Available online at IJTID Website: https://e-journal.unair.ac.id/IJTID/

Indonesian Journal of
Tropical and Infectious Disease

Vol. 11 No. 3 September – December 2023

Original Article

Examining convalescent plasma transfusion in severe COVID-19 patients, recent research highlights the significance of S-RBD antibodies and IL-10 levels

Aditea Etnawati Putri[1*], Betty Agustina Tambunan[1], Bambang Pujo Semedi[2], Narazah Mohd Yusoff [1,3], Siti Salmah Bt Noordin[4]

[1] MD, Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo Hospital, Surabaya, Indonesia

[2] PhD, Department of Anesthesiology and Reanimation, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo Hospital, Surabaya, Indonesia

[3] MBBS, PhD, Advanced Medical and Dental Institute, Universiti Sains Malaysia (USM), Bertam 13200 Kepala Batas, Penang Malaysia

[4] MD, Advanced Medical and Dental Institute, Universiti Sains Malaysia (USM), Bertam 13200 Kepala Batas, Penang Malaysia

Received: 2nd November 2023; Revised: 6th November 2023; Accepted: 21th November 2023

ABSTRACT

Convalescent plasma (CP) may be an option for people with severe COVID-19. However, its efficiency remains unknown. A study was done to determine whether the levels of Anti-SARS-CoV-2 Spike Receptor-Binding Domain (S-RBD) antibodies and IL-10 in COVID-19 patients who had CP transfusion were related to their survival status. The observational cohort study included 40 patients with severe COVID-19 who were followed for 28 days after receiving a CP transfusion. Antibody and IL-10 levels were assessed on Day 1 before to CP transfusion and on Days 1, 2, and 7 following CP transfusion. Twenty six (65%) of the 40 patients survived. Anti-SARS-CoV-2 S-RBD antibody levels were observed to be significantly higher on Days 1, 2, and 7 following CP transfusion (p-value 0.05). Furthermore, IL-10 levels dropped significantly on Days 2 and 7 (p-value 0.05). However, neither the CT value nor the patients' survival status were linked to greater antibody levels or changes in IL-10 levels. According to the findings, CP transfusion can greatly enhance anti-SARS-CoV-2 S-RBD antibody levels while drastically decreasing IL-10 levels. These findings may have therapeutic implications for the use of CP as a COVID-19 therapy option. More research is needed to determine its efficacy in enhancing the survival rate of COVID-19 patients with severe symptoms.

Keywords: Anti-SARS-CoV-2 S-RBD antibody, IL-10, infectious disease, convalescent plasma, and mortality.

Highlights: This study showed that there was a decreasing trend of IL-10 after CP transfusion, which suggest that the immunomodulating effect from CP transfusion had successfully reduced IL-10 level in severe COVID-19 patients.

How to Cite: Putri, A. E., Tambunan, B. A., Semedi, B. P., Yusoff, N. M., and Noordin, S. S. B. Examining convalescent plasma transfusion in severe COVID-19 patients, recent research highlights the significance of S-RBD antibodies and IL-10 levels. Indonesian Journal of Tropical and Infectious Disease. 11(3). 157–166. Dec. 2023.

DOI: 10.20473/ijtid.v11i3.50859

* Corresponding Author:
aditea.putri@gmail.com

INTRODUCTION

The coronavirus sickness 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It affects roughly 100 million people worldwide and poses a major threat to public health.[1] According to the World Health Organization (WHO), there were more than 21 million new cases in six regions during the most recent reporting period, reaching the highest weekly case total since the pandemic began. There were also approximately 50,000 additional fatalities reported. COVID-19 had been related to about 346 million verified illnesses and 5.5 million fatalities worldwide by January 23, 2022.[2]

The pathogenesis of COVID-19 is mediated by the host's immunological response.[3] Acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS) are symptoms of immunological dysregulation in severe cases.[4] The invasion of inflammatory cells and the massive production of proinflammatory cytokines or chemokines are the characteristics of this, which cause organ damage and patient death.

SARS-CoV-2 is not yet a definite therapeutic approved for the treatment of COVID-19, while a number of antiviral medications have been employed in different clinical trials.[5] Convalescent plasma (CP), however, is making a comeback as a potentially effective COVID-19 therapeutic option. Because it contains a variety of proteins, including albumin, cytokines, antibodies, and anti-coagulation proteins, CP has been used to treat coronavirus infections in the past with encouraging outcomes. Additionally, CP has antithrombotic capabilities, which can re-establish hemostasis and reverse hypercoagulable states in COVID-19 patients.[6,7,8] By neutralizing antibodies that bind to the receptor-binding domain of the S1 spike antigen (sRBD) of the SARs-CoV-2 virus, it provides passive protection by preventing virus entry and restricting its amplification. Because CP contains antibodies and anti-inflammatory cytokines that block complement, inflammatory cytokines, and autoantibodies, it also has immunomodulatory effects.[6,7]

Cytokine IL-10 (interleukin10) has anti-inflammatory properties and is thought to function as a negative feedback mechanism to reduce inflammation.[9] On the other hand, it has been demonstrated that elevated IL-10 plays a pathogenic part in the severity of COVID-19. Because of its anti-SARS-CoV-2 S-RBD concentration, CP transfusion has been recommended for the treatment of severely and critically ill COVID-19 patients.[10] Despite its advantages, CP administration is still debatable, and opinions differ. Furthermore, no research has been done to link the survival status following CP transfusion to the levels of IL-10 and Anti-SARS-CoV-2 S-RBD antibody.[11] As a result, numerous laboratory markers are being studied to determine the utility of CP transfusion, and numerous clinical trials are still being conducted to determine its effectiveness. The purpose of this study is to assess the anti-SARS-CoV-2 S-RBD antibody and IL-10 levels, as well as their relationship to the survival status of patients with severe COVID-19 after CP transfusion.

MATERIALS AND METHODS

Study Design

This study used a prospective cohort design and was an observational analytical investigation. Patients with COVID-19 who were hospitalized in the isolation ward of the Dr. Soetomo Hospital in Surabaya, Indonesia between June and December 2020 comprised the study population. This hospital treats severe COVID-19 cases and serves as a teaching hospital as well as one of East Indonesia's referral hospitals. The Dr. Soetomo Hospital's health research ethics committee granted ethical permission. Using

a successive sampling strategy, 40 patients were recruited who fulfilled the inclusion criteria. The recipients' positive COVID-19 status was confirmed by a polymerase chain reaction (PCR), analysis of the nasopharyngeal swab, and they were also required to receive therapy at the Special Inpatient Installation (Isolation Ward) and had severe or critical disease. Participants in this study were split into two groups: those who survived and those who succumbed, based on mortality rates.

COVID-19 severity can be determined using the following criteria:[12]

a. Breathing difficulty accompanied by a respiration rate of 30 breaths per minute.
b. A saturation of oxygen (SpO2) of 93% or below while breathing room air.
c. A PaO2/FiO2 ratio of no more than 300 mmHg.
d. Chest X-ray lesions that have worsened by more than 50% in the last 24-48 hours.

The following criteria are utilized to identify critically ill COVID-19 patients at Dr. Soetomo Hospital:[12]

a. Severe pneumonia that advances swiftly and has frequent increases in viral load while receiving hospital-prescribed COVID-19 medication on a regular basis.
b. Acute Respiratory Distress Syndrome (ARDS) with a PaO2/FiO2 ratio less than 300.
c. Requiring or receiving mechanical ventilation therapy

Procurement of Convalescent Plasma (CP)

This study's convalescent plasma was acquired through apheresis donation utilizing Haemonetics MCS+ machine technology, in accordance with National Standards for Blood Transfusion Service and blood bank protocols. Each donor donated 200-400 mL of convalescent plasma, which was then transfused to each recipient in 200 mL increments over two days.

To be eligible for donating convalescent plasma, the following criteria must be met:

a. Age must be between 17 and 60.
b. The donor must have recovered from COVID-19 and provide two consecutive negative PCR test results for nasopharyngeal swabs.
c. The donor must not have any symptoms of COVID-19 or must have completed a 14-day symptom-free period before donating plasma.
d. Patients who have tested negative on re-PCR results of nasopharyngeal swabs 24 hours before plasma donation will not be eligible for donation if they are outpatients or self-isolation patients.
e. The donor must not have any comorbidities such as diabetes, hypertension with target organ damage (stroke, coronary heart disease, and renal disease), CKD, and inadequate vascular access.
f. Negative test results for hepatitis B, hepatitis C, human immunodeficiency virus, and syphilis are required.
g. The donor must have a blood antibody titer to SARS-CoV-2 more than 1:320, as measured by a rapid test assay using the PANBIO COVID-19 IgG rapid test equipment.

Exclusion criteria for convalescent plasma (CP) donors:

a. Donors who are getting COVID-19 treatment but have insufficient clinical information
b. Positive antibody screening test donor

Laboratory parameters

On Day 1 before CP transfusion, we tested for Anti-SARS-CoV-2 S-RBD antibody, IL-10, and rt-PCR (real time-

Polymerase Chain Reaction), as well as on Day 1, Day 2, and Day 7 following CP transfusion. Blood was taken using BD Vacutainer® SSTTM Tubes to determine antibody and IL-10 levels. The tests were performed using the sCOVG ADVIA Centaur for anti-SARS-CoV-2 antibody levels, the Cytometric Beads Array (CBA) method with the BD FACS Calibur TM flow cytometry for IL-10 levels, and the PCR SARS-CoV-2 by Abbott m2000 for rt-PCR analysis of nasopharyngeal swab. Prior to testing, serum antibody and IL-10 analysis samples were maintained at -80°C. After collecting all of the samples, the tests were carried out.

Patient monitoring and evaluation

On Day1, we assessed the demographics and clinical features of 40 COVID-19 patients before transfusing convalescent plasma. The patients' progress was tracked for 28 days after the transfusion.

Statistical analysis

The frequency of categorical variables was calculated, while quantitative data was provided as mean and standard deviation (SD) or median and interquartile range (IQR). To compare dependent samples, the Wilcoxon Sign Rank test was utilized, and the Mann-Whitney U test was used to compare independent samples. The Spearman correlation test was employed to assess the link between anti-SARS CoV-2 S-RBD antibody levels, IL-10 levels, CT value, and survival status. The significance level was set at 0.05.

RESULTS

The inclusion criteria were met by 40 COVID-19 patients who were severely to critically ill. The patients were primarily male (75%), had comorbidities (72.5%), were ventilated (50%), and had COVID-19 problems (95%) as shown in Table 1.

Table 1. Details of 40 COVID-19 patients' demographics and clinical characteristics.

Characteristics	n (%)
Age* (years)	49.83 ± 9.159
BMI* (kg/m^2)	25.90 ± 3.970
Gender	
Male	30 (75%)
Female	10 (25%)
Severity of infection	
Non-ventilated	20 (50%)
Ventilated	20 (50%)
Comorbid	
Yes	29 (72.5%)
No	11 (27.5%)
Comorbid Type	
DM	14 (48.3%)
Hypertension	14 (48.3%)
Overweight - Obesity	7 (14.9%)
CHD	2 (4.3%)
Hypothyroid	2 (4.3%)
Others	8 (17%)
Complications	
Yes	38 (95%)
No	2 (5%)
Complication type	
Respiratory failure	37 (97.4%)

Septic shock	10 (26.3%)
Non-specific hepatitis	6 (15.8%)
AKI	6 (15.8%)
Hypoalbuminemia	5 (10.5%)
Others	4 (7.4%)

BMI = Body Mass Index, DM = Diabetes Mellitus, CHD = Chronic Heart Disease, AKI = Acute Kidney Injury(*)Mean ± Standard deviation

From Day 1 to Day 7, the anti-SARS-CoV-2 S-RBD antibody considerably increased (p<0.001) (Table 2). The highest antibody level (723.67 U/mL) was recorded on Day 7 following CP transfusion. Table 3 revealed that IL-10 levels differed significantly on Day 2 and Day 7 (p<0.05). Pre-CP transfusion, the median baseline concentration of IL-10 was 5.64 pg/mL, and it gradually declined until Day 7.

Table 2. Differences in anti-SARS-CoV-2 S-RBD antibody levels before and after receiving CP tranfusion on Days 1, 2, and 7 in severe COVID-19 patients.

anti SARS CoV-2 S-RBD antibody levels	Median (min – max)	Differences of antibody level from baseline Median (min – max)	p-*value**
Day-1	4.96 (0.05 – 362.44)		
Day 1	16.78 (0.26 – 557.18)	8.51 (-13.05 – 411.93)	< 0.001
Day 2	31.99 (0.38 – 709.01)	16.13 (-37.49 – 632.83)	< 0.001
Day 7	75.31 (0.59 – 723.67)	37.81 (-90.65 – 497.50)	< 0.001

* Results showed statistical analysis were significant, with P < 0.05 using Wilcoxon Sign Rank test

Table 3. Differences in IL-10 levels before and after receiving CP tranfusion on Days 1, 2, and 7 in severe COVID-19 patients

IL-10 levels	Median (min – max)	Differences of IL-10 level from baseline Median (min – max)	p *value**
Day-1	5.64 (2.92 – 25.48)		
Day 1	4.64 (2.82 – 33.11)	0.95 (17.92 – 26.05)	0.090
Day 2	4.24 (2.24 – 25.48)	1.56 (20.68 – 19.84)	0.003
Day 7	4.09 (1.00 – 36.23)	1.49 (19.50 – 30.59)	0.003

* Results showed statistical analysis were significant at Day 2 and Day 7 , with p < 0.05 using Wilcoxon Sign Rank test

On Day 2, our investigation found median changes in antibody levels in both the recovered and succumbed groups (Figure 1a), as well as median changes in IL-10 levels (Figure 1b).

Further statistical analysis, however, revealed a statistically negligible connection between antibody or IL-10 levels and survival state, with p = 0.411 and p = 0.734, respectively.

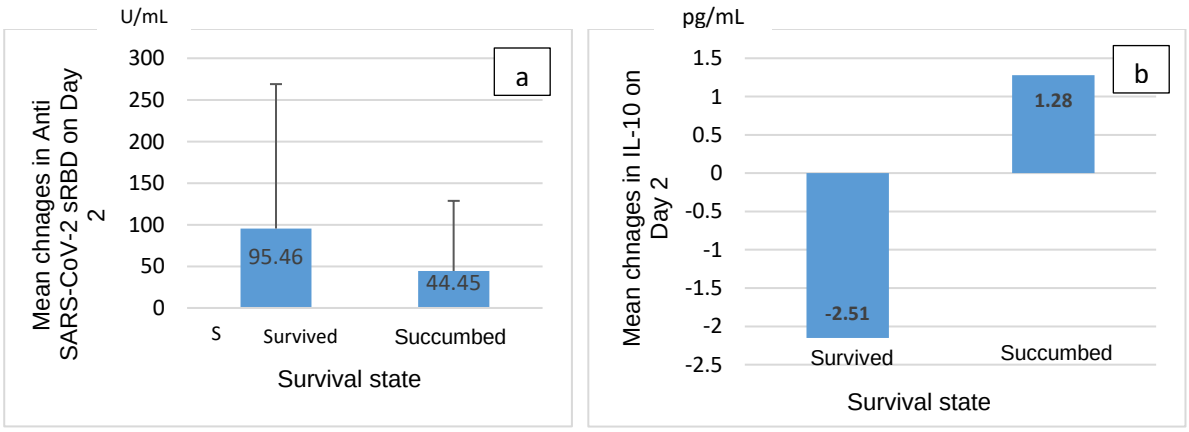

Figure 1. (a) Mean changes in anti-SARS-CoV-2 S-RBD antibody levels after receiving CP transfusion on Day 2 and survival state (b) Mean changes in IL-10 levels after receiving CP transfusion on Day 2 and survival state. Results of the Mann Whitney U test showed that there was no significant difference in antibody and IL-10 levels before and after receiving CP transfusion on Day 2 between those who recovered and deceased ($p > 0.05$).

Table 4 demonstrates a significant relationship ($p<0.05$) between anti-SARS-CoV-2 S-RBD antibody and IL-10 levels following CP transfusion on Days 2 and 7. Figure 2 shows a small but significant positive relationship between the two variables ($r = 0.31$, $r = 0.27$).

The Mann Whitney U test demonstrated that there was no significant connection between changes in anti-SARS-CoV-2 S-RBD antibody and IL-10 levels after receiving CP transfusion on Day 2 for both survivors and non-survivors ($p > 0.05$). Furthermore, Table 5 reveals that there was no significant association between changes in anti-SARS-CoV-2 S-RBD antibody on Day 7 and changes in CT value prior to receiving CP transfusion on Day 7 ($p > 0.05$).

Table 4. Correlation between anti-SARS-CoV-2 S-RBD antibody with IL-10 levels following CP transfusion on Days 1, 2, and 7 in severe COVID-19 patients.

Variable	*Spearman Correlation*	
	r_s	p-value*
Delta* anti SARS CoV-2 S-RBD Day 1 – Delta IL-10 Day 1	0.244	0.064
Delta anti SARS CoV-2 S-RBD Day 2 – Delta IL-10 Day 2	0.311	0.025
Delta anti SARS CoV-2 S-RBD Day 7 – Delta IL-10 Day 7	0.273	0.044

* Delta means changes in anti-SARS-CoV-2 S-RBD antibody and IL-10

* Results showed statistical analysis were significant, with $P < 0.05$ using *Spearman Correlation test*

Table 5. Correlation of Delta sCOVG changes with CT values

Variable	*Spearman Correlation*	
	r	p-value
Delta sCOVG Day 7 – CT Day 1	-0.131	0.210
Delta sCOVG Day 7 – CT Day 7	0.049	0.383

* Delta means changes in anti-SARS-CoV-2 S-RBD antibody and Cycle Threshold on rt-PCR

* Results showed statistical analysis were significant, with P < 0.05 using *Spearman Correlation test*

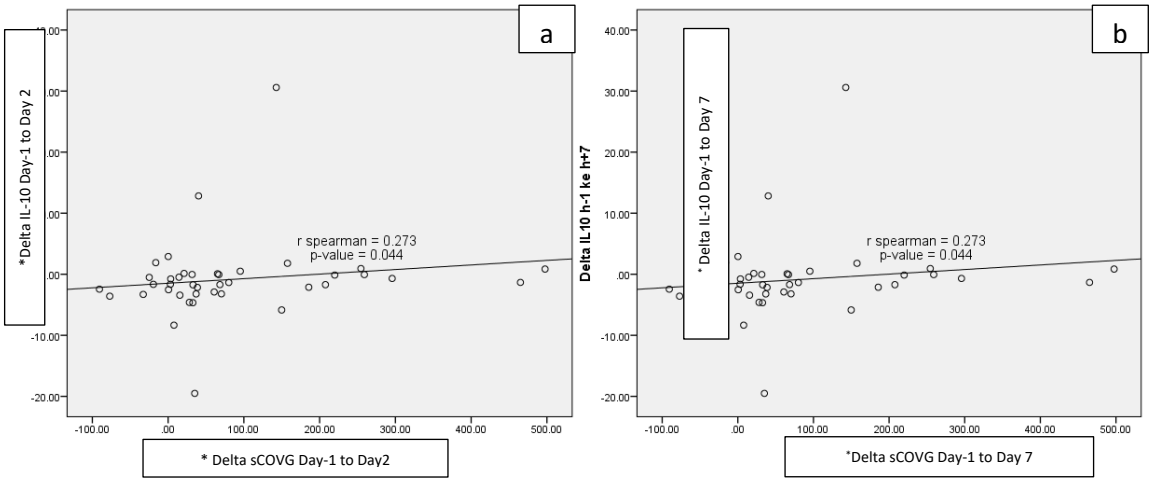

Figure 2. (a) Scatter Plot correlation of anti-SARS-CoV-2 S-RBD antibody with IL-10 on Day 2. (b) Scatter Plot correlation of anti-SARS-CoV-2 S-RBD antibody with IL-10 on Day 7. Both figures showed significant correlation using the Spearman correlation test with p<0.05. * Delta means changes in anti-SARS-CoV-2 S-RBD antibody and IL-10.

DISCUSSION

In this study, anti-SARS-CoV-2 (S-RBD) antibody and IL-10 levels were connected to survival status following CP transfusion in severe COVID-19 patients. The patients in our study were almost mostly male (75%). This is consistent with a previous study, which discovered that men were more likely than women to acquire substantial COVID-19 (69.8%).[13] There were two non-identical routes for viral entrance in gender susceptibility to COVID-19 via sex hormonal stabilization of angiotensin-converting enzyme 2 (ACE2). On the one hand, estrogens or X chromosomal inactivation escape can enhance ACE2 expression in women, allowing for a larger supply of ACE2 to maintain the elemental balancing axis of the Renin-Angiotensin System (RAS). Nonetheless, because the X regulatory genes were activated, women had not only lower viral loads but also greater CD4 T-cell counts and higher expression of Toll-like receptor 7 (TLR7), making them more resistant to severe COVID-19 than men.[14]

According to our findings, the majority of patients who received CP infusions had underlying comorbidities such as diabetes, hypertension, or obesity. In prior research, diabetes and hyperglycemia were linked to COVID-19 severity and death. Furthermore, COVID-19 patients comorbidities can lengthen their stay in the ICU and increase patient mortality.[15] COVID-19 patients with cardiovascular comorbidities are also more likely to suffer from sudden cardiac death and heart failure.[17] This is because viruses that reach the lungs may have direct or indirect consequences, such as cytokine storms.[18]

Antibody levels increased after Convalescent Plasma (CP) transfusion, according to our findings. This is in keeping with the notion that CP is a type of passive vaccination containing antibodies, cytokines, and coagulation factors.[10,11,19] The antibodies in CP neutralize infections before eradicating the virus, leading in a decrease in clinical symptoms. Another study discovered a decreasing trend in IL-10 levels after CP transfusion, demonstrating that the immunomodulatory effect of CP transfusion

successfully reduced IL-10 levels in severe COVID-19 patients. However, a previous study discovered that IL-10 levels increased after CP transfusion. High IL-10 expression in COVID-19 patients was found to predict poor outcomes. In addition to IL-10, patients with severe COVID-19 had increased levels of IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, monocyte chemoattractant protein-1, tumor necrosis factor, macrophage inflammatory protein 1 alpha, and C-reactive protein.[21]

Although earlier administration of CP may reduce severity and mortality, high anti-SARS-CoV-2 S-RBD titers had no effect on viral load kinetics. This occurrence does not appear to be unique.[22] The period of delivery influences the efficacy of CP, and it is recommended that CP be provided within 72 hours after the onset of symptoms. A prior study found that CP infusions could decrease the mortality of ICU patients, and their success was impacted by characteristics such as disease severity, comorbidities, complications, and duration of stay.[23,24] Patients with underlying comorbidities showed inappropriate and inadequate immune responses, which may encourage viral replication and heighten the consequences associated with SARS-CoV-2 infection.[23]

The researchers discovered no link between changes in anti-SARS-CoV-2 S-RBD antibody levels and Ct values on Day 7 after receiving convalescent plasma (CP).[19] The mean Ct value before the CP transfusion was 18.61, but it jumped to 24.62 after the transfusion. This implies that antibody levels have no effect on viral clearance and that Ct value is unrelated to a patient's clinical status. Aranha et al. revealed in a prior study that COVID-19 positive cases with Ct values of 31 or above were later tested negative for SARS-CoV-2 RNA within 7 days of initial identification. However, the clinical conditions of the individuals were not disclosed.[25]

STRENGTH AND LIMITATION

Our study highlights the impact of CP transfusion as passive immunization involving antibodies, cytokines, and coagulation factors. This antibody level in CP neutralizes pathogens, which subsequently eliminates the virus resulting in improvement in clinical manifestations.

The study has some limitations, including insufficient data on the date of infection, which makes assessing the onset of symptoms difficult and may affect anti-SARS-CoV-2 S-RBD antibody, IL-10, and Ct value levels. Furthermore, because there was no control group (severe COVID-19 patients who did not get CP transfusion), no comparison between anti-SARS-CoV-2 S-RBD antibody, IL-10, and Ct value could be made. The study's small sample size is also an issue. Future research should include larger sample sizes, multi-center investigations, and more biological markers.

CONCLUSIONS

Transfusion with CP significantly increased the level of anti-SARS-CoV-2 S-RBD antibody and significantly reduced the level of IL-10. However, these parameters are not significant in predicting the survival state among severe COVID-19 patients transfused with CP.

ACKNOWLEDGEMENT

All authors approved the final manuscript and Siemens Healthiness Indonesia provided reagents without influencing study design or analysis.

ETCHICAL CLEARANCE

This study was approved by the Health Research Ethics Committee of Dr. Soetomo Hospital, Surabaya, Indonesia (approval number: 0001/KEPK/V/2020).

FUNDING

There is no funding for this research.

CONFLICT OF INTEREST

The author declares that they have no conflict of interest.

AUTHOR CONTRIBUTION

AEP, BAT and BPS contributed in the study conceptualization, methodology, data curation, writing - review & editing. NMY and SSN contributed to the writing - review & editing. All authors read and approved the final version of the manuscript.

REFERENCES

1. WHO Indonesia. Coronavirus Disease Coronavirus Disease Coronavirus Disease World Health World Health Organization Organization. World Heal Organ [Internet]. 2020;19(May):2. Available from: https://covid19.who.int/
2. Asia S. Weekly epidemiological update on COVID-19 - 25 January 2022 Edition 76. 25 January 2022. 2022;(January):22. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-january-2022
3. Hojyo S, Uchida M, Tanaka K, Hasebe R, Tanaka Y, Murakami M, et al. How COVID-19 induces cytokine storm with high mortality. Inflamm Regen. 2020;40(1).
4. Mahdi BA, Suryantoro SD, Romadhon PZ, Windradi C, Widiyastuti KN, Novendrianto D, Widiasi ED, Agustin ED, Firdausa S. Convalescent plasma therapy: The early use in moderate to severe COVID-19 patients in hospitals with limited resources. Journal of Tropical and Infectious Disease. 2021;9:3.
5. Natarajan H, Crowley AR, Butler SE, Xu S, Weiner JA, Bloch EM, et al. SARS-CoV-2 antibody signatures robustly predict diverse antiviral functions relevant for convalescent plasma therapy. medRxiv Prepr Serv Heal Sci [Internet]. 2020;9922:1–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32995801%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7523138
6. Sun M, Xu Y, He H, Zhang L, Wang X, Qiu Q, et al. A potentially effective treatment for COVID-19: A systematic review and meta-analysis of convalescent plasma therapy in treating severe infectious disease. Int J Infect Dis [Internet]. 2020;98:334–46. Available from: https://doi.org/10.1016/j.ijid.2020.06.107
7. Langhi DM, Santis GC De, Bordin JO. COVID-19 convalescent plasma transfusion. Hematol Transfus Cell Ther [Internet]. 2020;42(2):113–5. Available from: https://doi.org/10.1016/j.htct.2020.04.003
8. Franchini M, Glingani C, Liumbruno GM. Potential mechanisms of action of convalescent plasma in COVID-19. Diagnosis. 2021;8(4):413–20.
9. Riwu1a AG, Nugaraha J, Dachlan YP. Differences of Interleukin-18 and Interleukin-10 Levels in Pulmonary Rifampicin Resistant dan Rifampicin Sensitive Tuberculosis Patients in Dr. Soetomo Hospital Surabaya
10. Lu L, Zhang H, Dauphars DJ, He YW. A Potential Role of Interleukin 10 in COVID-19 Pathogenesis. Trends Immunol [Internet]. 2021;42(1):3–5. Available from: https://doi.org/10.1016/j.it.2020.10.012

11. Harvala H, Robb ML, Watkins N, Ijaz S, Dicks S, Patel M, et al. Convalescent plasma therapy for the treatment of patients with COVID-19: Assessment of methods available for antibody detection and their correlation with neutralising antibody levels. medRxiv. 2020;
12. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA - J Am Med Assoc. 2020;323(13):1239–42.
13. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Heal. 2020;8(April):1–6.
14. Lakbar I, Luque-Paz D, Mege JL, Einav S, Leone M. COVID-19 gender susceptibility and outcomes: A systematic review. PLoS One [Internet]. 2020;15(11 November):1–15. Available from: http://dx.doi.org/10.1371/journal.pone.0241827
15. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol [Internet]. 2020;8(10):823–33. Available from: http://dx.doi.org/10.1016/S2213-8587(20)30271-0
16. Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J. 2021;97(1147):312–20.
17. Herman H, Gharini PPR, Dinarti LK. Clinical cardiac manifestations in coronavirus disease 2019 (COVID-19) patients with. 2020;52(3):120–37.
18. Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, et al. Cytokine Storm in COVID-19—Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. Front Immunol. 2020;11(July).
19. 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.
20. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect. 2020;9(1):1123–30.
21. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm'' in COVID-19.' J Infect [Internet]. 2020;80(6):607–13. Available from: https://doi.org/10.1016/j.jinf.2020.03.037
22. Sewell HF, Agius RM, Kendrick D, Stewart M. Vaccines, convalescent plasma, and monoclonal antibodies for covid-19. BMJ. 2020;370:1–2.
23. French MA, Moodley Y. The role of SARS-CoV-2 antibodies in COVID-19: Healing in most, harm at times. Vol. 25, Respirology. 2020. p. 680–2.
24. 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 U S A. 2020;117(17):9490–6.
25. Aranha C, Patel V, Bhor V, Gogoi D. Cycle threshold values in RT-PCR to determine dynamics of SARS-CoV-2 viral load: An approach to reduce the isolation period for COVID-19 patients. J Med Virol. 2021;93(12):6794–