JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Efficacy of COVID convalescent plasma therapy in hospitalized moderate coronavirus disease 2019 patients

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Abstract

Introduction: Covid Convalescent Plasma (CCP) failed to demonstrate its efficacy in severe and life-threatening coronavirus disease 2019 (COVID-19) cases. However, the role of CCP in hospitalized moderate cases is unclear. This study aims to examine the efficacy of administering CCP to hospitalized moderate coronavirus disease 2019 patients.

Methodology: An open-label randomized controlled clinical trial design was used from November 2020 – August 2021 at two referral hospitals in Jakarta, Indonesia, and the primary outcome was mortality at 14 days. The secondary outcomes were mortality at 28 days, the time-to-discontinuation of supplemental oxygen, and the time-to-hospital discharge.

Results: This study recruited 44 subjects, and the intervention arm consisted of 21 respondents who received CCP. The control arm consisted of 23 subjects who received standard-of-care treatment. All subjects survived during the fourteen-day follow-up period, and the 28-day mortality rate in the intervention group was lower than the control (4.8% vs 13.0%; $p = 0.16$, HR = 4.39 (95% CI = 0.45-42.71). There was no statistically significant difference in the time-to-discontinuation of supplemental oxygen and time-to-hospital discharge. During the total follow-up period (41 days), the mortality rate in the intervention group was also lower than the control (4.8% vs 17.4%, $p = 0.13$, HR = 5.47, 95% CI = 0.60–49.55).

Conclusions: This study concluded that in hospitalized moderate COVID-19 patients, CCP did not reduce 14-day mortality compared to the control. Mortality during 28 days and total length of stay (41 days) were lower in the CCP group compared to the control, although they did not reach statistical significance.

Key words: COVID Convalescent plasma; COVID-19; mortality.

J Infect Dev Ctries 2023; 17(1):43-51. doi:10.3855/jidc.17146

(Received 22 July 2022 – Accepted 31 October 2022)

Introduction

Coronavirus Disease (COVID-19) cases continue to increase globally, and confirmed cases reached 618,507,182, with 6,535,944 deaths [1]. Since the first two cases were detected in Indonesia, within two and a half years, the number of detected and confirmed cases has reached nearly 6,475,672, of which about 0.3% are in treatment, 97.2% have recovered, and 2.4% died [2].

No specific therapy exists for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. Treatment protocol for the management of COVID-19 has been published and revised periodically as new evidence emerged [3]. Current established therapy consists of antivirals, such as favipiravir, remdesivir, or molnupiravir, and supportive therapy by administrating vitamins [3,4]. The growing incidence of cases with a rapid increase in the mortality rate, specifically in Indonesia, indicates the need for other potential therapeutic modalities.

The clinical spectrum is grouped into five categories: asymptomatic, mild, moderate, severe, and critical/life-threatening disease [5]. In moderate COVID-19, it is recommended to exercise close monitoring because patients can deteriorate rapidly [5]. The incidence and pathogenesis progressing to severe and critical diseases are not fully understood. Aksel *et al.* [6] showed that dyspnea, comorbid disease, elevated CRP level and low pulse O_2 saturation predict mortality

in moderate to severe disease. A report from Wuhan reported a high mortality rate, around 28% and 81% in severe and critical/life-threatening diseases, respectively, with 81% requiring mechanical ventilation [7]. Other treatment modalities are needed to prevent disease progression such as worsening respiratory failure from moderate to severe COVID-19 disease. Therefore, this study is expected to help answer the question regarding whether CCP reduces mortality in hospitalized moderate COVID-19 patients.

Despite its controversial issue, CCP is an alternative treatment option. Several publications have reported its efficacy and safety [8–10]. Most of these publications were case reports which utilized CCP administration in severe COVID-19. They reported improvement in clinical status, radiological lesions, laboratory parameters (lymphocytopenia and C-reactive protein (CRP)), increased neutralizing antibodies, and loss of SARS-CoV-2 RNA. However, no adverse or threatening side effects were reported [8–10], and the administration of CCP has also been reported in patients without severe symptoms but with persistent infection [11]. The administration of CCP has been recommended in various viral outbreaks, such as in the Ebola virus and Middle East Respiratory Syndrome (MERS) outbreaks. Convalescent plasma has also been reported to be effective against SARS-CoV, H5N1, and H1N1 viruses [12–17]. Reports on the efficacy and safety of existing trials and studies regarding CCP are still minimal due to the small study sample size or flaws in the design. The latest evidence from the PlasmAr study group shows no evidence supporting the use of CCP in severe COVID-19 Pneumonia [18]. Meanwhile, CCP has not yet been approved by the Food and Drug Administration for the treatment of hospitalized patients. it was designated as an investigational product. Thus, the use of this product must be under the emergency use authorization (EUA) or investigational new drug (IND) [19].

Some patients are affected by COVID-19 with symptoms that will progress into severe fatal diseases. We hypothesized that CCP administration prevents severe disease progression from reducing mortality. This study aims to examine the efficacy of CCP for COVID-19 patients who exhibit clinical worsening during hospitalization.

Methodology

Study Subjects

An open-label randomized controlled clinical trial design was used involving hospitalized moderate coronavirus disease 2019 patients treated at two referral hospitals in Jakarta, Indonesia, namely Dr. Cipto Mangunkusumo and Pertamina Hospitals. The subjects were divided into control and intervention groups. Furthermore, those assigned to the intervention group received CCP on top of standard treatment, while the control only received the standard therapy. This study was conducted under the guidelines of the Declaration of Helsinki, and the protocol used was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, with the number: KET-550/UN2.F1/ETIK/PPM.00.02/2020. Informed consent was obtained from all patients/family representatives and plasma donors.

The inclusion criteria were 1) age 18 years, 2) positive for COVID-19 infection confirmed by SARS CoV-2 RT-PCR, and 3) Hospitalized moderate coronavirus disease 2019 patients. Meanwhile, the exclusion criteria included 1) known contraindications to plasma transfusion, 2) other uncontrolled infections (sepsis). 3) disseminated intravascular coagulation (DIC) requiring clotting factor replacement (fresh frozen plasma), 4) hemodialysis patients, 5) active intracranial bleeding, 6) active cancer or post-chemotherapy, and patients undergoing immunotherapy ≤ 1 month, and 7) patients who did not agree to participate in this study.

According to the World Health Organization, moderate COVID-19 is defined as follows 1) respiratory rate $20 < x < 30$x/min, 2) moderate respiratory distress, 3) oxygen saturation (SpO_2) $93 < x < 95\%$ in room air, and 4) PaO_2/FiO_2 ratio $300 < x \leq 400$.

Source of COVID Convalescent Plasma (CCP)

CCP was obtained from donors who met the following criteria 1) male; 2) at least aged 18 years; 3) history of COVID-19 infection, confirmed by SARS CoV-2 RT-PCR; 4) symptom-free for at least 14 days; 5) negative SARS CoV-2 RT-PCR swab test results at least two consecutive times, minimal 24 hours from the first test; 6) positive COVID-19, positive IgG, and negative IgM rapid test results; 7) haemoglobin 12.5 – 17 g/dL; 8) platelets > 150,000 mm^3; and 9) albumin 3.5 – 5.5 g/dL. The exclusion criteria for donors were 1) the presence of blood-borne infections (Hepatitis B, Hepatitis C, HIV, or Syphilis).

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 23 software for Windows. A comparison of clinical and laboratory data before and after transfusion was presented

descriptively. The independent T-test used normal data distribution to observe differences in the mean of the numerical parameters obtained, such as hematological parameters, oxygen saturation, and CRP levels. Mann-Whitney test was used when the distribution was abnormal. The Chi-square test observed the differences in outcomes between intervention and control groups with categorical parameters, such as incidence of complications and mortality, while Kaplan-Meier analysed survival with the log-rank test.

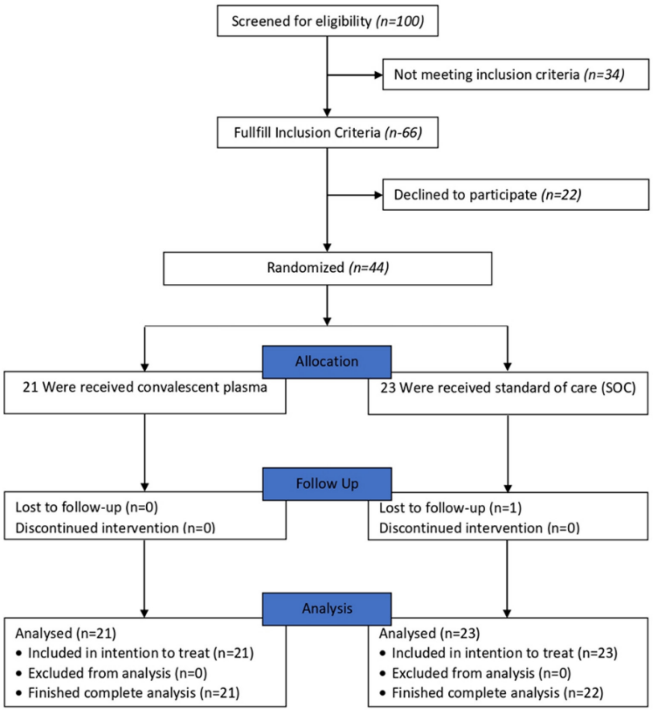
COVID Convalescent Plasma (CCP) Procedure

In this study, prospective donors had a history of being treated either as inpatients, or outpatients at Dr. Cipto Mangunkusumo and Pertamina Hospitals. The study team recruited donors through flyers, direct recruitment, or social media and contacted prospective donors for a pre-screening assessment. Questions prepared using Google Forms or by telephone were asked to determine the screening of prospective donors. Furthermore, further evaluation was conducted to determine eligibility to donate plasma. At initial screening, the study team obtained written consent to participate in this study from prospective donors at the Dr. Cipto Mangunkusumo Hospital.

After obtaining informed consent, the study team conducted history taking and laboratory tests. The blood volume of approximately 18 mL (six tubes consisting of five purple tubes/K3-EDTA and one red tube/clot activator), of which two tubes (one purple tube and one red tube) were used to examine haemoglobin, platelets, and albumin in the Dr. Cipto Mangunkusumo Hospital. The remaining four purple tubes were utilized to investigate ABO blood type, screening for HIV, Hepatitis B, Hepatitis C, Syphilis, and other transfusion-transmissible-infections (TTIs) using CLIA (chemiluminescence immunoassay) and NAT (nucleic acid test) at the CBTU Indonesian Red Cross. These tests were performed on positive and negative SARS CoV-2 IgG and IgM donors. These rapid antibody tests were performed using the lateral flow assay (LFA) method, and prospective donors were subjected to the swab RT PCR. The study team contacted prospective donors to inform them of the laboratory results from Dr. Cipto Mangunkusumo Hospital and CBTU Indonesian Red Cross. Donors who met the inclusion criteria were scheduled for a one-day plasma donation at the CBTU-Indonesian Red Cross. Meanwhile, the plasma was obtained using the apheresis method (plasmapheresis), and about 400-600 ml were divided into 2-3 bags, 200 mL each. The donor's blood was drawn using a kit connected to an apheresis machine (Haemonetics® MCS®+/Trima Accel®). The donor's blood goes through apheresis, and the cellular components of the blood are returned to circulation. ACDA (acid citrate dextrose adenine) was used as an anticoagulant for the donor plasma, and the process took about one to two hours. The plasma was frozen (fresh frozen plasma) and stored at the Jakarta BTU (blood transfusion unit) of the Indonesian Red Cross at a temperature of -30 °C.

COVID-19 patients treated from November 2020 – August 2021 at Dr. Cipto Mangunkusumo and Pertamina Hospitals who met the inclusion criteria were asked for their informed consent. Patients in the control and intervention groups were subjected to laboratory tests before being monitored. In addition, the intervention group was given two bags of CCP intravenously (one bag contained 200 mL of plasma) for two to four hours and monitored for adverse effects during and after transfusion. The second CCP transfusion was given four hours after the first, while the control and intervention groups were monitored for 7-28 days. In both treatment arms, when subjects' condition worsened and additional therapies such as 1) mechanical ventilation, 2) Intravenous Immunoglobulin (IVIG), and 3) tocilizumab were planned, a blood test was performed before these procedures. In patients who experienced clinical improvement and were planned to be discharged, a blood test was performed within 14 days before the patients were discharged. The examinations included

Figure 1. Enrollment and Randomization.



clinical, blood gas analysis, routine blood (haemoglobin, leukocytes, platelets), prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, CRP, and ferritin. The control and intervention groups received standard therapy for the treatment of COVID-19, including antivirals (favipiravir, oseltamivir, or remdesivir), anticoagulants, antibiotics, and anti-inflammatory drugs (methylprednisolone or dexamethasone).

Outcomes Measurement

The primary outcome was mortality at 14 days after the hospital admission, while the secondary outcomes were mortality at 28 days, the time-to-discontinuation of supplemental oxygen, and the time-to-hospital discharge.

Results

This study screened 100 patients across 2 hospitals from November 18th, 2020 to August 29th, 2021. Furthermore, 44 patients met the inclusion criteria and were randomized into 21 receiving CCP with the standard of care treatment (intervention group) and 23 receiving only standard of care treatment (control group) (Figure 1).

Each patient's demographical and clinical characteristics can be seen in Table 1. The mean age in the intervention group was 57 years (interquartile range [IQR] of 53-69), with 15 (71.4%) were male. The mean age was 56 years (IQR of 42-59.5) in the control group, with 13 (56.5%) were male. The groups' most frequently complained symptoms were breathlessness, cough, fatigue, and fever.

Table 1. Demographic and baseline characteristics of hospitalized moderate COVID-19 patients.

Characteristics	COVID Convalescent Plasma (CCP) Arm (n = 21)	Control Arm (n = 23)
Age, years, Median (IQR)	57 (53 – 69)	56 (42 – 59.5)
Sex		
Men	15 (71.4)	13 (56.5)
Women	6 (28.6)	10 (43.5)
ABO Blood Group		
A Rhesus Positive	7 (33.3)	6 (26.1)
B Rhesus Positive	6 (28.6)	4 (17.4)
O Rhesus Positive	8 (38.1)	12 (52.2)
AB Rhesus Positive	0 (0)	1 (4.3)
Body Mass Index (BMI)		
Mean (SD)	26.94 (4.17)	26.77 (3.32)
Number of Comorbidity		
No Comorbidity	11 (52.4)	9 (39.1)
1 Comorbidity	6 (28.6)	7 (30.4)
2 Comorbidities	3 (14.3)	5 (21.7)
3 or more Comorbidities	1 (4.8)	2 (8.7)
Comorbidity		
No Comorbidity	11 (52.4)	9 (39.1)
Diabetes Mellitus	3 (14.3)	8 (34.8)
Cardiovascular Disease	2 (9.5)	2 (8.7)
Hypertension	8 (38.1)	10 (43.5)
Malignancy	1 (4.8)	2 (8.7)
Autoimmune Disease	0 (0)	1 (4.3)
Asthma	1 (4.8)	0 (0)
Sign and Symptoms		
Fever	19 (90.5)	17 (73.9)
Cough	20 (95.2)	23 (100)
Cold	8 (38.1)	2 (8.7)
Sore Throat	8 (38.1)	9 (39.1)
Shortness of Breath	21 (100)	21 (91.3)
Shivering	4 (19)	7 (30.4)
Headache	14 (66.7)	12 (52.2)
Fatigue	19 (90.5)	18 (78.3)
Muscle Pain	7 (33.3)	9 (39.1)
Nausea	9 (42.9)	11 (47.8)
Vomiting	1 (4.8)	4 (17.4)
Abdominal Pain	0 (0)	4 (17.4)
Diarrhea	2 (9.5)	6 (26.1)
Anosmia	8 (38.1)	6 (26.1)

IQR: interquartile range; SD: standard deviation.

Pre- and post-observational assessment of laboratory values such as PO_2/FiO_2 ratio, haemoglobin, leukocytes, thrombocytes, NLCR, PT, aPTT, D-dimer, CRP, and ferritin were conducted during admission, as seen in Tables 2 and 3 for control and intervention groups, respectively. Table 4 shows the ratio comparison of each laboratory parameter of each group and found no significant differences between the two.

Primary Outcome

During the 14-day follow-up, no subjects in both group experienced the event, as shown in Table 5.

Secondary Outcomes

During 28 days of hospital admission, all cause mortality was higher in control (13.0%) compared to the intervention group (4.8%). However, they had no statistically significant difference ($p = 0.16$, HR = 4.39, 95% CI = 0.45-42.71). Figure 2 shows the cumulative survival with observation until 28 days between the two groups. Cumulative survival was 88.9% and 26.7% in intervention and control groups, respectively.

There was no statistically significant difference in the amount of time supplemental oxygen (13 days [IQR of 9-18 days] vs. 10 days [IQR of 9-14 days], $p = 0.16$). The same result was also observed in the time it took before patients were discharged (14 days [IQR of 9-20 days] vs. 11 days [IQR of 9-15 days], $p = 0.27$).

During the total follow-up with the most prolonged stay of 41 days, 5 patients consisting of 4 from the control (17.4%) and 1 from the intervention group (4.8%) died, thereby making the proportion of patients

Figure 2. Cumulative survival curve between CCP arm and control arm at 28 days.

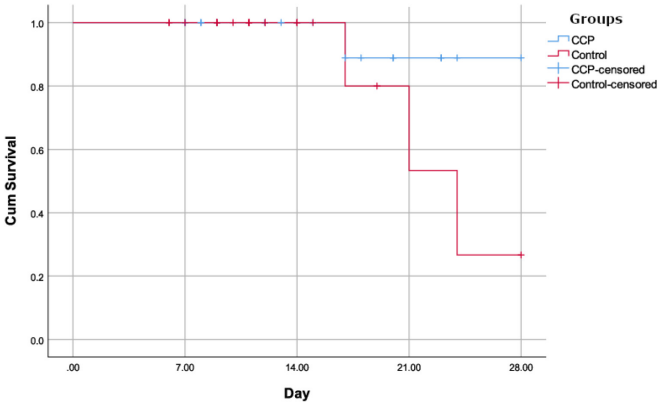


Table 2. Comparison of laboratory parameters between pre- and post-observation in control groups.

	Control Arm (n = 22)	
	Pre-observation	**Post-observation**
Ratio pO_2/FiO_2, Median (IQR)	210 (140.5 – 356.5)	299 (187.75 – 467.25)
Hb (g/dL), Median (IQR)	13.45 (12.92 – 14.60)	12.55 (12.08 – 13.93)
White blood cell ($\times 10^3$), Mean (SD)	8.6932 (5.55)	12.36 (6.29)
NLCR, Mean (SD)	9.44 (17.57)	13.36 (13.19)
Platelets ($\times 10^3$), Median (IQR)	206 (170.75 – 320.50)	363 (284 – 414.75)
PT (Seconds), Median (IQR)	10.3 (10 – 11)	11 (10.7 – 11.7)
aPTT (Seconds), Median (IQR)	31.7 (26.5 – 35.3)	28 (25.6 – 32.75)
D-Dimer (mg/L), Median (IQR)	580 (340 – 1330)	680 (360 – 1580)
CRP (mg/L), Median (IQR)	540 (337.5 – 1360)	3.80 (2.85 – 17.13)
Ferritin (ng/mL), Median (IQR)	553.24 (384.66 – 1094.04)	651.07 (462.17 – 1520.22)

pO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen; Hb: haemoglobin; IQR: interquartile range; SD: standard deviation; NLCR: neutrophil to lymphocyte count; PT: prothrombin time; aPTT: activated partial thromboplastin time; CRP = c-reactive protein.

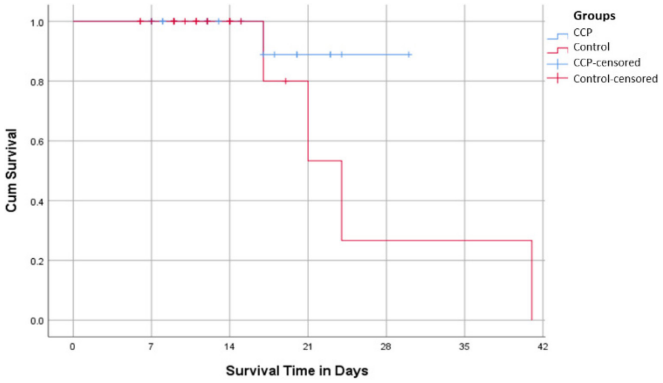
Table 3. Comparison of laboratory parameters between pre- and post-observation in plasma CCP groups.

	COVID Convalescent Plasma (CCP) Arm (n = 21)	
	Pre-observation	**Post-observation**
Ratio pO_2/FiO_2, Median (IQR)	210 (140.5 – 356.5)	299 (187.75 – 467.25)
Hb (g/dL), Mean (SD)	14.3 (13.45 – 15.35)	13.6 (12.6 – 14.5)
White blood cell ($\times 10^3$), Mean (SD)	7.54 (3.30)	10.23 (3.56)
NLCR, Median (IQR)	6.52 (2.52 – 9.89)	6.86 (5.37 – 12.23)
Platelets ($\times 10^3$), Median (IQR)	207 (172.5 – 269.5)	298 (246 – 385.5)
PT (Seconds)	10.5 (10 – 11)	11 (10.52 – 11)
aPTT (Seconds), Median (IQR)	29 (24.9 – 36.5)	29 (24 – 40.1)
D-Dimer (mg/L), Median (IQR)	460 (315 – 965)	410 (290 – 720)
CRP (mg/L), Median (IQR)	460 (315 – 965)	3.5 (1 – 7.6)
Ferritin (ng/mL), Median (IQR)	609 (371.7 – 1440.5)	649.9 (435.1 – 1198.47)

pO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen; Hb: haemoglobin; IQR: interquartile range; SD: standard deviation; NLCR: neutrophil to lymphocyte count; PT: prothrombin time; aPTT: activated partial thromboplastin time; CRP: C-reactive protein.

who recovered from being 82.6% and 95.2%, respectively (p = 0.13, HR = 5.47, 95%CI = 0.60 – 49.55). On the other hand, Figure 3 shows a similar result to Figure 2, and the cumulative survival rate between the intervention and control during the total length of care was 88.9% and 0%, respectively.

Figure 3. Cumulative survival curve between CCP arm and control arm during the total follow up period stay.



Discussion

This study focused on hospitalized moderate COVID-19 patients, most of whom are male. Same-sex predominance was found in previous studies, one of which was by Johan *et al.* [20] In this study, the screening process was conducted in 100 patients, with 44 matching the inclusion criteria, while 56 were excluded. Furthermore, 22 subjects were excluded because they refused to obtain CCP due to negative public stigma regarding the effect of therapy. The other reason for exclusion is some subjects refused to be randomized and might fall into the control group.

The study by Yang *et al.* [21] stated that COVID-19 patients with moderate symptoms and comorbidities had a higher risk of worsening critical conditions. In moderately-ill patients, the prevalence presented with or without comorbidities is relatively similar. However, a higher mortality rate was observed in those with comorbidities. The most frequent comorbid conditions were the same as those found in Yang *et al.* [21], namely hypertension and diabetes.

CCP did not give survival benefits during the 14-day follow-up, and the 28-day mortality rate in the intervention group was lower than the control (4.8% vs 13.0%). Even though they did not reach statistical significance, probably due to the small sample size, the proportion of patients who died between those groups reached three-fold, which should be considered clinically significant. This result is consistent with Simonovich *et al.* [18] in Argentina, where 288 patients received CCP (SARS-CoV-2 antibody titer mean of 1:3200). In addition, there was no difference in the 30-day mortality rate between the control and intervention groups (10.96% vs. 11.43%, respectively; 95% CI: -7.8 to 6.8).

Other similar studies by Ortigoza *et al.* or the RECOVERY trial [22] did not show the difference in 14- and 28-day mortality rates between the intervention and control group (24% vs. 24%; rate ratio 1.00, 95% CI 0.93-1.07, p = 0.95). They did not show any difference in the length of outpatient care after hospital admission between the intervention (66%) and control

Table 4. Comparison of laboratory parameters between control groups and CCP arm.

	Control Arm (n = 22)	COVID Convalescent Plasma (CCP) Arm (n = 21)	*p* value
Δ Ratio pO_2/FiO_2, Median (IQR)	132.5 (-34 – 209.5)	148 (13 – 358)	0.230$^+$
Δ Hb (g/dL), Median (IQR)	-0.65 (-1.22 – 0.65)	-0.2 (-1.8 – 0.2)	0.431$^+$
Δ WBC ($\times 10^3$)	2.86 (0.06 – 6.09)	1.58 (-0.25 – 6.11)	0.480$^+$
Δ NLCR, Median (IQR)	2.41 (0.54 – 6.95)	-0.7 (-2 – 4.46)	0.505$^+$
Δ Platelet ($\times 10^3$), Median (IQR)	91 (15.75 – 161.5)	89 (-14 – 152)	0.999$^+$
Δ PT (Seconds), Mean (SD)	0.54 (0.75)	0.33 (0.80)	0.371^
Δ aPTT (Seconds), Mean (SD)	2.15 (18.19)	0.33 (14.28)	0.920^
Δ D-Dimer (mg/L), Mean (SD)	244.44 (1393.06)	-611.62 (2350.79)	0.188^
Δ CRP (mg/L), Mean (SD)	-38.66 (64.99)	-55.55 (50.44)	0.159^
Δ Ferritin (ng/mL), Mean (SD)	-44.39 (554.96)	-28.06 (539.19)	0.910^

^Independent T test; + Mann Whitney Test. pO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen; Hb: haemoglobin; IQR: interquartile range; SD: standard deviation; NLCR: neutrophil to lymphocyte count; PT: prothrombin time; aPTT: activated partial thromboplastin time; CRP: C-reactive protein.

Table 5. Comparison of primary outcomes between CCP arm and standard of care (control arm).

Primary Outcome	Control Arm (n = 23)	COVID Convalescent Plasma (CCP) Arm (n = 21)	*p* value
All-cause mortality at 14 days	0 (0.0)	0 (0.0)	-

group (66%) (rate ratio 0.99, 95% CI 0.94-1.03 p = 0.57). The result is in line with RECOVERY, which showed no difference in length of outpatient care after discharge between the intervention and control groups with median of 14 and 11 days, respectively (p = 0.27) [22].

Since the RECOVERY trial failed to demonstrate the survival benefit of CCP, patients were followed up until they were discharged from the hospital, with the longest stay of 41 days. During this period, 4 (17.4%) and 1 (4.8%) patients in the control and intervention groups died. This additional data increases the hazard ratio between the groups, giving additional survival benefits in favor of CCP.

Laboratory examinations can also be utilized to assess clinical improvement. The groups did not improve values of surrogate markers such as D-dimer, prothrombin time, CRP, and other laboratory markers (Table 4). Sekine *et al.* [23] conducted an open-label, randomized study in which 160 patients were divided into groups getting CCP in addition to conventional and those receiving only standard treatment. The study found no difference in terms of 14- and 28-day clinical improvement of 61.3% and 65.0% in the intervention and control groups, respectively (difference -3.7%; 95% CI -18.8% - 11.3%).

The cumulative survival rate in the intervention group has a better outcome than the control (Figures 2 and 3). Rejeki *et al.* [24] showed that patients with moderate symptoms of COVID-19 had significant clinical improvement after CCP. Another case report by Mahdi *et al*. [25] described the patient given CCP for 3 days in a row as replacement therapy. This is because Favipiravir shortages showed improvement in symptoms such as shortness of breath, fever, and weakness. In Alsharidah *et al.* [26], moderate COVID-19 patients with CCP show faster recovery than in the control group (7 days vs 8 days, p = 0.006). The mortality rate decreased significantly after 30 days of treatment, oxygen saturation improved after day 3, and lymphocyte recovery was at day 7.

The experimental design is an "open-label randomized clinical trial", which is advantageous because it is the first time this method has been applied in Indonesia. However, this study also has some limitations, and the first is the total number of subjects. Secondly, the standard parameter cannot ensure the quality and quantity of the antibody titer in the donor plasma.

Conclusions

In conclusion, COVID CCP did not reduce 14-day mortality compared to the control group in hospitalized moderate COVID 19 patients. Mortality during 28-day and total length of stay (41 days) were lower in the CCP group compared to the control, although they did not reach statistical significance.

Acknowledgements

The authors are grateful to the healthcare workers, donors, patients, and their families, which with full encouragement, are consistently providing care for patients during the COVID-19 pandemic. Furthermore, the authors thank Nova Hippy, MD, and team (CBTU Indonesian Red Cross), Pierlita Rini, MD, and team (Jakarta BTU Indonesian Red Cross), Prof. Pustika Amalia Wahidiyat, MD. PhD and team (Dr. Cipto Mangunkusumo Blood Bank Unit), Suwarsih and team (BTU Indonesian Red Cross, Pertamina Hospital), Wibowo Soepomo, MD., Goretty Lusya Angelita, MD., Fery Murtopo, MD., Febianza Mawaddah Putri, MD. and team (Pertamina Hospital), Parbety Mustika Agustin, Ria Maryani, Melly Oktaviani, Bona Pratama Putra and team (Integrated Laboratory Dr. Cipto Mangunkusumo Hospital), Ika Wijayanti and team (Madya Outpatient Clinic Dr. Cipto Mangunkusumo Hospital), Ardhi Rahman Ahani, MD., Erwin Christian Susanto, MD., Edwin Ti Ramadan, MD., Muhammad Farhan Maruli, MD., Utami Susilowati (Research Co-ordinator unit), as well as Yasmin and Dewi Sawitri for their contributions.

Data Availability

Additional data can be requested when needed by contacting the corresponding paper. Requests for access to these data should be made by e-mail to Cosphiadi Irawan, MD, Ph.D. cosphiadi.irawan@ui.ac.id.

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Conflict of interests: No conflict of interests is declared.