ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

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ABSTRACT

BACKGROUND

Convalescent plasma is frequently administered to patients with Covid-19 and has been reported, largely on the basis of observational data, to improve clinical outcomes. Minimal data are available from adequately powered randomized, controlled trials.

METHODS

We randomly assigned hospitalized adult patients with severe Covid-19 pneumonia in a 2:1 ratio to receive convalescent plasma or placebo. The primary outcome was the patient's clinical status 30 days after the intervention, as measured on a six-point ordinal scale ranging from total recovery to death.

RESULTS

A total of 228 patients were assigned to receive convalescent plasma and 105 to receive placebo. The median time from the onset of symptoms to enrollment in the trial was 8 days (interquartile range, 5 to 10), and hypoxemia was the most frequent severity criterion for enrollment. The infused convalescent plasma had a median titer of 1:3200 of total SARS-CoV-2 antibodies (interquartile range, 1:800 to 1:3200]. No patients were lost to follow-up. At day 30 day, no significant difference was noted between the convalescent plasma group and the placebo group in the distribution of clinical outcomes according to the ordinal scale (odds ratio, 0.83 (95% confidence interval [CI], 0.52 to 1.35; P=0.46). Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of −0.46 percentage points (95% CI, −7.8 to 6.8). Total SARS-CoV-2 antibody titers tended to be higher in the convalescent plasma group at day 2 after the intervention. Adverse events and serious adverse events were similar in the two groups.

CONCLUSIONS

No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo. (PlasmAr ClinicalTrials.gov number, NCT04383535.)

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In late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, and has spread worldwide since then, infecting millions of people. Coronavirus disease 2019 (Covid-19), the disease caused by SARS-CoV-2, has clinical manifestations ranging from no symptoms to respiratory failure. So far, only two agents have shown a degree of clinical efficacy in large randomized, controlled trials: remdesivir, in hospitalized patients with pulmonary disease, and dexamethasone, in hospitalized patients receiving oxygen.[1,2]

Convalescent plasma has been used for the treatment of infectious diseases for more than a century, under the assumption that passive immunization can "jump start" the immune system to control the evolution of the disease until a specific immune response is established in the infected person.[3] Despite great interest, convalescent plasma has been clearly demonstrated to be of value only in the treatment of Argentine hemorrhagic fever, for which it is considered standard of care.[4] Although predominantly open-label, nonrandomized trials have claimed efficacy of convalescent plasma in SARS, Middle East respiratory syndrome (MERS), influenza A (H1N1) in 2009, avian influenza (H5N1) and Ebola, conclusive data from randomized, controlled trials are lacking.[5-8]

Observational studies have consistently shown that convalescent plasma has an adequate safety profile in patients with Covid-19. An exploratory analysis in 4330 patients showed no significant difference in 7-day mortality between patients who received high-titer plasma and those who received low-titer plasma in the overall population, whereas 20% lower 7-day mortality was seen in the predefined subgroup of nonintubated patients who received higher-titer plasma than in those who received lower-titer plasma (14%, vs. 11%; P=0.03). In a post hoc analysis, 7-day mortality in nonintubated patients who were younger than 80 years of age and were treated within 72 hours after diagnosis was 6.3% in those receiving high-titer plasma and 11.3% in those receiving low-titer plasma (P=0.0008).[9] A similar efficacy analysis from the Mayo Clinic included 3082 participants receiving a single unit of plasma among the 35,322 patients who had received plasma through the expanded-access program.[10] After adjustment for baseline characteristics, the 30-day mortality rate was 29.1% in the low-titer group and 24.7% in the high-titer group; the difference did not reach statistical significance. A post hoc subgroup analysis also suggested a benefit of high-titer plasma in patients who received plasma within 3 days after Covid-19 diagnosis. On the basis of all available data, convalescent plasma is currently available for use in the United States under an Emergency Use Authorization (EUA) and has been widely used worldwide in the context of extended and compassionate use.[11,12]

In February 2020, the first imported case of Covid-19 was reported in Buenos Aires, and since then, the number of cases has been increasing steadily, reaching a total of more than 417,700 cases by the end of August.[13] In an attempt to more clearly determine the effect of convalescent plasma in Covid-19, we planned and conducted the PlasmAr trial to evaluate the safety and efficacy of convalescent plasma in the treatment of SARS-CoV-2 pneumonia. The main hypothesis of this trial was that in patients with severe SARS-CoV-2 pneumonia, treatment with convalescent plasma would be associated with improved clinical outcomes at 30 days.

Patients and Methods

Trial Design

PlasmAr was a double-blind, placebo-controlled, multicenter trial conducted at 12 clinical sites in Argentina and coordinated by Hospital Italiano de Buenos Aires. Eligible participants were randomly assigned in a 2:1 ratio to receive either convalescent plasma or placebo. The trial protocol, available with the full text of this article at NEJM.org, was approved by the institutional review boards at all the clinical sites and by regional or jurisdictional ethics committees, as applicable. Written informed consent was obtained from all participants, and the trial was conducted in accordance with the principles stated in 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, the analysis of the data, and the adherence of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

Inclusion and Exclusion Criteria

Hospitalized adults (at least 18 years of age) at each participating site were screened for enroll-

ment if they had a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a respiratory tract sample that was positive for SARS-CoV-2, radiologically confirmed pneumonia, no previous directives rejecting advanced life support, and at least one of the following severity criteria: oxygen saturation (SaO_2) below 93% while they were at rest and breathing ambient air, a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) below 300 mm Hg (PaO_2:FiO_2), or a Sequential Organ Failure Assessment (SOFA) or modified SOFA (mSOFA) score of two or more points above baseline status (scores range from 0 to 24, with higher scores indicating more severe disease). Patients who were pregnant or lactating, patients of reproductive age who were not willing to use contraceptive measures for a period of 30 days after enrollment, and patients with a history of blood component allergies, an infectious cause of pneumonia other than SARS-CoV-2, a requirement for mechanical ventilation, multiorgan failure, or any other condition that would impede the provision of informed consent were excluded.

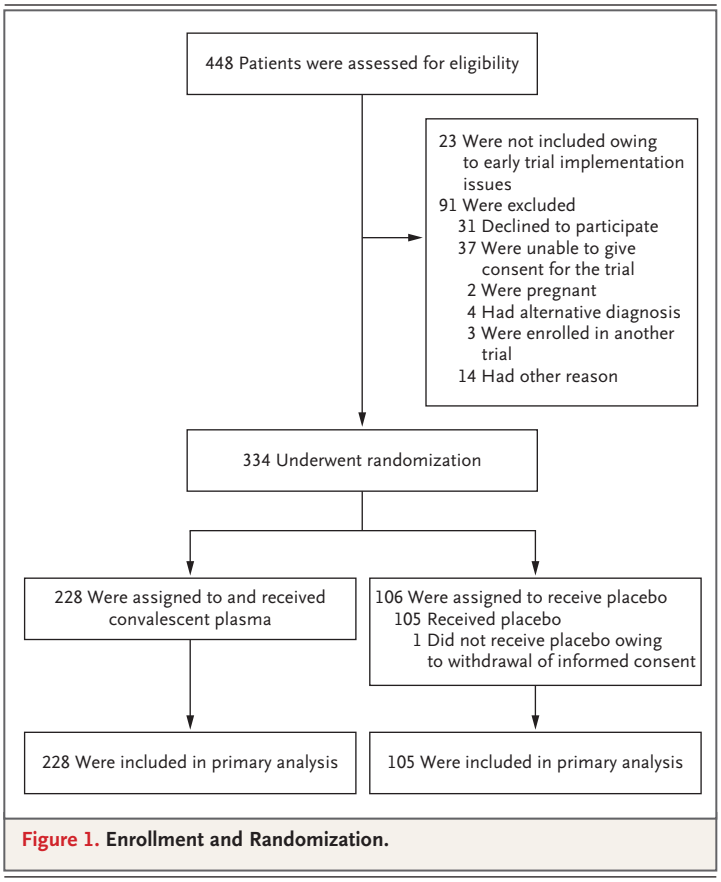


Figure 1. Enrollment and Randomization.

INTERVENTION

Eligible patients underwent treatment allocation and concealment through a randomization program (REDCap)[14] and were assigned in a 2:1 ratio to receive either a single administration of Covid-19 convalescent plasma or placebo (normal saline solution) in addition to standard treatment. The entire clinical team, the data collectors, and the outcome adjudicators were unaware of the treatment assignments. Patients were allowed to receive antiviral agents, glucocorticoids, or both according to the standard of care at the provider health care institution. Convalescent patients with a minimum SARS-CoV-2 total antibody titer of 1:400 were accepted as plasma donors after they had provided informed consent. Convalescent plasma was from a single donor or from a pool of two to five donors. Specific SARS-CoV-2 IgG antibody titer was measured in each convalescent plasma pool before transfusion. The total antibody titer goal in convalescent plasma was above 1:800 in all cases. For details of the intervention, see the Supplementary Appendix, available at NEJM.org.

CLINICAL OUTCOMES

The primary outcome was clinical status 30 days after intervention, as represented by one of six mutually exclusive ordinal categories on an adapted version of the World Health Organization (WHO) clinical scale: 1 indicated death, 2 invasive ventilatory support, 3 hospitalized with supplemental oxygen requirement, 4 hospitalized without supplemental oxygen requirement, 5 discharged without full return to baseline physical function, and 6 discharged with full return to baseline physical function.[15] Secondary outcomes were the clinical status on the ordinal scale at days 7 and 14 and the time (in days) to discharge from the hospital, the time to discharge from the intensive care unit (ICU), the time to improvement in at least two categories on the ordinal scale, the time to death, and the time to full functional recovery. The incidence of adverse events and serious adverse events was analyzed in the two groups. After the trial intervention, patients were followed in person during in-hospital admission and by telephone after hospital discharge. Details regarding data collection, patient follow-up, randomization, the data blinding and masking process, and plasma donation, col-

Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Convalescent Plasma (N=228)	Placebo (N=105)
Median age (IQR) — yr	62.5 (53–72.5)	62 (49–71)
Age category — no. (%)		
<65 yr	126 (55.3)	54 (51.4)
≥65 to <80 yr	75 (32.9)	43 (41)
≥80 yr	27 (11.8)	8 (7.6)
Female sex — no. (%)	67 (29.4)	41 (39.0)
Median time to onset of symptoms (IQR) — days	8 (5–10)	8 (5–10)
Coexisting conditions — no. (%)		
No other conditions	80 (35.1)	37 (35.2)
Body-mass index >30	104 (45.6)	52 (49.5)
Hypertension	111 (48.7)	48 (45.7)
Diabetes	40 (17.5)	21 (20)
Chronic obstructive pulmonary disease	23 (10.1)	2 (1.9)
Asthma	9 (3.9)	5 (4.8)
Chronic renal failure	10 (4.4)	4 (3.8)
Hematologic cancer	4 (1.8)	3 (2.9)
Solid tumors	23 (10.1)	11 (10.5)
Current tobacco use	6 (2.6)	6 (5.7)
Previous tobacco use	101 (44.3)	37 (35.2)
Congestive heart failure	8 (3.5)	3 (2.9)
Thromboembolic disease	5 (2.2)	2 (1.9)
Previous medications used — no. (%)		
ACEI or ARB 2	69 (30.3)	32 (30.5)
Frequent or recent use of NSAID	37 (16.2)	13 (12.4)
Anticoagulation	14 (6.1)	6 (5.7)
Corticosteroids	7 (3.1)	2 (1.9)
Immunosuppressants	6 (2.6)	3 (2.9)
Statins	61 (26.8)	21 (20)
Laboratory values		
Median total SARS-CoV-2 antibody titer (IQR)	1/50 (0–1:800)	1:50 (0–1:1600)
Negative total SARS-CoV-2 antibody titer — no./total no. (%)	65/145 (44.8)	34/70 (48.6)
Median D-dimer level (IQR) — ng/ml	697 (470–1150)	797 (550–1224)
Median ferritin level (IQR) — ng/ml	939 (441–1634)	645 (362–1180)
Severity inclusion criteria — no. (%)		
Oxygen saturation <93% at FiO_2 0.21	224 (98.2)	100 (95.2)
mSOFA or SOFA ≥2	32 (14)	17 (16.2)
Hospitalization area at enrollment — no. (%)		
Emergency department	11 (4.8)	3 (2.9)
General ward	150 (65.8)	77 (73.3)
Critical care unit	67 (29.4)	25 (23.8)

Table 1. (Continued.)

Characteristics	Convalescent Plasma (N=228)	Placebo (N=105)
Use of oxygen supplementation devices (n=299) — no. (%)		
Low-flow nasal cannula	146 (64.0)	70 (66.7)
Venturi or nonrebreather mask	49 (21.5)	16 (15.2)
High-flow nasal cannula	11 (4.8)	7 (6.7)
Noninvasive ventilatory support	0	0
Treatments during trial† — no. (%)		
Supplemental oxygen	206 (90.4)	93 (88.6)
Glucocorticoids‡	209 (91.7)	101 (96.2)
Lopinavir–ritonavir	7 (3.1)	3 (2.9)
Tocilizumab	6 (2.6)	8 (7.6)
Ivermectin	4 (1.8)	1 (1)
Hydroxychloroquine	1 (0.4)	0

* ACEI or ARB 2 denotes angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker, mSOFA modified Sequential Organ Failure Assessment, and NSAID nonsteroidal antiinflammatory drug.
† Remdesivir was not available in Argentina during the trial.
‡ Glucocorticoids included low-dose dexamethasone or equivalent doses of other glucocorticoids.

lection, processing, and storage are provided in the Supplementary Appendix.

IgG Titers and Neutralizing Antibody Measurements

End-point IgG titrations of specific antibodies against the SARS-CoV-2 spike and receptor-binding domain were performed with the COVIDAR Argentina Consortium enzyme-linked immunosorbent assay (ELISA) test. Neutralizing activity was measured through a standardized replication-defective pseudotyped particle system that mimics entry of live SARS-CoV-2, as previously described.[16]

Laboratory Evaluation

All the patients were tested for total IgG SARS-CoV-2 antibodies against spike protein on day 0 (before infusion) and subsequently on days 2, 7, and 14. Ferritin and D-dimer levels were analyzed at baseline and on day 14.

Statistical Analysis

The trial was designed to enroll 333 patients (222 in the plasma group and 111 in the placebo group). We calculated that this sample size would provide 80% power to detect a proportional odds ratio of 1.8 for plasma as compared with placebo on the clinical ordinal scale at the 0.05 (two-sided) level of significance.[17] More details are provided in Table S1, available in the Supplementary Appendix. An odds ratio greater than 1.0 would correspond to more favorable outcomes with the use of plasma as compared with placebo. The analysis was performed with the STATA statistical software, version 15.1 MP, Parallel Edition (StataCorp). See the Supplementary Appendix for details regarding the overall statistical analysis, interim analysis, and unblinding criteria.

RESULTS

Patients

Between May 28 and August 27, 2020, a total of 448 patients were assessed for inclusion criteria at 12 participating centers, and 334 patients were enrolled. One patient withdrew informed consent before receiving the intervention. Consequently, 228 patients were assigned to convalescent plasma and 105 to placebo (Fig. 1), and each patient received the assigned infusion.

The median age of the patient population was 62 years (interquartile range, 52 to 72); 67.6% of

Table 2. Clinical Outcomes in Patients Who Received Convalescent Plasma as Compared with Placebo.*

Outcomes	Convalescent Plasma (N=228)	Placebo (N=105)	Odds Ratio or Hazard Ratio (95% CI)	P value
Primary outcome, clinical status at 30 days — no. of patients (%)			Odds ratio, 0.81 (0.50–1.31)	0.396
Death	25 (11)	12 (11.4)		
Invasive ventilatory support	19 (8.3)	10 (9.5)		
Hospitalized with supplemental oxygen requirement	5 (2.2)	2 (1.9)		
Hospitalized without supplemental oxygen requirement	8 (3.5)	1 (1)		
Discharged without full return to baseline physical function	30 (13.2)	8 (7.6)		
Discharged with full return to baseline physical function	141 (61.8)	72 (68.6)		
Secondary Outcomes				
Median time from intervention (IQR) — days				
To hospital discharge	13 (8–30)	12 (7–ND)	Subhazard ratio, 1 (0.76–1.32)	—
To discharge from the ICU	ND (8–ND)	ND (6–ND)	Subhazard ratio, 0.94 (0.48–1.82)	—
To complete restoration of physical functions†	15 (9–ND)	15 (7–ND)	Subhazard ratio, 0.89 (0.66–1.18)	—
To start of invasive ventilation	ND (9–ND)	ND	Subhazard ratio, 1.14 (0.72–1.81)	—
To death	ND	ND	Hazard ratio, 0.93 (0.47–1.86)	—
To improvement of 2 categories in the ordinal outcome or hospital discharge within 30 days	12 (7–29)	12 (6–ND)	Hazard ratio, 1 (0.76–1.32)	—
Adverse events — no (%)				
Any event	153 (67.1)	66 (62.9)	Odds ratio, 1.21 (0.74–1.95)	—
Serious event	54 (23.7)	19 (18.1)	Odds ratio, 1.40 (0.78–2.51)	—
Infusion-related event	13 (5.7)	2 (1.9)	Odds ratio, 3.13 (0.69–14.11)	—

* ND denotes could not be determined.
† Restitution refers to the patient's status at baseline.

the patients were men, and 64.9% had a coexisting condition at entry into the trial. The median time from the onset of Covid-19 symptoms to enrollment was 8 days (interquartile range, 5 to 10). An oxygen saturation below 93% while the patient was breathing ambient air was the most common severity criterion for enrollment, and more than 90% of the patients were receiving oxygen and glucocorticoids at the time of entry into the trial (Table 1).

The median volume of infused convalescent plasma was 500 ml (interquartile range, 415 to 600). Of the 215 patients from whom a baseline total anti–SARS-CoV-2 IgG antibody level could be obtained, the median titer was 1:50 (interquartile range, 0 to 1:800); 46.0% of patients had no detectable antibody level.

Total IgG and neutralizing SARS-CoV-2 antibody titers were also analyzed in the infused convalescent plasma pools, using the COVIDAR assay. The total IgG antibody median value of all pools was 1:3200 (interquartile range, 1:800 to 1:3200). Analysis of SARS-CoV-2 neutralizing antibody titers was available for 125 of the infused convalescent plasma doses (56%), with an 80% inhibitory concentration median titer of 1:300 (interquartile range, 1:136 to 1:511). The correlation analysis between the total SARS-CoV-2 anti-

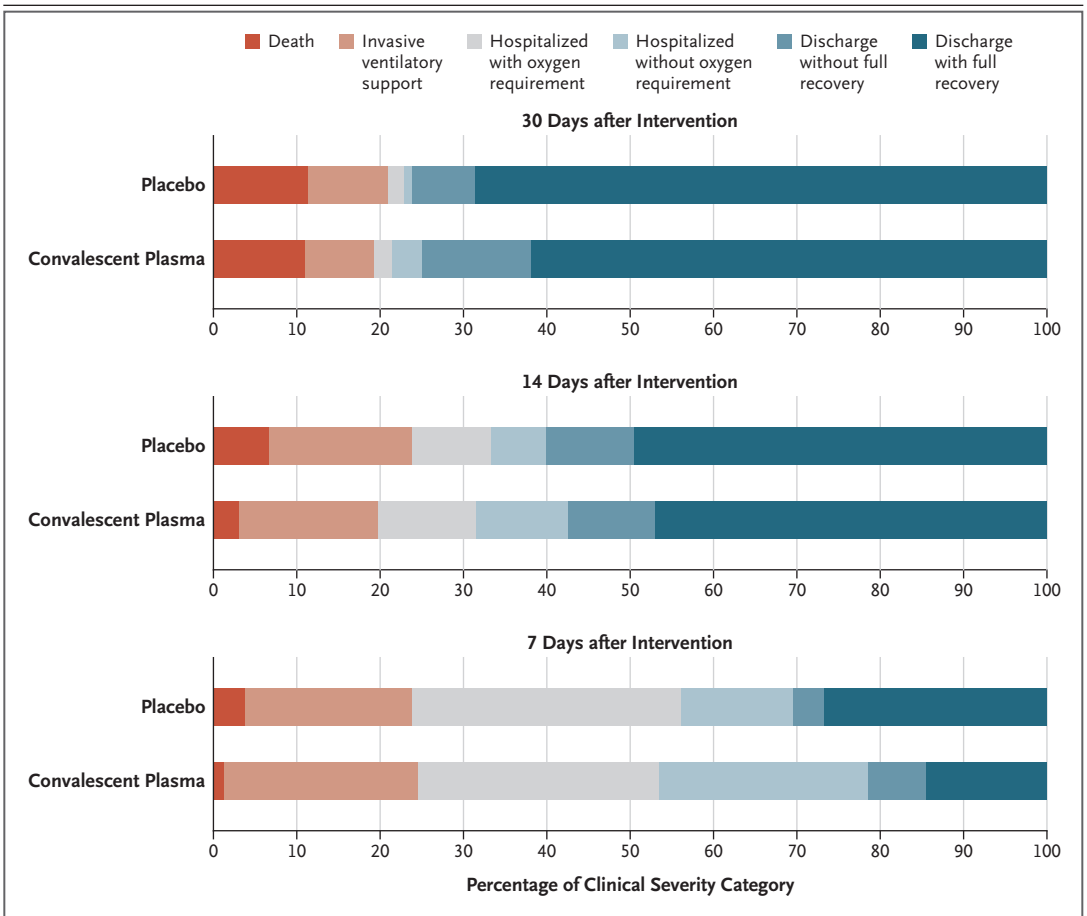


Figure 2. Clinical Outcomes among Patients Treated with Convalescent Plasma as Compared with Placebo.
The distribution of the clinical status according to the ordinal scale is shown at 30 days, 14 days, and 7 days after the intervention.

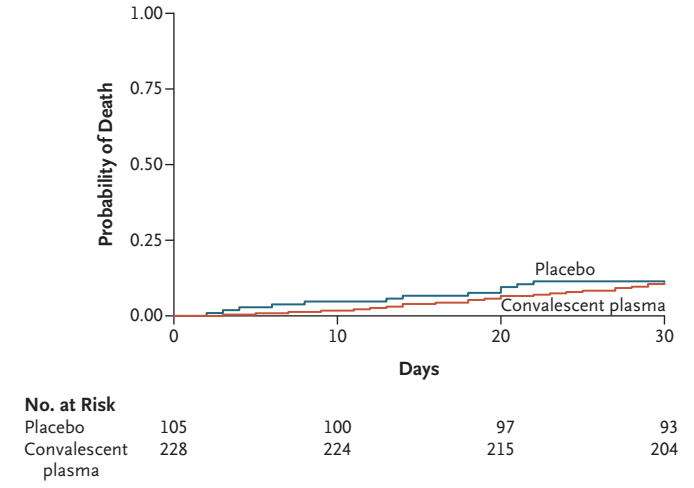
body titer and the neutralizing antibody titer in the convalescent plasma pools is provided in the Figure S1.

PRIMARY OUTCOME

At day 30, no significant difference was noted between the convalescent plasma group and the placebo group in the distribution of clinical outcomes according to the ordinal scale (odds ratio, 0.83; 95% confidence interval [CI], 0.52 to 1.35; P=0.46) (Table 2 and Fig. 2). The assumption of the proportional odds ratio for the primary outcome was supported by the nonsignificant results of the Brant test (P=0.34). After adjustment for sex, history of COPD, and history of tobacco use, the odds ratio for the score on the ordinal scale between the convalescent plasma and placebo groups was 0.92 (95% CI, 0.59 to 1.42; P=0.70).

SECONDARY OUTCOMES

The 30-day mortality was 10.96% (25 of 228 patients) in the convalescent plasma group and 11.43% (12 of 105) in the placebo group, for a risk difference of −0.46 percentage points (95% CI, −7.8 to 6.8). No significant between-group differences in clinical status on the ordinal scale were seen either at day 7 (odds ratio, 0.88; 95% CI, 0.58 to 1.34) or at day 14 (odds ratio, 1.00; 95% CI, 0.65 to 1.55) (Fig. 2 and Table S2). The median time from enrollment to hospital discharge was 13 days (interquartile range, 8 to 30) in the convalescent plasma group and 12 days (interquartile range, 7 to 30) in the placebo group (subhazard ratio, 0.99; 95% CI, 0.75 to 1.32). Throughout the trial, the proportion of ICU admissions and invasive ventilatory support requirements was 53.9% (123 of 228 patients)



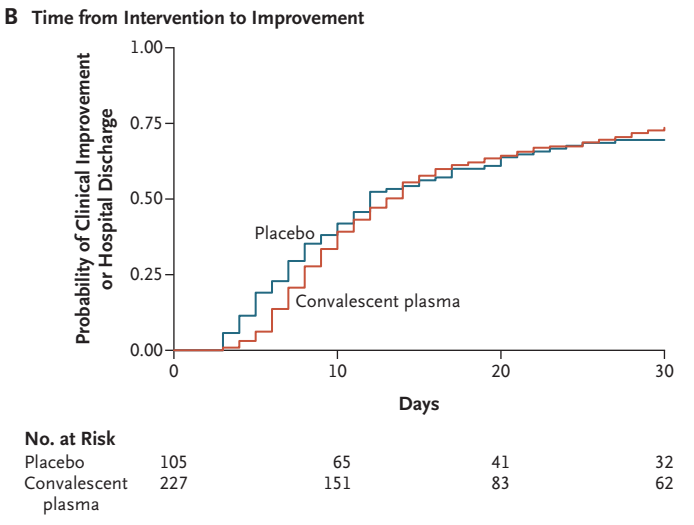


Figure 3. Time to Death or to Improvement after Treatment with Convalescent Plasma or Placebo.

Shown are the Kaplan–Meier failure estimates of the time from intervention (administration of convalescent plasma or placebo) to death or to improvement in at least two categories in the ordinal scale or hospital discharge. The ordinal scale, an adapted version of the World Health Organization clinical scale, has six mutually exclusive categories ranging from category 1 (death) to category 6 (discharged with full return to baseline physical function).

and 26.8% (61 of 228 patients), respectively, in the convalescent plasma group and 60% (63 of 105 patients) and 22.9% (24 of 105 patients), respectively, in the placebo group. No significant differences were noted in the time to death or in the time to clinical improvement of at least two categories on the ordinal scale or hospital discharge (Fig. 3 and Table 2).

No differences in ferritin and D-dimer levels were noted between the patient groups at day 14. Although baseline median titers were identical, patients receiving convalescent plasma had SARS-CoV-2 total antibody levels that were higher at day 2 than levels in patients receiving placebo. No differences in antibody titers were noted at days 7 or 14 (Table S3).

SUBGROUP ANALYSIS

The prespecified subgroup analyses failed to suggest any credible subgroup effects. Convalescent plasma appeared to be associated with a worse clinical outcome in the subgroup of patients younger than 65 years of age. However, the rest of the outcome analyses for this subgroup did not show similar results (Fig. S2 and S3). Analyses of the primary outcome and of clinical improvement of at least two ordinal categories in relation to total and neutralizing antibody titers in the infused plasma pools are provided in the Supplementary Appendix.

SAFETY RESULTS

Infusion-related adverse events were slightly more common in the convalescent plasma group (4.8%; 11 of 228 patients) than in the placebo group (1.9%; 2 of 105 patients) (odds ratio, 2.62; 95% CI, 0.57 to 12.04). Five patients in the convalescent plasma group and none in the placebo group had nonhemolytic febrile reactions. No significant differences were found in the overall incidence of adverse events (odds ratio, 1.21; 95% CI, 0.74 to 1.95) or serious adverse events (Table 2 and Table S4).

DISCUSSION

The use of convalescent plasma did not result in a significant clinical benefit as compared with placebo in patients with severe Covid-19 pneumonia. Our trial ensured that more than 95% of the transfused convalescent plasma units had a total anti–SARS-CoV-2 antibody titer of at least 1:800 and that the plasma volume infused had a correction factor according to the participant's weight. This finding is in contrast to the findings of a series of nonrandomized studies claiming convalescent plasma to be of substantial benefit and illustrates the importance of randomized, controlled trials, especially in the context of a pandemic.[18]

Our data are consistent with the recently published results of a randomized, controlled trial in patients with moderate Covid-19 that showed no difference in severe disease or death at day 30, although the intervention was not blinded and the infused convalescent plasma had very low titers of specific antibodies.[19]

In a randomized, open-label clinical study of treatment with convalescent plasma in patients with severe and life-threatening Covid-19 that had to be interrupted, Li et al. found no differences in the time to hospital discharge, clinical improvement, or day-28 mortality in comparison with placebo.[20] An open-label randomized, controlled clinical trial in the Netherlands was stopped prematurely owing to detection of baseline neutralizing antibodies in 79% of the patients tested, with median titers similar to those of the donors.[21] In this regard, for the 215 patients in the present trial in whom pretreatment SARS-CoV-2 measurements were made, titers were less than 1:50 in 46.0% of the patients. As expected, antibody titers trend higher in the intervention group at day 2, but this difference was diluted later in the trial. The median SARS-CoV-2 neutralizing antibody titers of the infused plasma in the PlasmAr trial were high, in concordance with the general recommendations of regulatory authorities.[22] The ConPlas-19 trial, an open-label randomized, controlled trial also failed to complete enrollment and thus cannot provide firm conclusions about efficacy.[23]

Our trial had a number of prespecified subgroup analyses in an attempt to detect patient subpopulations for which previous reports had suggested that the use of convalescent plasma might have a potential benefit. No differences in favor of convalescent plasma were noted in either the primary or the secondary outcomes in any of these subgroups, including the 39 patients who received the intervention within 72 hours after the onset of symptoms. We did find a difference in the primary outcome, in favor of placebo, for patients younger than 65 years of age (odds ratio 0.18; 95% CI, 0.06 to 0.54). Additional analysis of this subgroup failed to reveal any clear explanation, and we interpret this as a chance finding, although further confirmation in other studies may be warranted.

Our trial has limitations. All enrolled patients had severe Covid-19 pneumonia. As such, no conclusion should be extrapolated to other clinical groups, including patients with mild-to-moderate cases of Covid-19 or patients with life-threatening disease. The median time from the onset of symptoms to progression to respiratory failure is around 7 days.[24] This time frame is similar to the median time from the beginning of symptoms to enrollment in our trial. Thus, no firm conclusion can be drawn regarding the potential efficacy of passive immune therapy earlier than the median time of entry to this trial or in patients with milder forms of the disease. Indeed, studies with specific antibodies administered within 72 hours of Covid-19 diagnosis in patients with risk factors for severe disease are currently ongoing or planned.

Although the use of usual therapy was allowed in both groups, it was not standardized among participating sites. Nevertheless, no significant differences were detected in the subgroup analyses performed in this trial. Dexamethasone or other glucocorticoids were heavily used in both trial groups.[2] Nevertheless, no suggestion for interaction between convalescent plasma and concomitant therapies was found.

Specific postinfusion reactions, such as transfusion-associated cardiac overload and transfusion-related acute lung injury, were difficult to assess and differentiate from Covid-19 progression in this spectrum of patients with severe pneumonia. Similarly, the true effect of fluid overload on cardiovascular function in these patients may have been underestimated. In addition, convalescent plasma therapy is intrinsically heterogeneous. Different antibody-response phenotypes and immune signatures could have different effects on disease progression.[25] A recent study suggests that some autoantibodies that have developed in patients with life-threatening Covid-19 may be harmful by decreasing interferon-mediated immune responses.[26]

In our trial, the use of convalescent plasma therapy in addition to standard treatment in patients with severe pneumonia due to Covid-19 did not reduce mortality or improve other clinical outcomes at day 30 as compared with placebo. We believe the use of convalescent plasma as a standard of care in such patients should be reevaluated. Further studies regarding antibody therapy may be best focused on other populations or on interventions with other types of preparations, such as intravenous immunoglobulin or anti–SARS-CoV-2 monoclonal antibodies.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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