Efficacy and safety of convalescent plasma versus standard care in hospitalized patients with COVID-19 from the Peruvian Social Security Health System: open-label, randomized, controlled clinical trial

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Conflicts of interest

The authors declare not to have any interest conflicts.

Data availability

The raw data was generated at the Institute for the Evaluation of Technologies in Health and Research - IETSI of Peru's Social Security of Health (EsSalud). Restrictions apply to the public availability of these data due to institutional patient data sharing policies. However, the data is available upon reasonable request from the author.

Clinical Trial Registration Number: This clinical trial has been registered in the Peruvian Registry of Clinical Trials (REPEC, by Spanish acronym) with the following ID: PER-013-20.

ABSTRACT

OBJECTIVES: To assess the efficacy and safety of convalescent plasma plus standard of care (CP + SoC) compared with standard of care (SoC) alone in patients hospitalized for moderate to severe COVID-19 who do not yet require mechanical ventilation.

METHODS: Phase 2 randomized, parallel-group, randomized, open-label, controlled, superiority, single-center clinical trial. This clinical trial has been registered in REPEC with the following ID: 013-20. Hospitalized adult patients with moderate to severe COVID-19 were enrolled. The allocation ratio was 1:1 in a variable-size permuted block randomization scheme. The primary outcome was death 28 days after the intervention. Secondary outcomes were mortality at 14 and 56 days, time to death at 56 days, time in the ICU at 28 days, time on a mechanical ventilator at 28 days, frequency of adverse events, and frequency of serious adverse events.

RESULTS: A total of 64 participants were enrolled, 32 were assigned to CP + SoC, and 32 to SoC. One participant assigned to CP + SoC withdrew his informed consent before applying the treatment. At day 28, there were no statistically significant differences for the primary outcome between the CP + SoC and SoC groups (relative risk: 2.06; 95%CI 0.73 to 7.11; p = 0.190). No differences were found in the incidences of mortality at 56 days (hazard ratio: 2.21; 95%CI 0.66 to 7.33; p = 0.182), admission to the ICU at 28 days (sub-hazard ratio: 2.06; 95%CI 0.57 to 8.55; p = 0.250), admission to mechanical ventilation at 28 days (sub-hazard ratio: 2.19; 95%CI 0.57 to 8.51; p = 0.260). Estimates for days 14 were similar. No infusion-related adverse events were reported during the study. There were no statistically significant differences in the frequency of any adverse events (odds ratio: 2.74; 95%CI 0.90 to 9.10; p = 0.085) or the frequency of serious adverse events (odds ratio: 3.60; 95%CI 0.75 to 26.1; p = 0.75).

CONCLUSIONS: No evidence was found that CP had a significant effect in reducing 28-day mortality. There was also no evidence that the frequency of adverse events was higher in those who received CP + SoC than those who received only SoC.

Key Words: Convalescent plasma, COVID-19, SARS-CoV-2, clinical trial.

Introduction

The SARS-CoV-2 virus causes coronavirus disease 2019 (COVID-19), identified in Wuhan, China, in December 2019 and declared a pandemic on March 12, 2020, a few months after the first case was reported (1–3). In the absence of available treatments, clinical trials initially focused on evaluating the replacement of interventions with recognized efficacy for other infectious diseases, such as antiparasitic, antiviral, anti-inflammatory drugs, anticoagulants, and convalescent plasma, among others (4).

For more than a century, convalescent plasma (CP) has been used in the treatment of various diseases of viral origin: severe acute respiratory syndrome (SARS), Eastern respiratory syndrome (MERS), avian influenza A (H5N1), Spanish flu A H1N1 pandemic, among others (5,6). Theoretically, antibodies in the plasma of recovered COVID-19 individuals would be passive immunization agents for the immune system of patients with active disease (7); however, empirical evidence about its efficacy on important outcomes was anecdotal, coming mainly from case series or observational studies (5).

Initially, the studies showed conflicting evidence, and even the available systematic reviews and meta-analyses did not find consistent results (8–12). Some systematic reviews and meta-analyses concluded that PC shows a potential reduction in mortality, although with statistically uncertain estimates (8–10). However, other systematic reviews and meta-analyses concluded that PC does not offer any benefit to adverse outcomes of COVID-19 (11,12), but the quality of the evidence reviewed was low. These inconsistent results showed the need for more controlled clinical trials to clarify the uncertainty about the efficacy of PC in the treatment of COVID-19.

This clinical trial was conducted in this context of uncertainty about the efficacy of PC. However, as scientific evidence accumulated, it became increasingly clear that PC was ineffective in treating patients hospitalized for COVID-19 (13). For this reason, this study was terminated early. Although the current consensus indicates that there is high certainty that treatment with PC is not effective in reducing outcomes of death, admission to the ICU, or mechanical ventilation (13–15), there are still some controversies about whether these studies evaluated the doses, appropriate application times (16–21) and uncertainties about their safety (13). As of May 20, 2021, 100 clinical trials on CP had been registered, but only under 33% had been published (13), so the publication of the findings will contribute to resolving the uncertainties associated with CP therapy.

This study reports the results of a clinical trial that aimed to evaluate the efficacy and safety of PC plus standard of care (SoC) compared to SoC alone in outcomes of patients hospitalized for COVID-19. The main hypothesis of this clinical trial was that convalescent plasma treatment in patients with moderate to severe COVID-19, who do not yet require a mechanical ventilator, is effective in reducing 28-day mortality. Efficacy against intensive care unit (ICU) admission, ventilator, and adverse events were also evaluated. The article was written following the CONSORT 2010 guidelines (Consolidated Standards of Reporting Trials) (22).

Methods

Study design

Phase 2, randomized, controlled, open-label, parallel-group, superiority, single-center clinical trial. The study was approved by the Transitory National Research Ethics

Committee (CNTEI) -COVID-19 through Certificate of Approval - CNTEI-007-2020 dated June 19, 2020. The study is registered in the Peruvian Registry of Clinical Trials (REPEC) with code PER-013-20 (23) and was approved by the National Institute of Health through Directorial Resolution 198-2020-OGITT-INS dated June 25, 2020. The last version of the approved protocol, translated to English for publication purposes, is available in S1 File. Ethical approval and informed consent form are in the S2 and S3 Files. A detailed description of procedures is available in the Manual of Procedures whose last version is in the S4 File. This study followed the CONSORT recommendations for reporting clinical trials (S5 File).

Study population

This trial was conducted in the Emergency Service and the Transfusion Medicine Service of the Edgardo Rebagliati Martins National Hospital (HNERM), a tertiary care hospital located in Lima, the capital of Peru. Between September 2020 and April 2021, patients who met the following inclusion criteria were enrolled:

1. Adult male or female patient ≥18 years of age requiring hospitalization or hospitalized for COVID-19 without the need for mechanical ventilation (invasive or non-invasive) at the time of enrollment.
2. Written informed consent before performing study procedures.
3. Laboratory-confirmed diagnosis of SARS-CoV-2 infection by RT-PCR in nasopharyngeal or oropharyngeal swabs.
4. Patients at risk of progression of COVID-19 defined as the presence of two or more of the following laboratory values:
    a. Ferritin > 500 ng/mL
    b. D-dimer > 1 mg/L

c. C-reactive protein > 15 mg/L

d. Total lymphocytes <1000/mm3 or neutrophil/lymphocyte ratio >3.13

5. Or patients with a clinical manifestation of pulmonary compromise defined by the presence of two or more of the following clinical parameters

a. Dyspnoea

b. Respiratory rate greater than or equal to 30 per minute

c. Oxygen saturation less than 93%

d. PaO2/FiO2 less than 300 and pulmonary infiltrate greater than 50% in the 24 to 48 hours after the initial evaluation

Likewise, patients who met any of the following criteria were excluded:

1. Transfusion of any blood product within 120 days before administration of convalescent plasma.

2. Active pregnancy detected by a qualitative test that detects the hormone human chorionic gonadotropin (hCG) in the urine.

3. Current participation in a randomized clinical trial or past involvement in a clinical trial, and less than 30 days have passed since your last study visit.

4. Patient has life-threatening COVID-19 illness defined as one or more of the following:

a. Respiratory failure, ventilatory type, defined as the need for invasive mechanical ventilation (with endotracheal intubation) or ECMO (extracorporeal oxygenation).

b. Septic shock, defined as having criteria for sepsis (an increase of two or more points on the Sequential Organ Failure Assessment (SOFA) scale) (17) and requiring vasopressors to maintain MAP $\geq$ 65 mmHg after adequate hydration.

c. Multiple organ dysfunction or failure, defined as the dysfunction of two or more systems other than the respiratory system. System dysfunction will be considered when a score of 2 or more is obtained on the SOFA scale in the following systems: coagulation, liver, cardiovascular, central nervous system, or kidney. The SOFA criteria used in this clinical trial are in the S1 Table.

Study intervention

All participants received SoC for COVID-19. In addition, the treatment arm received ABO blood group system-compatible convalescent plasma from recovered COVID-19 patients (called donors) as an add-on therapy to the SoC. Other compatibilities, such as the Rh factor, were unnecessary for the plasma transfusion since it is free of red blood cells. Once a patient was assigned to the CP treatment arm, the CP bag was thawed, stored at 2-6°C, and used within 24 hours. A complete unit of plasma was administered intravenously as one dose, with a volume between 200-400 mL of convalescent plasma contained in a transfusion bag, at a recommended flow rate of 150-200 mL/h or less depending on patient tolerance. The plasma transfusion was in charge of one health personnel from the Transfusion Medicine Service who fulfilled the role of transfuser and was not part of the research team. The control arm received only SoC for COVID-19.

Outcomes

The study's primary outcome was the cumulative incidence of mortality (all causes) through day 28 after CP administration. Secondary outcomes were:

- Cumulative incidence of ICU admission at 14 and 28 days.
- Cumulative incidence of mechanical ventilation or extracorporeal oxygenation (ECMO) on day 14 and day 28 after randomization.

196 • Cumulative incidence of mortality (all causes) on days 14 and 56 after CP
197 administration.
198 • Safety evaluations of CP + SoC compared to SoC alone up to day 28 considering
199 the cumulative incidence of serious adverse events (SAEs) and infusion-related
200 adverse reactions.

201 ***Sample size***

202 For an open-label, parallel-group, standard-of-care, controlled, randomized (1:1 ratio)
203 superiority clinical trial and cumulative incidence of all-cause mortality at day 28 as the
204 primary outcome, a sample size of 190 patients (95 per arm) assuming 21% mortality in
205 the SoC arm (18) and an absolute difference of ~14% (relative risk of 0.33 or ~7%
206 mortality in the CP arm), with a power statistic of 80% and a two-sided alpha level of 5%
207 for a chi-square test of homogeneity without continuity correction. In addition, he
208 estimated that approximately 63 PC donors would be needed.

209 ***Procedures***

210 The patients with COVID-19 were recruited at the HNERM Emergency Department
211 through daily screening of medical records or on-site identification of the patients. Donors
212 were invited through local print and audiovisual media advertising, which the Ethics
213 Committee previously approved. Potentially eligible candidates were invited for a
214 complete evaluation at the Blood Bank of the HNERM Transfusion Medicine Service.

215

216 The investigators of this study, certified and trained in Good Clinical Practices and Ethics
217 in Research in Humans, conducted the process of obtaining the subject's informed consent
218 in accordance with Peruvian regulations and internationally accepted standards.
219 The patients received a presentation with key aspects of the clinical trial, they read the
220 written informed consent document together with the investigator and their doubts were

answered by him. In the end, the researcher confirmed that the information provided in the consent has been understood. When there were no more questions and the patient expressed understanding of the informed consent document, they were asked if she wishes to participate in the study. If accepted, the informed consent form was signed in duplicate by the patient or her legal representative, in case the patient is incapacitated, and by one of the researchers. In case she did not want to sign but did consent, her fingerprint was placed. Finally, one original informed consent form was delivered to the patient, and the other original was filed in a safe place. When the condition and severity of the patients who cannot consent did not allow the taking of informed consent in writing, consent was taken orally, recording the process in audiovisual media or digital images; and then, when feasible, obtaining the signature of the research subject in the written informed consent format. Due to the impediment to receiving medical visits that the COVID-19 services have imposed on the relatives of hospitalized patients, it was possible to contact legal representatives or relatives by phone or instant messaging to request their support or consent if the participant is prevented from doing so. Donors also received information about the clinical trial and gave their written informed consent before donating convalescent plasma. Patients and donors were informed about the possibility of collecting and storing an additional serum and plasma sample for up to one year for future use in research related to SARS-CoV-2. If they accepted, the participant or her legal representative signed written informed consent for future use of the biological sample.

Participants were randomly assigned to SoC alone (control arm) or treatment group (CP + SoC) with a 1:1 allocation according to a computer random number generator program that used permuted blocks of random size to ensure the balance of arms and the unpredictability of treatment assignments at any time during the trial. The random

246 sequence was generated using the ado ralloc package (19) in Stata/SE version 16.1 for
247 Microsoft Windows Pro 10 (StataCorp. 2019. College Station, TX: StataCorp LLC.).
248 To ensure concealment, block sizes were not disclosed until endpoint analysis and a
249 central randomization scheme were implemented. The random assignment list was
250 generated by a randomization officer and was kept hidden without sharing with any
251 research team member until the clinical trial was completed. The randomization officer
252 was a member of the team who was not part of the staff of evaluators or therapists, so
253 integrity was guaranteed during the randomization process. A detailed timeline is
254 provided in S1 Fig.
255
256 ***Statistical analysis***
257 The primary outcome was the cumulative incidence of death at 28 days after
258 randomization. This analysis was by intention to treat. The effect of CP + SoC versus
259 SoC alone on the cumulative incidence of mortality at 28 days was estimated using an
260 adjusted relative risk (aRR) obtained from a log-binomial regression model that included
261 the treatment variable and the block variable. Estimating the effect on mortality at 14 days
262 followed the same approach described. However, the effect on 56-day mortality was
263 assessed using a Cox regression that included treatment and block factor as covariates.
264 The effect of CP + SoC versus SoC alone on these outcomes was estimated using adjusted
265 hazard rate (HR) ratios. Survival curves were calculated using the Kaplan-Meier method
266 and compared using the log-rank test. The effect of CP + SoC on admission to the ICU
267 (at 14 and 28 days) and admission to mechanical ventilation (at 14 and 28 days),
268 compared to SoC alone, was estimated using the sub-hazard ratio (subHR) considering
269 death as a competitive event and obtained from a Fine and Gray model. Cumulative
270 incidence functions were estimated and compared using Gray test. All analyzes were

estimated with a 95% confidence interval and a significance level of 5%. Statistical analyzes were performed with R version 4.1.3 software.

Results

Patients

Between September 2020 and April 2021, 64 research subjects who met the selection criteria were enrolled, randomly assigning 32 to each study arm; One participant randomized to the intervention arm withdrew from the study before the application of PC, so 31 patients were assigned to convalescent plasma plus standard treatment and 32 to standard treatment alone (Fig 1).

Fig 1. Enrollment and random assignment

The mean age of the patient population was 59.5 years (IQR: 46 to 72); 20.0% were women, and 20% had at least one comorbidity at study entry. The median time from onset of COVID-19 symptoms to enrollment was 13 days. The distribution of sociodemographic and clinical characteristics is shown in Table 1.

Table 1. Characteristics of the participants at enrollment

Characteristics	CP + SoC (n = 32)	Only SoC (n = 32)
Sex		
Male	23 (71.9%)	28 (87.5%)
Female	9 (28.1%)	4 (12.5%)
Age, years	62.5 (51.8, 72.0)	56.5 (46.0, 69.0)
Arterial hypertension	6 (18.8%)	6 (18.8%)
Mellitus diabetes	4 (12.5%)	6 (18.8%)
Pulmonary fibrosis	0 (0.0%)	1 (3.1%)
Asthma	0 (0.0%)	1 (3.1%)
Heart disease	1 (3.1%)	1 (3.1%)
Cerebrovascular disease	0 (0.0%)	1 (3.1%)

Obesity	9 (28.1%)	7 (21.9%)
Cancer	1 (3.1%)	1 (3.1%)
Hypothyroidism	0 (0.0%)	2 (6.2%)
Hemoglobin, g/dL	14.0 (13.2, 15.3)	14.4 (13.2, 15.3)
Hemoglobin categories		
<14 g/dL	14 (45.2%)	14 (43.8%)
14-18 g/dL	17 (54.8%)	17 (53.1%)
>=18 g/dL	0 (0.0%)	1 (3.1%)
Lymphocyte count, 1/uL	760.0 (625.0, 1,060.0)	890.0 (737.5, 1,542.5)
Hemoglobin categories		
<900/uL	19 (61.3%)	16 (50.0%)
900-5200/uL	12 (38.7%)	16 (50.0%)
Neutrophil count, 1/uL	9,360.0 (6,670.0, 12,845.0)	7,520.0 (4,495.0, 9,385.0)
Neutrophil Count Categories		
1800-8000/uL	12 (38.7%)	17 (53.1%)
>8000/uL	19 (61.3%)	15 (46.9%)
Platelet count, 1000/uL	318.0 (214.0, 420.5)	262.5 (179.5, 380.0)
Platelet Count Categories		
<130 x 1000/uL	2 (6.5%)	2 (6.2%)
130-400 x 1000/uL	19 (61.3%)	23 (71.9%)
>400 x 1000/uL	10 (32.3%)	7 (21.9%)
Prothrombin time, sec	11.1 (10.6, 11.9)	11.0 (10.6, 11.9)
PT Categories		
<10.5 seg	6 (20.0%)	5 (15.6%)
10.5-13.0 seg	22 (73.3%)	25 (78.1%)
>13.0 seg	2 (6.7%)	2 (6.2%)
Partial thromboplastin time, sec	36.1 (32.2, 39.6)	34.0 (31.7, 36.4)
TPT Categories		
24.0-37.0 seg	0 (0.0%)	0 (0.0%)
>37.0 seg	12 (100.0%)	7 (100.0%)
Serum glucose, mg/dL	136.0 (118.0, 183.0)	137.0 (99.8, 185.5)
Serum glucose categories		
74-106 mg/dL	3 (9.7%)	10 (31.2%)
>106 mg/dL	28 (90.3%)	22 (68.8%)
Serum creatinine, mg/dL	0.7 (0.6, 0.8)	0.8 (0.7, 0.9)
Glutamic-oxalacetic transaminase, U/L	50.0 (39.0, 82.5)	58.5 (41.0, 67.5)
TGO Categories		
0.0-34.9 U/L	0 (0.0%)	0 (0.0%)
>34.0 U/L	25 (100.0%)	25 (100.0%)
Glutamic-pyruvic transaminase, U/L	75.0 (48.0, 119.5)	69.5 (51.2, 116.5)
TGP Categories		
0.0-49.0 U/L	8 (25.8%)	8 (25.0%)
>49.0 U/L	23 (74.2%)	24 (75.0%)
Serum sodium, mmol/L	139.2 (136.8, 142.1)	139.2 (136.8, 140.8)
Serum sodium categories		

<132.0 mmol/L	1 (3.2%)	0 (0.0%)
132.0-146.0 mmol/L	30 (96.8%)	32 (100.0%)
Serum potassium, mmol/L	4.1 (3.9, 4.4)	4.2 (4.0, 4.4)
Serum potassium categories		
<3.5 mmol/L	1 (3.3%)	1 (3.1%)
3.5-5.5 mmol/L	29 (96.7%)	31 (96.9%)
C-Reactive Protein, mg/dL	9.2 (5.1, 15.4)	6.1 (3.2, 11.2)
PCR Categories		
0.0-100.0 mg/dL	31 (100.0%)	31 (100.0%)
Ferritin, ng/mL	822.0 (666.9, 1,446.0)	869.9 (575.6, 1,362.5)
Ferritin Categories		
28.0-365.0 ng/dL	3 (9.7%)	4 (12.5%)
>365.0 ng/dL	28 (90.3%)	28 (87.5%)
D-dimer, mg/mL	0.7 (0.4, 1.1)	0.6 (0.5, 0.9)
D-Dimer Category		
0.00-0.54 ug/mL	11 (39.3%)	12 (40.0%)
>0.54 ug/mL	17 (60.7%)	18 (60.0%)
Lactic dehydrogenase, U/L	390.0 (289.5, 479.0)	347.5 (245.0, 403.8)
DHL Categories		
120.0-246.0 U/L	5 (16.1%)	9 (28.1%)
>246.0 U/L	26 (83.9%)	23 (71.9%)
Quantification of anti-SARS-CoV-2 antibodies - IgG, AU/mL	39.5 (15.9, 69.1)	37.8 (16.7, 67.5)
Categories of Ab anti-SARS-CoV-2 IgG		
Non-reactive	4 (12.9%)	7 (21.9%)
Reactive	27 (87.1%)	25 (78.1%)
Quantification of anti-SARS-CoV-2 antibodies - IgM, AU/mL	10.7 (2.3, 59.7)	5.4 (2.0, 23.8)
Categories of Ab anti-SARS-CoV-2 IgM		
Non-reactive	15 (48.4%)	20 (62.5%)
Reactive	16 (51.6%)	12 (37.5%)
Pulmonary compromise by tomography	50.0 (40.0, 63.0)	50.0 (42.0, 55.0)

CP + SoC: Convalescent plasma plus standard of care; SoC: Standard of care alone.

290

291 ***Primary outcome and secondary mortality outcomes***

292 The 28-day mortality was 25.8% (8 of 26 patients) in the convalescent plasma plus
293 standard therapy group and 12.5% (4 of 12 patients) in the standard therapy alone group.
294 At day 28, although mortality in the CP + SoC group was twice that of SoC, these
295 differences were not statistically significant (RR = 2.06; 95% CI 0.73 to 7.11; p = 0.190).

296

297 **Table 2.** Clinical Results in patients who received CP + SoC compared with SoC only.

Outcomes	Only SoC (n = 32)	CP + SoC (n = 31)	Risk Ratio or Hazard Ratio (95% CI); valor p
Primary outcome, death at 28 days; No. events (%)	4 (12)	8 (26)	Risk ratio; 2.06 (0.73 a 7.11); 0.190
Secondary outcomes			
Death at 14 days; No. events (%)	4 (12)	7 (23)	Risk ratio; 2.06 (0.73 a 7.11); 0.190
Time to ICU admission in 14 days; n events/person-time	3 (384)	6 (311)	Subhazard ratio; 2.21 (0.57 a 8.55); 0.250
Time to ICU admission in 28 days; n events/person-time	3 (720)	6 (577)	Subhazard ratio; 2.21 (0.57 a 8.55); 0.250
Time to invasive mechanical ventilation in 14 days; n events/person-time	3 (382)	6 (311)	Subhazard ratio; 2.30 (0.60 a 8.84); 0.230
Time to invasive mechanical ventilation in 28 days; n events/person-time	3 (718)	6 (577)	Subhazard ratio; 2.19 (0.57 a 8.51); 0.260
Time to death in 56 days; n events / person days	4 (1473)	8 (1339)	Hazard ratio; 2.56 (0.72 a 9.08); 0.147
Adverse events; No. events (%)			
Any event	6 (19)	12 (39)	Odds ratio; 2.74 (0.90 a 9.10); 0.085
Serious event	2 (6.2)	6 (19)	Odds ratio; 3.60 (0.75 a 26.1); 0.14
Infusion related event	0	0	NA

NA: Not apply

In the 56 days after enrollment, no statistically significant differences were found in the cumulative incidence curves of both groups (p = 0.196) (Fig 2). Similarly, there were no significant differences in the incidences of mortality (HR 2.21, 95% CI 0.66 to 7.33; p value = 0.182) (Table 2). The proportionality assumption of the Cox regression hazards was supported by the Grambsch and Therneau test (p = 0.450) and the Schoenfeld residual inspection.

Fig 2. Inverse Kaplan-Meier curves for cumulative incidence of death after treatment with CP + SoC versus SoC alone

310 ***Secondary efficacy outcomes***

311 No statistically significant differences were found in the cumulative incidence curves for
312 admission to the ICU within 28 days (p = 0.251) (Fig 3A). The incidence rate of admission
313 to the ICU within 28 days was 10.4 per 1000 patient days in the CP + SoC group and 4.17
314 per 1000 patient days in the group that received only SoC. Considering death as a
315 competitive event, the Fine and Gray model revealed no statistically significant
316 differences in the incidence of ICU admission between both groups (subHR 2.06; 95%
317 CI 0.57 to 8.55; p = 0.250). Compared to standard treatment alone, the estimated effect
318 of convalescent plasma + standard treatment was the same for ICU admission at 14 days
319 (subHR 2.21; 95% CI 0.57 to 8.55; p = 0.250).

320

321 No statistically significant differences were found in the cumulative incidence curves for
322 admission to mechanical ventilation at 28 days (p = 0.256) (Fig 3B). The 28-day incidence
323 rate of invasive mechanical ventilation was 10.4 per 1,000 patient days in the
324 convalescent plasma plus standard therapy group and 4.18 per 1,000 patient days in the
325 standard therapy only group. Compared to standard treatment alone, the estimated effect
326 of convalescent plasma + standard treatment was the same for admission to mechanical
327 ventilation at 28 days (subHR 2.19; 95% CI 0.57 to 8.51; p = 0.260).

328

329 **Fig 3.** Cumulative incidence function curves for death (competing event) and (A) ICU
330 admission or (B) mechanical ventilator admission after treatment with CP + SoC versus
331 SoC alone

332

333 ***Safety results***

334 No infusion-related adverse events were reported in study participants. Adverse events

were more common in the CP + SoC group (39%; 12 of 31 patients) than in the SoC group (19%; 6 of 32 patients). Similarly, serious adverse events were slightly more common in the CP + SoC group (19%; 6 of 31 patients) than in the SoC group (6.2%; 2 of 32 patients). However, there is high uncertainty regards the differences in the incidence of adverse events (OR 2.74; 95% CI, 0.90 to 9.10; p = 0.085) or serious adverse events (OR 3.60; 95% CI 0.75 to 26.1; p = 0.75) (Table 2 and S1 Table) if we consider the precision of these estimates and statistical significance.

Discussion

This study aimed to assess the efficacy and safety of convalescent plasma (CP) plus standard of care (SoC) versus SoC alone in adult patients hospitalized with COVID-19 but not yet requiring mechanical ventilation. Our results found no evidence that PC had an effect in reducing mortality at 28 days. We also found no evidence that the frequency of adverse events was higher in those who received PC than those who received SoC.

Our results agree with those widely reported in the literature. Although initially, systematic reviews with meta-analyses (24-26) found evidence of benefit in favor of PC to reduce mortality, these included observational studies (27–30) and clinical trials with significant limitations (18,31). More recent clinical trials reported no evidence of the benefit of PC in reducing mortality, admission to the ICU, or mechanical ventilation (17,32-45). Later meta-analyses also concluded no evidence of PC efficacy in reducing the incidence of these outcomes (8,24,25,38,46–52). Clinical practice guidelines recommend against using PC in hospitalized patients with COVID-19 with a strong level of recommendation and a high certainty of evidence (14,15,53).

The RECOVERY (34), CONCOR-1 (44), and REMAP-CAP (45) studies were the three largest clinical trials conducted to assess the efficacy and safety of convalescent plasma, and none found evidence of a benefit of high-dose CP in reducing mortality, ICU admission or mechanical ventilation in patients with COVID-19. Like our study, all of them were open-label and were stopped early. The RECOVERY trial (34) enrolled 11,558 patients (5,795 received CP + SoC and 5,763 received SoC). The study found evidence in favor of no significant differences (RR = 1.00; 95% CI 0.93-1.07) in 28-day mortality and other hospital outcomes such as mechanical ventilation. The CONCOR-1 trial (44), which enrolled 614 patients in the CP group and 307 in the SoC group, found no significant difference in its primary outcome of intubation or death at day 30 (RR = 1.16; 95%CI 0.94-1.43) nor in its secondary outcomes such as mortality, admission to intensive care and hospital stay. The REMAP-CAP trial (45), which enrolled 1084 critically ill patients in the PC group, and 916 in the control group, found no significant differences in in-hospital mortality outcomes. However, it did report potential for harm in patients who received convalescent plasma after the seven days of hospitalization.

Regarding the safety of PC, to date, 51 clinical trials have been published that evaluated the use of PC, concluding, through a meta-analysis, that with a low degree of certainty, PC does not increase the occurrence of adverse events (15). Consistent with existing evidence, our study did not find any transfusion-related SAEs and, although there was a higher frequency of adverse events of any kind in the group treated with PC + SoC compared to the SoC group, these differences were not statistically significant.

Observational surveillance studies suggest that adverse reactions are infrequent and related to conventional risks of plasma infusion for other indications. For example, a study

evaluating safety using records from 5,000 clinicians of hospitalized adult patients with severe COVID-19 found a low mortality rate of 0.3%. Likewise, the incidence of all serious adverse events (SAEs) in the first four hours after the transfusion was less than 1% (54). In addition to death (4 cases of 25 related SAEs), the main SAEs were transfusion-related circulatory overload (7 of 25 related SAEs), transfusion-related acute lung injury (11 of 25 SAEs), and severe transfusion-related allergic reactions (3 of 25 EAS). Months later, the update of this study extended the analysis to 20,000 patients, confirming the low frequency of adverse events: <1% for thrombotic and thromboembolic events and ~3% for cardiac events (55).

This study has limitations to be considered. All patients had moderate to severe COVID-19, so our conclusions cannot be extrapolated to other groups of patients with different degrees of severity, especially patients with mild COVID-19. Another limitation is that the trial was open label, which could have influenced more subjective outcomes such as the recognition and/or reporting of some adverse events. However, these results are unlikely to have influenced hard outcomes such as mortality, ICU admission, or admission to mechanical ventilation.

In conclusion, in our study, using CP + SoC in patients with moderate COVID-19 did not reduce mortality or improve other clinical outcomes at day 28 compared to SoC alone. Our results are consistent with the literature on the lack of benefit of CP and reinforce the evidence in favor of discouraging CP use in hospitalized patients with moderate to severe COVID-19.

References

1. Ciotti M, Angeletti S, Minieri M, Giovannetti M, Benvenuto D, Pascarella S, et al. COVID-19 Outbreak: An Overview. Chemotherapy. 2019;64(5–6):215–23.

2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727–33.

3. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet. 2020 Feb 22;395(10224):565–74.

4. Asili P, Mirahmad M, Tabatabaei-Malazy O, Manayi A, Haghighat E, Mahdavi M, et al. Characteristics of published/registered clinical trials on COVID-19 treatment: A systematic review. Daru J Fac Pharm Tehran Univ Med Sci. 2021 Dec;29(2):449–67.

5. Marson P, Cozza A, De Silvestro G. The true historical origin of convalescent plasma therapy. Transfus Apher Sci. 2020 Oct;59(5):102847.

6. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus. 2016 Mar;14(2):152–7.

7. Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, et al. Convalescent plasma in Covid-19: Possible mechanisms of action. Autoimmun Rev. 2020 Jul;19(7):102554.

8. Vegivinti CTR, Pederson JM, Saravu K, Gupta N, Evanson KW, Kamrowski S, et al. Efficacy of convalescent plasma therapy for COVID-19: A systematic review and meta-analysis. J Clin Apheresis [Internet]. [cited 2021 May 14];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jca.21881

9. Piechotta V, Chai KL, Valk SJ, Doree C, Monsef I, Wood EM, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev [Internet]. 2020 Jul 10 [cited 2021 Feb 8];(7). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013600.pub2/full

10. Wang Y, Huo P, Dai R, Lv X, Yuan S, Zhang Y, et al. Convalescent plasma may be a possible treatment for COVID-19: A systematic review. Int Immunopharmacol. 2021 Feb;91:107262.

11. Janiaud P, Axfors C, Schmitt AM, Gloy V, Ebrahimi F, Hepprich M, et al. Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. JAMA. 2021 Mar 23;325(12):1185–95.

12. Piscoya A, Ng-Sueng LF, Riego AP del, Cerna-Viacava R, Pasupuleti V, Thota P, et al. Efficacy and harms of convalescent plasma for treatment of hospitalized COVID-19 patients: a systematic review and meta-analysis. Arch Med Sci [Internet]. 2021 Feb 18 [cited 2021 May 14]; Available from:

https://www.archivesofmedicalscience.com/Efficacy-and-harms-of-convalescent-plasma-for-treatment-of-hospitalized-COVID-19,132492,0,2.html

13. Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev [Internet]. 2021 [cited 2022 Apr 19];(5). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013600.pub4/appendices

14. Bartoletti M, Azap O, Barac A, Bussini L, Ergonul O, Krause R, et al. ESCMID COVID-19 living guidelines: drug treatment and clinical management. Clin Microbiol Infect. 2022 Feb;28(2):222–38.

15. Therapeutics and COVID-19: living guideline [Internet]. [cited 2022 Apr 19]. Available from: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-therapeutics-2022.2

16. Bajpai M, Maheshwari A, Dogra V, Kumar S, Gupta E, Kale P, et al. Efficacy of convalescent plasma therapy in the patient with COVID-19: a randomised control trial (COPLA-II trial). BMJ Open. 2022 Apr 6;12(4):e055189.

17. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ. 2020 Oct 22;371:m3939.

18. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med. 2021 Feb 18;384(7):610–8.

19. Hartmann J, Bloch EM, Burnouf T. Experience with COVID-19 convalescent plasma provides vital guidance to future pandemics. Transfusion (Paris). 2022;62(3):681–4.

20. Paneth N, Casadevall A, Pirofski L anne, Henderson JP, Grossman BJ, Shoham S, et al. WHO covid-19 drugs guideline: reconsider using convalescent plasma. BMJ. 2022 Feb 8;376:o295.

21. Joyner MJ, Paneth NS, Senefeld JW, Fairweather D, Bruno KA, Wright RS, et al. Concerns about estimating relative risk of death associated with convalescent plasma for COVID-19. Nat Med. 2022 Jan;28(1):51–2.

22. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 24;340:c332.

23. ENSAYOS CLINICOS - INSTITUTO NACIONAL DE SALUD [Internet]. [cited 2022 May 4]. Available from: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=013-20

24. Meher BR, Padhy BM, Das S, Mohanty RR, Agrawal K. Effectiveness of Convalescent Plasma Therapy in the Treatment of Moderate to Severe COVID 19 Patients: A Systematic Review and Meta-Analysis. J Assoc Physicians India. 2020 Dec;68(12):35–43.

25. Kim MS, An MH, Kim WJ, Hwang TH. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis. PLOS Med. 2020 Dec 30;17(12):e1003501.

26. Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, et al. The Effect of Convalescent Plasma Therapy on Mortality Among Patients With COVID-19: Systematic Review and Meta-analysis. Mayo Clin Proc. 2021 May 1;96(5):1262–75.

27. Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. N Engl J Med. 2021 Mar 18;384(11):1015–27.

28. Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, et al. Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. Nat Med. 2020 Nov;26(11):1708–13.

29. Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, et al. Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti–Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG. Am J Pathol. 2021 Jan;191(1):90–107.

30. Briggs N, Gormally MV, Li F, Browning SL, Treggiari MM, Morrison A, et al. Early but not late convalescent plasma is associated with better survival in moderate-to-severe COVID-19. PloS One. 2021;16(7):e0254453.

31. O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest. 2021 Jul 1;131(13):150646.

32. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA. 2020 Aug 4;324(5):460–70.

33. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med. 2021 Feb 18;384(7):619–29.

34. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet Lond Engl. 2021 May 29;397(10289):2049–59.

35. Körper S, Weiss M, Zickler D, Wiesmann T, Zacharowski K, Corman VM, et al. Results of the CAPSID randomized trial for high-dose convalescent plasma in patients with severe COVID-19. J Clin Invest. 2021 Oct 15;131(20):e152264.

36. Avendaño-Solá C, Ramos-Martínez A, Muñez-Rubio E, Ruiz-Antorán B, Malo de Molina R, Torres F, et al. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. J Clin Invest. 2021 Oct 15;131(20):e152740.

37. Baldeón ME, Maldonado A, Ochoa-Andrade M, Largo C, Pesantez M, Herdoiza M, et al. Effect of convalescent plasma as complementary treatment in patients with moderate COVID-19 infection. Transfus Med Oxf Engl. 2022 Apr;32(2):153–61.

38. Sekine L, Arns B, Fabro BR, Cipolatt MM, Machado RRG, Durigon EL, et al. Convalescent plasma for COVID-19 in hospitalised patients: an open-label, randomised clinical trial. Eur Respir J. 2022 Feb;59(2):2101471.

39. van den Berg K, Glatt TN, Vermeulen M, Little F, Swanevelder R, Barrett C, et al. Convalescent plasma in the treatment of moderate to severe COVID-19 pneumonia: a randomized controlled trial (PROTECT-Patient Trial). Sci Rep. 2022 Feb 15;12(1):2552.

40. AlQahtani M, Abdulrahman A, Almadani A, Alali SY, Al Zamrooni AM, Hejab AH, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. Sci Rep. 2021 May 11;11:9927.

41. Rasheed AM, Fatak DF, Hashim HA, Maulood MF, Kabah KK, Almusawi YA, et al. The therapeutic potential of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. Infez Med. 2020 Sep 1;28(3):357–66.

42. Ortigoza MB, Yoon H, Goldfeld KS, Troxel AB, Daily JP, Wu Y, et al. Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients: A Randomized Clinical Trial. JAMA Intern Med. 2022 Feb 1;182(2):115–26.

43. Holm K, Lundgren MN, Kjeldsen-Kragh J, Ljungquist O, Böttiger B, Wikén C, et al. Convalescence plasma treatment of COVID-19: results from a prematurely terminated randomized controlled open-label study in Southern Sweden. BMC Res Notes. 2021 Dec 4;14(1):440.

44. Bégin P, Callum J, Jamula E, Cook R, Heddle NM, Tinmouth A, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med. 2021 Nov;27(11):2012–24.

45. Writing Committee for the REMAP-CAP Investigators, Estcourt LJ, Turgeon AF, McQuilten ZK, McVerry BJ, Al-Beidh F, et al. Effect of Convalescent Plasma on Organ Support-Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2021 Nov 2;326(17):1690–702.

46. Snow TAC, Saleem N, Ambler G, Nastouli E, McCoy LE, Singer M, et al. Convalescent plasma for COVID-19: a meta-analysis, trial sequential analysis, and meta-regression. Br J Anaesth. 2021 Dec;127(6):834–44.

47. Kloypan C, Saesong M, Sangsuemoon J, Chantharit P, Mongkhon P. CONVALESCENT plasma for COVID-19: A meta-analysis of clinical trials and real-world evidence. Eur J Clin Invest. 2021 Nov;51(11):e13663.

48. Peng HT, Rhind SG, Beckett A. Convalescent Plasma for the Prevention and Treatment of COVID-19: A Systematic Review and Quantitative Analysis. JMIR Public Health Surveill. 2021 Apr 7;7(4):e25500.

49. Axfors C, Janiaud P, Schmitt AM, Van't Hooft J, Smith ER, Haber NA, et al. Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. BMC Infect Dis. 2021 Nov 20;21(1):1170.

50. Yang P, Wang J, Zheng R, Tan R, Li X, Liu X, et al. Convalescent plasma may not be an effective treatment for severe and critically ill covid-19 patients: A Systematic Review & Meta-Analysis of Randomized Controlled Trials. Heart Lung J Crit Care. 2022 Jun;53:51–60.

51. Jorda A, Kussmann M, Kolenchery N, Siller-Matula JM, Zeitlinger M, Jilma B, et al. Convalescent Plasma Treatment in Patients with Covid-19: A Systematic Review and Meta-Analysis. Front Immunol. 2022;13:817829.

52. Troxel AB, Petkova E, Goldfeld K, Liu M, Tarpey T, Wu Y, et al. Association of Convalescent Plasma Treatment With Clinical Status in Patients Hospitalized With COVID-19: A Meta-analysis. JAMA Netw Open. 2022 Jan 4;5(1):e2147331.

53. Convalescent Plasma and Immune Globulins [Internet]. COVID-19 Treatment Guidelines. [cited 2022 Apr 20]. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/convalescent-plasma/

54. Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest. 2020 Sep 1;130(9):4791–7.

55. Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, et al. Safety Update. Mayo Clin Proc. 2020 Sep;95(9):1888–97.

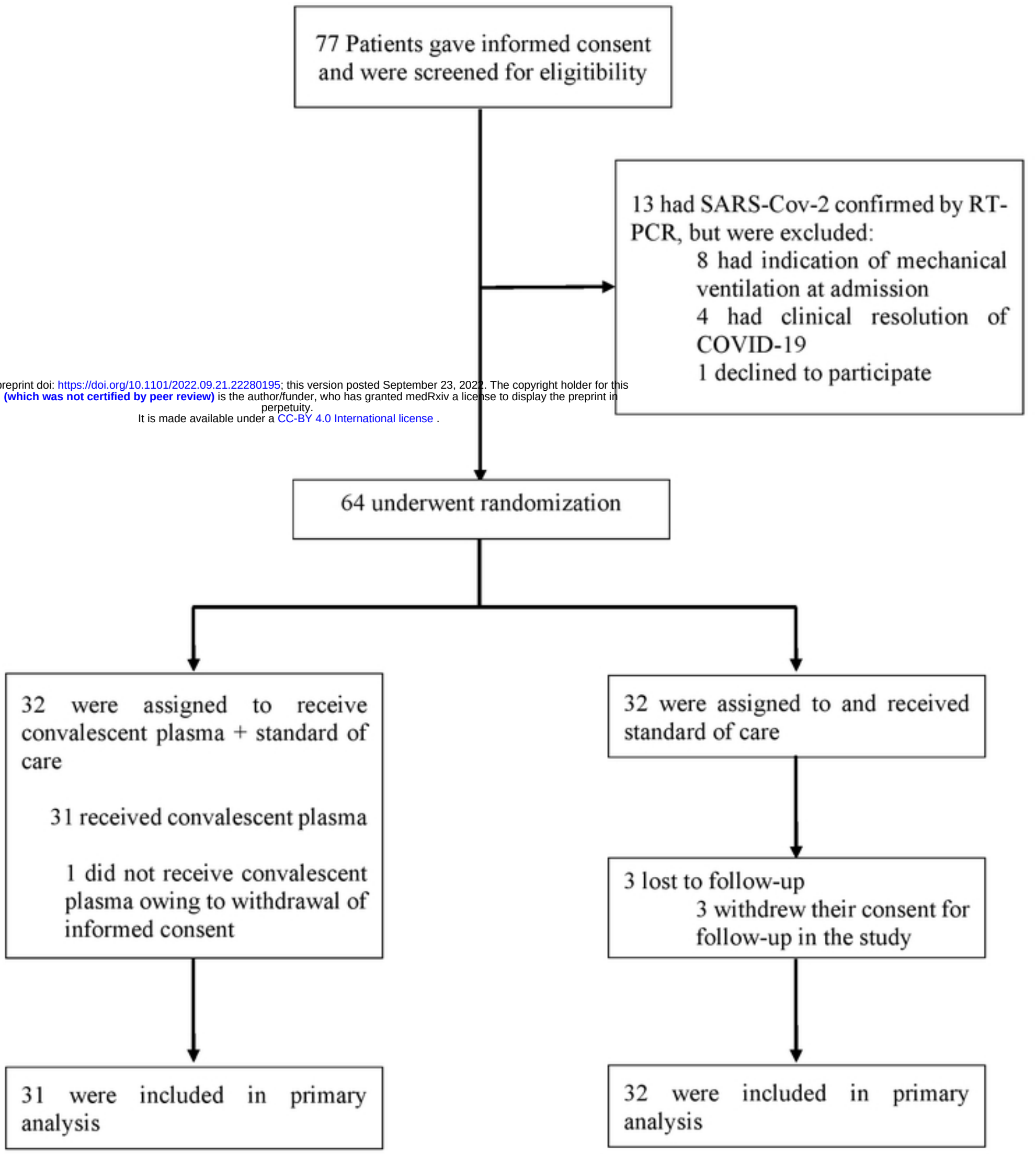
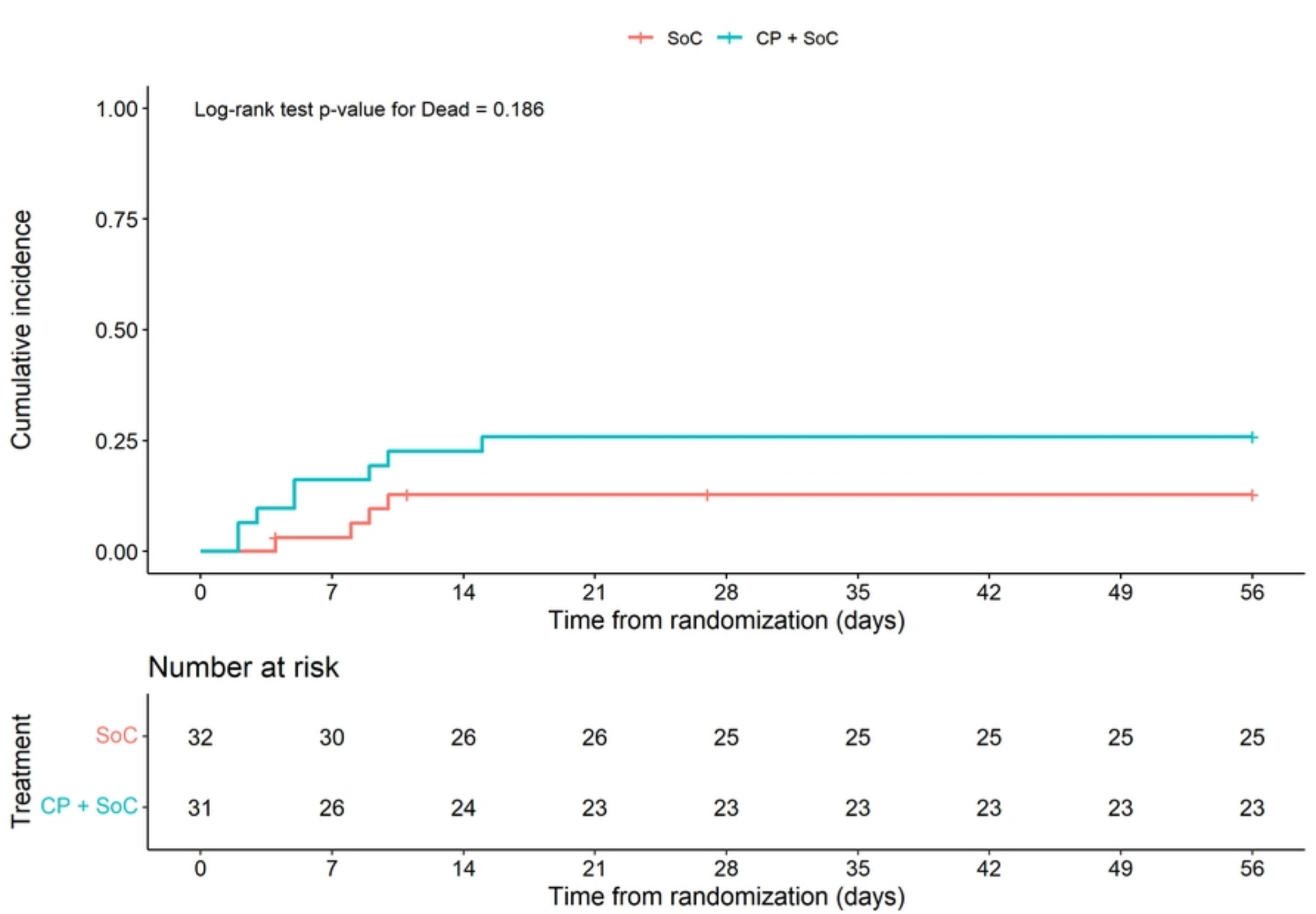


Figure1


SoC
CP + SoC
Log-rank test p-value for Dead = 0.186
Cumulative incidence
1.00
0.75
0.50
0.25
0.00
0
7
14
21
28
35
42
49
56
Time from randomization (days)
Number at risk
Treatment
SoC
CP + SoC
32
30
26
26
25
25
25
25
25
31
26
24
23
23
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23
0
7
14
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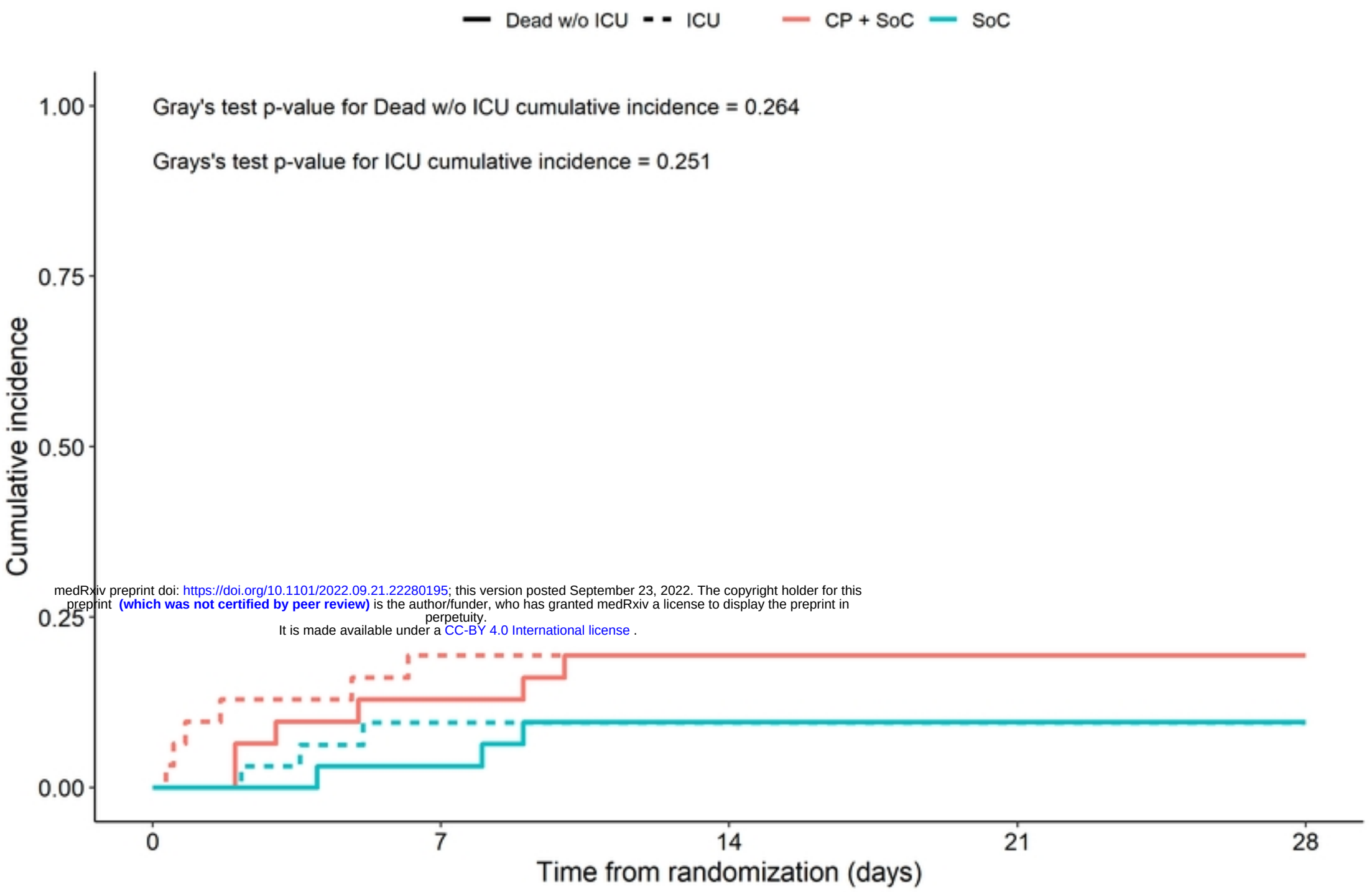
28
35
42
49
56
Time from randomization (days)

Figure2

A



B

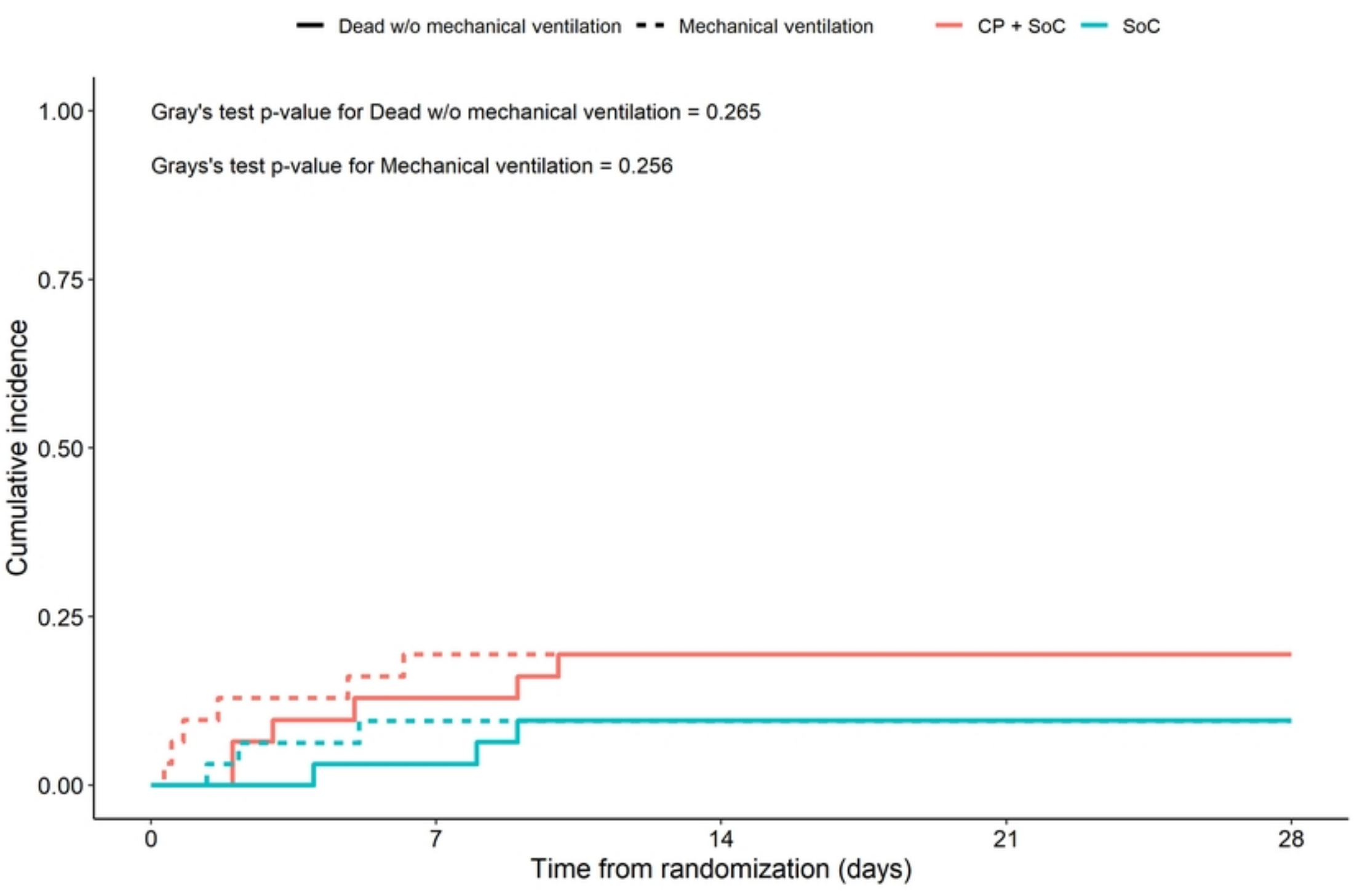


Figure3