FAST TRACK

Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)

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ABSTRACT

OBJECTIVE
To investigate the effectiveness of using convalescent plasma to treat moderate coronavirus disease 2019 (covid-19) in adults in India.

DESIGN
Open label, parallel arm, phase II, multicentre, randomised controlled trial.

SETTING
39 public and private hospitals across India.

PARTICIPANTS
464 adults (≥18 years) admitted to hospital (screened 22 April to 14 July 2020) with confirmed moderate covid-19 (partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio between 200 mm Hg and 300 mm Hg or a respiratory rate of more than 24/min with oxygen saturation 93% or less on room air): 235 were assigned to convalescent plasma with best standard of care (intervention arm) and 229 to best standard of care only (control arm).

INTERVENTIONS
Participants in the intervention arm received two doses of 200 mL convalescent plasma, transfused 24 hours apart. The presence and levels of neutralising antibodies were not measured a priori; stored samples were assayed at the end of the study.

MAIN OUTCOME MEASURE
Composite of progression to severe disease (PaO_2/FiO_2 <100 mm Hg) or all cause mortality at 28 days post-enrolment.

RESULTS
Progression to severe disease or all cause mortality at 28 days after enrolment occurred in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (risk difference 0.008 (95% confidence interval −0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54).

CONCLUSION
Convalescent plasma was not associated with a reduction in progression to severe covid-19 or all cause mortality. This trial has high generalisability and approximates convalescent plasma use in real life settings with limited laboratory capacity. A priori measurement of neutralising antibody titres in donors and participants might further clarify the role of convalescent plasma in the management of covid-19.

TRIAL REGISTRATION
Clinical Trial Registry of India CTRI/2020/04/024775.

WHAT IS ALREADY KNOWN ON THIS TOPIC

As of October 2020, multiple small case series, one large observational study (>35 000 patients), and three randomised trials have been published on the utility of convalescent plasma to treat coronavirus disease 2019 (covid-19)

Although the observational studies suggested clinical benefits in recipients of convalescent plasma, the trials were stopped early and failed to ascertain any mortality benefit from convalescent plasma treatment in patients with covid-19

WHAT THIS STUDY ADDS

In settings with limited laboratory capacity, convalescent plasma does not reduce 28 day mortality or progression to severe disease in patients admitted to hospital with moderate covid-19

Convalescent plasma treatment was associated with earlier resolution of shortness of breath and fatigue and higher negative conversion of SARS-CoV-2 RNA on day 7 of enrolment

As a potential treatment for patients with moderate covid-19, convalescent plasma showed limited effectiveness

Introduction

With few treatment options available to manage coronavirus disease 2019 (covid-19), the disease presents a unique set of challenges for healthcare providers globally. In addition to using non-drug interventions, health systems have devised strategies to manage covid-19 using repurposed drugs and revisiting older strategies, such as convalescent plasma. In the past, convalescent plasma was used as a passive immunisation strategy to treat viral diseases, raising expectations that potentially it could be used to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for covid-19 and a disease with no proven, effective interventions.[1]

Convalescent plasma is a source of antiviral neutralising antibodies. Other immune pathways, such as antibody dependent cellular cytotoxicity, complement activation, or phagocytosis are putative mechanisms through which convalescent plasma might exert its therapeutic effect in patients with covid-19.[2] Additionally, anti-inflammatory cytokines, defensins, pentraxins, and other immunomodulatory proteins might have a role in alleviating systemic inflammatory response syndrome, the main pathophysiological basis for acute respiratory distress syndrome and mortality from covid-19 related pneumonia.[2] In the pre-vaccine era, convalescent plasma was used to treat viral diseases such as poliomyelitis, measles, mumps, and influenza, and, more recently, influenza, Ebola virus disease, and severe acute respiratory syndrome coronavirus epidemics, with varying degrees of success.[3-6] Evidence suggests that convalescent

plasma collected from survivors of covid-19 contains receptor binding domain specific antibodies with potent antiviral activity.[7] However, effective titres of antiviral neutralising antibodies, optimal timing for convalescent plasma treatment, optimal timing for plasma donation, and the severity class of patients who are likely to benefit from convalescent plasma remains unclear.

Since the publication of the first case series from China, multiple observational studies have been published, some on preprint servers, reporting the association between convalescent plasma and reduced mortality, hospital stay, and viral load in patients with covid-19.[8-12] Only two randomised controlled trials on convalescent plasma use in covid-19 have been published, one from China and the other from the Netherlands.[13 14] Both were stopped prematurely—the China study because of inadequate patient enrolment, and the Dutch study because interim findings highlighted the need for a redesign of the trial. Neither study found a mortality benefit, and the Dutch study raised uncertainties about the pretransfusion antibody status of patients as a potential factor in identifying appropriate candidates for convalescent plasma treatment.[14] This uncertainty in the published evidence was reflected in a recent systematic review, which remained undecided on both the safety and the effectiveness of convalescent plasma as a treatment option in patients admitted to hospital with covid-19.[15] Meanwhile, convalescent plasma treatment has received regulatory approval for use in patients in several countries. This has resulted in its widespread adoption in real world clinical practice, where it is being used to treat patients with a wide spectrum of covid-19 severity.[16 17] Given these uncertainties, we determined the effectiveness and safety of convalescent plasma in patients with moderate covid-19 admitted to hospitals across India to limit progression to severe disease.

Methods

Study design

Our study (the PLACID Trial) was an open label, parallel arm, phase II, multicentre, randomised controlled trial conducted in 39 tertiary care hospitals across India (supplementary figure 1 shows the location of the trial sites). Of these, 29 were teaching public hospitals and 10 were private hospitals spread across 14 states and union territories representing 25 cities. Supplementary table 1 provides a detailed list of the study sites.

Participants

Patients aged at least 18 years who had confirmed covid-19 based on a positive reverse transcriptase polymerase chain reaction (RT-PCR) result for SARS-CoV-2 and had been admitted to the participating hospitals were screened for eligibility. Inclusion criteria were moderate illness with either a partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio between 200 mm Hg and 300 mm Hg or a respiratory rate of more than 24/min with oxygen saturation (SpO_2) 93% or less on room air,[17] and availability of a matched donor for convalescent plasma at the point of enrolment. These criteria were similar to those for patients with severe illness in studies from other countries. We excluded pregnant and lactating women, patients with known hypersensitivity to blood products, recipients of immunoglobulin in the past 30 days, patients with conditions precluding infusion of blood products, participants in any other clinical trials, and critically ill patients with PaO_2/ FiO_2 <200 mm Hg or shock (requiring vasopressors to maintain a mean arterial pressure (MAP) of ≥65 mm Hg or MAP of <65 mm Hg).

Eligible donors were men or nulliparous women who were aged between 18 and 65 years, weighed more than 50 kg, had received a diagnosis of covid-19 confirmed by a RT-PCR test result, and had experienced symptoms of covid-19 with at least fever and cough. Additionally, the symptoms must have completely resolved for 28 consecutive days before donation or a period of 14 days before donation with two negative RT-PCR test results for SARS-CoV-2 from nasopharyngeal swabs collected 24 hours apart. All routine screening tests, including ABO blood grouping; Rhesus phenotype; complete blood counts; screening for HIV, hepatitis B or C virus, syphilis, and malaria; and total serum protein were conducted according to the Drugs and Cosmetics (second amendment) Rules, 2020.[18]

All participants or their family members or legally authorised representatives were provided with information about the trial in a language with which they were familiar, and written informed consent was obtained before recruitment.

Randomisation and masking

An independent biostatistician from the Indian Council Medical Research-National Institute of Epidemiology, Chennai, India, generated the randomisation sequence using the RALLOC module in STATA v.14 (College Station, TX). A stratified block randomisation strategy was used to allocate participants in a 1:1 ratio to receive either convalescent plasma with the best standard of care (intervention arm) or best standard of care alone (control arm). Stratification was by sites; block randomisation was done with unequal block sizes. After written, informed consent had been obtained from eligible patients, the site investigators screened the participants for recruitment and contacted a member of the central trial coordinating team to receive the randomisation sequence, ensuring concealment of allocation.

Procedures

Patients enrolled in the control arm received best standard of care for covid-19 in keeping with the institutional protocol, which was dictated by the best available evidence at the time and guidelines for the management of covid-19 issued by health authorities of the Indian government. The range of treatment protocols followed by the participating clinical sites for the management of patients with covid-19 included antivirals (hydroxychloroquine, remdesivir, lopinavir/

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ritonavir, oseltamivir), broad spectrum antibiotics, immunomodulators (steroids, tocilizumab), and supportive management (oxygen through a nasal cannula, face mask, non-rebreathing face mask; non-invasive or invasive mechanical ventilation; awake proning). The decision to transfer to the intensive care unit depended on the policies of the individual trial sites.

Participants in the intervention arm received two doses of 200 mL of convalescent plasma, transfused 24 hours apart, in addition to the best standard of care. The first dose of convalescent plasma was transfused at randomisation. The two plasma units were collected preferably from different donors depending on availability and ABO compatibility to increase the chances of receiving convalescent plasma with neutralising antibodies.[19] If two different donors were not available, both units were collected from a single donor. Convalescent plasma was collected from patients who had recovered from covid-19 by centrifugal separation using the apheresis equipment available at the facility after obtaining written informed consent from the donors. At least 20 mL of the donated plasma was stored at −80°C for measurement of SARS-CoV-2 neutralising antibody titres, as reliable and approved qualitative and quantitative tests were not available at the start of the study. Commercial qualitative immunoassays for SARS-CoV-2 antibodies on chemiluminescent immunoassay or enzyme linked immunosorbent assay platforms approved by the Indian Council of Medical Research became available halfway through the trial. Trial sites were encouraged to use them once available before collection of convalescent plasma.

All participants underwent clinical examination and a range of laboratory investigations, including arterial blood gas analysis, complete blood count, renal and hepatic function tests, and a coagulation profile on the day of enrolment (day 0) and subsequently on days 1, 3, 5, 7, and 14. Chest imaging was carried out and biomarkers including serum ferritin, lactate dehydrogenase, C reactive protein, and D-dimer obtained on days 0, 3, and 7. Serum for antibody titre assays was collected on days 0, 3, and 7; these samples were stored at −80°C until further analysis at the Indian Council of Medical Research-National Institute of Virology, Pune, India. RT-PCR for SARS-CoV-2 antibodies from nasopharyngeal swabs was repeated on days 3 and 7. All participants were contacted by telephone on day 28 to assess health status.

A micro-neutralisation test for SARS-CoV-2 was performed for determining the neutralising antibody titres in stored donor convalescent plasma and participant serum from days 0, 3, and 7 at the Biosafety Level-3 facility at Indian Council of Medical Research-National Institute of Virology, Pune following standardised methods.[20] Vero CCL-81 adapted SARS-CoV-2 (strain NIV2020770) was isolated at the National Institute of Virology, Pune.[21] The detection range of neutralising antibody titres was 1:20 to 1:1280. Values reported as less than 1:20 were considered as undetectable neutralising antibody titres; values greater than 1:1280 were considered as 1:1280 for analysis. The supplementary file provides full details.

Outcomes

The primary outcome of the study was a composite of progression to severe disease (PaO_2/FiO_2 ratio <100 mm Hg) any time within 28 days of enrolment or all cause mortality at 28 days. If progression to severe disease or all cause mortality could be prevented in the 28 days post-enrolment, the primary outcome was considered as "good" and if not it was considered as "poor."

The secondary outcomes were time to symptom resolution, measured as the proportion of participants showing resolution of symptoms of fever, shortness of breath, or fatigue on day 7; change in oxygen requirement after plasma transfusion, measured as variation in fraction of inspired oxygen on days 1, 3, 5, 7, and 14; total duration of respiratory support during hospital admission, and post-enrolment duration of respiratory support until day 28 or discharge, whichever was earlier; proportion of participants requiring invasive or non-invasive ventilation post-enrolment; sequential organ failure assessment score over days 0, 3, and 7; conversion to a negative result for SARS-CoV-2 RNA on days 3 and 7; levels of biomarkers post-enrolment, measured as variation in levels over days 0, 3, and 7 in both groups; and requirement of vasopressor support. Also, we compared clinical improvement on the World Health Organization ordinal scale on days 0, 1, 3, 5, 7, 14, and 28 between the two study arms.[22] The WHO ordinal scale was not mentioned in the initial study protocol but was added midway through the trial as we thought it would be a key endpoint in future meta-analyses.

Safety outcomes were frequency of minor and serious adverse event (death and invasive mechanical ventilation, haemodynamic instability) within six hours of convalescent plasma transfusion. Relatedness of a serious adverse event with the trial was assessed according to published definitions.[23]

Statistical analysis

Assuming that 18% of the intervention arm would meet the composite primary outcome under the null hypothesis and 9% under the alternative hypothesis, for a power of 80% and significance level of 5%, we calculated that we would need a sample size of 226 participants in each arm, totalling 452 participants for the study. The assumption that 18% of the participants in the control arm would meet the composite primary outcome was based on the best available evidence at the time the trial was designed.[24]

Descriptive analysis was done by tabulation of data and presentation of continuous variables as means and standard deviations or medians and interquartile ranges, as appropriate, and categorical variables as proportions.

We performed an intention-to-treat analysis after imputing the missing composite outcomes for

progression to severe disease or mortality. For the composite outcome we calculated risk ratios with 95% confidence intervals.[25] A priori, it was decided to adjust for trial sites and any known prognostic covariate that might remain imbalanced between the two arms after randomisation.

Similarly, we calculated unadjusted and adjusted risk ratios for the secondary outcomes. Adjustment was done for trial sites and presence of diabetes mellitus. A per protocol analysis was performed for secondary outcomes. We compared changes in continuous variables such as oxygen requirement (FiO_2), laboratory variables (biomarker levels, neutralising antibody titres) over the period of hospital stay between both arms by using generalised estimating equations. To assess viral clearance, we compared the proportion of participants negative for SARS-CoV-2 RNA between the trial arms on days 3 and 7. For continuous variables such as duration of respiratory support or hospital stay, we applied the Mann-Whitney U test. The median score on the WHO ordinal scale was plotted for the two trial arms for days 0, 1, 3, 5, 7, and 14.

A modified intention-to treat analysis was performed on a subgroup of participants based on duration of symptoms at enrolment, detection of neutralising antibodies in the recipients or the transfused convalescent plasma. A post hoc subgroup analysis compared the composite outcome between participants who received convalescent plasma with detectable neutralising antibodies and participants in the control arm. We compared participants receiving convalescent plasma with a neutralising antibody titre of 1:80 or higher with control participants for the primary outcome. Stratified analysis was done for the primary outcome between intervention and control arms based on stratums such as detectable neutralising antibodies at enrolment and duration of symptoms at enrolment. To assess the effect of transfusing convalescent plasma early in covid-19, we carried out a subgroup analysis for the composite outcome in participants who had symptoms for three days or less at enrolment. Interaction was checked by including an interaction term in the models.

Data were collected in structured paper case record forms and then entered in the Research Electronic Data Capture system (REDCap, version 8.5 Vanderbilt University, TN). Data analysis was done using STATA v14 (College Station, TX). An independent data and safety monitoring board oversaw the study. The trial protocol was registered with the Clinical Trial Registry of India (CTRI/2020/04/024775).

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of our research.

Results

Of 1210 patients admitted across 39 trial sites and screened between 22 April and 14 July 2020, 464 eligible patients were recruited in the study; 235 were randomised to receive convalescent plasma and best standard of care (intervention arm) and 229 were randomised to receive best standard of care only (control arm). The primary outcome at 28 days was not available for two patients (one in each arm) who were lost to follow-up after discharge from hospital; nine patients (five in intervention arm, four in control arm) withdrew consent after randomisation. Two patients did not receive the intervention, convalescent plasma, after randomisation because no match for a donor was available. Figure 1 shows the flow of participants through the study. All 464 participants were included in the intention-to-treat analysis of the primary outcome. A per protocol analysis was performed for secondary outcomes in 451 participants. Supplementary table 1 provides details of enrolment at the study sites, and supplementary figure 1 shows the geographical spread of the study sites across India.

Baseline personal and clinical characteristics, available for all 464 participants, were similar across the trial arms, except for prevalence of diabetes mellitus and cough (table 1 and table 2). Patient management across the trial arms was similar except for convalescent plasma treatment (table 2).

Convalescent plasma was used from 262 of 433 donors in the trial. Most of the donors were men (n=247, 94%), with a mean age of 34.3 (SD 9.3) years. The median disease duration was 6 days (interquartile range 3-11 days) and most of the donors (n=245, 94%) had mild disease. Nearly two thirds (n=161, 64%) of the donors had a neutralising antibody titre of more than 1:20, with a median titre of 1:40 (interquartile range 1:30-1:80). Plasma was donated after a median of 41 (interquartile range 31-51) days from the RT-PCR confirmed diagnosis of covid-19 (see supplementary figure 2 and table 2 for details).

The primary outcome did not differ across the trial arms on intention-to-treat analysis; missing information on the composite outcome was imputed for 11 participants. The composite outcome occurred in 44 (19%) patients in the intervention arm and 41 (18%) in the control arm (unadjusted risk difference 0.008, 95% confidence interval −0.062 to 0.078; risk ratio 1.04, 95% confidence interval 0.71 to 1.54). Mortality within 28 days of enrolment was recorded in 34 participants (15%) in the intervention arm and 31 participants (14%) in the control arm (risk ratio1.04, 0.66 to 1.63). Progression to severe disease was recorded in 17 participants from each arm (risk ratio 1.04, 0.54 to 1.98; table 3).

A higher proportion of patients in the intervention arm showed resolution of shortness of breath and fatigue at day 7, whereas resolution of fever and cough did not differ between the two arms (table 4). Negative conversion of SARS-CoV-2 RNA at day 7 post-enrolment was significantly higher in the intervention arm compared with control arm (table 4).

Total and post-enrolment duration of respiratory support, the proportion of participants receiving invasive ventilation, and the proportion receiving vasopressor support did not differ between the arms

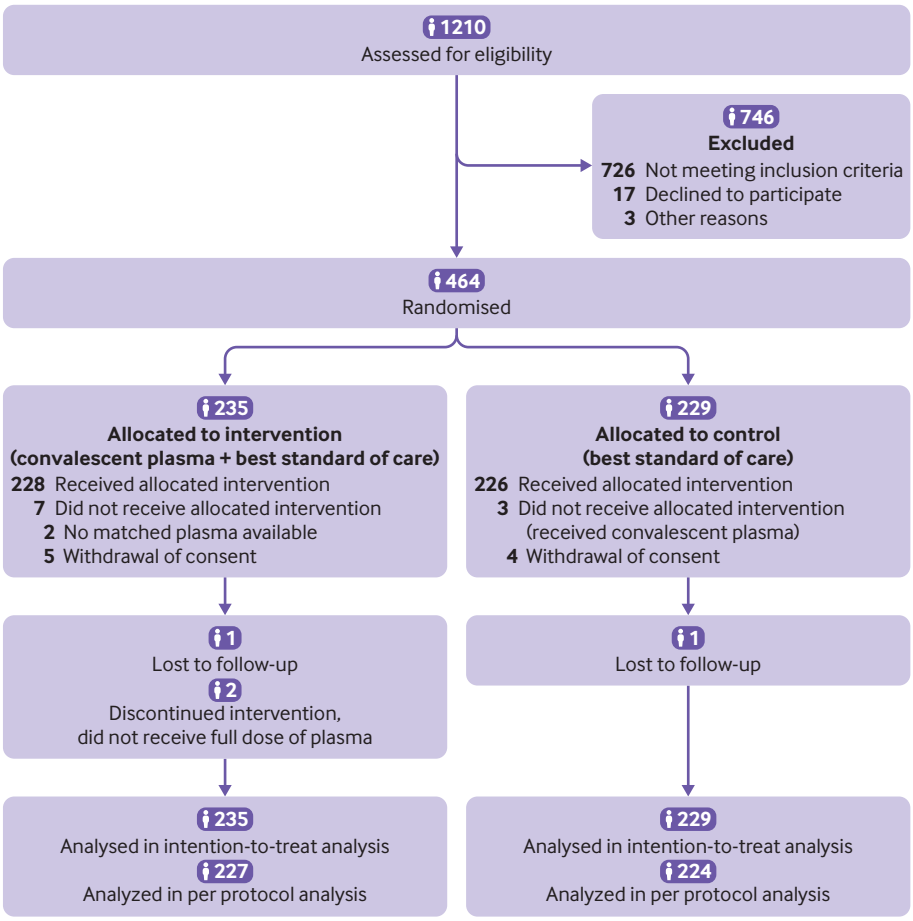

Fig 1 | Trial profile

Table 1 | Personal and baseline characteristics of study participants with moderate coronavirus disease 2019 assigned to convalescent plasma therapy (intervention arm) or to best standard of care (control arm). Values are numbers (percentages) unless stated otherwise

Characteristics	Intervention arm (n=235)	Control arm (n=229)
Median (interquartile range) age (years)	52 (42-60)	52 (41-60)
Men	177 (75)	177 (77)
Mean (SD) body mass index	26.2 (4.3)	26.1 (4.2)
Comorbidities:	167 (71)	147 (64)
Diabetes mellitus	113 (48)	87 (38)
Hypertension	92 (39)	81 (35)
Coronary artery disease	15 (6)	17 (7)
Obesity	16 (7)	17 (7)
Tuberculosis*	9 (4)	10 (4)
Chronic kidney disease	8 (3)	9 (4)
Chronic obstructive pulmonary disease	8 (3)	7 (3)
Cerebrovascular disease	3 (1)	1 (0.4)
Cirrhosis	0	2 (1)
History of cancer	1 (0.4)	0
Ever smoker	19 (8)	18 (8)
Blood group:		
A	55 (23)	51 (22)
B	87 (37)	83 (36)
O	79 (34)	83 (36)
AB	14 (6)	12 (5)
Median (interquartile range) symptom onset to admission (days)	4 (3-7)	4 (3-7)
Median (interquartile range) symptom onset to enrolment (days)	8 (6-11)	8 (6-11)
Detectable neutralisation antibody titre† (n=418)	185 (86)	163 (80)

*Only two patients, one in each arm, had active disease.
†Data not available for all randomised patients.

(table 4). Among the 38 participants who received invasive ventilation, only two survived until 28 days post-enrolment. The average fraction of inspired oxygen over 14 days of hospital stay did not differ between the arms (β=−0.1, 95% confidence interval −25 to 2.3; supplementary figure 3). Over a period of seven days from enrolment, the average levels of inflammatory markers showed no statistically significant difference between the two arms: lactate dehydrogenase (β=19.5, 95% confidence interval −43.3 to 82.4), ferritin (33.6, −49.5 to 116.7), C reactive protein (−19.4, −0.84.3 to 45.5), D-dimer (0.4, −0.2 to 0.9) (fig 2). The median scores on the sequential organ failure assessment for both arms were the same on days 0, 3, and 7 (2 (interquartile range 2-3), 2 (1-2), and 1 (0-2), respectively). WHO ordinal scale scores for clinical improvement did not differ between the trial arms at any observation point (supplementary fig 4). Supplementary table 4 provides the adjusted analysis for secondary outcomes.

Thirty four participants (15%) died in the intervention arm and 31 (14%) in the control arm. One participant each in the intervention group reported minor adverse events of pain at the infusion site, chills, nausea, bradycardia, and dizziness. Fever and tachycardia were reported in three patients. Dyspnoea and blockage of an intravenous catheter occurred in two participants each. Mortality was assessed as

Table 2 | Clinical and laboratory findings in study participants with moderate coronavirus disease 2019 assigned to convalescent plasma therapy (intervention arm) or to best standard of care (control arm) at baseline and drugs received during hospital stay. Values are numbers (percentages) unless stated otherwise

Clinical and laboratory findings	Intervention arm	Control arm
Shortness of breath	215/235 (91)	208/229 (91)
Fever	77/235 (32)	85/229 (37)
Cough	149/235 (63)	167/229 (73)
Fatigue	183/234 (78)	182/229 (79)
Radiography findings (n=432):		
Ground glass opacity	27/218 (12)	29/224 (13)
Local patchy shadows	12/218 (5)	9/224 (4)
Bilateral patchy shadows	140/218 (64)	139/224 (65)
Interstitial abnormalities	3/218 (1)	4 /224 (2)
Bilateral white out lung	2/218 (1)	2/224 (1)
Others	34/218 (16)	31/224 (14)
Mean (SD) SpO_2 on room air (%)	88.1 (4)	88.5 (4)
Mean (SD) FiO_2 required to maintain SpO_2 >92%	39.04 (13)	37.4 (11)
Mean (SD) PaO_2/F_IO2	255.4 (42)	251.6 (39.5)
Mean (SD) haemoglobin (g/L)	125 (21)	125 (18)
Median (interquartile range) WBC count (cells/mm^3)	8480 (6110-11 460)	8500 (6500-11 200)
Median (interquartile range) neutrophil:lymphocyte ratio	5.5 (3.5-10)	5.5 (3.4-9.4)
Median (interquartile range) ferritin (ng/mL)	529.8 (278.6-956)	539.5 (328.3-873)
Median (interquartile range) LDH (IU/L)	473.5 (335-661)	458.6 (342.5-638.5)
Median (interquartile range) C reactive protein (mg/L)	41.6 (14.2-90)	41.7 (12-126)
Median (interquartile range) D-dimer (mg/L)	0.8 (0.5-2.1)	0.7 (0.4-1.5)
WHO ordinal scale (n=463):		
4	180/234 (7)	181/229 (79)
5	54/234 (23)	47/229 (21)
6	0	1/229 (0.4)
Drug treatments:		
Hydroxychloroquine	159/235 (68)	155/229 (68)
Remdesivir	7/235 (3)	13/229 (6)
Lopinavir/ritonavir	36/235 (15)	30/229 (13)
Methylprednisolone	123/235 (52)	114/229 (50)
Dexamethasone	23/235 (10)	30/229 (13)
Hydrocortisone	4/235 (2)	5/229 (2)
Tocilizumab	16/235 (7)	26/229 (11)
Heparin (UFH/LMWH)	178/235 (76)	170/229 (74)
Azithromycin	156/235 (66)	140/229 (61)
Intravenous immunoglobulin	1/235 (0.4)	0
Other antibiotics	204/235 (87)	196/229 (86)

SpO_2=peripheral capillary oxygen saturation; FiO_2=fraction of inspired oxygen; PaO_2=partial pressure of oxygen in arterial blood; WBC=white blood cells; LDH=lactate dehydrogenase; WHO=World Health Organization; UFH=unfractionated heparin; LMWH=low molecular weight heparin.

possibly related to convalescent plasma transfusion in three participants (1%).

A modified intention-to-treat analysis was performed in a subgroup of participants based on duration of symptoms at enrolment, detection of neutralising antibodies in participants or recipients of convalescent plasma (table 5). For those with symptoms for three days or less at enrolment, the composite outcome did not differ between the intervention and control arms (n=24, risk ratio 0.8, 95% confidence interval 0.2 to 3.1). Titres of neutralising antibody in transfused convalescent plasma were available in 224 out of 235 participants in the intervention arm; 160 (71.4%) participants received at least one unit of convalescent plasma with detectable neutralising antibodies. The primary outcome did not differ between the subgroups of participants in the intervention arm who received convalescent plasma with detectable neutralising antibody titres (n=160) or convalescent plasma with neutralising antibody titres of 1:80 or higher (n=67) or convalescent plasma with no detectable neutralising antibodies (n=64) and the control arm (table 5).

Neutralising antibody titres were measured in 418 trial participants; 348 (83%) had detectable neutralising antibodies at enrolment. The median neutralising antibody titre at enrolment was 1:90 (interquartile range 1:30-1:240). In enrolled participants with detectable neutralising antibodies at baseline, the composite primary outcome did not differ between the intervention and control groups (29 (16%) *v* 27 (17%), risk ratio 0.9, 95% confidence interval 0.6 to 1.5). In participants with undetectable neutralising antibodies at baseline (n=70), no difference in the composite primary outcome could be discerned (9 (30%) *v* 10 (25%), risk ratio 1.2, 0.6 to 2.6). Figure 3 shows the neutralising antibody titres on days 0, 3, and 7 in both trial arms.

Discussion

This study found no difference in 28 day mortality or progression to severe disease among patients with moderate covid-19 treated with convalescent plasma along with best standard of care compared with best standard of care alone. Additionally, outcomes did not differ between participants receiving convalescent plasma with detectable neutralising antibody titres compared with participants receiving best standard of care alone; or between those receiving convalescent plasma with neutralising antibody titres of 1:80 or higher and those receiving best standard of care alone. Treatment with convalescent plasma was associated with a higher resolution of shortness of breath and fatigue on day 7. A higher proportion of participants in the intervention arm showed negative conversion of SARS-CoV-2 RNA on day 7 post-enrolment. The intervention did not, however, show anti-inflammatory properties as we could not detect any difference in the levels of inflammatory markers such as ferritin, C reactive protein, D-dimer, or lactate dehydrogenase between the trial arms.

Comparison with other studies

A recent Cochrane review, including 20 studies (one randomised controlled trial, three controlled non-randomised studies of intervention, 16 non-controlled non-randomised studies of intervention), concluded

Table 3 | Comparison of primary outcomes between convalescent plasma therapy (intervention arm) and best standard of care (control arm) in intention-to-treat analysis

Composite outcome	No (%) in intervention arm (n=235)	No (%) in control arm (n=229)	Unadjusted risk difference (95% CI)	Unadjusted risk ratio (95% CI)	Adjusted risk ratio (95% CI)
All cause mortality at 28 days or progression to severe disease	44 (19)	41 (18)	0.008 (−0.062 to 0.078)	1.04 (0.71 to 1.54)	1.07 (0.73 to 1.58)

Adjusted for trial sites and presence of diabetes mellitus.

Table 4 | Comparison of secondary outcomes between convalescent plasma therapy (intervention arm) and best standard of care (control arm) in per protocol analysis (n=451). Values are numbers (percentages) unless stated otherwise

Secondary outcomes	Intervention arm	Control arm	Unadjusted risk ratio (95% CI)
Resolution of symptoms on day 7:			
Shortness of breath (n=362)	140/183 (76)	119/181 (66)	1.16 (1.02 to 1.32)
Fever (n=138)	66/67 (98)	65/71 (92)	1.08 (0.99 to 1.16)
Cough (n=274)	102/127 (80)	111/147 (76)	1.06 (0.94 to 1.2)
Fatigue (n=306)	114/156 (73)	92/153 (60)	1.21 (1.02 to 1.42)
Negative conversion of SARS-CoV-2 RNA:			
Day 3 (n=367)	79/184 (43)	67/183 (37)	1.2 (0.9 to 1.5)
Day 7 (n=342)	117/173 (68)	93/169 (55)	1.2 (1.04 to 1.5)
Median (interquartile range) total hospital stay (days); No with event	14 (10-19); n=227	13 (10-18); n=224	0.2*
Median (interquartile range) total days of respiratory support; No with event	9 (6-13); n=227	10 (6-13); n=224	0.7*
Median (interquartile range) days of respiratory support post-enrolment; No with event	6 (3-9); n=227	6 (4-10); n=224	0.5*
Type of mechanical ventilation during hospital stay:			
Invasive	19/227 (8)	19/224 (8)	0.99 (0.54 to 1.81)
Non-invasive	31/227 (14)	37/224 (16)	0.8 (0.5 to 1.3)
Vasopressor support after enrolment	10/225 (4)	8/221 (4)	1.2 (0.5 to 3.05)

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; RNA=ribonucleic acid.
*Continuous variables—Mann-Whitney U test applied and P values reported. All changes are measured from day of enrolment.

that the effectiveness of convalescent plasma in improving mortality or clinical improvement is uncertain in patients with covid-19.[15] A randomised controlled trial of 103 patients with severe and life threatening covid-19 in China reported no effect of convalescent plasma treatment on time to clinical improvement. In that trial, a subgroup of 45 patients with severe disease, similar to patients with moderate disease in our study, showed increased clinical improvement in the convalescent plasma group.[13] The ConCOVID trial from the Netherlands, prematurely terminated after 86 patients had been enrolled, could not find any effect on mortality at 60 days, hospital stay, or disease severity at 15 days.[14] A large observational study advocated the usefulness of convalescent plasma to treat covid-19, reporting that 7 day mortality and 30 day mortality were lower in those who received convalescent plasma within three days of symptom onset. However, the absence of a controlled comparator weakens these findings as evidence of

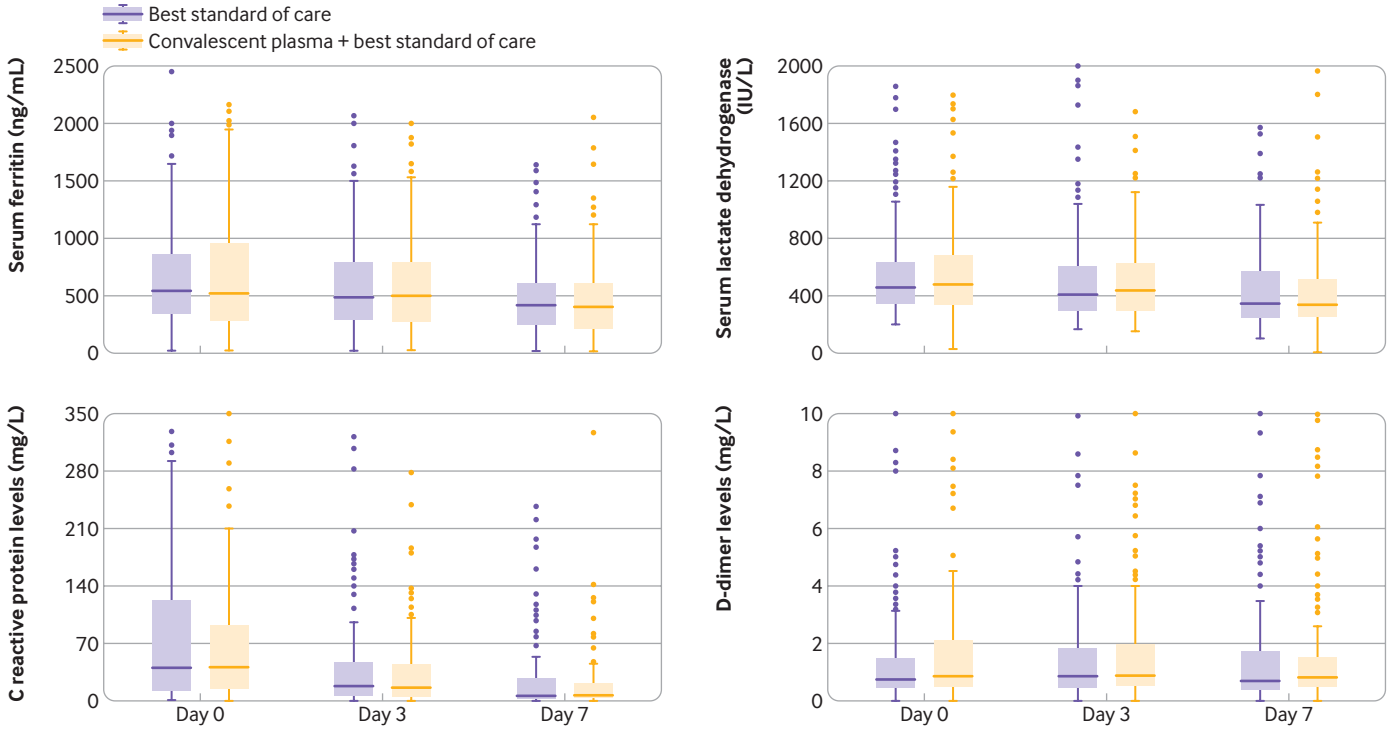

Fig 2 | Comparison of biomarkers between intervention (convalescent plasma therapy+best standard of care) and control (best standard of care) arms, by days post-enrolment. The dark line in the box represents the median and the upper and lower edges of the box represent the interquartile range. The upper and lower extreme of the whiskers represent the upper and lower range, respectively, excluding outliers

Table 5 | Subgroup analysis for primary outcome between convalescent plasma therapy (intervention arm) and best standard of care (control arm) in modified intention-to-treat analysis. Values are numbers (percentages) unless stated otherwise

Composite outcome	Intervention arm (detectable NAbs in CP)* (n=160)	Control arm (n=229)	Unadjusted risk ratio (95% CI)	Intervention arm (NAbs ≥1:80 in CP)* (n=67)	Unadjusted risk ratio (95% CI)	Intervention arm (undetectable NAb in CP)* (n=64)	Unadjusted risk ratio (95% CI)
All cause mortality at 28 days or progression to severe disease	27 (17)	41 (18)	0.94 (0.61 to 1.47)	12 (18)	1.0004 (0.56 to 1.79)	13 (20)	1.13 (0.65 to 1.98)

Nab=neutralising antibodies; CP=convalescent plasma.
*Comparator was best standard of care.

efficacy.[26] Although our study was underpowered, we did not find any benefit from convalescent plasma being administered within three days of symptom onset in covid-19.

Our results concur with those of the ConCOVID trial, where 79% of the participants had detectable antibodies at baseline.[14] However, the neutralising antibody titres in convalescent plasma in our study were similar to those of another study, which found that 13-40% patients turned seronegative in the early convalescent phase.[27] In a series involving 175 patients, the researchers documented that 30% of patients generated low levels of neutralising antibodies, with titres correlating to increasing age and disease severity.[20] We found that participants had higher antibody positivity and median neutralising antibody titres than the donors of convalescent plasma. The difference in age and severity of illness between participants, with donors being younger and having milder disease, could have driven this difference. Although all survivors of covid-19 were encouraged to donate plasma, most of the donors were young and only had mild disease. Recovered patients who had moderate or severe disease were generally reluctant to return to hospitals for plasma donation. This has major implications for obvious operational reasons in the scaling up of convalescent plasma treatment for covid-19 not only in India but also globally.

Neutralising antibody titres did not differ between the two trial arms despite the transfusion of convalescent plasma. This suggests potentially no benefit of convalescent plasma collected from young survivors of mild covid-19 and administered to elderly patients with moderate or severe disease who have a robust antibody response.

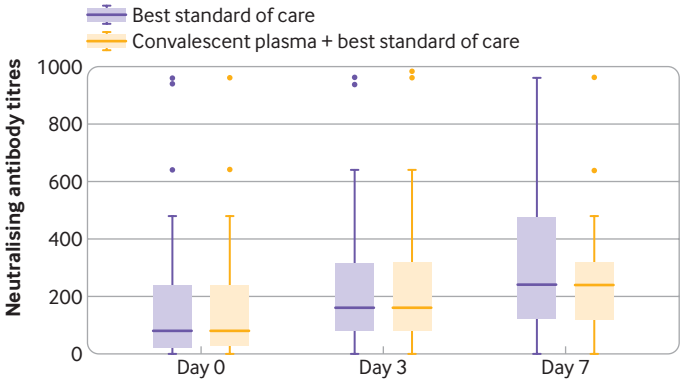

Fig 3 | Comparison of neutralising antibody titres between intervention (convalescent plasma therapy and best standard of care and control (best standard of care) arms, by days 0, 3, and 7 post-enrolment

The early conversion to viral RNA negativity in the intervention arm aligns with published evidence and further supports the fundamental hypothesis that convalescent plasma exerts virus neutralising effects.[11 13] The goal of achieving better clinical outcomes in our study, however, remained elusive. We did not find evidence to support the immunomodulator functions of convalescent plasma as we could not show differences in the levels of inflammatory markers. This could potentially explain why convalescent plasma treatment made no difference to the primary outcome despite early negativity for SARS-CoV-2 RNA.

Transfusion of convalescent plasma was deemed to be safe in our study as minimal non-life threatening adverse events were reported. Three deaths could possibly be related to transfusion, which is comparable to the other larger report on safety of convalescent plasma use to treat covid-19.[12] In our study we defined a "possible" adverse event as a clinical event that occurred within six hours of convalescent plasma transfusion but could also be explained by worsening covid-19.[23]

Strengths and limitations of this study

Our trial (the PLACID Trial) was conducted to generate context specific evidence relevant to all stakeholders, including policymakers, healthcare providers, and patients. To achieve this, we invited an expression of interest from hospitals across India, not just a few centres of excellence. Hospitals were chosen from both the public and the private sectors, lending heterogeneity in infrastructure and wide social, cultural, and economic representation of study participants, with a large range of comorbidities and presenting features. The best standard of care represented the care standards likely to be provided in a real world setting. Although this approach could have affected comparability across study sites, we believe this lends the trial more generalisability, approximates real world scenarios more closely, and in the methodological spectrum of clinical trials, shifts it towards pragmatic trials.

Our trial has several limitations. Because our study used an open label design, it was susceptible to anchoring bias of the treating doctors in outcome ascertainment. This might be reflected in the higher resolution of subjective symptoms such as shortness of breath and fatigue noted in the intervention arm. The trial was conducted in 39 hospitals across India, with some level of heterogeneity across the trial sites for best standard of care and participant enrolment. The biomarker assays for ferritin, lactate

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dehydrogenase, C reactive protein, and D-dimer were conducted using tests from different manufacturers. Also, as the pandemic was in different stages across the country, the numbers enrolled varied between sites, with a possibility of selection bias arising from clustering of enrolment. We dealt with this bias by statistically adjusting the primary outcome for trial sites. Furthermore, the discharge criteria for covid-19 was based on Indian government guidelines and not on clinician discretion and patient condition, hence we chose not to analyse discharge as a secondary outcome. We could not measure the antibody titres in convalescent plasma before transfusion because validated, reliable commercial tests for qualitative or quantitative antibody measurement were not available when our trial started. However, this practice remains a close approximation of the manner in which convalescent plasma treatment has largely been used in regions with limited laboratory capacity.

Policy implications

Use of convalescent plasma as treatment for covid-19 is authorised for off-label use in India.[29] This authorisation has been paralleled by questionable practices such as calls for donors on social media and the sale of convalescent plasma on the black market with exorbitant price tags in India.[30] Additionally, although convalescent plasma is a safe form of treatment when transfused in accordance to the regulations appropriate for the transfusion of blood and blood products, plasmapheresis, plasma storage, and measurement of neutralising antibodies are all resource intensive processes, with a limited number of institutes in India having the capacity to undertake these procedures in a quality assured manner.

Conclusion

Although the use of convalescent plasma seemed to improve resolution of shortness of breath and fatigue in patients with moderate covid-19 and led to higher negative conversion of SARS-CoV-2 RNA on day 7 post-enrolment, this did not translate into a reduction in 28 day mortality or progression to severe disease. Areas of future research could include effectiveness of convalescent plasma among neutralising antibody negative patients and the use of convalescent plasma with high neutralising antibody titres. The challenge will be to find both suitable patients and suitable plasma donors. Additionally, this challenge could limit the use of convalescent plasma to a small subset of patients.

See appendix 1 for the names and affiliations of the PLACID Trial Collaborators.

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Contributors: AM is the guarantor. Patient enrolment, conduct of study, clinical care and data collection: Madras Medical College, Chennai: BL, SS, SAMK, VR, AS, PB, RSUM, RJ, SR. SMS Medical College, Jaipur: SB, SB, AS, AP, AH, GR. Sir H.N Reliance Foundation Hospital and Research Centre: VK, KK, JR, DR, EP, NB, MHP, RJV. Sri Aurobindo Institute of Medical Science, Indore: RD, SP, AT, SJ, RK. Smt. NHL Municipal Medical College, Ahmedabad: JRK, NNS, NMS, HMP, CKS, MNP, SS, STS, TM, VRB. Topiwala National Medical College and BYL Nair Hospital: RDS, KJ, FE, SA, RB, AMN, TM, VK, RW, NV. Gandhi Medical College, Secunderabad: RRM, BTC, AVS, AKM, KH, KN, KS, TRC, KTR, JV. Government Institute of Medical Science, Noida: SS, RU, SB, RP, SS, BRG. Gandhi Medical College, Bhopal: SD, RS, PD, RM, DC, JL, UMS, JLM. ABVIMS and RML Hospital, New Delhi: KC, AS, VK, RK, PK, BPA, KKG, AG, PS, SD. Satguru Pratap Singh hospitals, Punjab: AJ, MJJ, ASD, RK, NS, NK, DK, RK, RM, GS, JK, RPS, RB Kasturba Hospital: SP, OS, JS, MD, SU. Rajarshree Chhatrapati Shahu Maharaj Govt Medical College: VAF, VB, RM, SY All Institute of Medical Sciences, Jodhpur: SM, AB, MKG, GKB, VN, PBA, MN, PS, RN Post Graduate Institute of Medical Education and Research, Chandigarh: NSK, PM, RS, MPS, NS, SS, RH, VS, LNY, PVML All Institute of Medical Sciences, Patna: NS, DB, NK Byramjee Jeejeebhoy Medical College, Pune: MT, SS, NK, SS, LN, SJ, RK, SG ESIC Medical College and Hospital, Faridabad: NS, NV, AD; Clinical Development Services Agency: MB, NW Smt. Kashi Bai Navale Medical College: SB, SD, VW, AK, TY Karnataka Institute of Medical Sciences, Hubballi: RSK, PR, KY, PG, VM, MS, MHN Lady Hardinge Medical College and SSK Hospital, New Delhi: AG, RS, SP, AP, PG, SS King George's Medical University, Lucknow: DHR, CT, SP, PM, AW, VK Byramjee Jeejeebhoy Medical College, Ahmedabad: KU, NB, NS, MS, TP Mahatma Gandhi University of Medical Sciences Technology, Jaipur: RMJ, AJ, SS, PR, NG Government Medical College, Surat: TCP, MGS, JP, YRS, MJ GMERS Medical College and Hospital, Gotri, Vadodara: VG, MS, RR, IN Sumandeep Vidyapeeth and Dhiraj Hospital, Vadodara: PRJ, ADS, GY, AJ, RKG Sri Venkateshwara Institute of Medical Sciences, Tirupati: KVSB, BSB, AM, BV, KCS Kurnool Medical College, Kurnool: SD, KN, CA, GB, RRK, PC Madurai Medical College, Madurai: MN, MS, DPK, FR Government Medical College, Bhavnagar: SJP, PHS, MB, KD, PJA MGM Indore: MB, AY, MG, NR, DC Poona Hospital and Research Centre: VKK, DP, SM, CDS, VT Super Specialty Paediatric Hospital and Post Graduate Teaching Institute, Noida: SA, DKG, SD SN Medical College, Agra: NC, ASC Christian Medical College, Vellore: JJM, SK, DD Aditya Birla Memorial Hospital: RS, VD, YA, SA RD Gardi Medical College, Ujjain: AP, MP, AS Seth GS Medical college and KEM Hospital, Mumbai: JS, KJ, SB; National Institute of Immunohaematology: MM, RMY Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai: NDK, YAG, LN, SM Study design, data analysis, data interpretation and manuscript writing team: AA, AM, GK, PC, TB, SD, PM. Data Management Team: KK, RS. Generation of randomisation sequence: VSK. Central Implementation Team: AA, AM, GK, AT. Laboratory Analysis Team: GD, SS, RG, AS, DP, CP, SS, KJ, HK, PDY, GS, PA.

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interpretation, and writing of the report. Patient enrolment, data collection, and the conduct of the study was done at public and private hospitals independently, and the investigators in ICMR had no role in these activities. The funding source has no financial interest in the investigational product.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that: TB is a member of the National Task Force for covid-19, which approved the protocol. AM, AA, GK, AT, TB, VS, KK, RS, SD, GD, SS, RG, AS, DP, CP, SS, KJ, HK, PDY, GS, PA, MM, and RMY are employed by the Indian Council of Medical Research (ICMR), the funding source for the trial. PC was an employee of ICMR during the trial.

Ethical approval: This study was approved by the Indian Council of Medical Research Central Ethics Committee on Human Research (CECHR-002/2020) based in the National Center for Disease Informatics and Research, Indian Council of Medical Research, Bengaluru, Karnataka, India, as well as from the institutional review boards or institutional ethics committees of all the participating hospitals.

Data sharing: Individual patient level data, collected in connection with the PLACID Trial, along with a data dictionary defining the variable fields have been developed and are available from the corresponding author. Deidentified participant level data with data dictionary, or a subset thereof, may be made available upon written request to the corresponding author. Additional documents, including the study protocol and statistical analysis plan have been made available as supplementary files within the original submission. Results of secondary or subgroup analyses will be provided on request. Data will be made available, upon request, once the trial is published. Data requests should be accompanied by a brief proposal outlining the analysis plan, which may be carried out with investigator support. A signed data access agreement might be needed to ensure data safety and compliance with national rules about data sharing.

The corresponding author (AM) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research. The study results will be disseminated to the study participants via their treating doctors.

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Supplementary information: Additional tables and figures

Supplementary information: Detailed list of PLACID Trial collaborators