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► To cite this version:

Karine Lacombe, Thomas Hueso, Raphael Porcher, Arsene Mekinian, Thibault Chiarabini, et al.. Use of covid-19 convalescent plasma to treat patients admitted to hospital for covid-19 with or without underlying immunodeficiency: open label, randomised clinical trial. *BMJ Medicine*, 2023, 2 (1), pp.e000427. 10.1136/bmjmed-2022-000427. hal-04335160

HAL Id: hal-04335160

<https://hal.science/hal-04335160>

Submitted on 11 Dec 2023

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Use of covid-19 convalescent plasma to treat patients admitted to hospital for covid-19 with or without underlying immunodeficiency: open label, randomised clinical trial

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjmed-2022-000427>).

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Cite this as: *BMJMED* 2023;2: doi:10.1136/bmjmed-2022-000427

Received: 3 November 2022
Accepted: 5 September 2023

ABSTRACT

OBJECTIVE To evaluate the efficacy of covid-19 convalescent plasma to treat patients admitted to hospital for moderate covid-19 disease with or without underlying immunodeficiency (CORIPLASMA trial).

DESIGN Open label, randomised clinical trial.

SETTING CORIMUNO-19 cohort (publicly supported platform of open label, randomised controlled trials of immune modulatory drugs in patients admitted to hospital with moderate or severe covid-19 disease)

based on 19 university and general hospitals across France, from 16 April 2020 to 21 April 2021.

PARTICIPANTS 120 adults (n=60 in the covid-19 convalescent plasma group, n=60 in the usual care group) admitted to hospital with a positive SARS-CoV2 test result, duration of symptoms <9 days, and World Health Organization score of 4 or 5. 49 patients (n=22, n=27) had underlying immunosuppression.

INTERVENTIONS Open label randomisation to usual care or four units (200–220 mL/unit, 2 units/day over two consecutive days) of covid-19 convalescent plasma with a seroneutralisation titre >40.

MAIN OUTCOME MEASURES Primary outcomes were proportion of patients with a WHO Clinical Progression Scale score of ≥6 on the 10 point scale on day 4 (higher values indicate a worse outcome), and survival without assisted ventilation or additional immunomodulatory treatment by day 14. Secondary outcomes were changes in WHO Clinical Progression Scale scores, overall survival, time to discharge, and time to end of dependence on oxygen supply. Predefined subgroups analyses included immunosuppression status, duration of symptoms before randomisation, and use of steroids.

RESULTS 120 patients were recruited and assigned to covid-19 convalescent plasma (n=60) or usual care (n=60), including 22 (covid-19 convalescent plasma) and 27 (usual care) patients who were immunocompromised. 13 (22%) patients who received convalescent plasma had a WHO Clinical Progression Scale score of ≥6 at day 4 versus eight (13%) patients who received usual care (adjusted odds ratio 1.88, 95% credible interval 0.71 to 5.24). By day 14, 19 (31.6%) patients in the convalescent plasma group and 20 (33.3%) patients in the usual care group needed ventilation, additional immunomodulatory treatment, or had died. For cumulative incidence of death, three (5%) patients in the convalescent plasma group and eight (13%) in the usual care group died by day 14 (adjusted hazard ratio 0.40, 95% confidence interval 0.10 to

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Treatment with convalescent plasma (ie, passive polyclonal antibody administration to provide immediate immunity) has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral causes in emergency settings and when no specific antiviral treatment is available
- ⇒ At the early stages of the covid-19 pandemic, using high titre covid-19 convalescent plasma seemed to be an immediate therapeutic option, but many randomised clinical trials and observational studies have reported conflicting results on the efficacy of convalescent plasma
- ⇒ Evaluation of the efficacy of covid-19 convalescent plasma in patients with underlying immunosuppression has been limited and the emergence of variants resistant to other passive immunotherapies (ie, monoclonal antibodies) has restricted the treatment options for these patients

WHAT THIS STUDY ADDS

- ⇒ This multicentre, randomised clinical trial indicates that transfusion of high titre covid-19 convalescent plasma to patients admitted to hospital with mild-to-moderate covid-19 within nine days of the onset of symptoms might not improve early outcomes
- ⇒ In the subgroup of patients with immunosuppression, the evidence indicated a lower odds of death at 14 and 28 days after transfusion of covid-19 convalescent plasma, but this finding was not significant

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- ⇒ This study, and other trials and cohort studies, support further evaluation of transfusion of covid-19 convalescent plasma in patients with underlying immunosuppression
- ⇒ Treatment options for patients who are immunocompromised are scarce if non-existent because of the changing genetic variability of the SARS-CoV2 virus

1.53), and seven (12%) patients in the convalescent plasma group and 12 (20%) in the usual care group by day 28 (adjusted hazard ratio 0.51, 0.20 to 1.32). In a subgroup analysis performed in patients who were immunocompromised, transfusion of covid-19 convalescent plasma was associated with mortality (hazard ratio 0.39, 95% confidence interval 0.14 to 1.10).

CONCLUSIONS In this study, covid-19 convalescent plasma did not improve early outcomes in patients with moderate covid-19 disease. The efficacy of convalescent plasma in patients who are immunocompromised should be investigated further.

TRIAL REGISTRATION ClinicalTrials.gov
NCT04345991.

Introduction

Early in the covid-19 pandemic, transfusion of covid-19 convalescent plasma was identified as a potential treatment that needed evaluation.¹ The overall efficacy of covid-19 convalescent plasma in patients admitted to hospital for covid-19 has not been established.² High titre convalescent plasma might be beneficial, however, particularly if used early before seroconversion^{3,4} or in patients who lack an effective humoral response.^{5,6} Treatment with monoclonal antibodies has been shown to be effective as an early intervention⁷ or later in seronegative patients admitted to hospital.⁸ Major limitations exist for monoclonal antibodies, however, including accessibility and cost,⁹ as well as loss of efficacy, as recently shown with the emergence of the immune evading omicron subvariants of the SARS-CoV-2 virus.¹⁰

By contrast with monoclonal antibodies, covid-19 convalescent plasma, from convalescent donors who have been vaccinated, is cheaper, readily available, and adaptable to a changing viral landscape, and potentially less prone to immune resistance. Although the recent omicron variant dominant periods have been associated with a decrease in the efficacy of almost all available monoclonal antibodies,¹¹ high titre convalescent plasma (before the omicron dominant period) from convalescent donors who were vaccinated might retain anti-omicron neutralisation activity.¹² This anti-omicron neutralisation capacity is further increased in plasma from donors convalescing after the omicron variant of the virus who were vaccinated.¹³

As well as immunomodulating drugs that specifically target the inflammatory phase of the disease, oral direct antiviral agents, such as molnupiravir¹⁴ or nirmatrelvir with ritonavir,¹⁵ are another therapeutic option. These drugs have drawbacks, however, such as the need to start treatment within five days of the onset of symptoms and drug interactions for

nirmatrelvir-ritonavir, particularly in patients who are immunosuppressed. The intravenous antiviral agent, remdesivir, has shown only limited efficacy against the SARS-CoV-2 virus in patients admitted to hospital with covid-19.¹⁶ Careful assessment of the efficacy and safety of covid-19 convalescent plasma therefore is an important aspect of public health, particularly in patients who are immunosuppressed and do not have a vaccine mediated immune response. These patients are at risk of severe disease and have limited treatment options. We report the results of a randomised controlled trial that assessed the efficacy of covid-19 convalescent plasma (four units, about 840 mL) in patients with and without immunosuppression, who were admitted to hospital with moderate SARS-CoV-2 infection associated with pneumonia but who did not require assisted ventilation at the time of inclusion.

Methods

Trial design

CORIMUNO-19 is a publicly supported platform, established by Assistance Publique-Hôpitaux de Paris, France, at the beginning of the covid-19 pandemic, dedicated to performing cohort, open label, randomised controlled trials of immune modulatory drugs in patients admitted to hospital with moderate or severe covid-19 disease.¹⁷ CORIPLASM (Efficacy of Convalescent Plasma to Treat Covid-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort) was an embedded multicentre, open label, randomised controlled trial in patients with moderate covid-19 pneumonia conducted in French hospitals. Online supplemental appendix II and III have the full trial protocol and statistical analysis plan.

Study population and randomisation

At hospital admission, patients were evaluated for eligibility criteria: adults aged ≥ 18 years admitted to hospital, positive test result for the SARS-CoV-2 virus by nasopharyngeal polymerase chain reaction or computed tomography scan, or both, before randomisation, onset of symptoms < 9 days, illness of mild or moderate severity according to the WHO Clinical Progression Scale (admitted to hospital, mild disease, no oxygen needed; admitted to hospital, moderate disease, oxygen < 3 litres needed, online supplemental appendix I), not pregnant, no previous severe grade 3 allergic reaction to plasma transfusion, and no current bacterial infection reported.

ABO compatibility with available covid-19 convalescent plasma was verified before inclusion of patients. Written informed consent was obtained from all patients or their legal representatives at inclusion in CORIMUNO-19. Specific written informed consent was sought from eligible patients before inclusion in the CORIPLASM trial. The independent clinical research organisation compiled the computerised

randomisation list, and the patient's randomisation number was accessed through a secure site by a site study team member. Randomisation was performed within two hours of enrolment. Eligible patients were randomised 1:1 to receive convalescent plasma or usual care. Usual care could include the use of dexamethasone, tocilizumab, supportive care, including supplemental oxygen, antiviral agents, and antibiotics. A data and safety monitoring board provided guidance on the trial after inclusion of every 60 patients.

Study product

Convalescent donors were eligible for plasma donation 15 days after the end of symptoms related to covid-19 disease. Apheresis plasma was collected by Etablissement Français du Sang and underwent pathogen reduction (Intercept Blood System, Cerus, Concord, CA) and standard testing according to current regulations in France. Anti-SARS-CoV-2 potency was assessed in each donation, with a requirement for a SARS-CoV-2 seroneutralisation titre ≥ 40 , as described by Gallian et al.¹⁸ Antibody content was determined by immunoglobulin G enzyme linked immunosorbent assay (Euroimmun, Bussy-Saint-Martin, France). Covid-19 convalescent plasma with a seroneutralisation titre ≥ 40 , made available for the trial and collected between April and June 2020, gave a mean enzyme linked immunosorbent assay ratio of 6.1 (standard deviation 2.9, range 0.4-13.0). After the first three patients received two units of ABO compatible covid-19 convalescent plasma according to the protocol, all subsequent patients randomised to the convalescent plasma group received four units of convalescent plasma (200-220 mL/unit, 2 units/day over two consecutive days) provided by different donors.

Study endpoints

As in all of the CORIMUNO-19 nested trials, an early primary endpoint was defined as a WHO Clinical Progression Scale score of ≥ 6 (online supplemental appendix I) on day 4 of randomisation. Higher values on the WHO Clinical Progression Scale indicate a worse outcome. The primary endpoint specific to the CORIPLASM trial was survival without the need for assisted ventilation (including non-invasive ventilation or high flow oxygen) at day 14 of randomisation (WHO Clinical Progression Scale score < 6) or additional immunomodulatory treatment, with the exception of corticosteroids included within the standard of care (changes to the protocol, online supplemental file 1). Secondary endpoints were WHO Clinical Progression Scale score on days 4, 7, and 14 after randomisation, overall survival on days 14 and 28 after randomisation (ie, for the periods days 1-14 and days 1-28, respectively), time to discharge, time to end of dependence on oxygen supply, and

changes to a series of biological parameters at days 4, 7, and 14 after randomisation.

Predefined subgroup analyses included immunosuppression status (underlying immunodeficiency: yes/no), duration of symptoms before randomisation (≤ 5 days, > 5 days), and use of steroids. Safety data included all clinical and biological adverse events observed during the study follow-up. Immunodeficiency was defined as the presence of at least one of these medical conditions: active malignant neoplasm, lymphoid or myeloid neoplasms, haematopoietic stem cell or solid organ transplantation, or HIV/AIDS and not receiving highly active antiretroviral treatment.

Statistical analysis

The sample size was set at 120 participants (60 per group), with a bayesian interim analysis after 60 participants were randomised. We computed that the trial would have a frequentist power of 97.2% to detect a decrease in event proportions from 0.50 to 0.20, and 73.9% to detect a decrease in event proportions from 0.50 to 0.30. The study statisticians, who were masked to the group assignments, oversaw the interim and final analyses. Interim analysis reports were shared only with members of the data and safety monitoring board and not with the trial investigators. The trial investigators were blinded to all results during the trial.

The treatment effect was mainly expressed as an absolute risk difference for the early primary endpoint, and a hazard ratio for the longer term primary endpoint. Both were analysed in a bayesian framework. A posterior probability of absolute risk difference < 0 or hazard ratio < 1 but > 0.99 at the interim analysis or > 0.95 at the final analysis, indicated efficacy. We also computed posterior probabilities of absolute risk difference $< -5.5\%$ and hazard ratio < 0.85 , denoting a moderate or greater effect. At the interim analysis, a posterior probability of moderate or greater impact < 0.20 defined a futility boundary. The treatment effect was summarised by the posterior median and equal tail credible intervals.

Because decision rules are one sided, consistent credible intervals would theoretically be one sided 95% credible intervals, but we chose to report two sided 90% credible intervals with the same upper boundary. For the early primary endpoint, the posterior distribution of absolute risk difference was computed analytically, with a beta prior distribution, with parameters one and one for the proportion in each group. An odds ratio adjusted for age and centre (centre being treated as a random effect) was also estimated with a bayesian logistic regression model. For the longer term primary endpoint, the posterior hazard ratio distribution adjusted for age and centre was computed with Markov chain Monte Carlo with normal prior distributions, with mean 0 and variance

10^6 for the log hazard ratio. Different prior distributions were used as sensitivity analyses.

Secondary outcomes were analysed in a frequentist framework, except for WHO Clinical Progression Scale scores, analysed as an ordinal variable with a bayesian proportional odds model. Analyses of secondary outcomes were also adjusted for age and centre. For time to discharge and time to end of dependence on oxygen supply, we estimated adjusted subdistribution hazard ratios with Fine-Grey models, death being the competing event. Estimating subdistribution hazard ratios was preferred over cause specific hazard ratios because subdistribution hazard ratios have a one-to-one relation with the cumulative incidence (ie, the proportion) of events, and we considered that subdistribution hazard ratios would therefore be more relevant than the ratio of rates at which these events occur in time. We used interaction tests between the treatment group and subgroups to test for treatment effect heterogeneity between the subgroups, with similar regression models as the main adjusted analyses. The statistical analysis plan has full details of the statistical analyses (online supplemental appendix III).

Analyses were done on an intention-to-treat basis. The original protocol specified a modified intention-to-treat analysis excluding patients declining the intervention and those who could not receive the planned plasma treatment because ABO compatible covid-19 convalescent plasma was not available. Because those situations did not occur, no modified intention-to-treat analysis was performed. No correction for multiplicity was done for secondary outcomes, and corresponding results should be regarded as exploratory. Two interim analyses were conducted (online supplemental table S1). Statistical analyses were done with SAS (version 9.4, SAS Institute) and R (version 4.0.5, R Foundation) statistical software.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research, because the trial has been designed in an emergency setting. However, according to the French law, the results have been sent to all participants or to their families.

Results

Between 16 April 2020 and 21 April 2021, 120 patients (60 in the covid-19 convalescent plasma group and 60 in the usual care group) were enrolled (online supplemental figure S1). Table 1 shows the characteristics of the study participants, which were well balanced between the two groups.

Median time from onset of symptoms to randomisation (transfusion of covid-19 convalescent plasma or usual care) was seven days in both groups. We saw a positive anti-S and anti-N SARS-CoV-2 serology in

10/23 (44%) evaluable patients receiving convalescent plasma and in 9/27 (33%) evaluable patients receiving usual care. Underlying immunodeficiency was present in 22/60 (37%) and 27/60 (45%) patients in the convalescent plasma and usual care groups, respectively. One patient was thought to have covid-19 disease based on a typical chest computed tomography scan at inclusion, but was later reclassified as non-indicative of SARS-CoV-2 infection, and pulmonary oedema from cardiac origin was diagnosed. Online supplemental table S2 reports other treatments received before and after randomisation until day 14.

An intention-to-treat analysis was performed on 120 patients; two patients in each group were lost to follow-up at the day 28 evaluation but discharged alive before day 28 (figure 1). One patient did not receive a plasma infusion because of sudden worsening after randomisation and transfer to the intensive care unit. Nine patients received two units of convalescent plasma (three based on the protocol and six because of worsening of clinical status leading to admission to the intensive care unit), and 50 received four units of convalescent plasma. Same day transfusion was performed in 78% of patients, whereas 12 (20%) and one (2%) patient received a transfusion one and three days after randomisation, respectively.

Primary outcomes

Thirteen (22%) patients in the covid-19 convalescent plasma group versus eight (13%) patients in the usual care group had a WHO Clinical Progression Scale score of ≥ 6 at day 4 (median posterior absolute risk difference 8.0%, 90% credible interval -3.2% to 19.4% ; adjusted odds ratio 1.88, 95% credible interval 0.71 to 5.24; table 2, online supplemental table S3, and online supplemental figure S2). The WHO Clinical Progression Scale score on day 4 was analysed as an ordinal outcome in a proportional odds model, giving a median posterior adjusted odds ratio of 1.42 (95% credible interval 0.70 to 2.91), hence showing higher scores in the covid-19 convalescent plasma group, although the difference was not significant. By day 14, patients in the convalescent plasma and usual care groups needed non-invasive or high flow ventilation ($n=15$ in the convalescent plasma group and $n=13$ in the usual care group) or additional immunomodulatory treatment in the form of anti-interleukin 6 receptor monoclonal antibody ($n=0$ in the convalescent plasma group and $n=5$ in the usual care group), or had died ($n=2$ in each group). Also, one and five patients died after reaching the primary outcome in the convalescent plasma and usual care groups, respectively. Figure 2 shows the cumulative incidence of assisted ventilation or death. The median posterior adjusted hazard ratio was 1.04 (95% credible interval 0.55 to 1.97), and the posterior probability of a moderate or

Table 1 | Characteristics of participants at baseline in the two groups. Total group numbers that are not n=60 are indicated

	Covid-19 convalescent plasma group (n=60)	Usual care group (n=60)
Age (years)	64.5 (55.7-76.6)	67.0 (58.3-78.9)
Men	37/60 (62)	39/60 (65)
Weight (kg)	80.0 (68.5-93.5)	78.5 (67.0-89.5) (n=56)
Body mass index	27.8 (24.2-32.3) (n=55)	27.7 (22.9-32.3) (n=52)
Obesity (body mass index \geq 30)	21/60 (35)	15/58 (26)
WHO Clinical Progression Scale score (0-10)*:	5.0 (5.0-5.0)	5.0 (4.5-5.0)
Score 4	9/60 (15)	15/60 (25)
Score 5	51/60 (85)	44/60 (73)
Score 6	0/60	1/60 (2)
Temperature (°C)	37.2 (36.7-38.1)	37.4 (36.7-38.7)
Respiratory rate (breaths/min)	22.0 (20.0-28.0) (n=43)	24.0 (18.0-28.0) (n=39)
Oxygen flow (L/min)	2.0 (2.0-5.0) (n=50)	3.0 (2.0-4.0) (n=45)
SpO ₂ (%)	95.0 (94.0-96.0)	95.0 (93.0-96.0)
Time from onset of symptoms to randomisation (days)	7.0 (5.0-9.0)	7.0 (4.0-8.5)
Diagnosis of SARS-CoV-2 infection:		
Positive rRT-PCR test result	58/60 (97)	58/60 (97)
Typical chest CT scan only	2/60 (3)	1/60 (2)
None of the above†	0/60	1/60 (2)
Positive SARS-Cov-2 serology	10/23 (44)	9/27 (33)
Chronic cardiac disease	17/60 (28)	15/60 (25)
Diabetes	18/60 (30)	14/60 (23)
Chronic kidney disease (stages 1-3)	5/60 (8)	10/60 (17)
Asthma	4/60 (7)	7/60 (12)
Chronic pulmonary disease (except asthma)	4/60 (7)	7/60 (12)
Active malignant neoplasm	15/60 (25)	16/60 (27)
Lymphoid neoplasm	8/60 (13)	10/60 (17)
Myeloid neoplasm	4/60 (7)	7/60 (12)
Haematopoietic stem cell transplantation	2/60 (3)	1/60 (2)
Solid organ transplantation	1/60 (2)	1/60 (2)
AIDS/HIV not on HAART	0/60	1/60 (2)
Immunodeficiency‡	22/60 (37)	27/60 (45)
Current or former smoker	11/56 (20)	17/60 (25)
Laboratory values:		
C reactive protein (mg/L)	74.1 (27.7-108.7) (n=58)	84.4 (40.3-166.0) (n=58)
D-Dimer (µg/L)	580 (380-1070) (n=41)	921 (580-1650) (n=44)
Neutrophil count (10 ⁹ /L)	4.5 (2.5-6.3) (n=47)	3.8 (2.7-5.4) (n=55)
Lymphocyte count (10 ⁹ /L)	0.7 (0.6-1.1) (n=48)	0.8 (0.5-1.1) (n=54)
Lymphocytes to neutrophils ratio	0.2 (0.1-0.3) (n=47)	0.2 (0.1-0.4) (n=54)
Haemoglobin (g/dL)	12.4 (10.8-13.4) (n=57)	12.2 (10.1-13.7) (n=59)
Platelet count (g/L)	192 (145-263)(n=57)	153 (117-213) (n=59)
Alanine aminotransferase (IU/L)	40.0 (23.0-74.0) (n=54)	32.5 (22.0-47.5) (n=48)
Aspartate aminotransferase (IU/L)	44.0 (30.0-68.0) (n=54)	37.5 (28.0-52.0) (n=48)
Albumin (g/L)	34.2 (29.7-37.9) (n=32)	33.8 (30.2-39.0) (n=31)
Creatinine (µmol/L)	67.5 (55.0-84.0) (n=58)	77.0 (55.0-100.0) (n=59)
Ferritin (mg/L)	1137 (461-1472) (n=33)	945 (416-2160) (n=31)
Lactate dehydrogenase (g/L)	432 (344-535) (n=38)	366 (295-475) (n=36)
Creatine phosphokinase (IU/L)	78 (47-355) (n=24)	62 (41-141) (n=27)

Values are number/total number (%) or median (interquartile range).

CT=computed tomography; HAART=highly active antiretroviral therapy; rRT-PCR=real time reverse transcription polymerase chain reaction; SpO₂=oxygen saturation measured by pulse oximeter.

*Score 4: admitted to hospital, no oxygen treatment; score 5: admitted to hospital, oxygen by mask or nasal prongs; score 6: admitted to hospital, oxygen by non-invasive ventilation or high flow.

†Patient was included based on typical covid-19 chest CT scan at inclusion, but then reclassified as non-indicative of SARS-CoV-2 infection.

‡Active malignant neoplasm, lymphoid neoplasm, myeloid neoplasm, haematopoietic stem cell or solid organ transplantation, AIDS/HIV not on antiretroviral treatment (patients might have more than one of these conditions).

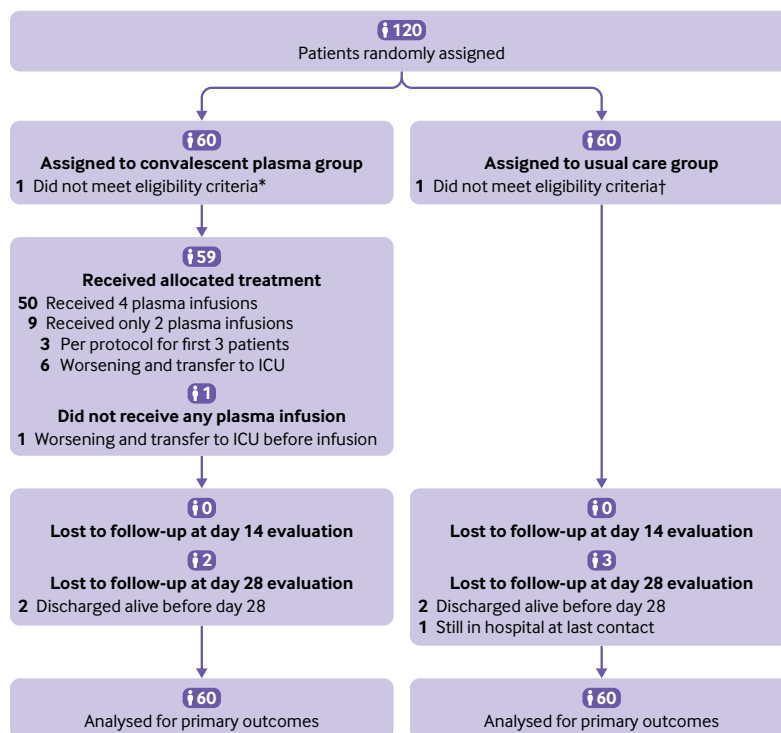


Figure 1 | Flowchart of CORIPLASM (Efficacy of Convalescent Plasma to Treat COVID-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort) clinical trial. *No SARS-CoV-2 infection. †Received non-invasive ventilation. ICU=intensive care unit

greater benefit was 0.269 (table 2 and online supplemental table S4). The results were consistent across the range of prior distributions used in the sensitivity analyses (online supplemental figure S3).

Secondary outcomes

At day 14, three (5%) and eight (13%) patients had died in the covid-19 convalescent plasma and usual care groups, respectively (adjusted hazard ratio 0.40, 95% confidence interval 0.10 to 1.53) (figure 3 and online supplemental table S5). At day 28, nine (12%) and 12 (20%) patients had died in the convalescent plasma and usual care groups, respectively (0.51, 0.20 to 1.32). The distribution of WHO Clinical Progression Scale scores from day 1 to day 14 did not differ significantly within groups, with a posterior odds ratio of 1.04 (95% credible interval 0.37 to 2.86) for the convalescent plasma group compared with the usual care group in a longitudinal ordinal model. The WHO Clinical Progression Scale scores tended to be higher in the convalescent plasma group between days 3 and 5, and then lower at day 14, with lower mortality (figure 4 and online supplemental table S6), although these findings were not significant. At day 14 and day 28, 38 and 48 patients in the convalescent plasma group and 36 and 45 in the usual care group, respectively, were discharged, with an adjusted day 28 subdistribution hazard ratio of 0.99 (95% confidence interval 0.65 to 1.49) adjusted for age and centre (online supplemental table S7). The incidence of not needing oxygen by day 28 was

not different between the groups: 76% and 62% by day 14 and 82% and 71% by day 28 in the convalescent plasma and usual care groups, respectively (subdistribution hazard ratio 1.18, 95% confidence interval 0.73 to 1.91) (online supplemental table S7).

Subgroup analyses

Figure 5 shows the primary outcome at day 14 (need for non-invasive or mechanical ventilation, use of additional immunomodulatory drugs, or death), with no difference in the subgroups. In the 47 patients who had an underlying immunodeficiency, the rate of a WHO Clinical Progression Scale score of ≥ 6 at day 4 was not significantly different in the covid-19 convalescent plasma group compared with the usual care group (24% v 15%, adjusted odds ratio 1.97, 95% confidence interval 0.53 to 7.39). At day 28, four of 21 patients had died in the convalescent plasma group versus nine of 26 patients in the usual care group (hazard ratio 0.39, 95% confidence interval 0.14 to 1.10) (figure 6). Despite these findings favouring convalescent plasma, we found no evidence of an interaction between immunodeficiency status and treatment ($P=0.34$): 4/21 patients died in the covid-19 convalescent plasma group versus 9/26 in the usual care group (hazard ratio 0.39, 95% confidence interval 0.14 to 1.10) (figure 6). We found limited mortality in the absence of underlying immunodeficiency (figure 7). Duration of symptoms or use of dexamethasone had no effect on day 28 survival (figure 5). Post hoc analysis of

Table 2 | Primary and secondary efficacy outcomes

	Convalescent plasma group (n=60)	Usual care group (n=60)	Treatment effect
Primary outcomes			
No (%) of patients with WHO Clinical Progression Scale score ≥ 6 at day 4:	13 (22)	8 (13)	8.0% (90% CrI -3.2% to 19.4%)*
Posterior probability of any benefit (%)			11.9
Posterior probability of moderate or greater benefit (%)†			2.4
No (%) of patients needing ventilation, additional immunomodulators, or death up to day 14:	19 (32)	20 (33)	1.04 (90% CrI 0.61 to 1.78)‡
Posterior probability of any benefit (%)			45.2
Posterior probability of moderate or greater benefit†			26.9
Secondary outcomes			
Overall survival:			
No (%) of patients who died days 0-14	3 (5)	8 (13)	0.40 (95% CI 0.10 to 1.53)§
No (%) of patients who died days 0-28	7 (12)	12 (20)	0.51 (95% CI 0.20 to 1.32)§
Median (IQR) WHO Clinical Progression Scale score:			
Day 4	5 (5-5)	5 (4-5)	1.42 (95% CrI 0.70 to 2.91)¶
Day 7	5 (4-5)**	5 (4-5)††	1.20 (95% CrI 0.61 to 2.37)¶
Day 14	3 (2-4)††	3 (2-5)††	0.59 (95% CrI 0.30 to 1.13)¶
Days 2-14 (longitudinal analysis)	—	—	1.04 (95% CrI 0.37 to 2.86)¶
Time to discharge:			
No (%) of patients discharged at day 28	48 (80)	45 (75)	0.99 (95% CI 0.65 to 1.49)‡‡
Time to end of dependence on oxygen supply:†			
No/total No (%) of patients not needing oxygen at day 28	42/51 (82)	32/45 (71)	1.18 (95% CI 0.73 to 1.91)‡‡
CI=confidence interval (frequentist analysis); CrI=credible interval (bayesian analysis); IQR=interquartile range. Moderate or greater benefit was defined as an absolute risk difference $< -5.5\%$ for day 4 outcome and hazard ratio < 0.85 for day 14 outcome. *Median posterior absolute risk difference; median posterior odds ratio adjusted for age and centre was 1.88 (90% credible interval 0.83 to 4.44). †For participants needing oxygen at randomisation (WHO Clinical Progression Scale score ≥ 5). ‡Median posterior hazard ratio adjusted for age and centre. §Hazard ratio adjusted for age and centre. ¶Median posterior odds ratio in a proportional odds model adjusted for age and centre. **n=58 with available data. ††n=59 with available data. ‡‡Subdistribution hazard ratio adjusted for age and centre.			

antibody potency in transfused covid-19 convalescent plasma in relation to outcome did not show a significant dose effect (online supplemental table S8).

Adverse events

Adverse events were reported in 44 (73%) and 36 (60%) patients in the covid-19 convalescent plasma (n=124 events) and usual care (n=103 events) groups, respectively (incidence rate ratio 1.06, 95% confidence interval 0.63 to 1.77; online supplemental table S9). We found serious adverse events in 30 (50%) and 26 (43%) patients in the convalescent plasma (n=46 events) and usual care (n=48 events) groups, respectively (incidence rate ratio 0.84, 95% confidence interval 0.46 to 1.54). We found 10 sepsis related events with usual care (six with convalescent plasma) and four incidences of acute pulmonary oedema with convalescent plasma (none with usual care).

Causes of death were covid-19 related acute respiratory distress syndrome (n=3 in the convalescent plasma group and n=10 in the usual care group), cardiac origin (n=2 convalescent plasma,

n=0 usual care), sepsis (n=2 convalescent plasma, n=3 usual care), gastrointestinal (n=0 convalescent plasma, n=1 usual care), vascular (n=1 convalescent plasma, n=0 usual care), and one of unknown origin (convalescent plasma).

Discussion

Principal findings

In this CORIPLASM trial, we found no difference in early outcomes between the covid-19 convalescent plasma and usual care groups for patients admitted to hospital for covid-19 disease not requiring assisted ventilation. The survival rate at day 14 and day 28 was higher in the convalescent plasma group but this finding was not significant.

The lack of efficacy associated with covid-19 convalescent plasma agrees with the results of most prospective randomised clinical trials of patients admitted to hospital for covid-19 disease.¹⁹ Only a small number of randomised studies have reported better survival after treatment with convalescent plasma,^{20 21} whereas several other trials, notably the large RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial,²² found no evidence of

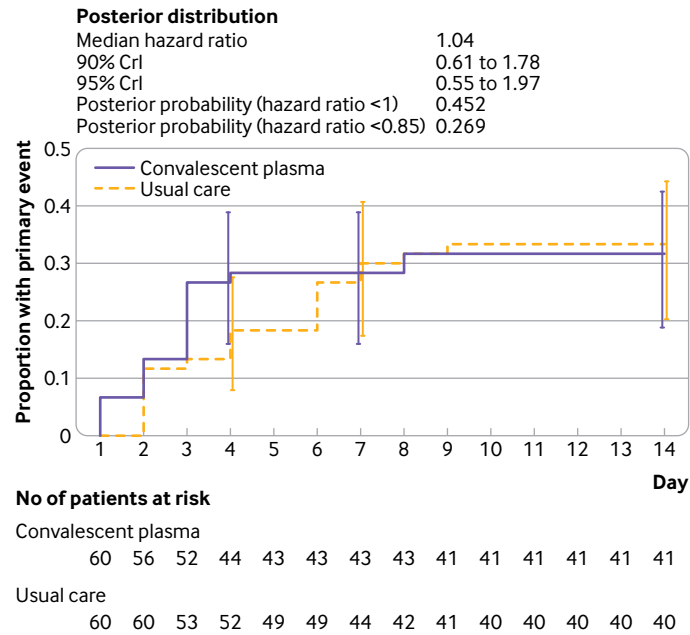


Figure 2 | Study outcomes in covid-19 convalescent plasma and usual care groups. Cumulative incidence of non-invasive or mechanical ventilation, use of additional immunomodulatory drugs, or death over 14 days (events on day 1 of randomisation occurred on the same day but after randomisation). CrI=credible interval

survival benefit with convalescent plasma. Large retrospective studies in the US reported evidence of reduced mortality associated with treatment with covid-19 convalescent plasma in patients admitted to hospital with covid-19.^{23 24} The reasons for these discrepancies might be related to the characteristics of the convalescent plasma, time to treatment from first symptoms, treatment modalities, and patient characteristics.

Our study included a substantial proportion of patients with underlying immunosuppression. Similar to previous findings,²⁵ we found that these patients with covid-19 have a worse prognosis, as seen in the usual care group. Several studies have suggested that convalescent plasma might be particularly effective in patients who lack an immune response, particularly a humoral response. We reported previously that treatment with covid-19

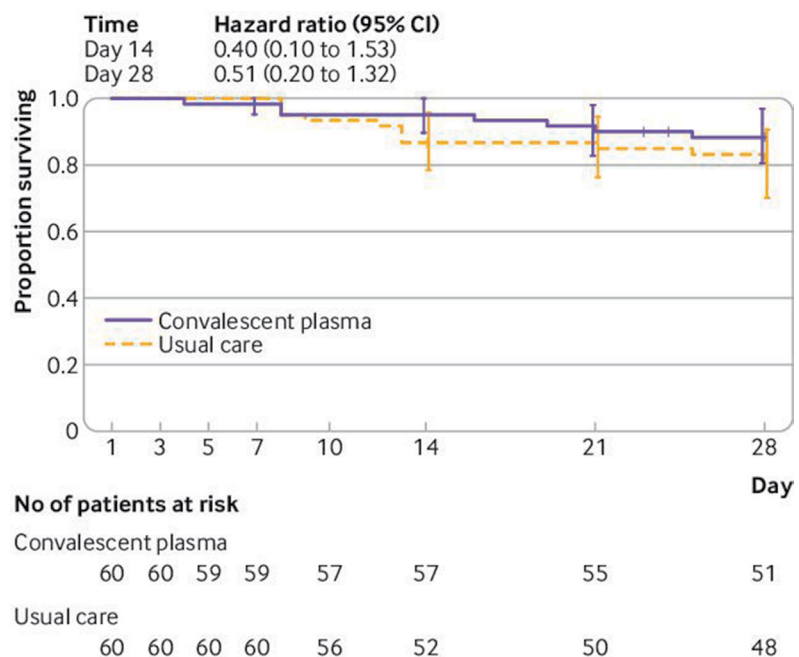


Figure 3 | Overall survival during follow-up in covid-19 convalescent plasma and usual care groups. CI=confidence interval

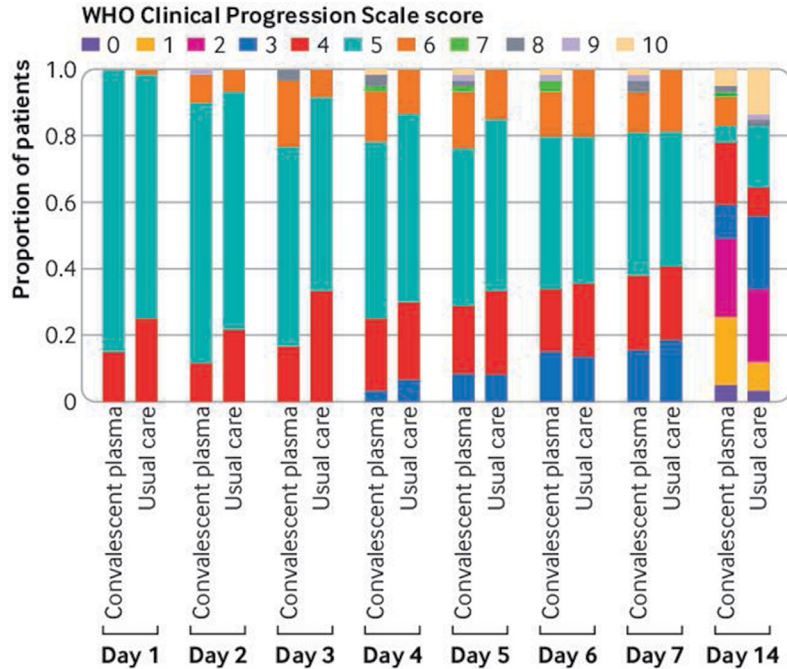


Figure 4 | Distribution of World Health Organization Clinical Progression Scale scores during follow-up in covid-19 convalescent plasma and usual care groups

convalescent plasma was associated with a favourable outcome in patients who were immunosuppressed (mainly B cell haematological malignancies treated with anti-CD-20 monoclonal antibodies).⁶ Further evidence was provided by two independent exposed and non-exposed studies with propensity score in patients with underlying immunosuppression. Hazard ratios of 0.52 (95% confidence interval 0.29 to 0.92) and 0.50 (0.34 to 0.72) were reported in favour of convalescent plasma treatment, respectively.^{6,7} This reduction in mortality was similar to patients with immunosuppression randomised to the convalescent plasma group in the CORIPLASM trial.

Comparison with other studies

Most other randomised trials published so far did not report subgroup analyses for patients with underlying immunosuppression. One exception is the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community Acquired Pneumonia) trial that investigated convalescent plasma in critically ill patients with covid-19.²² Although the overall results of this study did not provide evidence of the efficacy of covid-19 convalescent plasma in these patients, a prespecified subgroup analysis showed a potential benefit of convalescent plasma in patients with immunodeficiency. Another

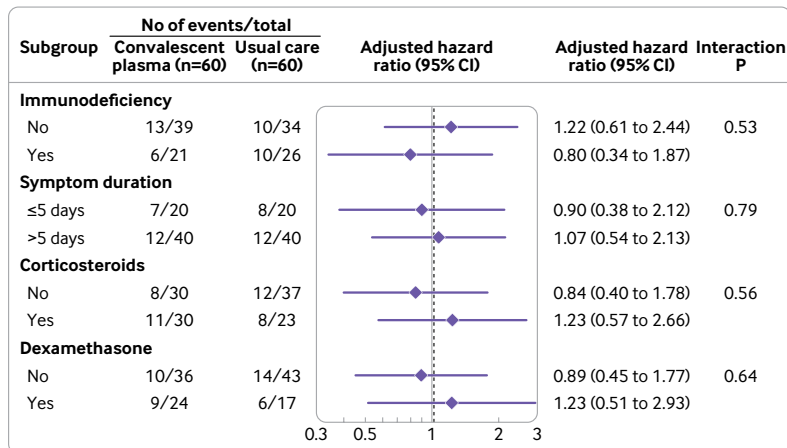


Figure 5 | Subgroup analyses. Day 14 primary outcomes (need for non-invasive or mechanical ventilation, use of additional immunomodulatory drugs, or death) in covid-19 convalescent plasma and usual care groups. Dashed line indicates overall estimate of treatment effect. Because only one patient was receiving antiviral agents at randomisation, no subgroup analysis according to antiviral agents was done. CI=confidence interval

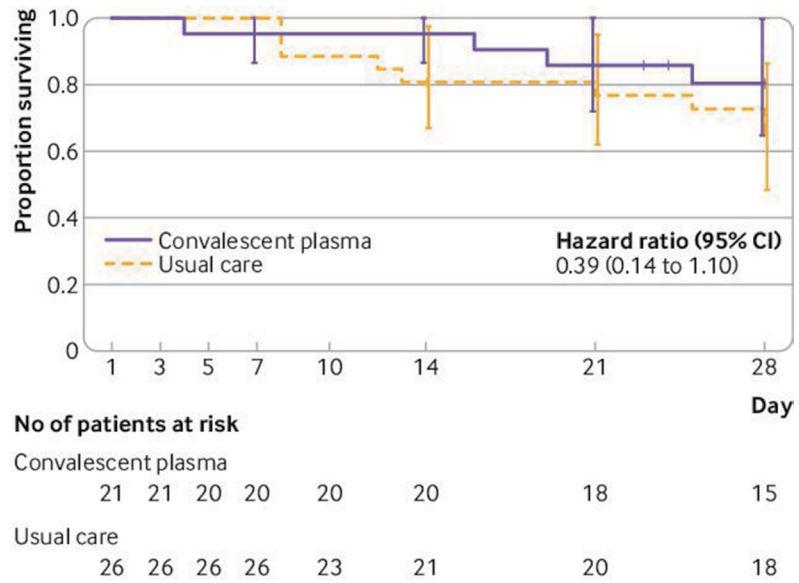


Figure 6 | Overall survival during follow-up in patients with immunosuppression in covid-19 convalescent plasma and usual care groups. CI=confidence interval

randomised trial performed in patients with a diverse range of clinical conditions reported a significant effect of covid-19 convalescent plasma on clinical improvement and survival in the subgroup of 56 individuals with cancer.²⁶ Finally, a meta-analysis incorporating the CORIPLASM trial has confirmed the potential benefit of covid-19 convalescent plasma in individuals with immunosuppression with mild-to-moderate covid-19 disease, based on greater statistical power because of the large number of individuals with immunosuppression included in the meta-analysis (1487 from randomised trials, 265 from case series, and 368 from cohorts).²⁷

An antibody dose effect has been reported in several randomised studies^{3 28} as well as in the early access

programme in the US.²³ In the CORIPLASM trial, 800-880 mL of covid-19 convalescent plasma were transfused to patients randomised to the convalescent plasma group. In most studies so far, patients most often received 250-500 mL of convalescent plasma, except in the CAPSID (A Clinical Trial of Convalescent Plasma Compared to Best Supportive Care for Treatment of Patients With Severe Covid-19) trial where patients received 700-750 mL of convalescent plasma.^{24 28} The CAPSID trial reported a significant antibody dose effect for several outcomes, including survival at day 28. By contrast, the CORIPLASM protocol recommended four covid-19 convalescent plasma units provided by different donors for each patient, which resulted in less variation in mean

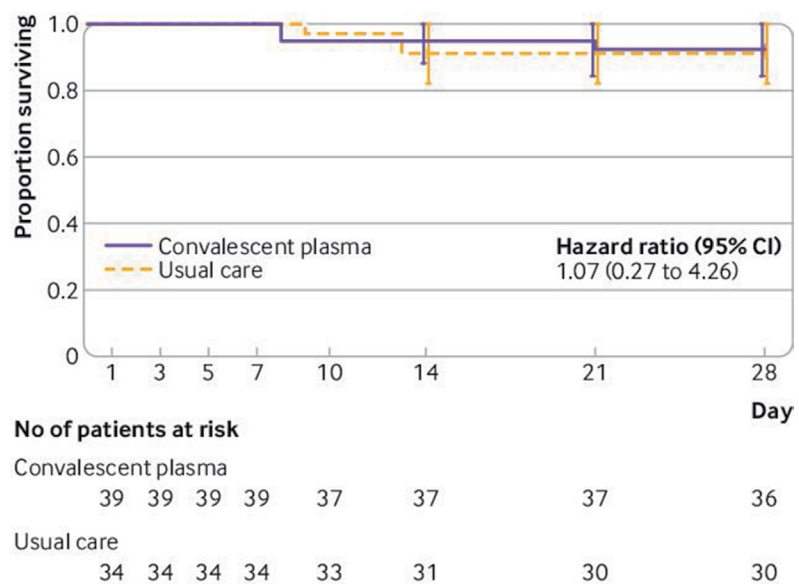


Figure 7 | Overall survival during follow-up in patients with no underlying immunodeficiency in covid-19 convalescent plasma and usual care groups. CI=confidence interval

antibody content in transfused convalescent plasma from patient to patient. This difference in transfusion practice might explain why we did not see an antibody dose effect in our study. Furthermore, convalescent plasma for the CORIPLASM study was collected early in the covid-19 crisis when vaccination was not available and before the occurrence of relevant SARS-CoV-2 variants.

Several studies have shown that plasma provided by convalescent donors who were vaccinated strongly increased anti-SARS-CoV-2 antibody titres and seroneutralisation ratios and also increased cross reactivity with a broader spectrum for variants to which the donor had not been exposed.^{12 29} High titre plasma from these convalescent donors who were vaccinated might have increased clinical efficacy. Early intervention with covid-19 convalescent plasma has been associated with improved outcome.^{3 4} Patients in our study had a median duration of symptoms of seven days at the time of inclusion, a short time period compared with most trials of patients admitted to hospital. Prespecified subgroup analyses, however, did not favour increased efficacy of convalescent plasma associated with a shorter time since onset of symptoms. The high number of patients with underlying immunosuppression, for whom seroconversion is not expected early on, might have contributed to this finding. Also, and as found in other covid-19 trials, early admission to hospital might be associated with more severe disease.^{8 22}

Patients in the covid-19 convalescent plasma group tended to have worsening pulmonary clinical conditions than patients in the usual care group early after transfusion. The occurrence of early transient pulmonary worsening after transfusion of convalescent plasma has also been reported elsewhere,³⁰ and might be related to antibody dependent enhancement involving immune complex mediated inflammatory immunopathology in infected tissues.³¹ Also, an antibody dependent Fc receptor mediated infection of tissues macrophages (and circulating monocytes) might result in a massive inflammatory response, as recently reported,³² which could also contribute to pulmonary worsening after transfusion of convalescent plasma.

These early outcomes are seldom reported in clinical studies, and distinguishing early pulmonary worsening from transfusion associated circulatory overload, transfusion related acute lung injury, or overall disease worsening, possibly started before transfusion, can be challenging. The transfusion of four units of plasma might have contributed to circulatory overload in some patients. Further spacing of administration of convalescent plasma (ie, 1 unit/day over four days) could reduce this risk. Early worsening did not prevent subsequent improvement and increased survival as early as day 14 after randomisation, although this effect was not significant. Antibody mediated SARS-CoV-2 uptake

by monocytes and macrophages triggering inflammatory cell death and inhibition of viral replication might be a mechanism for subsequent improvement in disease.³³

Limitations of this study

Our study had some limitations. The relatively small size of the trial limited the ability to appropriately assess outcomes, such as patient mortality, but we did access treatment with covid-19 convalescent plasma in immunosuppressed patients. Also, information on patient serostatus at inclusion was often not available. Although the mean antibody ratio in transfused convalescent plasma in our study was well above the US Food and Drug Administration threshold for high titre convalescent plasma (Euroimmun anti-SARS-CoV-2 immunoglobulin G ratio >3.5),³⁴ transfusion of higher titre plasma from convalescent donors who were vaccinated might improve efficacy.^{3 12 23 26}

The emergence of the omicron variant of the SARS-CoV-2 virus with its BA.1-BA.5 subvariants has highlighted the risks associated with immune resistant SARS-CoV-2 and loss of efficacy of available monoclonal antibodies.¹¹ Whereas several months are necessary to produce one or more new monoclonal antibodies more suited to changes in circulating viral strains, convalescent plasma, particularly from donors who are vaccinated, has shown increased resilience to immune resistant SARS-CoV-2 variants,^{12 30} increased scalability because of the existing collection infrastructure, as well as increased adaptability. The time between the onset of a covid-19 variant and the availability of convalescent plasma from donors infected with the variant disease is about four weeks.

Conclusions

The results of the CORIPLASM trial, along with recent data from other trials and cohort studies, support further evaluation and consequent use of convalescent plasma in patients who are immunocompromised for whom treatment options are limited. Recent guidelines from the Association for the Advancement of Blood and Biotherapies suggest transfusion of covid-19 convalescent plasma in addition to standard of care for patients admitted to hospital with covid-19 and pre-existing immunosuppression.³⁴

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Acknowledgements The authors thank the physicians, nurses, and assistant nurses who took care of the patients, clinical research assistants and clinical research doctors who included and followed the patients during the trial, physicians, nurses, and staff involved in convalescent plasma collection, manufacturing, testing, and issuing, and the patients who agreed to participate in the study and the convalescent donors who generously gave their plasma. Special thanks to the International Direction of Clinical Research (DRCI) of Assistance Publique-Hôpitaux de Paris (APHP), the trial sponsor, and the Unité de Recherche de l'Est Parisien (URC-EST, APHP.SU, site St Antoine site), who managed the trial.

Contributors KL and PT were involved in the protocol and study design, including conceptualisation, methodology, funding acquisition, and resources. NS and TS did the data curation, investigation, project administration, supervision, and validation. RP and GB did the data analysis. TH, AM, TC, SG-L, FA, JS, GM-B, FB, CC, OH, VP, MM, XL, PB, FP, PS, SR, LP, and J-MM included the patients. OH, XM, P-LT, MR-R, and PR designed the CORIMUNO-19 platform trial and conceptualised the embedded trials. The manuscript was drafted by KL and PT, and read and edited by all authors who approved the final manuscript. RP and GB had direct access to the data. KL is the

guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) 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.

Funding The study was funded by Programme Hospitalier de recherche Clinique (DGOS-French Ministry of Health, grant No 750712184), Fondation pour la Recherche Médicale (RSUB 210252 - PLASMACOV: REA202010012516), Sorbonne Université AAP 2020 (RSUB 200963), and Emergency Support Instrument (ESI), Direction Générale de la Santé, European Commission (PPPA-ECI-CCP-2020-Sl2.839209). The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from Programme Hospitalier de recherche Clinique (DGOS-French Ministry of Health), Fondation pour la Recherche Médicale, Sorbonne Université AAP 2020, and Emergency Support Instrument (ESI), Direction Générale de la Santé, European Commission for the submitted work; PT, PM, and AF are employees of Etablissement Français du Sang (EFS), the French public transfusion service, which collects, manufactures, tests and issues all blood components in France; KL is contributing to the development of monoclonal and polyclonal anti-SARS-CoV Antibodies (Spikimm, Xenothera, Fabentech); no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval This study involves human participants and was approved by CPP Ile de France VI on 10 April 2020 (No 26-20 Med.1°). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data for this article will be made available after publication on request from any qualified researchers or academics. The data include: analysed deidentified participant data, data dictionary, study protocol, statistical analysis plan, and informed consent form, among other data. The data will be shared for two years after publication on receipt of a request sent to raphael.porcher@aphp.fr.

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