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Original Article

Efficacy and safety of convalescent plasma therapy in patients with moderate-to-severe COVID-19: A non-randomized comparative study with historical control in a referral hospital in Indonesia

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ABSTRACT

Background: Studies to confirm the efficacy and safety of convalescent plasma (CP) as an adjunctive treatment for COVID-19 are still required especially for the countries where standard treatments are unevenly distributed.

Methods: A non-randomized comparative study was done from June – September 2020 in Dr. Sardjito Hospital, Yogyakarta, Indonesia. Plasma with anti-SARS-CoV-2 specific IgG titer of >1:320 were used. Primary end points were clinical and laboratory parameters outcome including BGA, chest X-ray, CT value, CRP, procalcitonin, IL-6, D-Dimer and ALC examined on day 1, 2 and 7 post-transfusion.

Results: The experimental arm of this study consisted of 15 patients who received CP: 3 (20%) with moderate COVID-19 and 12 (80%) with severe COVID-19. There were 15 historical controls in this study. Ten recipients survived and 5 deceased (survival rate was 66.7%). There were higher rate of pneumonia resolution (OR 1.54, CI95% 0.33–7.23), ARDS resolution (OR 1.20, CI95% 0.25–5.84) and shorter median length of stay (20 vs 22 days, $p = 0.41$) among recipients compared to controls. Lower mortality rate was observed in recipients vs controls (33.3% vs 46.7% (OR 0.75, CI95% 0.17–3.33)). Median death onset was longer in recipient vs control (7th vs 1st day, $p = 0.13$). Survival analysis showed protective effect of CP (HR 0.69, CI 95% 0.21–2.27, $p = 0.545$). Higher CT value improvement ($p = 0.51$) and negative conversion rate (OR 1.20, CI95% 0.25–5.84) were observed in recipients compared to controls. Sub-analysis showed more number of comorbidities, higher procalcitonin and higher D-Dimer among CP recipients who did not survive ($p = 0.02$ and $p = 0.02$ respectively). Lower CRP and procalcitonin, and higher ALC were found in survivors compared to non-survivors ($p = 0.0437$; $p = 0.0049$; and $p = 0.0002$ respectively).

Conclusion: This study showed promising results for CP marked by improvements in clinical outcome, as well as significant reduction of inflammatory markers among recipients.

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Introduction

Coronavirus disease 2019 (COVID-19) has spread across more than 100 countries worldwide with a cumulative sum of over 209,000,000 cases globally as of August 2021 [1]. Indonesia had its first case of local transmission in early March 2020 and since

then, more than 3,930,000 cases has been reported [2]. Besides the steep rise in active cases during its recent second wave in July 2021, Indonesia recorded the second highest cumulative death toll among Asian Countries with 122,633 deaths and death rate of 3.1% per August 2021 [1,2].

Implementation of health protocols, subject testing and tracing, and vaccination program are substantial for COVID-19 control and prevention. Current guideline recommends the use of anti-SARS-CoV-2 Monoclonal Antibody such as Sotrovimab or Casirivimab plus Imdevimab in addition to supportive treatment for non-hospitalized COVID-19 patients, while corticosteroids, Remdesivir and Baricitinib or Tocilizumab are recommended for hospitalized patients depending on patient's condition [3]. However, access to some of these medication is still difficult in developing countries such as Indonesia, especially in rural areas. Besides that, the high communicability and increased virulence of COVID-19 warrant any other potential treatments as adjunctive to standard treatment, especially for patients with moderate, severe and critical COVID-19.

Convalescent plasma (CP) as a form of passive antibody immunotherapy had been intensively explored during the COVID-19 pandemic. This is due to its strong scientific basis supported by previous successes in pandemics such as the 1918 influenza, influenza A (H1N1), avian influenza A (H5N1), Ebola, and other viral infections [4–7]. Studies on the efficacy and safety of CP were initially limited to patients with severe to critical COVID-19 and reported promising results shown by improved clinical symptoms and laboratory parameters of patients, and was well tolerated [8–10]. More recent studies on CP efficacy and safety from both high and low income countries had also included patients in earlier course of infection [11–14]. Following these studies, an Emergency Use Authorization (EUA) was granted by FDA in March 2021 for the use of high titer COVID-19 CP as treatment for hospitalized patients with COVID-19 early in the course of disease and those hospitalized with impaired humoral immunity [15].

In this study, we implemented standard CP treatment protocol for moderate and severe COVID-19 patients. Substantial baseline data and detailed improvement of clinical symptoms and laboratory parameters were recorded with the aim of providing reference regarding the application of CP as adjunctive treatment, especially for countries facing similar challenges as Indonesia where the vast geographical expanse hinders uniform distribution of standard COVID-19 medication and on-going vaccination program that has not reached minimum population required for herd immunity.

Materials and methods

Study subjects

We conducted a non-randomized comparative study with historical control group in Dr. Sardjito Hospital, Yogyakarta, Indonesia. This study is a part of a bigger multicenter clinical trial supported by the National COVID-19 Consortium under Ministry of Research and Technology (Kemenristek/BRIN), Indonesia, involving 8 referral centers spread throughout Indonesia. Ethical clearance was obtained from the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito General Hospital with approval letter number: KE/FK/0604/EC/2020. This study was also supervised by the Indonesian Food and Drug Authority (Badan Pengawas Obat dan Makanan) with clinical trial approval number: R-RG.01.06.1.3.05.20.156. Informed consent was obtained from all recipients/ authorized family members and donors prior to recruitment.

A total of 15 moderate and severe COVID-19 patients were recruited. The inclusion criteria were: 1) age >18 years old, 2)

positive SARS-CoV-2 infection by Real Time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) test from nasopharyngeal swab, 3) moderate, severe or critical COVID-19 and 4) signed informed consent form. Exclusion criteria were: 1) incomplete clinical and therapeutical data, 2) previous severe adverse reaction to plasma or blood component, 3) critical COVID-19 patients with poor prognosis (SOFA > 11 has mortality rate as high as 53% [16]) and 4) refusal to participate in study. The historical control group in this study consisted of 15 patients who underwent standard COVID-19 treatment in the same hospital, whose data were compiled retrospectively from medical records. They were matched to each recipient based on their age and clinical severity.

Definition of COVID-19 severity used in this study are: 1) Moderate [17,18]: signs and symptoms of pneumonia, does not require oxygen supplementation and does not meet criteria of severe pneumonia; 2) Severe [19]: respiratory rate ≥ 30 x/ min, oxygen saturation (SpO₂) of $\leq 93\%$, PaO₂/FiO₂ ratio ≤ 300 mmHg and/or worsening chest X-ray of >50% within 24–48 h; 3) Critical [20]: severe pneumonia with rapid progression and increase in viral load despite standard COVID-19 therapy, Acute Respiratory Distress Syndrome (ARDS) with PaO₂/FiO₂ < 300, requires mechanical ventilation, septic shock and/ or organ dysfunction or failure.

Convalescent plasma donor

CP was obtained from donors who met selection criteria of 1) age 18–60 years old, 2) male or nulligravid women, 3) confirmed resolution of COVID-19 infection by negative SARS-CoV-2 PCR nasopharyngeal swabs, 4) symptom free for a minimum of 14 days prior to plasma donation, 5) negative SARS-CoV-2 PCR nasopharyngeal swab prior to plasma donation, 6) no comorbidities such as diabetes mellitus on insulin therapy, severe hypertension, chronic kidney disease or difficult vascular access, 7) no transfusion related infections (Hepatitis B, Hepatitis C, HIV and Syphilis), 8) compatible blood group and rhesus with recipient candidate, 9) anti-SARS-CoV-2 specific IgG titer of >1:320 and 10) gave informed consent. Exclusion criteria for donor were: 1) refusal to participate, 2) incomplete clinical data during active COVID-19 infection, 3) incompatible blood with candidate recipient, 4) hemoglobin <12.5 g/dL, 5) pregnant, 6) hypotension, 7) history of cancer and history of injection drug abuse.

Statistical analysis

Continuous variables were expressed in terms of median and range, while categorical variables were summarized as total counts and percentages. There was no imputation procedure conducted for any missing data. Mann–Whitney test was performed for comparison of the continuous variables, while Chi-square test or Fisher's exact test was used to compare any ordinal and categorical variables, according to the assumptions met. Linear regression along with related plot was represented to demonstrate serial trend of any numerical variables. Two-way ANOVA was performed to analyze any trend difference of numerical variables between patients who died and survived, termed as 'survival factors'.

Mortality analysis including resolution of COVID-19 was evaluated within 28 days of admission. Survival analysis was delineated using Kaplan Meier curve and Hazard Ratio (HR) of the intervention calculated using Cox-regression. The analysis was considered statistically significant if $P < 0.05$ with 95% confidence interval (CI). All analysis was performed using R software version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism version 8.4.3 (San Diego, California).

Procedure of plasma donation and transfusion

A list of potential donors was obtained from hospitals in Yogyakarta. These potential donors were contacted and screened for donor eligibility after providing informed consent. Two 5 ml blood samples were obtained from each potential donor for transfusion related infection examination, anti-SARS-CoV-2 specific IgG titer measurement and future cross-matching with recipients.

COVID-19 patients admitted to Dr. Sardjito Hospital from June 2020 – September 2020 who met inclusion criteria as recipients were recruited after providing written informed consent. Laboratory examination was done prior to transfusion to establish baseline parameters. Each patient received 2 units of 200 ml CP and was monitored during transfusion until 20 min post-transfusion for any adverse effects. Clinical and laboratory parameters were evaluated on days 1, 2 and 7 post-transfusion. These include clinical status, inflammatory markers such as CRP, Procalcitonin, IL-6 and D-dimer, blood gas analysis (BGA) and chest X-ray. In addition to CP treatment, all patients received standard COVID-19 treatment of antiviral, anticoagulant, antibiotic and anti-inflammation.

Results

A total of 30 subjects (15 recipients and 15 historical controls) were enrolled in this study. Initially, there were 19 potential recipients, however only 15 included as 2 patients died, 1 patient showed clinical improvement prior to transfusion and 1 patient had no compatible donor. Each historical control recruited was matched based on age and clinical severity with their respective recipient. The median duration of CP collection from donors since recovery was 58 days (21–158 days).

Recipient

Characteristics of the 15 recipients are shown in Table 1. Median age was 50 years old (range: 28–88 years old) with 13 (86.5%) male and 2 (13.5%) female. Upon admission, 12 patients (80%) had severe infection, 3 (20%) had moderate infection and none of the patients were critically ill. Most of the recipients (12 recipients; 80%) had at least one comorbid disease; 5 recipients (33%) had 1 comorbidity, 3 recipients (20%) had 3 comorbidities, 2 recipients (13%) had 2 comorbidities and 2 recipients (13%) had 4 comorbidities. Only 3 (20%) of the recipients had no comorbidity.

All recipients were given standard treatment of antiviral, anticoagulant, anti-inflammatory medication and antibiotics. Median day of CP transfusion was on day 3 (range: day 1–20) since admission.

The estimated median length of stay (Fig. 1a) among recipients was 20 days vs 22 days among controls without any statistical difference between two groups ($p = 0.41$). No statistical difference was also observed for pneumonia resolution and ARDS improvement (Fig. 1b and c), where 8 recipients (64% of 14 patients) had pneumonia improvement vs 7 controls (54% of 13 patients) ($p = 0.70$) and 7 recipients (58% of 12 patients) vs 7 controls (54% of 13 patients) had ARDS improvement. Five CP recipients (33.3%) were intubated and put on mechanical ventilation support with median onset of intubation on day 7 since admission (range: day 6–10). Eventually, all five of these recipients died.

The clinical status improvement observed in CP recipients who survived in this trial was accordant with the improvement of serial laboratory parameters recorded. There were significant improvements of CRP ($p = 0.0041$) and absolute lymphocyte count (ALC) ($p = 0.0241$) after CP transfusion, while other laboratory parameters including CT value, IL-6, procalcitonin and BGA showed improving trends, although these trends were not statistically significant (Fig. 2).

No adverse effect related to CP transfusion was observed in this study.

Convalescent plasma recipient vs historical control

Patients who were characteristically and clinically similar to recipients were recruited as historical controls of our study (Table 2). Nine (60%) controls survived while 6 (40%) died. There was lower mortality rate among recipients compared to control (33.3% vs 40.0%; OR 0.75, CI95% 0.17–3.33) (Fig. 3a). Median death onset among CP recipient is longer than that in control group (7th day vs 1st day, $p = 0.13$) (Fig. 3b). Although not significant, survival analysis between recipients and historical controls showed protective effect of CP therapy (HR 0.69, CI 95% 0.21–2.27, $p = 0.545$) (not shown in figure).

The waterfall plot (Fig. 4a) showed overall difference in CT value during admission and discharge (delta CT value) of surviving recipients and historical controls. Delta CT value in the positive arm represented improvement and vice versa. More CP recipients had improved CT value upon discharge as illustrated by the violin plot available in the same figure ($p = 0.51$). Negative conversion rate was found to be slightly higher among CP recipients than historical controls (OR1.20, CI95% 0.25–5.84) (Fig. 4b).

Surviving vs non-surviving CP recipients

The survival rate of recipients in our study is 66.7% with median discharge day on day 10 since admission (range: 15–46 day). Median death onset of non-surviving recipients was on day 7 since admission (range: 7–12). Although not significant, we observed higher number of comorbidities among non-survivors (Table 3). Among the 5 non-survivors, 4 had diabetes and hypertension, while 3 were elderly (Table 1). Significantly higher levels of inflammatory markers i.e. procalcitonin (0.60 vs 0.05, $p = 0.02$) and D-dimer (1483 vs 431.5, $p = 0.02$) were observed among non-survivors (Table 3).

Serial evaluation of laboratory parameters of surviving recipients compared to non-surviving recipients also showed significantly lower CRP ($p = 0.0049$) and procalcitonin ($p = 0.0002$). Significantly higher ALC was also observed among survivors ($p = 0.0437$) (Fig. 2).

Discussion

Our study on moderate and severe COVID-19 patients has recruited mostly male subjects. Similar gender distribution was reported in prior multicenter trials conducted in Kuwait and Netherland [11,21]. A meta-analysis conducted on 7 researches with a total of 1576 patients in China also described higher portion of male than female (890:696) [22]. This suggests that men may be more susceptible to severe COVID-19 [23,24], possibly related to women having stronger innate and adaptive immune responses [22].

The survival rate of recipients recruited in our study was 67%. This is similar to findings conducted on severe COVID-19 patients in Kuwait [11] and New York [13] with survival rate of 69.6% and 71.8% respectively. Compared to historical control group, we observed lower mortality rate. However, similar to previous studies, this result is not statistically significant [21,25–27]. On contrary, Liu et al. had reported significant improvement in survival of patients with severe COVID-19 who received CP in their propensity score-matched control study involving 39 subjects (HR 0.31; 95% CI, 0.12–0.82; chi-squared test, $P = 0.018$) [13]. Nevertheless, the study also reported a higher portion of anticoagulant treatment among recipients compared to matched control group.

Death onset in CP recipients was found to be longer than controls. The presence of an outlier (a patient died on day 13)

Table 1
Characteristics of convalescent plasma recipients.

	Patient														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Initials	MAH	PUD	WAH	PRA	BAK	AGU	KUS	AZZ	NUR	TOT	WIR	ASM	KIA	DAR	BAG
Sex	Male	Male	Male	Male	Male	Male	Female	Male	Male	Male	Male	Male	Male	Female	Male
Age, years	42	60	38	47	60	47	45	28	58	88	58	42	72	67	50
Blood group	O	AB	O	O	B	B	B	O	O	B	B	B	O	O	B
Comorbid number	0	1	0	0	3	1	1	1	4	4	1	2	3	3	2
Comorbidity	None	Elderly	None	None	Elderly, DM, HTN	DM	Obesity	Obesity	DM, HTN, Asthma, Obesity	Elderly, DM, HTN, Stroke	CAD	DM, HTN	Elderly, CHF, HTN	Elderly, DM, HTN	DM, HTN
Body weight, kg	60	55	70	70	65	65	80	100	101	60	74	60	65	63	60
Admission date	16/07/2020	14/07/2020	23/07/2020	23/07/2020	28/07/2020	01/08/2020	05/08/2020	13/08/2020	16/08/2020	19/08/2020	06/09/2020	30/08/2020	25/08/2020	10/09/2020	16/09/2020
Severity	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Moderate	Moderate	Severe	Severe	Moderate	Severe
Tranfusion onset, day	2	6	2	5	2	1	2	4	6	2	3	12	20	4	3
Observed major tranfusion Rx	None	None	None	None	None	None	None	None	None	None	None	None	None	None	None
Complication prior plasma tranfusion	ARDS	ARDS, AKI	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	None	ARDS, Cerebellar Syndrome	ARDS	None	ARDS
Antibiotics	Meropenem, Levofloxacin	Meropenem, Levofloxacin	Meropenem, Levofloxacin	Meropenem, Azithromycin	Meropenem, Levofloxacin	Meropenem, Levofloxacin	Meropenem	Meropenem, Levofloxacin	Meropenem, Levofloxacin	Meropenem, Gentamicin, Cefepime	Azithromycin, Levofloxacin	Ceftriaxone, Azithromycin, Meropenem	Meropenem, Cefoperazone	Azithromycin, Levofloxacin	Meropenem, Levofloxacin
Tocilizumab	None	None	None	None	Yes	Yes	Yes	Yes	Yes	None	None	None	None	None	Yes
Anticoagulant	Enoxaparin	UFH	Enoxaparin	UFH	UFH	Enoxaparin	Enoxaparin	Enoxaparin	Enoxaparin	Enoxaparin	Enoxaparin	Enoxaparin	Enoxaparin	Enoxaparin	Enoxaparin
Antiviral	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Favipiravir	Remdesivir	Remdesivir	Remdesivir	Remdesivir	Remdesivir	Favipiravir	Favipiravir	Remdesivir
Hydroxychloroquine	None	None	None	None	Yes	Yes	Yes	None	None	None	None	Yes	Yes	None	None
Steroid	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	Dexamethasone	None	Dexamethasone
Outcome	Discharged	Dead	Discharged	Discharged	Dead	Discharged	Discharged	Discharged	Dead	Dead	Discharged	Discharged	Discharged	Discharged	Dead
Length of stay, day	22		16	27		18	18	29			15	46	40	15	
Dead, day		7			10				7	12					7

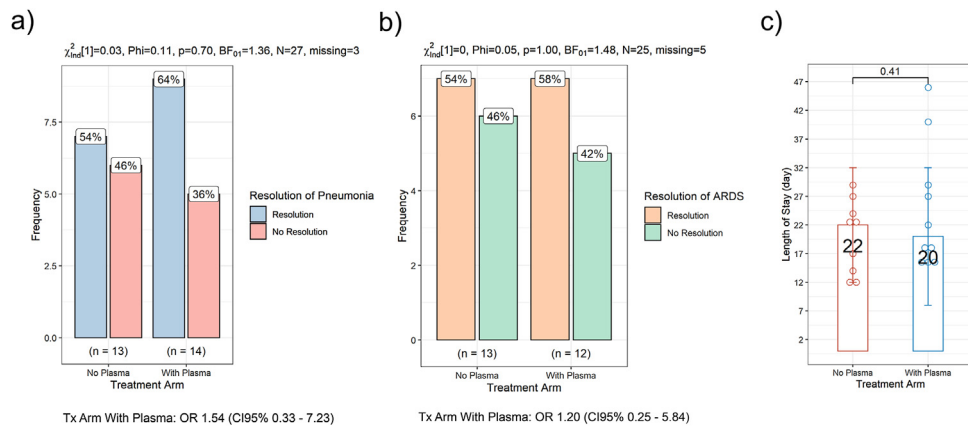


Fig. 1. Comparison of clinical outcomes between convalescent plasma recipients and historical control: a) resolution of pneumonia, b) resolution of ARDS, c) median length of stay.

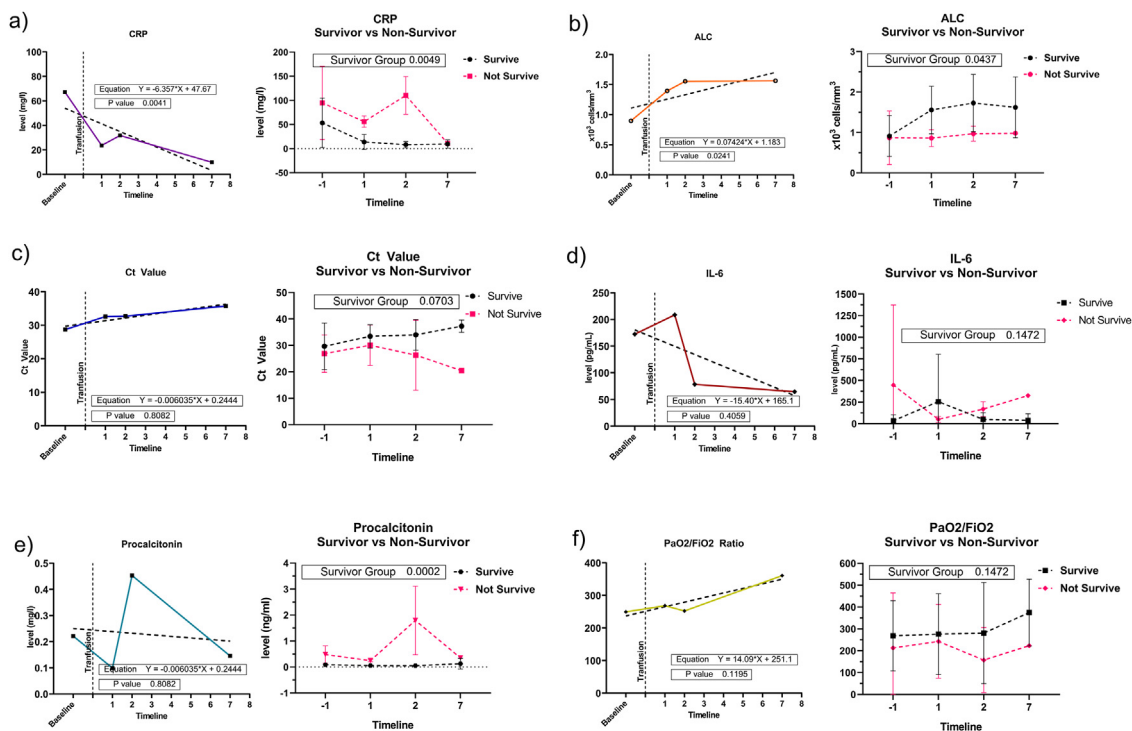


Fig. 2. Serial evaluation of laboratory parameters among convalescent plasma recipients (left: overall; right: survivor vs non-survivor): a) C-reactive protein (CRP), b) absolute lymphocyte count (ALC), c) Ct value, d) interleukin-6 (IL-6), e) procalcitonin, f) PaO₂/FiO₂ ratio.

in control group may contribute to the overall non-significant result. Shenoy et al. observed drastic increase in mortality rate among CP recipients from 7-day adjusted mortality rate of 9.13%, 14-day adjusted mortality rate of 14.83% and finally to 28-day mortality rate of 25.48%. This is in contrast to the relatively stagnant mortality rate of control group since early course of study with 19.77%–23.57% and finally 27.00%. Generally, the study observed significantly lower 7 day and 14 day mortality rates but not 28 day mortality rate among recipients when compared to control [28]. CP may contribute to lengthening time till death among COVID-19 patients. This may provide attending physicians more time to possibly improve patients' outcomes through additional/adjunctive treatment and intervention that may still be ongoing and continuously developed. This observation may also explain the increased length of stay among CP recipients compared to their controls as reported in previous studies [13,28,29].

Although not statistically significant, we observed tendency towards clinical improvement in terms of pneumonia resolution, ARDS resolution and length of stay among CP recipients compared to control. These observations are comparable to results from previous studies [10,21,30].

There was higher negative conversion rate of SARS-CoV-2 viral PCR result among CP recipients compared to historical controls. However, this result is not statistically significant. Unlike our study, prior studies showed significantly higher negative conversion rate of SARS-CoV-2 viral PCR results among CP recipients compared to controls [10,24,25]. This difference may be attributed to the small sample size in our study.

Significant CRP reduction among CP recipients in our study may be related to the presence of anti-inflammatory cytokines and antibodies in CP, which could modulate immune response and prevent innate immune cells (such as macrophages) from migrating to the lungs [31]. In addition to that, downward trend for other inflam-

Table 2
Comparison of baseline characteristics between plasma convalescent recipients and historical control.

n	Convalescent plasma 15	Historical control 15	p
Male (%)	13 (86.7)	13 (86.7)	1
Age (median [range])	50 [28–88]	53 [33–89]	0.618
Severe COVID-19 (%)	12 (80.0)	13 (86.7)	1
Blood group (%)			0.046
O	7 (46.7)	2 (15.4)	
B	7 (46.7)	5 (38.5)	
AB	1 (6.7)	1 (7.7)	
A	0 (0.0)	5 (38.5)	
Comorbid number (%)			0.579
0	4 (26.7)	5 (33.3)	
1	4 (26.7)	3 (20.0)	
2	2 (13.3)	5 (33.3)	
3	3 (20.0)	1 (6.7)	
4	2 (13.3)	1 (6.7)	
<i>Baseline parameter</i>			
Temperature (median [range])	36.70 [36–37]	36.70 [36–37.50]	0.15
Ct Value (median [range])	30.78 [7.78–38.39]	33.27 [19.10–38.02]	0.322
SOFA (median [range])	3 [0–6]	4 [0–5]	0.03
PaO ₂ /FiO ₂ ratio (median [range])	147.60 [62.10–660.50]	114.40 [39.20–464]	0.13
WBC (median [range])	9.43 [5.27–29.10]	10.27 [5.30–35.26]	0.756
ANC (median [range])	7.31 [0.87–26.77]	7.38 [3.90–29.97]	0.59
ALC (median [range])	0.71 [0.29–2.01]	1.11 [0.63–4.51]	0.033
AMC (median [range])	0.44 [0.11–1.04]	0.63 [0.20–2.44]	0.097
Stab (median [range])	0.11 [0.01–0.87]	0.06 [0–1.50]	0.25
CRP (median [range])	69 [5–150]	80 [13–150]	0.253
Procalcitonin (median [range])	0.06 [0.05–0.90]	0.21 [0.05–28.96]	0.118
D-Dimer (median [range])	617 [216–5670]	613.50 [200–2044]	0.77

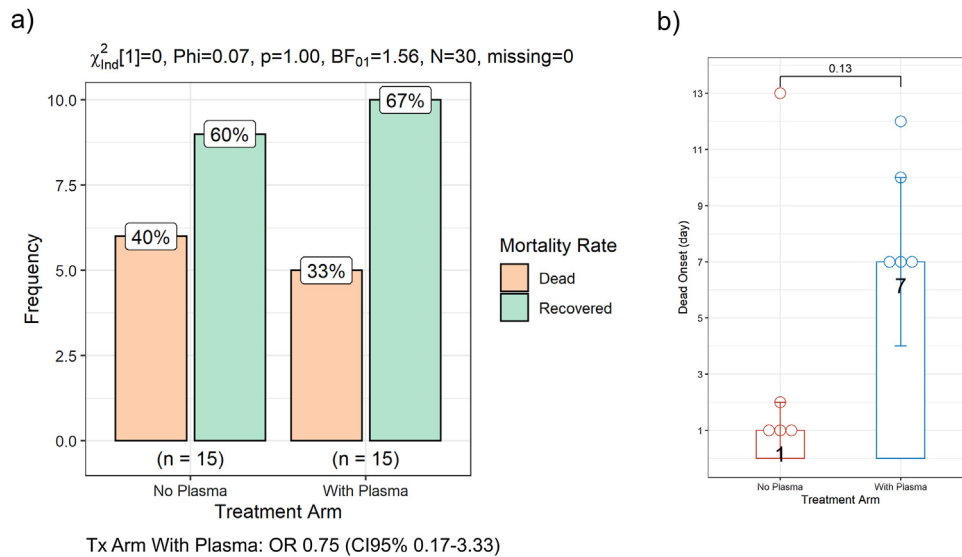


Fig. 3. Comparison between convalescent plasma recipients and historical control; a) mortality rate b) median dead onset.

matory markers such as procalcitonin and IL-6 was also observed. Similar to our study, a prospective multicenter interventional study conducted in Kuwait reported significant reduction in CRP among CP recipients ($p = 0.001$) [11]. There was a significant increase in ALC among recipient post CP transfusion in our study. Same result was reported by Alsharidah et al. that reported significant increase of ALC on day 7 post admission ($\beta = 0.46$; 95% CI 0.15–0.78) [11].

Sub-analysis comparing surviving and non-surviving CP recipients was done to investigate the interplay of various variables, which may relate to results observed in this study. This will aid more objective interpretation of data for consideration of CP as adjuvant treatment for moderate to severe COVID-19 patients.

Through this sub-analysis, we observed more number of comorbidities among non-surviving recipients, although this result is not statistically significant. Liu et al. also described strong link between comorbidity and COVID-19 severity [23]. However, similar to our findings, comorbidities were not significantly associated with mortality rate. Besides that, previous systematic review and meta analysis showed that older patients and those with more comorbidities had more severe COVID-19 infection [22,32]. The same review described hypertension and diabetes as the most common comorbidities among severely ill patients, which was similar to our study's observation [32]. It is postulated that chronic diseases induce pro-inflammatory state that reduce immune response especially macrophage and lymphocyte functions [22].

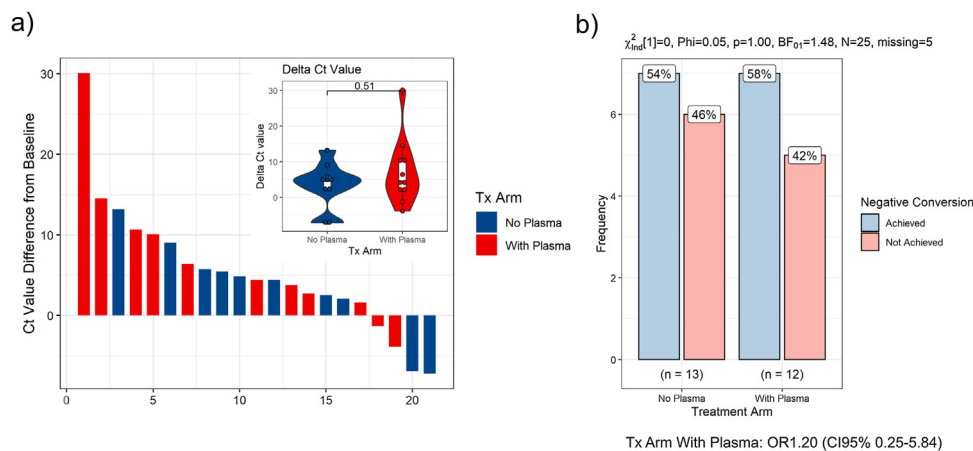


Fig. 4. Analysis of viral load among convalescent plasma recipients and historical control; a) delta CT value, b) negative conversion rate.

Table 3
Comparison of surviving and non-surviving convalescent plasma recipients.

n	Survivor 10	Non-survivor 5	p
Male (%)	8 (80.0)	5 (100.0)	0.524
Age (median [range]) – years old	46 [28–72]	60 [50–88]	0.057
Blood group (%)			0.364
O	6 (60.0)	1 (20.0)	
B	4 (40.0)	3 (60.0)	
AB	0 (0.0)	1 (20.0)	
Comorbid number (%)			0.248
0	3 (30.0)	0 (0.0)	
1	4 (40.0)	1 (20.0)	
2	1 (10.0)	1 (20.0)	
3	2 (20.0)	1 (20.0)	
4	0 (0.0)	2 (40.0)	
Body weight (median [range]), kg	67.50 [60–100]	60 [55–101]	0.264
Severe COVID-19 (%)	8 (80.0)	4 (80.0)	1
Tranfusion onset (median [range])	3.50 [1–20]	3 [2–6]	0.901
Baseline parameter			
Temperature (median [range])	36.5 [36–37]	36.7 [36–36.9]	0.496
Ct value (median [range])	30.88 [7.78–38.39]	25.91 [17.69–35.75]	0.391
SOFA (median [range])	2 [0–4]	3 [0–6]	0.187
PaO ₂ /FiO ₂ ratio (median [range])	265.90 [92.20–553.30]	101.70 [62.10–660.5]	0.221
WBC (median [range])	9.21 [5.27–12.30]	11.41 [6.11–29.10]	0.244
ANC (median [range])	6.08 [0.87–11.40]	10.32 [4.90–26.77]	0.086
ALC (median [range])	0.79 [0.39–1.78]	0.71 [0.29–2.01]	0.759
NLR (median [range])	9.45 [1–18.50]	16.50 [2.60–92.30]	0.27
LMR (median [range])	2 [0.80–4.5]	1.40 [1–1.90]	0.086
IL-6 (median [IQR])	8.30 [1.50–219.80]	25.47 [10.73–2104]	0.176
CRP (median [range])	39 [5–122]	150 [5–150]	0.154
Procalcitonin (median [range])	0.05 [0.05–0.21]	0.60 [0.05–0.90]	0.02
D-Dimer (median [range])	431.5 [216–1730]	1483 [617–5670]	0.02
Creatinin (median [range])	0.95 [0.49–1.58]	0.89 [0.72–2.76]	0.806
ALT/SGPT (median [range])	51 [22–406]	32 [19–309]	0.386
AST/SGOT (median [range])	50 [19–295]	30 [23–338]	0.593

We observed significantly lower inflammatory markers, namely CRP and procalcitonin among surviving CP recipients compared to non-survivors. This result is comparable to a prior clinical trial conducted in Iran that reported significant linear correlation of APACHE II score to CRP among CP recipients ($r = 0.456$; $p = 0.025$) [33]. The higher inflammatory markers observed in recipients with poorer prognosis may relate to pulmonary fibrosis and lung capacity reduction as the result of immune system over-activation known as cytokine storm [31].

Concerns were raised regarding safety of CP due to potential transfusion-related reactions (including transfusion-related acute lung injury and transfusion-associated circulatory overload) and antibody mediated pro-inflammatory response known as

antibody-dependent enhancement (ADE) caused by prior infection of different viral serotype in donors [29,34]. However, we observed no adverse events related to CP therapy. This result is accordant with previous studies which concluded that CP is a relatively safe adjuvant treatment among COVID-19 patients with very low incidence of adverse event [10,13,21,24,26].

Study limitation

Our study was conducted during the early phase of COVID-19 infection in Indonesia, when there were limited data on the optimal timing of CP administration. Hence, the time of CP administration among our recipients varied and might have contributed to the non-

significant reduction in mortality rate. Recent studies reported that CP may be more beneficial when administered earlier in the course of COVID-19 infection [35,36]. These studies found that patients who received CP within 3 days after diagnosis or 12.6 days after onset of symptoms had lower mortality rate. This may attribute to the presence of anti-SARS-CoV-2 antibodies in recipients prior to transfusion when CP is administered later in course of disease [26].

We acknowledged that there may be other confounding variables to be considered in this study. Our supplementary analysis using ROC curve showed that SOFA score may significantly predict the survival of COVID-19 patients (AUC 0.739; CI95% 0.549–0.930) (Supplementary Fig. S1). This is similar to result reported by a previous study with ROC curve showing AUC 0.890; CI95% 0.826–0.955 [37]. The historical control group in our study had higher baseline SOFA score compared to CP recipients but further analysis showed no statistically significant difference in mortality rate among recipients and controls with SOFA score >3 (HR 6.80; CI95% 0.87–53.29). Nevertheless, as the sample size in this study is limited, further investigation may be required to confirm the relationship of SOFA score and outcome of moderate/severe COVID-19 patients regardless of CP administration.

Recently, Tocilizumab treatment was found to have survival benefit for COVID-19 patients [38]. Our supplementary analysis showed that co-treatment with anti-IL6 may reduce systemic inflammation (two-way ANOVA $p = 0.002$). Significant negative correlation also denoted improvement of CRP among CP recipient co-treated with Tocilizumab ($r = -0.54$; $p = 0.0074$) (Supplementary Fig. S2). Since some of the recipients in our study received Tocilizumab, the protective effect of CP adjunctive treatment observed in this study may be partly underestimated as anti-IL6 can suppress devastating systemic inflammation that occur during severe COVID-19 progression. However, this assumption needs further confirmation by referring to any study that specifically aims to delineate the efficacy of anti-IL6 with or without CP adjunctive treatment, which is almost out of the scope of this study.

Randomization was not done in our study due to the limited availability of CP donors at the time of study. However, we did add the historical control arm as comparison. In addition to that, a bigger sample size may be required to further confirm the trend of improvement in clinical and laboratory outcomes in our study.

Conclusion

Our study demonstrated significant reduction of inflammatory markers among CP recipients. There was no significant effect on the mortality rate. Possible lengthening of time to death was observed, which may be a quite valuable “buying time” for physicians in improving outcome of CP recipients with other additional treatment strategies to come. More number of comorbidities may indicate worse prognosis among CP recipients. There was trend towards improvement of clinical and laboratory parameters among CP recipients compared to control, however, this needs further investigation with uniformly earlier administration of CP and bigger sample size.

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Conflict of interest

All authors have nothing to disclose.

Authors' contributions

JK, MS, TT, JAT initiated and designed the study.

IT, TT, SA, FA, MU, AB performed sample collection.

IT, CF, JK, MS managed the patients.

TT, FA, US performed plasma collection – administration and laboratory work.

SA, AF, MU, YS did data management, analysis and literature searching.

MS, SA, YS, JK worked on the preparation of the manuscript.

JK, MS, TT and JAT participated in data management, analysis, interpretation of results, overall supervision, and manuscript writing.

All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jiph.2021.10.028>.

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