ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ*) 2021, Volume 10, Number 3: 851-859
P-ISSN.2089-1180, E-ISSN: 2302-2914

Bali Medical Journal
www.BaliMedicalJournal.org
Published by Bali Medical Journal

Convalescent plasma as an adjunctive treatment for severe and critically ill COVID-19

Damai Santosa,[1*] Muchlis Achsan Udji Sofro,[2] Retnaningsih,[3,4] Eko Adhi Pangarsa,[1] Budi Setiawan,[1] Nur Farhanah,[1] Fathur Nur Kholis,[5] Thomas Handoyo,[5] Sofyan Rahardjo,[6] Like Rahayu Nindhita,[7] Iva Puspitasari,[8] Ridho M. Naibaho,[1] Retty Kharismasari,[2] Ika Kartiyani,[1] Vina Yunarvika,[1] Daniel Rizky,[1] Suhartono[9]

[1]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro and Dr. Kariadi Hospital, Semarang, Indonesia
[2]Division of Infection and Tropical Disease, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro and Dr. Kariadi Hospital, Semarang, Indonesia
[3]Department of Neurology, Faculty of Medicine, Universitas Diponegoro and Dr. Kariadi Hospital, Semarang, Indonesia
[4]Intensive Care Department, Dr. Kariadi Hospital, Semarang, Indonesia
[5]Division of Pulmonary Disease and Critical Care Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro and Dr. Kariadi Hospital, Semarang, Indonesia
[6]Pulmonology Department, Dr. Kariadi Hospital, Semarang, Indonesia
[7]Department of Clinical Laboratory, Blood Transfusion Unit, Dr. Kariadi Hospital, Semarang, Indonesia
[8]Department of Clinical Microbiology, Dr. Kariadi Hospital, Semarang, Indonesia
[9]Faculty of Public Health, Universitas Diponegoro, Semarang, Indonesia

*Corresponding to:
Damai Santosa; Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro and Dr. Kariadi Hospital, Semarang, Indonesia;
santosaiva@yahoo.com

Received: 2021-07-23
Accepted: 2021-08-28
Published:2021-09-07

ABSTRACT

Introduction: The historical treatment of convalescent plasma was successful against RNA viruses. However, the significance of COVID-19 convalescent plasma therapy has not been clinically proven consistently in most studies and the available data showed contradictory results so far. Our study aims to evaluate the role of convalescent plasma therapy as an adjunctive treatment for severe and critically ill COVID-19 patients.

Methods: This study was an open-label, non-randomized comparative clinical trial that was conducted at Dr. Kariadi Hospital, Semarang, Indonesia. This study sample are hospitalized severe and critically ill COVID-19 patients were assigned with a 2:1 ratio to receive convalescent plasma and local standard of care. The primary outcome was the clinical status 30 days after the intervention

Results: A total of 73 patients received convalescent plasma and 38 patients received local standards of care. Both of the groups had similar clinical ordinal scales (median was 5, p=0.65), while patients in the study groups had significantly higher SOFA scores and P/F ratio. The control group had a worse overall mortality rate (61.1% vs 18.4%) with a hazard ratio of 3.5 (95%CI, 2.1-5.9) compared to the study group. From the subgroup analysis, we found that patients in the study group without mechanical ventilation support had the best survival rate compared to other groups HR: 0.0047 (95%CI, 0.01-0.19). The clinical outcome 7 days after convalescent plasma infusion was also significantly improved in the study group (median baseline & day-7, 5 & 3, p<0.001). From the multivariate analysis of therapeutic variables, convalescent plasma was the most significant variable for survival outcome (OR=0.089, 95%CI, 0.029-0.27; p<0.001). There was one case of anaphylactic shock and was excluded.

Conclusions: The convalescent plasma administration significantly improved clinical outcomes and overall survival rates compared to those who received local standards of care.

Keywords: Adjunctive treatment, convalescent plasma therapy, COVID-19
Cite This Article: Santosa, D., Sofro, M.A.U., Retnaningsih. Pangarsa, E.A., Setiawan, B., Farhanah, N., Kholis, F.N., Handoyo, T., Rahardjo, S., Nindhita, L.R., Puspitasari, I., Naibaho, R.M., Kharismasari, R., Kartiyani, I., Yunarvika, V., Rizky, D., Suhartono. 2021. Convalescent plasma as an adjunctive treatment for severe and critically ill COVID-19. *Bali Medical Journal* 10(3): 851-859. DOI: 10.15562/bmj.v10i3.2590

INTRODUCTION

Coronavirus disease of 2019 (COVID-19) have the characteristic of a high rate of transmissibility associated with considerable mortality rate which the World Health Organization (WHO) declared COVID-19 pandemic on March 11, 2020.[1,2] By December 2020, one year after the first case of SARS-CoV-2 infection emerged in Wuhan, China, a total of 101,053,721 confirmed cases and 2,182,867 deaths (2.1%) had been reported worldwide at the time of writing this article.[3,4] In Indonesia, the COVID-19 escalated from week to week in January 2021 with daily cases hitting records. We are undoubtedly overwhelmed with COVID-19 cases with case fatality rate (CFR) once reaches 8.9% in some areas.[5,6]

It is needed an effort to develop effective therapies for COVID-19, especially in a particular population with a severe and life-threatening disease. Fifteen to forty-four percent of the hospitalized patients required intensive care and 49.0% of these patients eventually succumbing to death.[7–9] Antiviral treatment, anticoagulant, dexamethasone, intensive care support, and the application of ECMO have been advocated. However, no single treatment modality has proven efficacy consistently.[10,11]

The historical treatment of convalescent plasma was successful against RNA viruses.[12] The use of plasma in other CoVs like SARS-CoV resulted in the decreased duration of invasive ventilation and lesser day hospitalization in a severely ill patient.[13,14] Convalescent plasma refers to a non-cellular component of blood containing specific antibodies against SARS-CoV-2 antigen with virus neutralization capability, collected from recovered patients from a similar

disease.[15,16] The neutralizing antibodies play a role by binding to the spike proteins of the SARS-CoV-2 and hence inhibiting viral entry and replication. Convalescent plasma provided passive immunomodulatory property that helps the recipient will control the excessive inflammatory cascade induced by the SARS-CoV-2 infection.[17,18] Recent study by Joyner et al. revealed that convalescent plasma was safe with small incidents of serious adverse reactions. The preliminary results have shown a decrease in fever and clinical improvement among patients receiving this therapy.[19–21] Another experience announced that seriously ill COVID-19 patients demonstrated improved oxygenation, reduced inflammation, and viral load.[22–24] However, the significance of COVID-19 convalescent plasma therapy has not been clinically proven consistently in most studies and the available data showed contradictory results so far.[15,25–27]

The convalescent plasma therapy (CPT) decent exploration for an effective line treatment as part of critical COVID-19 management. We evaluated clinical outcome and mortality among a subgroup of hospitalized with COVID-19 who received CPT as an adjunctive therapy compared to the local standard protocol.

METHODS

Research design

This open-label study was a non-randomized clinical trial conducted at Dr. Kariadi Hospital, Indonesia. The Ethical Clearance was obtained from the Ministry of Health of Republic Indonesia (Ethical Clearance (EC) no. LB.02.01/2/KE.351/2020) and the Food and Drug Advisory Agency (approval no. R-RG.01.06.1.3.05.20.156). The protocol was approved by the institutional review board (EC no. 528/ECX/KEPK-RSDK/2020) and registered in the International Standard Randomised Controlled Trial (ISRCTN16842454). All convalescent plasma donor and recipients or their surrogates gave written informed consent.

The variables collected in this study included demographic data and basic characteristics of SARS-CoV-2 patients, including age, covid severity, SOFA score, P/F ratio, D-dimer level, procalcitonin level, CRP level, and comorbid status. Also, therapeutic variables including CPT, Azithromycin, Levofloxacin, Amikacin, Meropenem, Moxifloxacin, Fluconazole, Micafungin, Favipiravir, Remdesivir, Lopinavir-Ritonavir, Dexamethasone, Vitamin C 1000 mg, Colchicine, and no anticoagulant.

Serology test and RT-PCR detection of SARS-CoV-2

The diagnosis COVID-19 was performed according to WHO interim guidance. The SARS-CoV-2 RNA was extracted using the MagNA Pure LC total nucleic acid isolation kit (Roche, Mannheim, Germany). Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 RNA was using Nucleic Acid Detection Kit (PCR Fluorescence Probing). A positive result was determined by a Ct (cycle threshold) value of less than 40.

Anti-IgG SARS-CoV-2 antibody was detected by chemiluminescence microparticle immunoassay (CLIA) by qualitative indirect immunofluorescence assay (ARCHITECHT® SARS-CoV-2 assay, Abbott Laboratories, Abbott Park, IL 60064, USA). The assay is designed to detect antibodies to the nucleocapsid protein in serum and plasma. Serum specimens were tested at a dilution of 1:80 (S/CO cutoff < 3.5).

Inclusion and exclusion criteria

This study included hospitalized patients age ≥18 years with the confirmed laboratory diagnosis of SARS-CoV-2 infection or COVID-19. Patients are eligible for CPT if they had severe or critical COVID-19 determined according to the WHO classification. Severe COVID-19 included at least one of the following: the presence of dyspnea, respiratory frequency ≥30 breaths/minutes, blood oxygen saturation ≤93%, a ratio of arterial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2 ratio) <300, or lung infiltrates >50% within 24-48 hours. Critical disease is defined as the presence of respiratory failure, septic shock, or multiple organ dysfunction.

The exclusion criteria for CPT were the history of an allergic reaction to blood product, medical condition which contraindicated for transfusion (e.g. decompensated heart failure or renal failure with fluid overload), patients with a critical degree of COVID-19 who have a worse prognosis estimate with Sequential Organ Failure Assessment (SOFA) score >11.

Control sampling criteria

The systematic stratified sampling techniques were used to identify control patients for the COVID-19 hospital registry. In general, we used all patients with similar characteristics before the team incorporate convalescent plasma as adjunctive treatment to severe and critical COVID-19. The control group would consist of patients who had been admitted for COVID-19 during the preparatory period for the CPT protocol was being set up, also for those for whom ABO-compatible plasma was not available during the study.

Donor selection and plasma collection

Convalescent plasma was collected from individuals who have recovered from COVID-19. Inclusion criteria for COVID-19 plasma donors were: adult males aged 18-60 years, a negative result of COVID 19 from of PCR evaluation of the naso-oropharyngeal swab, no other comorbidities (diabetes mellitus, hypertension, chronic kidney disease), seronegative from hepatitis B, hepatitis C, HIV, and syphilis, ABO compatibility, and rhesus blood groups matched with the plasma recipient, and the SARS-CoV-2 specific serum antibody titers ≥ 1: 80.

Plasmapheresis was performed using an apheresis machine (PCS®2 Plasma Collecting System from Haemonetics Co., Massachusetts, USA) connected via peripheral venous access. The amount of plasma collected was adjusted according to the donor's body weight and hematocrit level at approximately 400-mL for every plasmapheresis session. Upon donation, the convalescent plasma product was treated with amotosalen and illuminated with ultraviolet light (INTERCEPT, Cerus) before distribution into the 200-mL bag. Each bag of convalescent plasma was frozen within 6 hours of collection and stored below -18□C until thawed to ambient temperature, immediately before transfusion.

Convalescent plasma transfusion

We gave a 200-mL as single or multiple CPT, the dose could be repeated every

48 hours up to 5 doses unless the patients were considered to have clinical improvement. ABO-compatible CPT was administered at approximately 10-mL for the first 15 minutes, which then increased to approximately 100-mL per hour with close monitoring. Adjustments in the infusion rate were allowed based on the patient's risk for fluid overload and tolerance at the discretion of the clinician. The routine premedication was furosemide, diphenhydramine, and dexamethasone intravenously.

Co-intervention and standard treatment

The standard treatment protocol consisted of symptomatic control and supportive care for COVID-19 was based on our institutional protocol, evolving Indonesian Joint Expert Committee on COVID-19 Management, and International guidelines. COVID-19 patients were always treated by a multidisciplinary team consisted of infectious disease specialists, pulmonologists, hematologist-medical oncologists, cardiologists, nutritionists, intensivists, internal medicine, and nursing team.

Clinical data collection

Clinical and laboratory data were extracted from patient's electronic medical records using a predesigned data collection sheet. We captured pre-existing medical conditions, including cardiovascular disease, diabetes, hypertension, and obesity. Data on specific therapies were also collected. Complete blood count, C-reactive protein (CRP), D-dimer, procalcitonin, were collected on days 1, 3, and 7 hospitalizations. We followed the patient's progress daily from day 1 until discharge or in-hospital or 30-day mortality.

Primary and secondary outcome

The primary endpoint was time for clinical improvement within 30 days. Clinical improvement was defined as patient discharge or a reduction of 2 points on a 6-point disease severity scale. The scale described as follows: point 6-death; 5-hospitalization plus ECMO or invasive mechanical ventilation; 4-hospitalization plus non-invasive ventilation or high-flow supplemental oxygen; 3-hospitalization plus supplemental oxygen; 2-hospitalization with no supplemental oxygen; 1-hospital discharge. The secondary outcome of the current study was 1) the mortality, including analysis of time from inclusion to death or recovery, 2) duration of hospitalization, and 3) conversion of nasopharyngeal swab PCR results from positive at baseline to negative at follow-up assessed every 72 hours.

Sample size calculation

The trial was designed to enroll 42 patients (21 patients in the CPT group and 21 in the control group). We calculated that this sample size would provide 80% power to detect a proportional Hazard ratio of 1.8 for CPT as compared with placebo on the clinical ordinal scale at the 0.05 level of significance.

Statistical analysis

Pairwise comparisons were performed using Pearson's chi-squared test for categorical variables and the Kruskal-Wallis test or Mann-Whitney U test for continuous variables. In the primary analysis strategy, we used the Kaplan-Meier product-limit estimates to compare the time to reach the end-point (mortality) in the trial group. A Cox proportional hazards model was used to assess the overall 30-day clinical improvement, the Hazard ratio (HR) with 95% confidence interval (CI) were reported in the Cox model. For the secondary endpoint, we calculated the OR and 95% CI using logistic regression analysis. The Statistical Package for Social Science (IBM v. 21.0; SPSS Inc., Chicago, USA) was used. All tests were two-sided with p values <0.05 were considered significant. The method process is showed in Figure 1.

RESULT

Characteristics patients

Between July and December 2020, a total of 143 severe to critically ill COVID-19 patients were screened at Dr. Kariadi Hospital Semarang. A total of 113 eligible patients were recruited; 73 patients received CPT as a study group and 38 patients received local standard of care as the control group. One patient was excluded due to anaphylactic shock and was treated as per local protocol. The median age for the study population was 52 years (min-max, 21-79 y.o) and 57 years (28-75 y.o) for the control group and was not statistically different. Male patients were more often included in the study group (n=56, 77%) compared to the control group (n=19, 50%) p=0.006. There were no significant differences in comorbid characteristics between the study and the control group. For the severity of COVID-19, patients in the study group tended to have more severe conditions, p=0.003, and higher SOFA score p=0.08. For the concurrent treatments, there were a significant differences in patients receiving azithromycin (n=45 (62.5%) vs n=11 (28.9%) p=0.002), dexamethasone (n=64 (88.9%) vs n=18 (47.4%), p<0.001), colchicine (n=29 (40.3%) vs n=4 (10.5%), p=0.003) and anticoagulant dosages (p<0.001) in study versus control group respectively (Table 1).

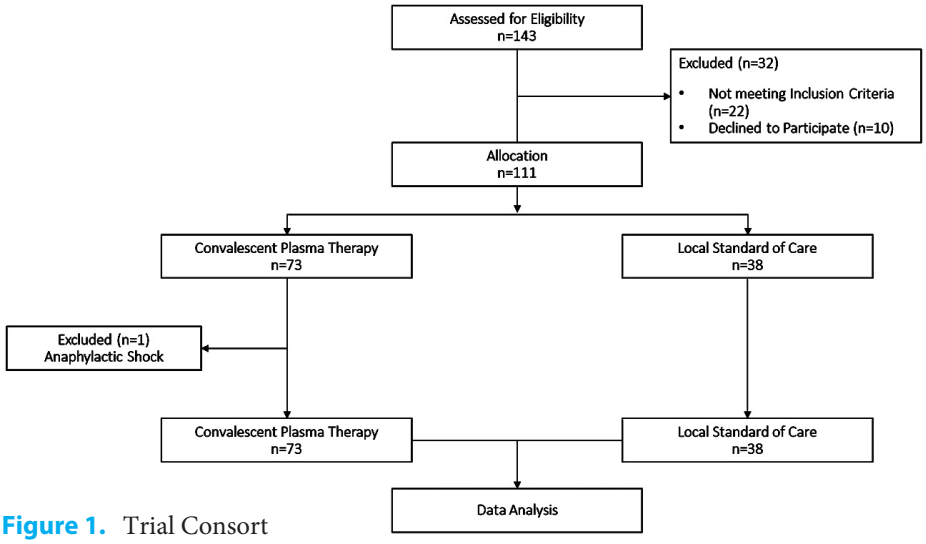

Figure 1. Trial Consort

Table 1. Baseline characteristics of the study group as compared with the control group

	Convalescent Plasma Therapy Group N = 72	Local Standard of Care Group N = 38	P Value
Age (median, min - max)	52 (21 – 79) years old	57 (28 – 75) Years old	0.127*
Sex			
Male (%)	56 (77%)	19 (50%)	0.006⁋
Female (%)	16 (23%)	19 (50%)	
Comorbidity			
Hypertension	33 (45.8%)	12 (31.6%)	
Diabetes Melitus	25 (34.7%)	17 (44.7%)	0.214⁋
CHF	5 (6.9%)	3 (7.9%)	0.411⁋
Obese	25 (34.7%)	6 (19.4%)	1.000†
Pregnancy	4 (5.6%)	1 (2.6%)	0.061⁋
Chronic liver disease	2 (2.8%)	0 (0%)	0.657†
Cancer	2 (2.8%)	2 (5.3%)	0.544†
Stroke	7 (9.7%)	3 (7.9%)	0.607†
No comorbid	9 (12.5%)	10 (26.3%)	1.000†
1 comorbid	31 (43.1%)	15 (39.5%)	
2 comorbidities	25 (34.7%)	10 (26.3%)	0.134□
3 comorbidities	7 (9.7%)	3 (7.9%)	
COVID-19 severity			
Severe (%)	45 (62.5%)	34 (89.5%)	0.003⁋
Critically ill (%)	27 (37.5%)	4 (10.5%)	
Clinical Ordinal Scale (median, min - max)	5 (4-5)	5 (4-5)	0.65⁋
SOFA score (median, min - max)	5 (2-11)	4 (2 – 7)	0.015*
P/F Ratio (median, min-max)	123 (35-381)	137 (72-290)	0.08*
D-dimer level (ng/mL)	2055 (300-20000)	1915 (270-20000)	0.486*
CRP level (mg/dL)	10 (0.05-40)	9.68 (1.96-39)	0.451*
Procalcitonin level (ng/mL)	0.2 (0.01-9.54)	0.2 (0.04-17.25)	0.332*
Therapy			
Azithromycin	45 (62.5%)	11 (28.9%)	0.002⁋
Levofloxacin	24 (33.3%)	13 (34.2%)	1.000⁋
Amikacin	10 (13.9%)	2 (5.3%)	0.212⁋
Meropenem	39 (54.2%)	14 (36.8%)	0.082⁋
Moxifloxacin	15 (20.8%)	5 (13.2%)	0.464⁋
Fluconazole	11 (15.3%)	1 (2.6%)	0.054⁋
Micafungin	4 (5.6%)	0 (0%)	0.296⁋
Favipiravir	42 (58.3%)	15 (39.5%)	0.093⁋
Remdesivir	12 (16.7%)	3 (7.9%)	0.326⁋
Lopinavir-Ritonavir	25 (34.7%)	9 (23.7%)	0.330⁋
Dexamethasone	64 (88.9%)	18 (47.4%)	<0.001⁋
Vitamin C 1000 mg	72 (100%)	38 (100%)	1.000⁋
Colchicine	29 (40.3%)	4 (10.5%)	0.003⁋
Anticoagulant			
No anticoagulant	0	5 (13.2%)	
Standard prophylactic dose	10 (13.9%)	6 (15.8%)	<0.001⁋
High prophylactic dose	19 (26.4%)	18 (47.4%)	
Therapeutic dose	43 (59.7%)	9 (23.7%)	
ICU admission	63 (87.5%)	38 (100%)	0.026†
Mechanical ventilator	38 (52.8%)	27 (71.1%)	0.099⁋

*Independent T-test
⁋Chi Square
†Fisher Exact test
□Mann Whitney test
CP, Convalescent plasma; P/F ratio, PaO2/FiO2 ratio; CRP, C-reactive protein

Table 2. Clinical outcomes among patients treated with convalescent plasma

	Convalescent plasma (n=72)	Local standard of care (n=38)	P Value
Not Survived	28 (38,9%)	31 (81,6%)	<0.001*
Survived	44 (61.1%)	7 (18.4%)	
PCR conversion to negative	45 (62.5%)	8 (21.1%)	<0.001*
Not converted	27 (37.5%)	30 (78.9%)	
Ordinal Scale			
	Ordinal scale baseline (median, min-max)	**Ordinal scale day-7 (median, min-max)**	**P Value**
Convalescent Plasma Therapy	5 (4-5)	3 (2-6)	<0.001⁋
Local standard of care	5(4-5)	5(3-6)	0.147⁋

*Chi-Square
⁋Wilcoxon Test

Convalescent plasma dose and time from diagnosis to treatment

The median volume of infused plasma was 400 ml (minimum-maximum, 200 cc – 1000 cc) with minimum titer anti-SARS-CoV-2 IgG antibody above 1:80. And all the patients in the study group had a median of 6 days (1 – 23 days) from diagnosis to infusion.

Primary outcome

On day 30, there was a significant difference in overall mortality rate between the study group (28 of 76 patients, 38.9%) and the control group (31 of 38 patients, 81.6%), p<0.001. With cox regression analysis, the hazard ratio for 30 days mortality rate was 3.5 (95% CI, 2.1-5.9); p<0.001 in the control group. The clinical ordinal scale was significantly improved on day-7 after infusion in the study group (p<0.001), while the result was in contrast for the control group (p=0.147) (Table 2). The 30 days survival rate curve is showed in Figure 2.

From the subgroup analysis based on CPT and mechanical ventilator support on enrollment status, We found that patients who received CPT without mechanical ventilator support had the best overall survival rate compared to the other group (HR 0.047; 95% CI, 0.01-0.09) followed by patients in the control group without mechanical ventilator support. Patients with mechanical ventilator support in both the intervention and control group showed the worst outcome respectively in terms of 30-days survival.

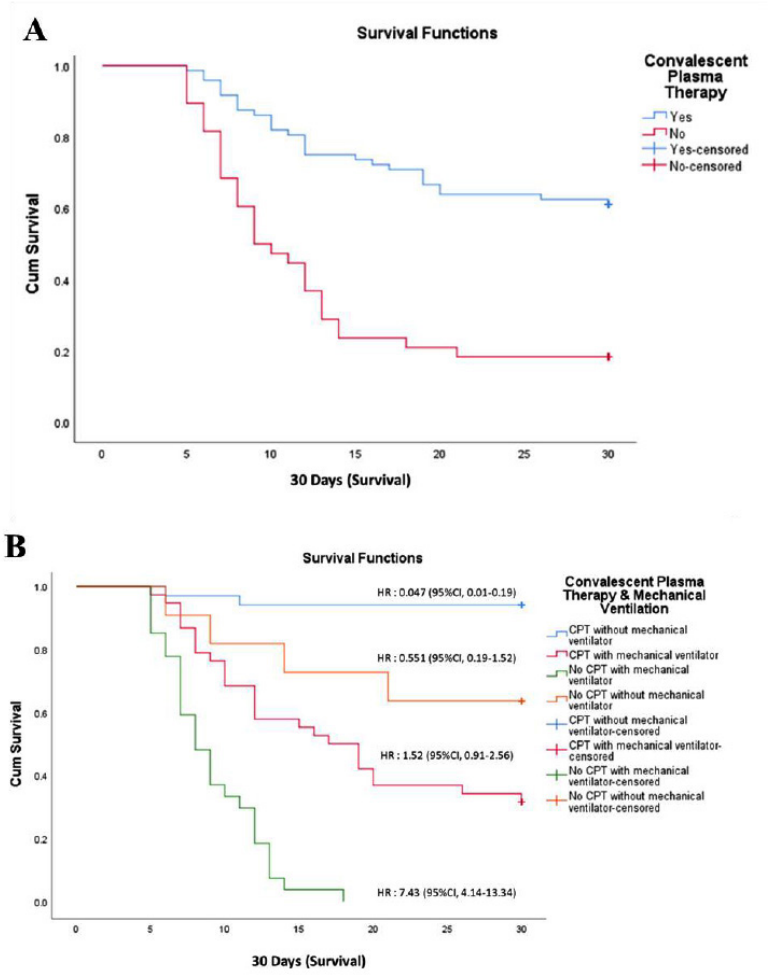

Figure 2. Kaplan meier 30 days survival rate curve. (A) Overall survival convalescent plasma therapy vs control; (B) Overall survival based on subgroup analysis

Secondary outcomes

We found that the conversion rate of polymerase-chain-reaction was significantly higher in patients in the study group (44 of 72 (62.5%) vs 8 of 38 (21.1%); p<0.001). Patients with mechanical ventilator support also tend to had a better improvement in the study group as shown with the extubated rate, from all 65 patients that were intubated and received mechanical ventilator, 12 patients had successfully extubated and survive, and all of the CPT (p=0.001) (Table 3).

Table 3. Correlation of baseline characteristics and the clinical outcomes

Variables	Status		p-Value
	Not survived (n=59)	Survived (n=51)	
Age	56 (25-77)	49 (21-79)	0.029*
Covid Severity			
Moderate	1 (1,7%)	1 (2%)	0.027⁋
Severe	36 (61%)	41 (80,4%)	
Critically ill	22 (37,3%)	9 (17,6%)	
SOFA Score	5 (2-11)	4 (2-8)	0.01⁋
P/F Ratio	110 (35-271)	151 (50-381)	0.013⁋
D-dimer level (ng/mL)	2780 (270-20.000)	1240 (300-20.000)	<0.001⁋
Procalcitonin level (ng/mL)	0.27 (0.02-17.25)	0.2 (0.01-3.7)	<0.01⁋
CRP level (mg/dL)	14 (3-40)	7 (0.05-33)	0.01⁋
Comorbid status			
No comorbid	12 (20.3%)	7 (13,7%)	0.32†
1 comorbid	25 (42,4%)	21 (41,2%)	
2 comorbidities	17 (28.8%)	18 (35,3%)	
3 comorbidities	5 (8,5%)	5 (9,8%)	
Therapeutic Variables			
CPT (n=72)	28 (38.9%)	44 (61.1%)	<0.001†
Azithromycin (n=56)	28 (50%)	28 (50%)	0.452†
Levofloxacin (n=37)	14 (37.8%)	23 (62.2%)	0.031†
Amikacin (n=12)	7 (58.3%)	5 (41.7%)	0.969†
Meropenem (n=53)	32 (60.4%)	21 (39.6%)	0.24†
Moxifloxacin (n=20)	10 (50%)	10 (50%)	0.91†
Fluconazole (n=12)	4 (33.3%)	8 (66.7%)	0.235†
Micafungin (n=4)	3 (75%)	1 (25%)	0.622†
Favipiravir (n=57)	27 (47.4%)	30 (52.6%)	0.24†
Remdesivir (n=15)	9 (60%)	6 (40%)	0.80†
Lopinavir-Ritonavir (n=34)	17 (50%)	17 (50%)	0.76†
Dexamethasone (n=82)	37 (45.1%)	45 (54.9%)	0.004†
Vitamin C 1000 mg (n=110)	59 (53.5%)	51 (46.4%)	1†
Colchicine (n=33)	12 (36.4%)	21 (63.6%)	0.03†
No anticoagulant Standard dose High dose Therapeutic dose	5 (8.5%) 9 (15.3%) 21 (35.6%) 24 (40.6%)	0 (0%) 7 (13.7%) 16 (31.4%) 28 (54.9%)	0.08†

*T-test
⁋Mann Whitney
†Chi Square
CP, Convalescent plasma; P/F ratio, PaO2/FiO2 ratio; CRP, C-reactive protein

From the bivariate analysis between baseline characteristics to survival outcome, there were significant differences in variables such as age, the severity of COVID-19, SOFA score, PaO2/FiO2 (P/F) ratio, D-dimer level, Procalcitonin level, CRP level, and patients with obese and cardiac heart failure. From the multivariate analysis of therapeutic variables, we found the adjusted OR for CPT was 0.089 (95% CI, 0.029-0.27; p<0.001) and it was the most significant variable for survival outcome as compared to other variables.

From Wilcoxon analysis, there were significant differences in SOFA score (median, min-max; 4, 2-10 and 2.5, 0-9; <0.001, before and after), P/F ratio (144, 35-296 and 223, 47-416; p<0.001), and CRP levels (7.35, 0.05-33 and 1.27, 0.06-3.6; p<0.001) before and 7 days after CPT infusion. While we found no significant differences for D-dimer and procalcitonin levels before CPT infusion and 7 days after (Figure 3).

Convalescent plasma dose and time from diagnosis to treatment

Median convalescent plasma volume infusion in the study group was 400

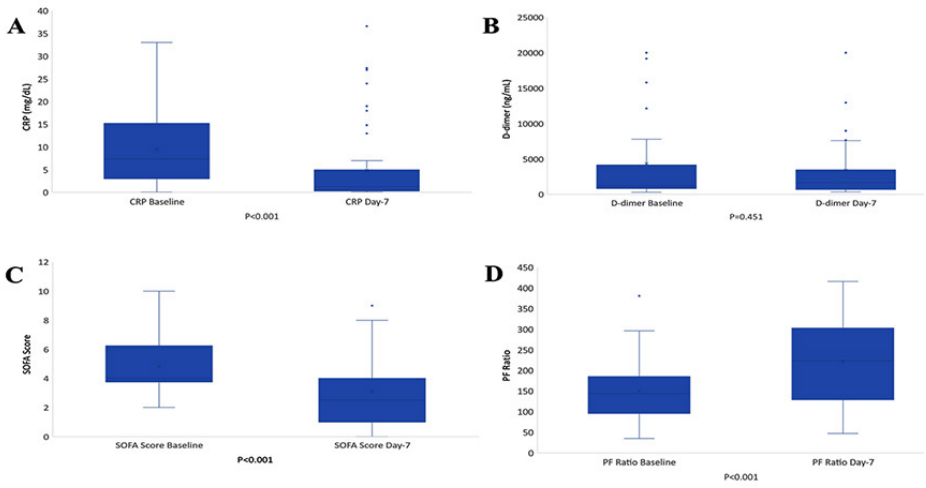

Figure 3. Comparison of biomarker levels before and 7 days after CPT. (A) CRP evaluation, (B) D-dimer evaluation, (C) SOFA score evaluation, (D). PF ratio evaluation.

cc, there was no significant difference in duration from diagnosis to plasma infusion (6 days, 1-23 days vs 6 days, 1-17 days; p=0.166) and survival rate. There was also no significant differences in the patient that received infusion before and after 7 days from diagnosis with survival rate (p=0.074).

DISCUSSION

CPT has been a promising yet debatable treatment in COVID-19 patients. Numerous earlier nonrandomized studies have shown a glimpse of hope in this pandemic era. In August 2020, The US Food and Drug Administration had approved CPT as emergency therapy in COVID-19 patients.[28] This approval lead many researchers to study its efficacies and safety in a large sample population.[26,29] From the Cochrane systematic review, there have been 57 trials that analyze the same issue as presented in this study and the results vary between trials.[30]

In this study, we found a significant difference in the 28-day mortality rate among patients with severe and critically ill COVID-19 infection treated with CPT compared to the control group. The study group had a much better overall mortality and PCR conversion rate. We also admit that patients without mechanical ventilator support and who received CPT had the best clinical outcome. These findings are in contrast to other randomized controlled trials which claimed that CPT had a similar outcome to the placebo result.[26,29,31] In our study, patients with more severe conditions, higher SOFA scores, P/F ratios, D-dimer, and CRP levels tended to receive CPT.

The local standard of care in our study consisted of antibiotics, antivirus, vitamin C, dexamethasone, and anticoagulant. But these therapeutic variables were not in the same proportion administered between the study and control groups. From the multivariate analysis, we noticed that CPT is the most prominent game-changer in the COVID-19 management according to our study. Patients in the CPT group received a median 400 ml plasma volume during their hospitalization, this amount of the infusion dose is similar to the PLACID trial.[29] In addition we found no significant differences between the total of diagnosis-to-infusion-time or the infusion volume to mortality rate. These findings differ from another study which concluded that CPT administration within 3 days of COVID-19 diagnosis had a better clinical outcome.[32] In our study group, CPT also significantly improved SOFA score, P/F ratio, and CRP level 7 days after administration. SOFA score describes the severity of multiple organ dysfunction and CRP levels are correlated with the inflammatory state,[33,34] we conclude that CPT could resolve the inflammation process thus helping to reduce the pulmonary distress and the COVID-19 severity.

From the subgroup analysis, we found that patients who received CPT and were not on mechanical ventilator support had the best overall survival rate compared to other groups. We conclude that CPT has a protective effect especially if it is given in severe patients within timepoint before mechanical ventilator support becomes mandatory. These data have changed our clinical decision-making to give CPT in the medical ward even before patients fall into clinical deterioration before ICU admission.

We only found one case of a serious adverse event of anaphylactic shock after 5 minutes of CPT. This complication was included as one of the transfusion-related complications. The patient was managed using our local protocol and survived. There were no reports of incidence of transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) following CPT, these findings were also very difficult to differentiate from the clinical symptoms of COVID-19 itself. There were no thrombotic events reported in our study, as has been reported could happen due to CPT.[29] Therefore we conclude that CPT administration is considered safe.

Limitations of this study are not randomized and the variables criteria were not equal between these 2 groups especially concerning severity status, although our data show that the study group was in more severe condition while the overall survival rate was better than the control group. The heterogeneity of these sample variables and the standardized local standards of care could have caused a bias between the results even though we tried to adjust it statistically. The strength of this study is the strictness of antibody plasma donor screening titer which had to be met for our donor inclusion criteria.

Although our findings are in contrast with most randomized controlled trial findings, we conclude that CPT may still be efficacious in our setting. The remarkably high number of coronavirus variant mutations worldwide which have also been found in Indonesia may also play a role in this difference in the outcome.[35,36]

CONCLUSION

We found that CPT still gives us hope to overcome COVID-19 infection in this pandemic era until specific drugs have been developed. The convalescent plasma administration significantly improved clinical outcomes and overall survival rates compared to those who received local standards of care. Furthermore, another randomized clinical trial with better sample selection will be required for better results. However, CPT remains a very compelling treatment for severe to critically ill COVID-19 patients at our center.

ACKNOWLEDGMENTS

The authors would like to thank the Blood Transfusion Unit personnel who conducted both the donor screening and plasmapheresis procedures. Special thanks to all the health care providers who have risked their lives caring for COVID-19 patients including giving convalescent plasma transfusion during the study. Also, we must consider the value and contribution of all volunteers, nonremunerated convalescent plasma donors who have willingly supported this research, for their time, their gift, and their solidarity, even after their traumatic period of being affected by the virus.

Data presented in this study is part of a multicentre study as a preliminary report. Any views or opinion that are expressed in this manuscript are those of the authors and represents the result from a single center; it may or may not represent the whole data interpretation which partly in data collection stage at this time.

DISCLOSURE

Ethical Statement

The Ethical Clearance was obtained from the Ministry of Health of Republic Indonesia (Ethical Clearance (EC) no. LB.02.01/2/KE.351/2020) and the Food and Drug Advisory Agency (approval no. R-RG.01.06.1.3.05.20.156). The protocol was approved by the institutional review board (EC no. 528/ECX/KEPK-RSDK/2020) and registered in the International Standard Randomised Controlled Trial (ISRCTN16842454).

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The researchers also confirm their independence from funders and sponsors.

Funding

This work was supported by research funding from the Indonesian Ministry of Research and Technology/National Foundation in Research and Innovation (Kemenristek/BRIN) (Grant number: PRJ-11/LPDP/2020).

Author contribution

All authors contributed equally in the preparation of the manuscript, seen, revised, and approved the final version herewith submitted for publication.

REFERENCES

1. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2. Emerg Infect Dis. 2020;26(7):1470–7.
2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020;91(1):157–60.
3. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. Eurosurveillance. 2020;25(4).
4. Muhyiddin, M., & Nugroho H. A Year of Covid-19: A Long Road to Recovery and Acceleration of Indonesia's Development. J Perenc Pembang Indones J Dev Plan. 2021;5(1)(1):1–19. Available from: https://doi.org/10.36574/jpp.v5i1.181
5. Ariawan I, Jusril H. COVID-19 in Indonesia: Where Are We? Acta Medica Indones Indones J Intern Med. 2020;52:193–4.
6. Setiati S, Azwar MK. COVID-19 and Indonesia. Acta Med Indones. 2020;52(1):84–9.
7. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.
8. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China. JAMA. 2020;323(13):1239.
9. Shang Y, Pan C, Yang X, Zhong M, Shang X, Wu Z, et al. Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan, China. Ann Intensive Care. 2020;10(1):73.
10. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Natl Institutes Heal. 2020;
11. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(8):693–704.
12. Soo YOY, Cheng Y, Wong R, Hui DS, Lee CK, Tsang KKS, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect. 2004;10(7):676–8.
13. Yeh K-M, Chiueh T-S, Siu LK, Lin J-C, Chan PKS, Peng M-Y, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother. 2005;56(5):919–22.
14. Wong SSY, Yuen K-Y. The management of coronavirus infections with particular reference to SARS. J Antimicrob Chemother. 2008;62(3):437–41.
15. Shankar-Hari M, Estcourt L, Harvala H, Roberts D, Menon DK. Convalescent plasma to treat critically ill patients with COVID-19: framing the need for randomised clinical trials. Crit Care. 2020;24(1):449.
16. Lagunas-Rangel FA, Chávez-Valencia V. What do we know about the antibody responses to SARS-CoV-2? Immunobiology. 2021;226(2):152054.
17. Acosta-Ampudia Y, Monsalve DM, Rojas M, Rodríguez Y, Gallo JE, Salazar-Uribe JC, et al. COVID-19 convalescent plasma composition and immunological effects in severe patients. J Autoimmun. 2021;118:102598.
18. 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;19(7):102554.
19. Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, et al. Safety Update. Mayo Clin Proc. 2020;95(9):1888–97.
20. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020;(29):1–8.
21. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci. 2020;117(17):9490–6.
22. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Crit Care. 2020;24(1):91.
23. Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, et al. Treatment of Coronavirus Disease 2019 (COVID-19) Patients with Convalescent Plasma. Am J Pathol. 2020;190(8):1680–90.
24. Xia X, Li K, Wu L, Wang Z, Zhu M, Huang B, et al. Improved clinical symptoms and mortality among patients with severe or critical COVID-19 after convalescent plasma transfusion. Blood. 2020;136(6):755–9.
25. 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 - J Am Med Assoc. 2020;324(5):460–70.

26. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto M V., Vallone MG, Vázquez C, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med. 2020;1–11.
27. 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;371:10–1.
28. Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. BMJ. 2020;368(August):m1256.
29. Pathak EB. Convalescent plasma is ineffective for covid-19. BMJ. 2020;371:4072.
30. Sj V, Piechotta V, Kl C, Doree C, Monsef I, Em W, et al. with COVID-19 : a rapid review (Review). 2020;
31. Gharbharan A, Jordans CCE, GeurtsvanKessel C, Hollander JG den, Karim F, Mollema FPN, et al. Convalescent Plasma for COVID-19. A randomized clinical trial. medRxiv. 2020;2020.07.01.20139857.
32. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. medRxiv Prepr Serv Heal Sci. 2020;1–31.
33. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020;50(4):332–4.
34. Liu S, Yao N, Qiu Y, He C. Predictive performance of SOFA and qSOFA for in-hospital mortality in severe novel coronavirus disease. Am J Emerg Med. 2020;38(10):2074–80.
35. ECDC. Rapid increase of a SARS-CoV-2 variant with multiple spike protein mutations observed in the United Kingdom. Eur Cent Dis Prev Control. 2020;1–13.
36. Nidom R V., Indrasari S, Normalina I, Kusala MKJ, Ansori ANM, Nidom CA. Investigation of the D614G mutation and antibody-dependent enhancement sequences in indonesian SARS-CoV-2 isolates and comparison to southeast Asian isolates. Syst Rev Pharm. 2020;11(8):203–13.