomization (days)		0	4	8	12	16	20	24	28
Control plasma	At risk	73	49	27	19	15	12	10	6
	Improving	1	27	46	47	47	48	48	53
Convalescent Plasma	At risk	147	96	46	39	30	25	21	16
	Improving	4	63	93	99	103	108	110	117

Figure 4: Subgroup analyses of primary outcome of clinical status at 28 days, adjusted for age and sex



*pOR = proportional odds ratio