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Efficacy of therapeutic plasma exchange and convalescent plasma therapy in moderate-to-severe COVID-19 patients

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has emerged as a global health catastrophe since its first reported cases in late December 2019. Critically ill COVID-19 patients have been related to cytokine storms leading to acute respiratory distress syndrome and high mortality rates. Therapeutic plasma exchange (TPE) and convalescent plasma (CP) therapy improve clinically by removing inflammatory cytokines excess and using passive antibody-containing blood, respectively. This study aimed to evaluate TPE and CP treatment for moderate-to-severe COVID-19 infection.

Method: The patients were randomly divided into TPE group (n = 10), CP group (n = 11), and control group (n = 10). This 1-week quasi-experimental study with a pretest–post-test control group design was conducted in the Intensive Care Unit (ICU) of Dr. Moewardi General Hospital and Universitas Sebelas Maret (UNS) Hospital. The study comparison between groups included blood gas analysis profile (pH, base excess, $PaCO_2$, PaO_2, hematocrit, HCO_3, total CO_2, SaO_2), FiO_2, P/F ratio, COVID-19 severity, and D-dimer. The paired t-test was used to analyze every group's pretest–post-test mean difference. One-way ANOVA was performed to analyze the mean difference across the three groups. SPSS version 22.0 for Windows was used to perform statistical analyses.

Result: TPE and CP groups showed significant clinical-laboratory improvement than control ($p > 0.05$). Furthermore, high clinical-laboratory improvement tendency was observed in CP therapy than TPE.

Conclusion: The use of TPE and CP in moderate-to-severe COVID-19 patients has been related to improving clinical-laboratory outcomes.

Keywords: acute respiratory distress syndrome, convalescent plasma, COVID-19, plasmapheresis, SARS-CoV-2, therapeutic plasma exchange.

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INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infects the lower respiratory airway epithelium and causes pneumonitis and severe systemic inflammation due to extensive epithelial damage via cytopathic effects.[1] SARS-CoV-2 or Coronavirus disease 2019 (COVID-19) arose as the most devastating global health catastrophe since its first reported cases in Wuhan, Hubei, China, in December 2019 and the influenza pandemic of 1918.[2] This novel coronavirus pandemic continues to spread with an approximated 554,066,515 cases and 6,360,840 deaths worldwide (as of July 03, 2022).[3] Although COVID-19 vaccination has significantly reduced the number of global cases, moderate-to-severe COVID-19 can still result in worsening conditions and death of the vaccinated patient.[4] Moderate-to-severe COVID-19 has been related to high lymphopenia concentration of C-reactive protein, ferritin, D-dimer, lactate dehydrogenase, and inflammatory cytokine of interleukin (IL)-6.[5]

Therapeutic Plasma Exchange (TPE) has been used to manage immune disorders, sepsis, and severe infections such as HIN1 influenza A with a trend of improving survival rates.[6] TPE was related to higher extubation rates than the non-TPE COVID-19 patient. Moreover, it had a lower post plasma exchange mortality than non-TPE.[7] Similarly, convalescent plasma (CP) therapy, a novel therapy, uses passive antibody-containing blood from patients who have recovered from COVID-19 to help others recover. It can be life-saving in moderate-to-severe COVID-19 because vaccination requires time to develop an immune response initiation.[8]

With Indonesia's geographically vast and dispersed archipelago, the accessibility to secondary-to-tertiary hospital-possessed TPE and CP becomes challenging. This problem causes a lack of data on TPE and CP therapy in Indonesia. Therefore, this study aims to examine the efficacy of TPE and CP as possible supportive treatment for moderate-to-severe COVID-19 infection.

METHOD

Study design and participant

This 1-week quasi-experimental study with pretest–post-test control group design was conducted from July 24 to August 29, 2020, at the COVID-19 Intensive Care Unit (ICU) of Dr. Moewardi General Hospital and Universitas Sebelas Maret (UNS) Hospital, Central Java, Indonesia. The participant inclusion criteria included: adult male-female aged more than 40 years old, polymerase chain reaction (PCR) swab of the nasopharyngeal confirmed positive result of SARS-CoV-2, moderate-to-severe (>100-200 to ≤100 mmHg) COVID-19 based on Horowitz Index (P/F Ratio). Study exclusion criteria such as patients with the acute coronary syndrome, patients with suspected or confirmed pulmonary embolism, and pregnancy.

Sample size and randomization

As of July 24, 2020, there have been 1,761 new cases of PCR-confirmed COVID-19 patients in Indonesia based on the online database of the Indonesia Ministry of Health. Severe-to-moderate COVID-19 patients who would receive TPE or CP in our ICU hospitals (n=63) were selected and included in the study. TPE or CP was planned to be given after seven days of illness. However, only 31 patients remain as of July 31, 2020. We conducted simple random sampling before the intervention. Then, the patients were randomly divided into TPE group (n=10), CP group (n=11), and control group (n=10).

Interventions and data collection

Prior to intervention of TPE or CP, we collected pretest (day-0) data including study demographics, smoking history, body mass index, blood type, medication history, comorbidity, antiviral therapy, blood gas analysis profile (normal reference value) of pH (7.350-7.450), base excess (-2 - +3 mmol/L), $PaCO_2$ (27.0-41.0 mmHg), PaO_2 (83.0-108.0 mmHg), hematocrit (37-50%), HCO_3 (21.0-28.0 mmol/L), total CO_2 (19.0-24.0 mmol/L), SaO_2 (94-99%), FiO2, P/F ratio (400-500 mmHg), COVID-19 severity, and D-dimer (<250 ng/mL). The duration of intervention was estimated at 5 days. In post-test (day 5), we collected the same data as performed in the pretest (day 0). We controlled the risk of performance bias by homogenizing the standardized treatment for all patients based on *Pedoman Tatalaksana* COVID-19 *Edisi 1*.[9] All patients received Vasopressor therapy, Vitamin C, and Dexamethasone; moreover, there were slight variations in medication history, comorbidity, and antiviral therapy.

We performed TPE using a standard plasma exchange kit with anticoagulant solution A and citrate dextrose solution. We used fresh frozen plasma as a replacement solution. Total plasma volume to be replaced was formulated: plasma replacement (liter) = (1/13) x (100-hematocrit) x body weight (kg). We performed TPE through a standard femoral central venous catheter of 12 Fr. Each patient in the TPE group underwent five therapeutic procedures.

We obtained written consent-approved CP donors using the following criteria: previously confirmed SARS-CoV-2 by PCR, aged 18-60 years, free from COVID-19-related symptoms for more than 14-days. The donors gave plasma donation through the plasmapheresis procedure. They met blood donation criteria: seronegative results for hepatitis B, hepatitis C, Syphilis, and human immunodeficiency virus. We collected 500-600 mL plasma through an apheresis procedure, then we divided the plasma into four units of 100-150 mL plasma and stored them at 20°C. CP therapy was given thrice at 2-day intervals or one dose every 16 hours. The CP dose was 3 mL/kg of body weight. Its transfusion rate in the first 15 minutes was 10-20 mL, then its rate increased gradually and was completed within 4 hours.

Meanwhile, the control group was defined as confirmed COVID-19 patients who received guideline-based COVID-19 treatment like the other study groups but received neither TPE nor CP intervention.

Statistical analyses

The paired t-test was used to analyze the pretest–post-test mean difference of blood gas analyses profile, P/F ratio, COVID-19 severity, and D-dimer from the TPE, CP, and control groups. Before numerical data analyses, we ensured that all data were normally distributed and homogeny (Saphiro-Wilk test p>0.05 and Levene test p>0.05, consecutively). The One-way ANOVA was performed to analyze the mean difference of blood gas analysis profile, P/F ratio, COVID-19 severity, and D-dimer from each study phase, including pretest and post-test intervention (Figure 1). Furthermore, the Post-Hoc Tukey test was also performed if we found a significant result of mean comparison in One-way ANOVA. P-values <0.05 were considered statistically significant. The statistical analyses were performed using IBM SPSS version 22.0 for Windows.

RESULTS

The study demographic profile is presented in Table 1. Furthermore, the pretest clinical-laboratory data of all participants (n=31) from three groups were analyzed for homogeneity using One-Way ANOVA (Table 2). The pretest data showed homogeneous results, with all p-values >0.05, so the Post-Hoc Tukey test did not need to be carried out.

The post-test variable of pH, PaO_2, hematocrit, P/F ratio, COVID-19 severity, and D-dimer from three groups showed significant results (p<0.05) in One-way ANOVA (Table 3). Subsequently, their significant Post-Hoc Tukey tests including: pH_{CP} vs. $pH_{control}$ (7.47±0.12 vs. 7.33±0.09, p=0.014); PaO_{2TPE} vs. $PaO_{2Control}$ (91.27 ± 18.37 vs. 102.17 ± 13.34, p = 0.001); $hematocrit_{CP}$ vs $hematocrit_{Control}$ (42.18 ± 4.35 vs. 55.50 ± 8.04, p = 0.001); P/F $ratio_{TPE}$ vs. P/F $ratio_{Control}$ (407.60 ± 106.77 vs. 227.40 ± 69.72, p = 0.001); P/F $ratio_{CP}$ vs. P/F $ratio_{Control}$ (475.09 ± 68.31 vs. 227.40 ± 69.72,p = 0.001); COVID-19 $severity_{TPE}$ vs COVID-19 $severity_{Control}$ (1.20 ± 0.42 vs. 2.20 ± 0.42, p = 0.001); COVID-19 $severity_{CP}$ vs COVID-19 $severity_{Control}$ (1.00 ± 0.01 vs. 2.20 ± 0.42, p = 0.001); D-$dimer_{TPE}$ vs D-$dimer_{Control}$ (112.3103 ± 80.63 vs. 408.2289 ± 120.71, p = 0.001); D-$dimer_{CP}$ vs D-$dimer_{Control}$ (88.9525 ± 73.23 vs. 408.2289 ± 120.71, p = 0.001).

In the pretest-post-test comparison, almost all study variable data improved significantly, except for base excess, total CO_2, SaO_2 in the TPE group, and total CO_2 in the CP group. Meanwhile, overall variable data of the control group's pretest-posttest comparison did not show significant improvement (Table 4A-C).

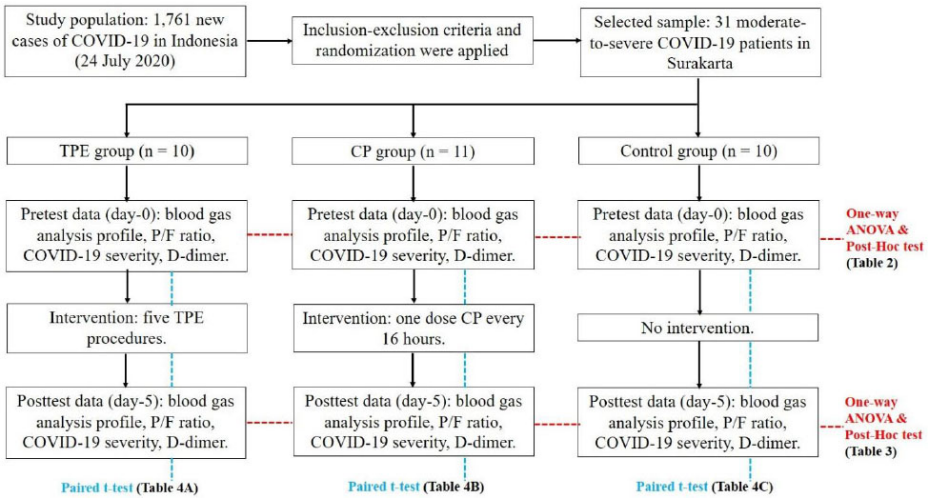

Figure 1. Flowchart diaphragm of the study design and the statistical analyses.

Table 1. Study demographic and clinical profiles.

Variable	n
Age (years)	
40-49	9 (29.03%)
50-59	8 (25.80%)
60-69	14 (45.17%)
Sex	
Male	18 (58.06%)
Female	13 (41.94%)
Smoking history for >1 year	
Yes	12 (38.70%)
No	19 (61.30%)
Body mass index	
Normal	13 (41.93%)
Overweight	5 (16.12%)
Obesity class I	5 (16.12%)
Obesity class II	6 (19.35%)
Obesity class III	2 (6.45%)
Blood type	
A+	6 (19.35%)
B+	5 (16.12%)
AB+	3 (9.67%)
O+	17 (54.86%)
Comorbidity	
Diabetes mellitus	9 (20.00%)
Hypertension	17 (37.78%)
Cardiovascular diseases	6 (13.33%)
Respiratory disorders	6 (13.33%)
Kidney diseases	7 (15.56)
Medication history	
Angiotensin-converting enzyme inhibitor	17 (28.33%)
Angiotensin receptor blocker	17 (28.33%)
Calcium channel blocker	3 (5.00%)
Diuretic	3 (5.00%)
β -Blocker	7 (11.67%)
Oral anti-diabetic	8 (13.33%)
β-Agonist	5 (8.33%)
Antiviral therapy	
Favipiravir	18 (37.50%)
Lopinavir + ritonavir	13 (27.08%)
Hydroxychloroquine	4 (8.33%)
Azithromycin	13 (27.08%)

DISCUSSION

Acute respiratory distress syndrome (ARDS) and cytokine storm are the major cause of death in COVID-19 patients.[6] TPE enables toxins clearance and reduces inflammatory cytokine serum levels, which provokes a cytokine storm. These main cytokines are TNF, IL-1, and IL-6. In the early stage of ARDS, IL-1 promotes chemokine production and vascular leakage. Meanwhile, elevated IL-6 in plasma bronchoalveolar lavage increases mortality in patients with ARDS. Reduced inflammatory cytokine in TPE helps to improve oxygenation and maintain homeostasis.[10] CP allowed antibodies from COVID-19 survivor patients to suppress the viral load. A primary immune response develops in normal conditions after 10-14 days of COVID-19 infection. These adaptive immunity perform virus clearance in COVID-19 patients. Based on theory, CP is more effective in the early stage of COVID-19 disease.[11]

Coagulation dysfunction in COVID-19 is likely to develop into a severe illness with high mortality. D-dimer as a coagulation biomarker will increase by excessive clots and hypoxemia secondary to COVID-19 infection. D-dimer describes the fibrin degradation process, and its elevation can predict deep vein thrombosis and pulmonary embolism.[12] In COVID-19 patients, TPE will eliminate anti-fibrinolytic mediators and reform anticoagulant proteins.[13] Antithrombotic properties of CP performed by substitution of missing coagulation factors and immunomodulatory action. Antiphospholipid antibodies are one of the autoantibodies that are neutralized by CP and lead to inhibition of the thrombotic process.[14]

Based on the laboratory profile in Table 3, Table 4A-B, the overall intervention study comparison showed that CP was superior to TPE. Great expectations have been placed on CP's ability to treat COVID-19. Studies showed that early administration of passive immunotherapy in CP usually results in greater efficacy; nevertheless, even low doses of this medication might be useful.[15] Early convalescent plasma transfusion is more useful than administered before both clinical-laboratory deteriorations.

Table 2. Pretest clinical-laboratory data of all three groups. Data were presented as mean±standard deviation.

Variable	TPE (n=10)	CP (n=11)	Control (n=10)	*p*-value*
Blood gas analyses				
pH	7.34 ± 0.05	7.31 ± 0.06	7.31 ± 0.05	0.320
BE	-1.96 ± 5.84	-4.46 ± 8.11	-2.27 ± 7.07	0.680
$PaCO_2$ (mmHg)	53.93 ± 14.24	51.81 ± 9.60	61.99 ± 14.94	0.194
PaO_2 (mmHg)	35.36 ± 13.29	36.00 ± 11.84	37.34 ± 13.57	0.940
Ht (%)	56.00 ± 3.74	56.09 ± 4.88	55.90 ± 7.96	0.997
HCO_3 (mmol/L)	13.55 ± 6.33	18.20 ± 4.93	17.02 ± 5.62	0.168
T-CO_2 (mmol/L)	26.73 ± 5.60	21.77 ± 6.71	23.05 ± 6.11	0.186
SaO_2 (%)	91.75 ± 4.18	91.50 ± 1.91	93.20 ± 3.52	0.464
FiO_2 (%)	30.50 ± 2.36	29.00 ± 2.68	30.60 ± 2.01	0.239
P/F ratio (mmHg)	115.90 ± 40.69	123.81 ± 38.24	124.50 ± 50.02	0.883
Severity	3.50 ± 0.52	3.36 ± 0.50	3.40 ± 0.51	0.825†
D-dimer (ng/mL)	158.03 ± 130.63	143.40 ± 141.05	447.98 ± 160.17	0.060

Note: TPE, Therapeutic Plasma Exchange; CP, Convalescent Plasma; BGA, blood gas analyses; BE, base excess; Ht, hematocrit; T-CO_2, total CO_2; Severity, COVID-19 Severity.
*One-way ANOVA, any significant results ($p < 0.05$) will be tested for Post-Hoc Tukey.
†Categorical variable data were analyzed by Chi square test, their mean-numerical values were defined as 1 = not ARDS, 2 = mild, 3 = moderate, 4 = severe.

Table 3. Posttest clinical-laboratory data of all three groups. Data were presented as mean ± standard deviation.

Variable	TPE (n=10)	CP (n=11)	Control (n=10)	*p*-value*
Blood gas analyses				
pH	7.41 ± 0.06	7.47 ± 0.12	7.33 ± 0.09	0.019
BE	1.12 ± 4.00	-0.35 ± 4.09	0.69 ± 2.99	0.650
$PaCO_2$ (mmHg)	43.97 ± 21.71	33.53 ± 5.55	47.36 ± 25.01	0.237
PaO_2 (mmHg)	91.27 ± 18.37	102.17 ± 13.34	52.52 ± 14.70	0.001
Ht (%)	47.70 ± 9.54	42.18 ± 4.35	55.50 ± 8.04	0.002
HCO_3 (mmol/L)	21.83 ± 7.57	24.78 ± 2.43	21.22 ± 1.51	0.182
T-CO_2 (mmol/L)	25.01 ± 4.82	21.27 ± 1.47	24.00 ± 3.63	0.057
SaO_2 (%)	94.00 ± 6.14	97.72 ± 1.10	92.80 ± 6.66	0.091
FiO_2 (%)	22.80 ± 2.85	21.54 ± 0.68	23.70 ± 3.23	0.154
P/F ratio (mmHg)	407.60 ± 106.77	475.09 ± 68.31	227.40 ± 69.72	0.001
Severity	1.20 ± 0.42	1.00 ± 0.01	2.20 ± 0.42	0.001†
D-dimer (ng/mL)	112.3103 ± 80.63	88.9525 ± 73.23	408.2289 ± 120.71	0.001

Note: TPE, Therapeutic Plasma Exchange; CP, Convalescent Plasma; BGA, blood gas analyses; BE, base excess; Ht, hematocrit; T-CO_2, total CO_2; Severity, COVID-19 Severity.
*One-way ANOVA, any significant results ($p < 0.05$) will be tested for Post-Hoc Tukey.
†Categorical variable data were analyzed by Chi square test, their mean-numerical values were defined as 1 = not ARDS, 2 = mild, 3 = moderate, 4 = severe.

CP treatment is also recommended as a curative therapeutic option in early-stage ARDS patients who do not need mechanical ventilation.[16] TPE may help to control the circulating inflammatory cytokines and hypercoagulable conditions by replacing the ADAMTS13 enzyme, whereas CP from recovered donors may aid in inactivating the virus by neutralizing antibodies.[17]

TPE can be challenging in the prone position, although it is a well-tolerated procedure by most reported studies. TPE in sepsis has been reported that both the disease severity and timing are important factors for TPE efficacy.[18] In our study, the detected TPE-associated adverse event was only hypotension; however, it can be resolved by vasopressor and hydrocortisone injection therapy. Hence, TPE should be considered for patients with COVID-19 because it reduces mortality in moderate-to-critical COVID-19 patients.[19]

Several meta-analyses and systematic review studies only reported CP-associated mortality causes in COVID-19 patients instead of the laboratory-clinical outcomes.[20] Thus, to determine CP efficacy, further CP-related studies are required to analyze the effect over the disease course, such as clinical-laboratory outcomes and prognosis. Moreover, further studies are needed to present the healthcare system's capacity to give optimal data to the larger population, especially in a low-income country. However, most studies remain uncertain about the adverse effects of convalescent plasma.[21,22]

Although protocol homogenization has been applied, this study may have several limitations and biases. First, the number of patients studied was small (n=31). Second, all groups of patients received antiviral and corticosteroid treatment, which may cause bias in the post-test. Third, the medical expenses consideration and several delays in informed consent approvals caused several TPE and CP treatment delays.

Table 4A. Pretest-posttest comparison of the clinical-laboratory data from TPE group (n = 10). Data were presented as mean ± standard deviation.

Variable	Pretest	Posttest	*p*-value*
BGA			
pH	7.34 ± 0.05	7.41 ± 0.06	0.047
BE	-1.96 ± 5.84	1.12 ± 4.01	0.116
$PaCO_2$ (mmHg)	53.93 ± 14.24	43.97 ± 21.71	0.024
PaO_2 (mmHg)	35.36 ± 13.29	91.27 ± 18.37	0.001
Ht (%)	56.00 ± 3.74	47.70 ± 9.54	0.022
HCO_3 (mmol/L)	13.55 ± 6.33	21.83 ± 7.57	0.009
T-CO_2 (mmol/L)	26.73 ± 5.60	25.01 ± 4.82	0.411
SaO_2 (%)	91.75 ± 4.18	94.00 ± 6.14	0.369
FiO_2 (%)	30.50 ± 2.36	22.80 ± 2.85	0.001
P/F ratio (mmHg)	115.90 ± 40.69	407.60 ± 106.77	0.001
Severity	3.50 ± 0.52	1.20 ± 0.42	0.001†
D-dimer (ng/mL)	158.03 ± 130.63	112.31 ± 80.63	0.034

Note: BGA, blood gas analyses; BE, base excess; Ht, hematocrit; T-CO_2, total CO_2; Severity, COVID-19 Severity.
*Paired t-test
†Categorical variable data were analyzed by Chi-square test, their mean-numerical values were defined as 1 = not ARDS, 2 = mild, 3 = moderate, 4 = severe.

Table 4B. Pretest-posttest comparison of the clinical-laboratory data from CP group (n = 11). Data were presented as mean ± standard deviation.

Variable	Pretest	Posttest	*p*-value*
BGA			
pH	7.31 ± 0.06	7.47 ± 0.12	0.001
BE	-4.46 ± 8.11	-0.35 ± 4.09	0.030
$PaCO_2$ (mmHg)	51.81 ± 9.60	33.53 ± 5.55	0.001
PaO_2 (mmHg)	36.00 ± 11.84	102.17 ± 13.34	0.001
Ht (%)	56.09 ± 4.88	42.18 ± 4.35	0.001
HCO_3 (mmol/L)	18.20 ± 4.93	24.78 ± 2.43	0.005
T-CO_2 (mmol/L)	21.77 ± 6.71	21.27 ± 1.47	0.794
SaO_2 (%)	91.50 ± 1.91	97.72 ± 1.10	0.001
FiO_2 (%)	29.00 ± 2.68	21.54 ± 0.68	0.001
P/F ratio (mmHg)	123.81 ± 38.24	475.09 ± 68.31	0.001
Severity	3.36 ± 0.50	1.00 ± 0.01	0.001†
D-dimer (ng/mL)	143.40 ± 141.05	88.95 ± 73.23	0.040

Note: BGA, blood gas analyses; BE, base excess; Ht, hematocrit; T-CO_2, total CO_2; Severity, COVID-19 Severity.
*Paired t-test
†Categorical variable data were analyzed by Chi square test, their mean-numerical values were defined as 1 = not ARDS, 2 = mild, 3 = moderate, 4 = severe.

Fourth, this study did not evaluate the inflammatory cytokines profile to justify the study results.

CONCLUSION

This intervention study highlights the benefit of TPE and CP therapy in moderate-to-severe patients, while a better clinical-laboratory improvement trend was observed in CP therapy. However, several studies reported CP therapy's uncertainty and safety controversy. Thus, this is urgent to perform further double-blind, randomized clinical trials of CP therapy in the larger sample size of moderate-to-severe COVID-19 patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

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ETHICAL CONSIDERATION

This study was approved by the Health Research Ethics Committee of Universitas Sebelas Maret (UNS) No.051/UN27.06.6.1/KEPK/EC/2020 and No.094/UN27.06.6.1/KEPK/EC/2020.

AUTHOR CONTRIBUTION

All authors contributed equally to this manuscript. All authors read and approved the final manuscript.

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Table 4C. Pretest-posttest comparison of the clinical-laboratory data from Control group (n = 10). Data were presented as mean ± standard deviation.

Variable	Pretest	Posttest	*p*-value*
BGA			
pH	7.31 ± 0.05	7.33 ± 0.09	0.605
BE	-2.27 ± 7.07	0.69 ± 2.99	0.309
$PaCO_2$ (mmHg)	61.99 ± 14.94	47.36 ± 25.01	0.022
PaO_2 (mmHg)	37.34 ± 13.57	52.52 ± 14.70	0.023
Ht (%)	55.90 ± 7.96	55.50 ± 8.04	0.857
HCO_3 (mmol/L)	17.02 ± 5.62	21.22 ± 1.51	0.018
T-CO_2 (mmol/L)	23.05 ± 6.11	24.00 ± 3.63	0.487
SaO_2 (%)	93.20 ± 3.52	92.80 ± 6.66	0.793
FiO_2 (%)	30.60 ± 2.01	23.70 ± 3.23	0.001
P/F ratio (mmHg)	124.50 ± 50.02	227.40 ± 69.72	0.001
Severity	3.40 ± 0.51	2.20 ± 0.42	0.001†
D-dimer (ng/mL)	447.98 ± 160.17	408.22 ± 120.71	0.467

Note: BGA, blood gas analyses; BE, base excess; Ht, hematocrit; T-CO_2, total CO_2; Severity, COVID-19 Severity.

*Paired t-test

†Categorical variable data were analyzed by Chi square test, their mean-numerical values were defined as 1 = not ARDS, 2 = mild, 3 = moderate, 4 = severe.

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