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Convalescent Plasma Therapy in Severe-Critical COVID-19 Patients at North Kalimantan Regional Public Hospital: Survival Analysis

Terapia de plasma de convalecientes en pacientes graves con COVID-19 en el hospital público regional del norte de Kalimantan: análisis de supervivencia

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SUMMARY

Background: *Convalescent plasma therapy (CPT) is one of the methods used in treatment in COVID-19, but the administration of CPT to COVID-19 patients is still controversial. This study aims to assess the difference in survival between CPT administration in severe-critical COVID-19 patients and standard therapy.* **Methods:** *This research was a retrospective cohort observational research. Survival analysis was carried out on the factor and outcome variables by estimating the median survival time and Kaplan-Meier survival curve.* **Results:** *There were 101 patients with an average age of 58.77±11.45 years, and 65 patients (64.36 %) were men. The median length of stay was 12 days (Q1; Q3 9; 21). A total of 42 patients received standard therapy plus CPT, while 59 patients received standard therapy only. The predictor of length of stay had a median difference of 9 days which was statistically significant (p <0.001), as was the mortality outcome with a relative risk in the CPT group of 0.457 (95 % CI 0.281; 0.741). Survival for the two groups was significantly different (p <0.01), with a hazard ratio for the CPT group of 0.276 (95 % CI 0.146; 0.519).* **Conclusion:** *There were a potential therapeutic effect and a low risk in the severe-critical COVID-19 patient's treatment.*

Keywords: *COVID-19, convalescent plasma therapy, survival*

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RESUMEN

Antecedentes: *La terapia con plasma de convalecientes (TPC) es uno de los métodos utilizados en el tratamiento de COVID-19, pero la administración de TPC a pacientes con COVID-19 aún es controvertida. Este estudio tiene como objetivo evaluar la diferencia en la supervivencia entre la administración de TPC en pacientes con COVID-19 grave-crítico y la terapia estándar.* **Métodos:** *Esta investigación fue una investigación observacional de cohorte retrospectiva. El análisis de supervivencia se llevó a cabo sobre las variables de factor y resultado estimando la mediana del tiempo de supervivencia y la curva de supervivencia de Kaplan-Meier.* **Resultados:** *Hubo 101 pacientes con una edad promedio de 58,77 ± 11,45 años, de los cuales 65 pacientes (64,36 %) eran hombres. La mediana de la estancia hospitalaria fue de 12 días (Q1; Q3 9; 21). Un total de 42 pacientes recibieron terapia estándar más TPC, mientras que 59 pacientes recibieron terapia estándar solamente. El predictor de la duración de la estancia hospitalaria tuvo una diferencia media de 9 días que fue estadísticamente significativa (p <0,001), al igual que el resultado de mortalidad con un riesgo relativo en el grupo TPC de 0,457 (IC del 95 %: 0,281; 0,741). La supervivencia para los dos grupos fue significativamente diferente (p <0,01), con una razón de riesgo para el grupo TPC de 0,276 (IC del 95 %: 0,146; 0,519).* **Conclusión:** *Hubo un efecto terapéutico potencial y un riesgo bajo en el tratamiento del paciente con COVID-19 grave-crítico.*

Palabras clave: *COVID-19, terapia con plasma de convalecientes, supervivencia*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2, a virus that shares the same shape and behavior as the 2003 SARS-CoV virus. Coronavirus is a member of the Coronaviridae family of viruses, with a single-stranded, positive-sense RNA genome measuring 26-32 kb in length, the largest genome for an RNA virus. The term "coronavirus" originated in reference to the virus's appearance on the viral membrane in the form of crown-like spurs, or corona in Latin (1). On January 30, 2020, only a few weeks after the cases were discovered, the World Health Organization declared COVID-19 a public health emergency of international concern (PHEIC) (2). This disease has infected at least 228 million people worldwide with 4.6 million deaths (3).

Based on the Indonesian COVID-19 Management Guidelines, the clinical manifestations of COVID-19 patients have a broad spectrum, from asymptomatic to severe symptoms in the form of severe to critical pneumonia which can end in death. COVID-19 clinical manifestations of severe symptoms/ severe pneumonia in the presence of clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) include at least one of the following: respiratory rate greater than 30 breaths per minute, severe respiratory distress, oxygen saturation level lower than 93 percent in room air at sea level, a PaO2 per FiO2 ratio of ≤ 300 mmHg, or lung infiltrates is greater than 50 %. Meanwhile, the acute symptoms of COVID-19 in patients are Acute Respiratory Distress Syndrome (ARDS), sepsis, and septic shock (4,5). Moreover, several new clinical symptoms of COVID-19 had also been reported, thus causing difficulties to determine COVID-19 based only on the clinical symptoms (6).

The number of new cases of COVID-19 keeps increasing, and the high case fatality rate is steadily above the global rate (7). This condition immediately requires the development of cost-effective technology platforms for the production of vaccines, drugs, and protein reagents for the precise diagnosis and treatment of the disease (8). In addition, a novel treatment plan is required to lessen the growing number of deaths caused by COVID-19 (9). Since the beginning of March 2020, Indonesia has been fighting the covid-19 pandemic, and the situation does not appear to be improving anytime soon. Another theurapeutic strategy is necessary in addition to the country's present initiatives to reduce the rising mortality rate. Besides the country's current strategies to minimize the rising mortality rate, a novel therapeutic intervention is required. As well as other diseases that are transmitted through viruses, convalescent plasma therapy (CPT) is one of the methods used in treatment (10). Convalescent plasma therapy is antibody therapy against certain infectious diseases to treat or prevent that person from disease by providing fast immunity (4). A previous study reports the antibody titer of SARS-CoV-2 in convalescent plasma donors in Malang (11). CPT was declared safe as a COVID-19 therapy and could reduce the viral load in the

blood, especially in severe COVID-19 patients in the early stages of the disease course (12)a vaccine or specific drug is absent up to this date and more attention has been focused on the use of convalescent plasma (CP. Thus, to the best of the author's knowledge, there is no published data regarding the ability of CPT in Indonesia to deal with COVID-19 clinically. Therefore, the present study aims to assess the difference in survival between CPT administration in severe-critical COVID-19 patients and standard therapy.

METHODS

This research was a retrospective cohort observational research located at the Tarakan Regional Public Hospital, North Kalimantan, Indonesia. Patients who meet the criteria for the severe-critical COVID-19 diagnosis who were treated in the intensive care unit from 23-11-2020 to 14-04-2021 were the research subjects with the inclusion criteria: 1) COVID-19 patients proven by swab results PCR/TCM SARS-CoV-2 Positive, 2) patients aged 18 years or older, 3) COVID-19 in severe – critical category, such as clinical manifestations of COVID-19 for severe pneumonia with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) plus at least one of the following: (a) respiratory rate >30 breaths/min, (b) severe respiratory distress, or (c) oxygen saturation <93 % of room air. Meanwhile, for COVID-19 acute symptoms in patients with acute respiratory distress syndrome (ARDS), sepsis, and septic shock. The required patient data in the incomplete research were excluded from the analysis.

The requirements for plasma donors are people who have been hospitalized (not more than 3-6 months ago), with moderate/severe COVID-19; has been declared cured, without symptoms for 14 days; 18 to 60 years old; male, weight greater than 55 kg, (if receiving a transfusion, the distance is 3 to 6 months); if female, unmarried and never pregnant; no history of the comorbid disease; willing to fill out the informed consent and plasma donation form; Preference will be given to those who have donated blood. Convalescent plasma preparation includes (a) The donor filling out the "Blood Donation and Informed Consent forms", Donor selection through history and physical examination, (b) donor laboratory examination: routine blood examination, blood type confirmation, antibody screening, transmitted infections through blood transfusion (HIV, Hepatitis B, Hepatitis C, Syphilis), (c) donor blood collection: using the apheresis engine.

CPT was the predictor in this research, while the outcome was the mortality of COVID-19 patients with severe-critical symptoms and the length of stay. Related co-variables in this research were age, sex, systolic and diastolic blood pressure, body temperature, body mass index, blood test results: hemoglobin, leukocytes, alanine aminotransferase, aspartate aminotransferase, urea, creatinine, glucose, sodium, potassium, chloride, and pH, as well as initial oxygen saturation, and PF ratio (PO_2/FiO_2). This study compared CPT administration in severe-critical COVID-19 patients with standard therapy and standard therapy only. Standard therapy of COVID-19 patients include: (a) one of the antiviral agents (favipiravir, remdesivir) (b) antibiotics such as azithromycin or levofloxacin, (c) LMWH/UFH anticoagulants based on physician evaluation (d) steroids, may use dexamethasone injection or other equivalent corticosteroids such as hydrocortisone in severe cases receiving oxygen therapy or in severe cases on a ventilator (e) vitamin B1, vitamin C, and vitamin D (d) therapy according to comorbidities.

Secondary data was collected from the medical records for COVID-19 patients who had been treated at the Tarakan Regional Public Hospital, North Kalimantan, Indonesia, with severe-critical symptoms. Data were described by means (SD) for continuous variables and frequency (percent) for categorical variables. Univariate analysis was performed on each factor to the mortality outcome. For continuous scale factors, an independent Student t-test was performed unless the assumption of a normal distribution was not met, the Mann-Whitney test was performed; meanwhile, for the categorical scale factor, Pearson's chi-square test was performed. Survival analysis was carried out on the factor and outcome variables by estimating the median survival time and Kaplan-Meier survival curve. Log-rank test between outcome curves and hazard ratio analysis based on Cox regression Statistical

analysis was performed using STATA 17.0 SE (StataCorp LLC). The Ethics Committee has approved this research of Tarakan Regional Public Hospital, North Kalimantan, Indonesia. Patient confidentiality was maintained throughout this research.

RESULTS

Table 1 presents the patient characteristics. There were 101 patients with severe-critical symptoms of COVID-19 treated in the intensive care unit of the Tarakan Regional Public Hospital, North Kalimantan, Indonesia during the accrual period with an average age of 58.77±11.45 years, from which 65 patients (64.36 %) were men. The median length of stay was 12 days (Q1; Q3 9; 21).

A total of 42 patients received standard therapy plus CPT, while 59 patients received standard therapy only. The two groups had characteristics that did not differ between the group given standard therapy and CPT with standard therapy alone except for initial oxygen saturation, where the group with CPT had a normal mean initial oxygen saturation. In contrast, the group without CPT had lower mean initial oxygen saturation. Therefore, the formation of the Cox regression model will consider the initial oxygen saturation co-variable. The predictor of length of stay had a median difference of 9 days which was statistically significant (p <0.001), as was the mortality outcome with a relative risk in the CPT group of 0.457 (95 % CI 0.281; 0.741).

Table 1

Patient characteristics

Variables	CPT N=42	Standard N=59	P-value
Age (year)	59.64 ± 10.25	58.15 ± 12.27	0.3379*
Male	30 (71.43)	35 (59.32)	0.211
Died	13 (30.95)	40 (67.80)	0.0003
SBP (mmHg)	128.45 ± 18.27	135.15 ± 29.39	0.1940
DBP (mmHg)	80.40 ± 12.24	82.86 ± 16.51	0.9231*
Temperature (°C)	36.76 ± 0.77	36.53 ± 0.56	0.1477*
BMI (kg/m^2)	25.34 ± 3.41	25.46 ± 4.04	0.8913
Hb (mg/dL)	13.23 ± 1.84	12.51± 2.77	0.4024*
Leucocyte (/µL)	9 761.43 ± 5 455.75	1 2019.66 ± 7 864.62	0.4024*
AST (mg/dL)	70.19 ± 44.83	81.51 ± 89.27	0.4104*
ALT (mg/dL)	66.28 ± 47.92	61.55 ± 68.84	0.0903*
Urea (mg/dL)	47.15 ± 41.38	67.74 ± 73.29	0.5306*
Creatinine (mg/dL)	0.88 ± 0.42	1.63 ± 1.78	0.4736*
Glucose (mg/dL)	174.71 ± 76.28	183.88 ± 110.11	0.7527*
Natrium (mg/dL)	130.37 ± 7.01	130.63 ± 8.32	0.8578*
Kalium (mg/dL)	3.74 ± 0.55	3.88 ± 0.75	0.4995*
Chloride (mg/dL)	99.49 ± 6.31	101.09 ± 8.62	0.3045*
pH	7.39 ± 0.06	7.36 ± 0.11	0.2238
O2 Saturation (%)	96.10 ± 3.63	93.15 ± 9.02	0.0479*
PF Ratio	144.65 ± 132.80	158.35 ± 131.29	0.3594*
Long stay (day)	21.57± 12.72	12.41 ± 11.74	<0.001*

Continuous data in mean ± standard deviation, categorical data in frequency (percent), SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, Hb: hemoglobin, AST: aspartate transaminase, ALT: alanine aminotransferase, p-value based on independent t-test for continuous data, except those marked * based on the Mann-Whitney test, while the categorical data performed with chi-square test.

Survival

The group also given CPT had a median survival of 64 days with a lower incidence of death (1.43 %) than the standard therapy group (5.46 %), which had a median survival of 10 days. Survival for the two groups was estimated on the Kaplan-Meier diagram (Figure 1) and based on the log-rank test, both were significantly different ($p < 0.01$) with a hazard ratio for the CPT group of 0.276 (95 % CI 0.146; 0.519).

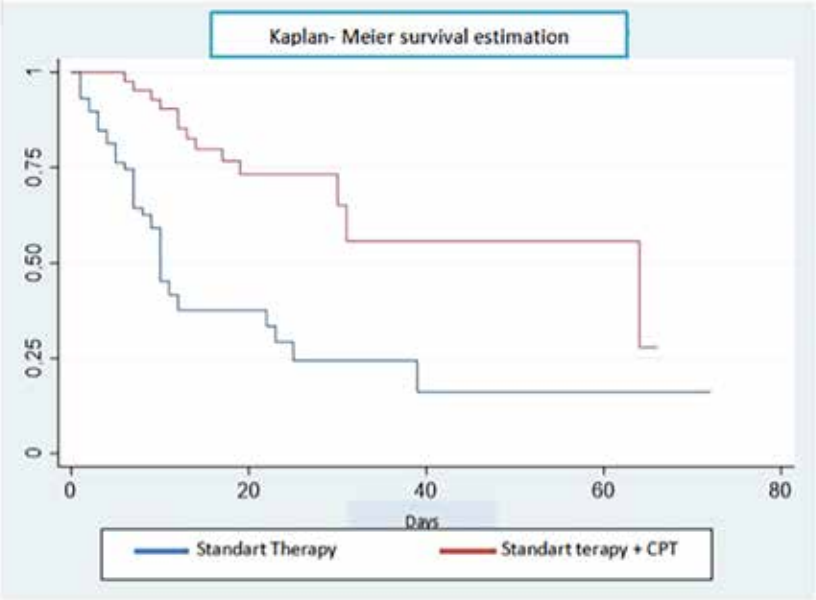

Figure 1. Kaplan-Meier survival estimation curve between standard therapy (blue) and standard therapy with the use of CPT (red).

Using the stepwise forward selection method, the Cox regression model formed with selected covariables (Table 2) resulted in a hazard ratio for sex-adjusted CPT and initial oxygen saturation of 0.312 (0.164; 0.595). This means a 68.8 % reduction in the risk of death in the CPT-treated group compared to the standard therapy group after adjusting for sex and initial oxygen saturation, and this reduction in risk in the population could range from 40.5 % to 83.6 %. This model fulfills the assumption of proportional hazard (global test p=0.2552).

Table 2

Predictors that significantly affect the survival of COVID-19 patients based on the Cox regression test

Predictors	**Adjusted hazard ratio (95% CI)**	**P-value of proportional hazard test**	**P-value of Global proportional hazard test**
CPT	0.312 (0.164; 0.595)	0.068	0.2562
Male	0.568 (0.324; 0.997)	0.696	
Initial oxygen saturation	0.934 (0.911; 0.977)	0.537	

DISCUSSION

The administration of CPT to COVID-19 patients is still controversial. Our cohort study showed that convalescent plasma therapy was associated with lower mortality, more prolonged survival, and a shorter duration of hospitalization than the standard therapy group. Convalescent plasma therapy is derived from blood plasma from COVID-19 survivors containing high titers of neutralizing antibodies. CPT also contains anti-inflammatory cytokines that can be useful for modulating severe immune responses to viruses (13). Passive immunization is expected to be a shortcut for the immune system to control disease progression until a specific immune response is formed in an infected person (14) largely on the basis of observational data, to improve clinical outcomes. Minimal data are available from adequately powered randomized, controlled trials. Antibodies directed against viruses have the potential to reduce viral entry into cells and increase virus elimination via antibody-dependent phagocytosis or antibody-dependent cellular toxicity (15). It may take two to three weeks for individuals who have never been exposed to a pathogen or vaccinated to develop an antibody response. Antibodies have the potential to prevent disease or significantly reduce the duration or severity of disease, thereby preventing serious or life-threatening complications.

CPT is considered in immunocompromised patients (particularly those receiving anti-CD20 monoclonal antibodies), the elderly (60 years), patients with comorbidities such as diabetes mellitus, hypertension, coronary heart disease, and obesity, CPT with high titer neutralizing antibodies (≥80), or high DO, and administered within 72 hours of symptom onset (16). The effect of CPT on COVID-19 still has varying research results (17). The available evidence for convalescent plasma in patients with severe COVID-19 is minimal. Observational studies using convalescent plasma for severe COVID-19 have shown that administration of convalescent plasma with higher antibody titers and earlier presentation is associated with better clinical effects. Overall, CPT with high antibody titers was found to be beneficial against SARS-CoV-2 infection in patients with a shorter duration of symptoms and who were not intubated. For example, in a report of 3 s082 patients who had or were at risk for severe COVID-19 and received convalescent plasma, administration of plasma with a higher antibody titer was associated with lower 30-day mortality rates (30, 27, and 22 percent) with low, medium, and high plasma titers; however, there was no association between antibody titers and mortality among patients on mechanical ventilation at the time of plasma transfusion. However, the clinical implications of this observational research are uncertain, given a large number of adverse findings from randomized trials (18,19).

Several factors affect the success rate of CPT in COVID-19 patients. The dose of CPT used in some studies tends to vary. In this research, a dose of 200 mL was given two times with an interval of 48 hours. In China, researchers demonstrated the use of a single 200 mL dose of convalescent plasma with a neutralizing antibody titer greater than 1:640 and a maximum dose of 2 400 mL of convalescent plasma administered to a 73-year-old male patient. Until now, the optimal CPT dose for COVID-19 has remained unknown (20).

If administered earlier, the effectiveness will be increased (ideally, within three days of the onset of symptoms) (21). A previous study (22) reported that 27 surviving patients received CPT between day 6 and day 50 after symptom onset or hospital admission. When administered late in the course of the disease, convalescent plasma is frequently ineffective. When the meta-analysis was restricted to trials that delivered plasma within three days of diagnosis, the evidence for benefit was strengthened (OR, 0.44; 95 % CI, 0.32–0.61). This is consistent with the mechanism of action, which involves inhibiting viral entry and/or increasing viral phagocytosis. There are two possible explanations for why late administration diminishes the efficacy of therapy. First, the majority of individuals will begin increasing their own antibody response within eight to ten days of infection, and donor plasma may not increase antibody levels above the endogenous response. Second, as the disease progresses, it is the inflammatory response to the virus that causes severe clinical manifestations, not the virus itself (22).

Antibody levels against SARS-CoV-2 are thought to be a significant predictor of effectiveness, as the virus's primary mode of action is antibody-mediated. The optimal antibody concentration or titer, on the other hand, is unknown. After removing one trial that included multiple individuals receiving plasma with low antibody titers, a meta-analysis determined that the benefit of CPT on mortality was statistically significant (death, 11 versus 16 percent; OR 0.65; 95 percent CI 0.43-0.98) (21).

There are several side effects of convalescent plasma therapy, including transfusion reactions, antibody-dependent enhancement (ADE), and interference with vaccination. Convalescent plasma is a type of human plasma that can result in a variety of transfusion reactions, including allergic and anaphylactic reactions, hemolysis, transfusion-associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI). Plasma, on the other hand, is generally well tolerated, with transfusion reactions being uncommon and easily controlled with supportive measures (23). Antibodies to infecting pathogens can paradoxically increase viral uptake by cells, exacerbating disease severity (24) such as severe acute respiratory syndrome coronavirus (SARS-CoV-2. ADEs have not been reported when convalescent plasma was used to treat individuals with COVID-19 or other viral infections. Early administration of convalescent plasma may increase the risk of developing ADE, and all patients, particularly those treated early in the course of infection, should be closely monitored (24) such as severe acute respiratory syndrome coronavirus (SARS-CoV-2. In theory, administering plasma containing antibodies to SARS-CoV-2 could impair the recipient's immune system's ability to recognize and produce antibodies against SARS-CoV-2, reducing the vaccine's effectiveness (21). In our research, there were no reports of any research subjects experiencing adverse effects.

There were some limitations in our study, such as the small sample size. In addition, this research did not report the duration of disease onset when receiving CPT therapy, and there was no standardization of the number of CPT titers given. Both can affect the analysis of the results.

CONCLUSION

This study demonstrated a possible therapeutic effect and a low risk in the treatment of severe COVID-19 patients. The optimal dose and timing of treatment administration, as well as the definitive clinical benefit of CPT therapy, should be investigated further in randomized clinical trials.

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