Original Article

Convalescent Plasma Therapy in Critically İll COVID-19 Patients: A Retrospective Cohort Study

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Abstract

Background: Convalescent plasma (CP) therapy can be defined as a passive immunity transfer approach involving the administration of plasma for therapeutic purposes to inpatients hospitalized due to an active virus infection. Passive immunity antibodies can reduce target organ damage and directly neutralize the responsible pathogens. A limited number of studies on the use of CP have reported that critically ill patients can benefit from CP therapy. **Aim:** We aimed in this study as the outcomes of CP therapy in critically ill coronavirus disease 2019 (COVID-19) patients in intensive care unit (ICU) and determine the differences between the recovery and mortality groups. **Patients and Methods:** This retrospective design study involved critically ill patients who were diagnosed with COVID-19 pneumonia or who were suspected of having COVID-19 in the ICU between April 1, 2020, and June 1, 2020. Comorbidity of patients, respiratory findings, hemodynamic data, laboratory data, and poor prognostic measures were compared between mortality and recovery group. **Results:** Convalescent plasma (CP) therapy was supplied for 41 (13.58%) patients in total of 302 COVID-19 patients. Twenty-nine patients were died in total of 41 COVID-19 patients who supplied CP therapy. The mortality rate is 70.73% in CP therapy. There was a significantly higher incidence ($P < 0.021$) of invasive mechanical ventilation (IMV) and significantly lower mean arterial pressure (MAP) values in mortality group ($P < 0.05$). There were significantly higher NLR values ($P < 0.05$), lower platelet count ($P < 0.05$), lower of glomerular filtration rate (GFR) level ($P < 0.05$), higher creatinine values ($P < 0.05$), higher lactate dehydrogenase (LDH) levels ($P < 0.05$), higher D-dimer levels ($P < 0.05$), higher level of pro-brain natriuretic peptide (BNP) ($P = 0.000$), rate of fever ($P = 0.031$), arrythmia ($P = 0.024$), and transfusion-associated circulatory overload (TACO) ($P = 0.008$) were more often in mortality group. **Conclusion:** Convalescent plasma therapy seems not useful in critically ill COVID-19 patients.

Keywords: *Convalescent plasma (CP), coronavirus disease 2019 (COVID-19), immunotherapy, transfusion*

Introduction

The novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) was described for the first time on January 13, 2020, after studies conducted in late December 2019 in the Wuhan province of China. The disease caused by SARS-CoV-2 was named coronavirus disease 2019 (COVID-19). COVID-19 infection begins with acute respiratory symptoms (fever, cough, shortness of breath) and progresses to more severe disease conditions such as SARS-CoV-2. The disease spreads rapidly to other provinces in the People's Republic of

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China through human-to-human transmission, and on to other countries, and the disease was declared a Public Health Emergency of International Concern on January 30, 2020. The pandemic continues to be threat to public health worldwide.[1,2]

There is as yet no definitive therapy or vaccine for the treatment of the disease, or to curb its rapid spread. There is a considerably high mortality rate associated with COVID-19, which can be attributed to the fact that not all aspects of the pathogenesis of COVID-19 have been fully explained, and no effective antiviral therapy has yet been developed. Recent treatment guidelines focus on supportive therapies, the treatment of secondary infections, and the prevention of complications.[3,4]

It has been suggested that the use of plasma, serum, or immunoglobulin concentrates recovered from patients who have survived and recovered from COVID-19 may be effective in the prevention and treatment of COVID-19.[5] The position statement declared by the World Health Organization (WHO) Blood Regulators Network on January 28, 2020, indicates that immune plasma, serum, or immunoglobulin concentrates can be used for those infected with SARS-CoV-2, as were administered in the previous Middle East Respiratory Syndrome (MERS) outbreak, in the absence of a vaccine and/or effective antiviral drugs. In relation to this, it has been emphasized that the competent authorities should enact the necessary legislation for the collection of immune plasma or serum.[6-8]

Prior to the SARS-CoV-2 outbreak, convalescent plasma (CP) therapy was applied successfully in the avian influenza A virus (H5N1) and swine influenza A virus **(**H1N1) influenza virus outbreaks, the Ebola virus outbreak, and the MERS-CoV outbreak in 2015.[9-13] CP therapy can be defined as a passive immunity transfer approach involving the administration of plasma for therapeutic purposes to inpatients hospitalized due to an active virus infection. Passive immunity antibodies can reduce target organ damage and directly neutralize the responsible pathogens.[3] A limited number of studies on the use of CP have reported that patients can benefit from this therapy.[14-17] There has yet to be controlled study clearly describing the target patient group for this treatment method. In light of early studies[16,17] published since the declaration of the pandemic, the Food and Drug Administration (FDA) has recommended the use of CP in COVID-19, preferably within the first 7–14 days of infection, in patients meeting certain criteria. The use of this therapy is not recommended after the onset of symptoms in the presence of a cytokine storm reaction.[18]

There must be a match between CP and the patient's ABO blood type (those with an AB blood type are universal plasma donors). The Rh factor compatibility can be overlooked. A minimum dose for a patient is one to two doses of a 200-ml CP unit, one unit daily, up to a maximum three doses (600 milliliter). Recent data related to the therapy suggest that a single dose of 200 milliliter could be effective. The decision on the total dose to be administered to a particular patient is at the discretion of the attending physician, who should take into account the clinical and laboratory findings of the patient. The scientific basis of this therapy is the avoidance of volume overload in a patient with an unstable cardiopulmonary status.[19]

The present study analyzes the outcomes of CP therapy in critically ill COVID-19 patients in intensive care unit (ICU) and determines the differences between the survivors and non-survivors.

Materials and Methods

Ethics

Ethics Committee approval was obtained for this study, dated May 29, 2020 and decision number 2020.05.2.14.070, from Istanbul Bagcilar Training and Research Hospital. Written informed consent was obtained from all of the participants and their legal representatives. Procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1975, as revised in 2000.

Study design

Selection and description of participants: This retrospective design study involved critically ill patients who were diagnosed with COVID-19 pneumonia or who were suspected of having COVID-19 in the ICU between April 1, 2020, and June 1, 2020.

Included in this study were patients with normal IgA levels and upper and with lower respiratory tract samples that tested positive for COVID-19; those with bilateral widespread pulmonary involvement and computerized tomography (CT) findings consistent with COVID-19; an increase of >50% in pulmonary infiltrates over the preceding 24–48 hours; a respiratory rate of >30 breaths per minute; arterial partial oxygen pressure PaO_2/fraction of inspired oxygen (FiO_2) (P/F) of <300 mmHg; oxygen saturation (SpO_2) of <90%, despite continuous oxygen supplementation via a nasal cannula at a flow rate of 5 liters/minute or higher; PaO_2 <70 mmHg, despite continuous oxygen supplementation via a nasal cannula at a flow rate of 5 liter/minute or higher; a need for mechanical ventilatory support and

the administration of vasopressors; an increase in Sequential Organ Failure Assessment (SOFA) Score; and those who are expected to exhibit rapid clinical progression (lymphopenia, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and elevated D-dimer). The study exclusion criteria were being under the age of 18; pregnant or breastfeeding; IgA deficiency; immunoglobulin deficiency; severe septic shock; severe decompensated congestive heart failure; P/F >300 mmHg; SpO_2 >90% with continuous oxygen supplementation via a nasal cannula at a flow rate of 5 liters/minute or higher; PaO_2 >70 mmHg with continuous oxygen supplementation via a nasal cannula at a flow rate of 5 liter/minute or higher; upper and lower respiratory tract samples testing negative for COVID-19; CT findings inconsistent with COVID-19; and rejection of the therapy by the patient or the legal representative.

The patients admitted to the ICU were monitored as a matter of routine. Those with reservoir oxygen masks (ROM), high-flow nasal oxygenation (HFNO), non-invasive mechanical ventilation (NIMV), and endotracheal intubation according to breathing patterns, blood gas analyses and vital sign monitoring were followed-up under invasive mechanical ventilation (IMV). The Acute Physiology and Chronic Health Evaluation (APACHE II) score and SOFA score were calculated and recorded to determine mortality and organ failure in the first 24 hours. The length of ICU stay (days), duration of mechanical ventilation (days), discharge from the ICU, and mortality were recorded. A blood type analysis was performed. A thoracic CT was obtained prior to hospitalization, and pulmonary condition was monitored through a weekly chest X-ray. Computed tomography scans of the lungs and/or chest X-ray were repeated in the event of any emergency. Therapy in the form of hydroxychloroquine in a 400 mg/day maintenance dose, followed by a loading dose of 400 mg, a favipiravir 1200 mg/day maintenance dose followed by a loading dose of 1600 mg/day, and antibacterial therapy with a beta-lactam antibiotic was initiated. Blood biochemistry and arterial blood gas analyses were obtained daily to monitor the course of the disease and the side effects of the medications. The vital findings and the monitorization data of the patients were recorded. In addition to this therapy, patients with normal IgA levels were planned to undergo CP therapy that had been harvested from male or female donors aged 18–60 years (having passed 19 years, but not passed 61 years) with no history of pregnancy, abortion, or curettage, who underwent serological testing as per the national legislation, who had not received a previous blood transfusion, and who had recovered from COVID-19.[3] In order for an individual to become a CP donor, the diagnosis of COVID-19 must have been established based on laboratory tests (positive PCR testing of nasopharyngeal swabs or positive antibody testing against SARS-CoV-2), at least 14 days must have elapsed since clinical recovery (cough, fever, shortness of breath, etc.), and at least two PCR testings of nasopharyngeal swabs must have revealed negative findings (one of the tests must have been performed within the last 48 hours). A negative test result was not a requirement if 28 days had elapsed since clinical recovery.[3]

As per the treatment recommended by the Ministry of Health of Turkey,[3] patients meeting the above-mentioned criteria were administered 200 ml CP therapy 7–14 days after diagnosis upon the joint decision of a pulmonologist, an infectious diseases specialist, and an anesthesiology and reanimation specialist. The ABO type of the transfused CP was compatible with the patient's ABO type. In addition, the CP was cross-matched with the patient's red blood cells to ensure compatibility. CP was administered at approximately 10 mL for the first 15 minutes and then increased to approximately 100 mL per hour with close monitoring. Adjustments in the infusion rates, based on the patient's risk of volume overload and tolerance, were at the discretion of the attending physicians. No premedication was given prior to CP therapy. If deemed appropriate, a second dose of 200 ml and a third dose of 200 ml CP therapy were added to the treatment, to be administered at 48 and 96 hours depending on the laboratory and vital findings of the patients, making a total dose of 600 ml. In patients who received CP therapy, body temperature (BT) (^{O}C), mean arterial pressure (MAP) (mmHg), heart rate (HR) (beat/min), FiO_2, PaO_2 (mmHg), SaO_2 (%), white blood cell count (WBC) (1000×10^3/uL), lymphocyte count (1000×10^3/uL), neutrophil-to-lymphocyte ratio, platelet count (1000×10^3/uL), ferritin (ug/L), D-dimer (ng/mL), (CRP) mg/dL, procalcitonin (ng/mL), fibrinogen (g/L), urea (mg/dL), creatinine (mg/dL), glomerular filtration rate (ml/min), potassium (mmol/L), lactate dehydrogenase (LDH) (U/L), triglyceride (g/dL), and Pro-BNP values were recorded at 24th, 48th, 72th, 96nd hours, and 5th and 7th days. Transfusion-Associated Circulatory Overload (TACO) complications, which occur in the presence of acute respiratory distress, pulmonary edema, high pro-BNP, evidence of left heart failure, and positive fluid balance within six hours of transfusion,[19] and a Transfusion-Related Acute Lung Injury (TRALI), characterized by fever, tachycardia, dyspnea, tachypnea and hypoxemia, also occurring within six hours of the transfusion,[20] in the geriatric patient population with predominant cardiovascular risk

factors and chronic renal failure who underwent CP therapy, were recorded.

Statistics: Descriptive statistics were expressed as mean, standard deviation, median, minimum, maximum, frequency, and ratio. A Kolmogorov–Smirnov test was used to test whether the variables were normally distributed. A Mann–Whitney U test and an independent samples *t*-test were used to analyze the quantitative data. Repeated measurements were analyzed using a paired-samples *t*-test, and Wilcoxon and McNemar tests. A Chi-square test was used for the analysis of qualitative data, and a Fisher's test was used when the conditions for a Chi-square test were not met. The SPSS 22.0 software package was used for the statistical analysis. The results were evaluated at a significance level of $P < 0.05$.

Results

Convalescent plasma (CP) therapy was supplied for 41 (13.58%) patients in total of 302 COVID-19 patients. Demographic data are shown in Table 1.

Twenty-nine patients were died in total of 41 COVID-19 patients who supplied CP therapy. The mortality rate is 70.73% in CP therapy.

The most prevalent comorbidity was hypertension (HT) (58.5%), followed by diabetes mellitus (DM) (48.8%), chronic obstructive pulmonary disease (COPD) (14.6%), cardiovascular disease (CVD) (12.2%), malignancy (12.2%), and chronic renal failure (CRF) (7.3%). There were no significant incidence differences between the groups ($P > 0.05$) [Table 2].

Mean of serum level of IgA, planned unit (s) of CP, and duration of reach to CP are shown in Table 3.

Respiratory findings are shown in Table 4. There was a significantly higher incidence of invasive mechanical ventilation (IMV) in mortality group ($P < 0.05$). At all times (baseline, 24th hour, 48th hour, 72nd hour, 96th hour, 120th hour, and 168th hour), PaO_2/FiO_2 ratios (P/F) were significantly lower in mortality group ($P < 0.05$).

Hemodynamic data are shown in Table 5. There were no differences in BT values at all times between the two groups ($P > 0.05$). There were significantly lower MA*P* values in mortality group ($P < 0.05$). There were no differences in HR values at all times between the two groups ($P > 0.05$). There were significantly lower SpO_2 values from the 24th hour between the two groups ($P < 0.05$).

Patients laboratory data are shown in Table 6. There were significantly higher NLR values at the 24th, 48th, 72nd, 96th, and 168th hours in mortality group ($P < 0.05$).

Table 1: Demographic data of the patients

	Mean±SD/*n* (%)	Median	Min.-Max.
Age (year)	61.5±11.8	61	37-87
Gender			
Male	27 (65.9%)		
Female	14 (34.1%)		
APACHE-II Score	27.8±4.2	28	19-38
Mean SOFA Scores	5.4±2.0	5	2-11
Duration of MV (day)	13.7±9.3	12	0-40
ICU length of stay (day)	16.8±9.9	14	5-40
Blood Type			
A Positive			20 (48.8%)
O Positive			9 (22%)
O Negative			4 (9.8%)
A Negative			3 (7.3%)
B Positive			2 (4.9%)
AB Positive			2 (4.9%)
B Negative			1 (2.4%)
AB Negative			0 (0%)

SD: Standard deviation, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential organ failure assessment score, MV: Mechanical ventilation, ICU: Intensive care unit

Table 2: Comorbidity of the patients

	Mean±SD/*n* (%)		*P*
	Mortality (*n*=29)	Recovery (*n*=12)	
HT			
(+)	19 (65.5%)	5 (41.7%)	0.158$^{\chi 2}$
(-)	10 (34.5%)	7 (58.3%)	
DM			
(+)	15 (51.7%)	5 (41.7%)	0.558$^{\chi 2}$
(-)	14 (48.3%)	7 (58.3%)	
COPD			
(+)	4 (13.8%)	2 (16.7%)	1.000$^{\chi 2}$
(-)	25 (86.2%)	10 (83.3%)	
CVD			
(+)	5 (17.2%)	12 (100%)	0.298$^{\chi 2}$
(-)	24 (82.8%)	0 (0%)	
Malignancy			
(+)	4 (13.8%)	1 (8.3%)	1.000$^{\chi 2}$
(-)	25 (86.2%)	11 (91.7%)	
CRF			
(+)	3 (10.3%)	0 (0%)	0.543$^{\chi 2}$
(-)	26 (89.7%)	12 (100%)	

HT: Hypertension, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, CVD: Cardiovascular Disease, CRF: Chronic Renal Failure, χ^2: Chi-squared Test (Fisher Test)

There were significantly lower platelet count at all times in mortality group ($P < 0.05$). There were significantly higher urea values at all times in mortality group ($P < 0.05$). There were significantly higher creatinine values at 96th and 168th hours in mortality

group ($P < 0.05$), and there were significantly lower of GFR level at baseline in mortality group ($P < 0.05$). There were significantly higher LDH levels at 48th, 72th, 96nd, and 120th hours in mortality group ($P < 0.05$).

Poor prognostic measures [blood lymphocyte count (c/µl), serum ferritin level (ng/ml), C-reactive protein (CRP) level (mg/dL), and D-dimer level (ng/ml)] are compared in Table 7. Only D-dimer levels of poor prognostic measures were significantly higher in mortality group ($P < 0.05$). There were no differences in blood lymphocyte count, serum ferritin level, and CRP between the two groups ($P > 0.05$).

There was no difference in transfusion related complications rate between the two groups ($P > 0.05$). Rate of fever, arrythmia, and TACO were more often in mortality group than recovery group ($P < 0.05$). There were significantly higher level of pro-BNP in mortality group ($P < 0.05$) [Table 8].

Table 3: Mean of serum level of IgA, planned unit (s) of CP, and duration of reach to CP

	Mean±SD/*n* (%)	Median	Min. Max
Serum level of IgA (mg/dL)	279.7±122.5	266	74-595
Planned unit			
I (one)	37 (90.2%)		
II (two)	4 (9.8%)		
Duration of reach to CP (day)	3.8±3.6	3	1-18

Discussion

There was limited literature knowledge about the CP therapy available when we began to feel the intensity of the COVID-19 pandemic at the end of March 2020.[21,22] CP therapy was the on the front burner after the publication of Republic of Turkey Ministry of Health COVID-19 National Guideline[3] and the information and explanations of our colleagues and members of the national scientific committee in news and talk programs on national television. In fact, we felt excessive pressure from patients' relatives on this matter and it was not easy to convince them that their patients were not suitable for CP therapy. However, the literature regarding the CP restricts its applicability especially in the countries with the acceleration stage and late accumulation stage of COVID-19.[23] CP therapy with antibodies against SARS-CoV-2 might be powerful against the infection.[24]

Limited information about for small number of drugs including anti-viral, antibiotics, anti-inflammatory drugs, and intensive supportive medication in the treatment strategies for COVID-19 patients that are in critical condition are present.[25] For the emergency cases of COVID-19, CP therapy is an alternative treatment option when there is no other specific treatment options.[15]

Our study was performed to evaluate the outcomes of CP therapy in critically ill COVID-19 patients who developed mortality and who did not. In critically ill

Table 4: Respiratory findings in two groups

	Mortality (*n*=29)			Recovery (*n*=12)			*P*
	Mean±SD/*n* (%)	Median	Min.-Max	Mean±SD/*n* (%)	Median	Min.-Max	
IMV							
(+)	29 (100%)			9 (75%)			0.021$^{\chi 2}$
(-)	0 (0%)			3 (25%)			
NIMV							
(+)	3 (10.3%)			4 (33.3%)			0.075$^{\chi 2}$
(-)	26 (89.7%)			8 (66.7%)			
HFNO							
(+)	29 (100%)			5 (58.3%)			0.001$^{\chi 2}$
(-)	0 (0%)			7 (41.7%)			
NBOM							
(+)	0 (0%)			12 (100%)			
(-)	29 (100%)			0 (0%)			
P/F baseline	143.2±55.8	136.0	71.0-278.0	203.5±43.8	199.0	118.0-276.0	0.003^{m}
P/F 24th h	129.7±55.2	120.0	54.0-276.0	215.5±63.7	232.5	120.0-300.0	0.001^{m}
P/F 48th h	144.5±79.0	131.5	45.0-352.0	234.3±76.7	210.0	145.0-371.0	0.002^{m}
P/F 72nd h	151.6±87.0	122.0	64.0-345.0	244.8±100.3	193.0	141.0-400.0	0.004^{m}
P/F 96th h	157.2±91.7	132.0	64.0-405.0	264.4±106.6	261.0	65.0-400.0	0.013^{m}
P/F 120th h	175.6±71.9	171.0	82.0-347.0	302.3±98.6	322.0	121.0-400.0	0.002^{m}
P/F 168th h	141.0±85.4	98.0	83.0-330.0	279.1±111.4	285.0	119.0-433.0	0.005^{m}

IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation, HFNO: High-Flow Nasal Oxygenation, NBOM: Non-breathing oxygen mask, P/F: PaO_2/FiO_2. χ^2: Chi-squared Test (Fisher Test), m: Mann–Whitney *U*-Test

Table 5: Hemodynamic data

	Mortality (*n*=29)			Recovery (*n*=12)			*P*
	Mean±SD/*n* (%)	Median	Min.-Max.	Mean±SD/*n* (%)	Median	Min.-Max.	
BT (°C)							
Baseline	36.5±0.2	36.5	36.0-37.2	36.5±0.2	36.5	36.4-37.0	0.959[m]
At 24th h	37.0±0.5	37.0	36.5-38.0	36.8±0.2	36.7	36.5-38.0	0.115[m]
At 48th h	36.9±0.5	36.9	36.0-38.0	36.8±0.5	36.8	36.5-37.5	0.350[m]
At 72nd h	37.0±0.5	37.0	36.5-38.5	36.8±0.4	36.8	36.4-38.0	0.200[m]
At 96th h	36.9±0.5	36.8	36.4-38.0	36.8±0.4	36.5	36.0-36.6	0.050[m]
At 120th h	36.7±0.5	36.5	36.0-38.0	36.5±0.2	36.5	36.0-36.7	0.056[m]
At 168th h	36.7±0.5	36.7	36.0-38.0	36.5±0.2	36.5	36.0-36.8	0.156[m]
MAP (mmHg)							
Baseline	69.9±3.5	70.0	60.0-76.0	73.2±4.7	74.0	63.0-80.0	0.017[m]
At 24th h	65.6±10.2	65.0	51.0-112.0	72.8±4.3	72.5	65.0-82.0	0.000[m]
At 48th h	64.0±6.7	66.0	48.0-71.0	70.0±4.2	70.0	60.0-79.0	0.002[m]
At 72nd h	65.3±5.2	65.0	55.0-74.0	70.3±4.4	70.0	65.0-81.0	0.017[m]
At 96th h	65.0±5.9	66.0	54.0-75.0	70.8±3.6	71.0	66.0-77.0	0.009[m]
At 120th h	65.5±5.0	65.0	58.0-75.0	69.8±3.9	70.0	61.0-76.0	0.021[m]
At 168th h	63.6±6.5	65.0	51.0-75.0	69.5±10.2	72.0	43.0-81.0	0.024[m]
HR (beat/min)							
Baseline	90.0±11.9	89.0	64.0-116.0	87.1±13.4	89.0	60.0-109.0	0.646[m]
At 24th h	97.0±14.9	99.0	66.0-124.0	94.9±11.5	93.0	77.0-121.0	0.557[m]
At 48th h	92.4±17.2	91.0	56.0-120.0	95.0±17.1	89.5	81.0-146.0	0.840[m]
At 72nd h	94.8±15.5	88.0	69.0-115.0	87.9±9.5	80.0	75.0-105.0	0.062[m]
At 96th h	90.4±19.5	85.0	62.0-140.0	84.2±9.4	83.0	70.0-99.0	0.516[m]
At 120th h	92.8±18.1	88.0	74.0-145.0	82.0±8.6	83.5	65.0-92.0	0.150[m]
At 168th h	97.8±23.3	90.0	74.0-146.0	80.4±8.1	79.0	65.0-94.0	0.121[m]
SpO_2 (%)							
Baseline	87.2±2.5	88.0	81.0-90.0	88.7±1.4	89.0	85.0-90.0	0.080[m]
At 24th h	87.5±4.4	88.0	76.0-94.0	91.1±1.6	91.0	89.0-95.0	0.007[m]
At 48th h	88.6±10.1	90.0	50.0-98.0	94.0±2.3	94.0	90.0-99.0	0.011[m]
At 72nd h	89.8±3.7	93.0	85.0-97.0	94.3±1.8	94.0	91.0-97.0	0.048[m]
At 96th h	92.4±3.7	94.0	85.0-96.0	95.8±1.4	96.0	93.0-98.0	0.003[m]
At 120th h	93.4±4.0	94.0	82.0-98.0	96.1±2.3	96.0	90.0-99.0	0.031[m]
At 168th h	93.3±4.4	96.0	86.0-98.0	97.1±4.8	96.5	84.0-99.9	0.049[m]

BT: Body temperature, MAP: Mean arterial pressure, HR: Heart rate, SpO_2: Oxygen saturation. m: Mann–Whitney *U*-Test

patients that received CP therapy, age, high SOFA scores, decreased thrombocyte counts, lessened lymphocyte counts after 72 h, diminished leukocyte counts after day seven, elevated plasma d-dimer levels within first 24 h, decreased plasma ferritin levels after day five, diminished plasma CRP levels after day 7, hypofibrinogenemia after 48 h, low GFR, hypokalemia after day five, elevated pro-BNP, presence of shock, and low Horowitz index are the remarkable markers in the development of mortality. In a large study conducted at Mayo Clinic in the USA by Joyner *et al*.,[26] the data of 5,000 patients who received transfusion were presented. The hypothesis behind this study was that the rate of serious adverse effects of CP therapy would diminish spontaneously and that mortality rate at Day 7 would not be elevated when compared to the other conditions related to COVID-19. They experienced 602 deaths within the first seven days after the patients received CP therapy. Product limit estimator revealed the estimation of seven-day mortality as 14.9% (95% CI: 13.8%, 16.0%) that was above the crude estimate of 12.0%. On the other hand, 456 mortalities were observed among the 3,316 ICU patients (16.7%, 95% CI: 15.3%, 18.1%). Moreover, 146 mortalities were encountered among the 1.682 hospitalized patients that did not admit to the ICU (11.2%, 95% CI: 9.5%, 12.9%).[26] Zeng Q-L *et al*. revealed the mortality in the treatment and control groups as 5/6 and 14/15, respectively, in their study

Table 6: Patients laboratory data

	Mortality (*n*=29)			Recovery (*n*=12)			*P*
	Mean±SD/*n* (%)	Median	Min.-Max.	Mean±SD/*n* (%)	Median	Min.-Max.	
WBCc (10^3/uL)							
Baseline	13.3±6.6	12.00	3.5-27.4	14.1±6.4	14.2	1.9-26.3	0.557[m]
At 24th h	13.7±6.6	12.50	2.5-27.7	15.3±10.3	13.5	1.7-43.2	0.637[m]
At 48th h	15.2±7.8	14.20	4.6-32.1	13.6±6.0	14.8	2.3-21.9	0.867[m]
At 72nd h	16.8±10.1	13.90	4.4-47.0	12.4±4.7	13.2	1.6-19.6	0.291[m]
At 96th h	20.6±14.7	13.90	6.8-56.4	12.5±5.1	12.5	1.7-20.7	0.201[m]
At 120th h	20.1±12.7	19.00	5.2-45.0	13.1±5.6	12.7	2.1-21.9	0.215[m]
At 168th h	14.6±7.3	11.20	7.3-27.2	11.3±5.4	9.90	1.8-20.3	0.398[m]
NLR							
Baseline	19.3±12.4	14.40	2.9-58.6	16.2±9.4	14.5	1.8-32.6	0.538[m]
At 24th h	20.7±12.4	18.10	3.0-54.6	12.4±7.4	11.2	2.1-26.1	0.034[m]
At 48th h	20.8±16.2	16.30	6.3-77.0	13.4±10.9	9.80	2.8-36.6	0.044[m]
At 72nd h	21.3±14.4	17.00	5.7-59.3	10.8±6.7	8.60	3.4-25.6	0.020[m]
At 96th h	21.2±16.4	18.50	5.1-74.4	9.7±5.5	9.90	2.7-21.9	0.013[m]
At 120th h	19.0±19.6	12.20	1.5-71.2	9.7±6.9	9.60	2.1-27.1	0.144[m]
At 168th h	15.5±5.3	15.30	5.4-23.1	9.2±6.5	8.60	1.3-22.6	0.020[m]
Platelet (10^3/uL)							
Baseline	272.9±114.0	295.0	48.0-477.0	468.4±236.8	461.0	52.0-846.0	0.010[m]
At 24th h	263.0±123.8	283.0	69.0-437.0	462.7±200.8	475.0	50.0-738.0	0.003[m]
At 48th h	273.7±131.8	285.0	73.0-538.0	461.8±195.4	475.0	70.0-752.0	0.009[m]
At 72nd h	264.2±126.8	299.0	75.0-507.0	421.1±176.7	438.5	99.0-696.0	0.017[m]
At 96th h	259.6±126.1	274.0	60.0-501.0	400.9±138.8	407.0	113.0-617.0	0.009[m]
At 120th h	258.2±129.2	256.0	55.0-488.0	390.0±142.4	388.0	149.0-696.0	0.027[m]
At 168th h	252.4±127.3	252.0	40.0-463.0	393.6±142.1	401.0	145.0-607.0	0.049[m]
PCT (ng/mL)							
Baseline	1.5±2.8	0.40	0.05-11.0	2.4±7.1	0.15	0.04-25.0	0.092[m]
At 24th h	1.2±2.0	0.40	0.05-8.8	2.4±7.2	0.10	0.02-25.0	0.072[m]
At 48th h	0.8±1.5	0.35	0.05-6.9	2.6±7.7	0.15	0.01-27.0	0.201[m]
At 72nd h	0.8±1.2	0.20	0.04-3.6	2.7±8.3	0.10	0.02-29.0	0.092[m]
At 96th h	1.4±2.5	0.25	0.04-10.6	3.0±8.9	0.10	0.01-31.0	0.070[m]
At 120th h	1.5±1.4	0.38	0.05-4.6	2.9±8.6	0.09	0.02-30.0	0.005[m]
At 168th h	1.2±1.1	0.28	0.04-3.0	2.8±6.9	0.09	0.03-22.0	0.487[m]
Fibrinogen (g/L)							
Baseline	400.6±135.3	413.0	150.0-670.0	460.9±144.2	437.5	275.0-691.0	0.217[m]
At 24th h	381.1±128.1	388.0	161.0-666.0	445.5±139.4	430.0	271.0-676.0	0.240[m]
At 48th h	362.2±137.1	347.0	83.0-661.0	440.0±134.2	433.5	268.0-650.0	0.163[m]
At 72nd h	376.4±135.6	374.5	85.0-659.0	432.0±126.5	412.5	261.0-661.0	0.330[m]
At 96th h	378.5±120.2	351.0	202.0-655.0	420.5±117.0	400.0	255.0-600.0	0.320[m]
At 120th h	362.7±122.4	331.0	221.0-641.0	403.9±119.0	366.0	250.0-591.0	0.278[m]
At 168th h	317.7±792.4	296.0	211.0-512.0	414.4±131.1	446.5	202.0-599.0	0.121[m]
Urea (mg/dl)							
Baseline	73.0±53.7	55.0	22.0-266.0	42.5±17.0	40.5	31.0-89.0	0.022[m]
At 24th h	71.3±45.8	57.5	17.0-204.0	43.9±19.1	35.5	28.0-90.0	0.021[m]
At 48th h	77.3±52.8	54.5	36.0-263.0	46.7±20.0	40.5	31.0-97.0	0.011[m]

Contd...

Table 6: Contd...

	Mortality (*n*=29)			Recovery (*n*=12)			*P*
	Mean±SD/*n* (%)	Median	Min.-Max.	Mean±SD/*n* (%)	Median	Min.-Max.	
At 72nd h	72.3±32.9	55.0	36.0-149.0	48.3±21.0	40.0	29.0-96.0	0.004m
At 96th h	80.6±43.1	70.0	26.0-188.0	51.4±27.8	42.0	29.0-126.0	0.013m
At 120th h	83.3±51.0	69.0	21.0-237.0	50.7±32.1	40.0	25.0-147.0	0.015m
At 168th h	75.5±30.7	66.0	37.0-140.0	50.7±31.1	42.5	25.0-135.0	0.012m
Creat. (mg/dl)							
Baseline	1.1±1.5	0.6	0.3-7.9	0.5±0.1	0.5	0.4-0.7	0.592m
At 24th h	1.2±1.9	0.6	0.2-10.0	0.5±0.1	0.6	0.3-0.7	0.312m
At 48th h	0.9±0.7	0.6	0.3-3.4	0.5±0.1	0.5	0.3-0.7	0.203m
At 72nd h	1.0±0.9	0.7	0.3-3.9	0.5±0.1	0.6	0.3-0.7	0.245m
At 96th h	0.9±0.7	0.7	0.2-2.3	0.5±0.2	0.5	0.2-0.9	0.046m
At 120th h	1.0±0.8	0.7	0.2-3.0	0.6±0.2	0.5	0.3-1.1	0.166m
At 168th h	0.9±0.4	0.7	0.3-1.4	0.5±0.2	0.5	0.2-0.8	0.033m
GFR (mL/min/1.73m^2)							
Baseline	91.7±35.1	99.0	13.0-146.0	115.9±12.5	115.5	93.0-142.0	0.014m
At 24th h	89.2±37.7	96.0	9.0-144.0	113.5±14.4	111.0	81.0-132.0	0.076m
At 48th h	92.6±37.7	91.5	11.0-142.0	116.8±16.9	115.5	85.0-151.0	0.087m
At 72nd h	91.3±36.5	92.0	22.0-148.0	114.4±13.4	115.5	84.0-137.0	0.071m
At 96th h	86.2±40.1	90.0	15.0-147.0	111.0±17.3	111.5	63.0-132.0	0.144m
At 120th h	85.6±36.6	94.0	10.0-125.0	110.1±23.1	114.0	61.0-144.0	0.097m
At 168th h	94.8±29.2	90.0	37.0-133.0	111.2±18.4	115.5	64.0-131.0	0.245m
K (mEq/L)							
Baseline	4.1±0.6	4.1	3.1-5.7	4.3±0.5	4.3	3.5-5.0	0.307m
At 24th h	5.9±8.3	4.2	2.8-4.9	4.4±0.5	4.4	3.5-5.1	0.574m
At 48th h	6.2±9.8	4.3	3.0-5.2	4.3±0.6	4.1	3.6-5.6	0.749m
At 72nd h	4.4±0.7	4.4	2.8-5.6	4.4±0.6	4.3	3.7-5.8	0.983m
At 96th h	4.4±0.8	4.2	3.3-6.6	4.3±0.6	4.3	3.2-5.3	0.984m
At 120th h	4.4±0.7	4.2	3.5-5.9	4.3±0.4	4.2	3.6-5.2	0.911m
At 168th h	4.4±0.6	4.3	3.7-5.7	4.3±0.3	4.2	3.9-4.8	0.749m
Triglyceride (mg/dL)							
Baseline	177.6±77.4	180.0	63.0-376.0	189.8±78.9	192.0	72.0-324.0	0.547m
At 24th h	178.7±78.3	183.0	78.0-388.0	181.0±72.2	182.0	76.0-319.0	0.886m
At 48th h	176.2±78.8	175.0	78.0-391.0	180.2±67.5	179.5	75.0-312.0	0.750m
At 72nd h	162.7±76.6	141.0	71.0-367.0	181.6±63.6	199.0	79.0-291.0	0.291m
At 96th h	170.5±97.1	151.0	63.0-496.0	176.3±57.7	200.0	81.0-268.0	0.361m
At 120th h	177.8±103.0	156.0	58.0-503.0	176.4±57.8	190.0	79.0-245.0	0.465m
At 168th h	217.5±143.2	180.0	55.0-550.0	168.7±63.7	181.0	75.0-250.0	0.647m
LDH (U/L)							
Baseline	563.9±216.9	534.0	336.0-133.5	523.6±159.2	500.0	345.0-902.0	0.616m
At 24th h	572.8±238.1	546.0	263.0-1270.0	511.7±193.4	416.0	361.0-1049.0	0.448m
At 48th h	780.2±848.8	590.0	234.0-4566.0	468.8±129.4	452.0	367.0-846.0	0.042m
At 72nd h	636.9±358.6	551.0	270.0-1880.0	467.4±134.6	439.5	366.0-869.0	0.030m
At 96th h	656.4±359.9	512.0	327.0-1925.0	404.5±87.8	394.5	292.0-593.0	0.003m
At 120th h	745.9±471.1	575.0	376.0-2161.0	448.9±103.0	456.0	302.0-579.0	0.017m
At 168th h	1143.5±1186.2	639.0	208.0-4072.0	437.0±125.7	445.5	209.0-601.0	0.057m

WBCc: White blood cell count, NLR: Neutrophil-to-lymphocyte ratio, PCT: Procalcitonin, GFR: Glomerular filtration rate, K: Serum potassium level, LDH: Lactate dehydrogenase. m: Mann–Whitney *U*-Test

Table 7: Poor prognostic measures

	Mortality (*n*=29)			Recovery (*n*=12)			*P*
	Mean±SD/*n* (%)	Median	Min.-Max.	Mean±SD/*n* (%)	Median	Min.-Max.	
bLc (10^3/uL)							
Baseline	1.0±0.9	0.7	0.1-4.0	0.9±0.6	0.8	0.2-2.1	0.626[m]
At 24th h	0.9±0.8	0.8	0.2-3.5	1.0±0.6	1.0	0.2-2.4	0.360[m]
At 48th h	0.9±0.6	0.9	0.3-2.6	1.0±0.8	0.8	0.1-2.7	0.893[m]
At 72nd h	1.0±0.9	0.8	0.2-3.5	1.3±0.8	1.2	0.1-3.2	0.239[m]
At 96th h	1.4±1.5	0.9	0.2-6.7	1.3±0.8	1.3	0.2-3.0	0.516[m]
At 120th h	1.3±1.2	0.9	0.3-4.1	1.3±0.6	1.5	0.3-2.4	0.341[m]
At 168th h	0.9±0.3	0.9	0.4-1.5	1.2±0.8	1.1	0.4-2.6	0.480[m]
Ferritin (ng/ml)							
Baseline	720.8±520.3	491.0	127.0-1500.0	658.1±394.0	580.5	85.0-1500.0	0.966[m]
At 24th h	731.8±513.8	454.0	103.0-1500.0	659.4±404.0	612.5	84.0-1500.0	0.841[m]
At 48th h	681.6±523.4	485.5	88.0-1500.0	638.6±420.9	543.0	83.0-1453.0	0.840[m]
At 72nd h	586.5±479.4	343.0	86.0-1500.0	606.6±429.2	426.0	81.0-1480.0	0.871[m]
At 96th h	586.8±512.6	343.0	107.0-1500.0	587.0±448.0	385.0	78.0-1459.0	0.968[m]
At 120th h	557.2±488.9	394.0	104.0-1500.0	534.9±432.3	336.0	69.0-1469.0	0.965[m]
At 168th h	561.0±489.6	312.0	151.0-1500.0	545.5±464.7	353.0	53.0-1489.0	0.944[m]
CRP (mg/dL)							
Baseline	102.4±88.6	77.0	5.1-287.0	111.4±116.7	63.0	5.6-386.0	0.989[m]
At 24th h	88.9±85.6	45.0	4.1-269.0	112.0±150.4	38.0	4.7-437.0	0.709[m]
At 48th h	97.9±95.4	57.0	8.0-308.0	114.6±164.0	42.5	4.2-539.0	0.750[m]
At 72nd h	100.0±107.0	53.0	6.6-382.0	103.6±151.6	25.0	3.0-499.0	0.543[m]
At 96th h	99.8±100.3	78.0	3.8-374.0	81.7±115.9	31.5	2.0-398.0	0.394[m]
At 120th h	120.6±1163	86.0	1.9-408.0	87.8±124.9	17.5	1.0-332.0	0.298[m]
At 168th h	134.9±1157	121.0	5.0-378.0	110.8±138.4	24.0	4.1-367.0	0.622[m]
D-dimer (ng/mL)							
Baseline	3.1±2.1	2.7	0.1-7.8	1.5±2.0	0.8	0.3-7.3	0.005[m]
At 24th h	3.1±2.0	3.0	0.4-7.1	1.7±1.4	1.1	0.3-4.9	0.034[m]
At 48th h	3.2±2.1	2.9	0.6-7.8	1.8±1.8	1.3	0.2-6.3	0.025[m]
At 72nd h	3.4±2.2	2.7	1.2-7.8	1.5±1.1	1.3	0.2-3.6	0.013[m]
At 96th h	3.1±2.1	2.5	0.7-7.1	1.3±0.9	1.4	0.2-2.7	0.011[m]
At 120th h	3.5±2.2	3.2	0.9-7.8	1.2±0.8	1.0	0.2-2.4	0.002[m]
At 168th h	3.4±2.4	3.4	0.6-7.9	1.3±0.9	1.3	0.2-2.5	0.022[m]

bLc: Blood lymphocyte count, CRP: C-reactive protein. m: Mann–Whitney *U*-Test

conducted in China (P = 0.184). The primary question should be asked before starting CP therapy is the early identification of the COVID-19 patients that have the potential of developing critical illness.[27]

One of the passive immunization techniques for the neutralization of the pathogen of SARS-CoV-2 is CP transfusion.[8] As with other virus infections, CP therapy is recommended for reducing COVID-19 mortality as early as possible after symptoms begin.[9] In order to prevent time loss in duration of reach to CP, we routinely request CP with hospitalization at ICU for all our patients. Although we could not provide data in our study about when the symptoms of our patients started, the time of the start of CP therapy in our patients was on the day 3.78 ± 3.52 of ICU hospitalization. Although we requested CP, our 18 patients resulted in mortality before CP therapy was started. The most important reasons for this are that CP therapy indications in our national guide are recommended in patients with severe lung findings and with life-threatening disease and that CP therapy is not performed in any place other than ICU in our hospital. So, these patients were deprived of CP therapy during their hospitalization. Therefore, in theory, CP transfusion should be more efficient in patients who receive the therapy at the early stages of the disease (e.g. before the day 14, or seronegative

Table 8: Transfusion-related complications

	Mortality (*n*=29)			Recovery (*n*=12)			*P*
	Mean±SD/*n* (%)	Median	Min.-Max.	Mean±SD/*n* (%)	Median	Min.-Max.	
Complication							
(-)	9 31.0%			7 58.3%			0.103$^{\chi 2}$
(+)	20 69.0%			5 41.7%			
Fever							
(-)	11 37.9%			9 75.0%			0.031$^{\chi 2}$
(+)	18 62.1%			3 25.0%			
Dyspnea							
(-)	26 89.7%			11 91.7%			1.000$^{\chi 2}$
(+)	3 10.3%			1 8.3%			
Arrhythmia							
(-)	13 44.8%			10 83.3%			0.024$^{\chi 2}$
(+)	16 55.2%			2 16.7%			
Hematuria							
(-)	29 100.0%			12 100.0%			0.000
(+)	0 0.0%			0 0.0%			
Vasopressor support							
(-)	8 27.6%			12 100.0%			0.000$^{\chi 2}$
(+)	21 72.4%			0 0.0%			
TACO							
(-)	11 37.9%			10 83.3%			0.008$^{\chi 2}$
(+)	18 62.1%			2 16.7%			
TRALI							
(-)	29 100.0%			12 100.0%			0.000
(+)	0 . 0.0.%			0 0.0%			
Cutaneous reactions							
(-)	29 100.0%			12 100.0%			0.000
(+)	0 0.0%			0 0.0%			
Pro-BNP	6076.0±9157.8	3369.0	32.0-35000.0	436.0±707.8	78.0	15.0-2030.0	0.000$^{\chi 2}$

S.D: Standard derivation, TACO: Transfusion-associated circulatory overload, TRALI: Transfusion-related acute lung injury, BNP: Brain natriuretic peptide. χ^2: Chi-square Test

and viremic stages).[28] The reason of the failure of decreasing the mortality rate may be due to the late CP therapy that was performed on the Day 21.5 of viral shedding period. However, when CP transfusion was performed on a single patient on day 11 during viral shedding, the patient eventually recovered. We believe that we are late to perform CP therapy. A randomized clinical trial indicated that the interval between the onset of the symptoms and randomization was between 22 and 39 days (27 days) and the time between the onset of the symptoms and admission was 5-20 days (12 days). No significant differences were observed in terms of outcomes of 28-day mortality, or time between randomization and discharge between the patient groups received CP transfusion or not.[2] Also, factors affecting CP therapy success include the number of transfusions, the volume, and its adjustment based on BMI and donor antibody titers.[16]

In a study conducted by Robert DJ *et al*. in UK,[5] COVID-19 patients in ICU on mechanical ventilation receive two doses of CP transfusion. The aim of this study is to investigate whether CP therapy is beneficial or harmful to the 2,000 patients that are included in the study. This trial is an adaptive trial and in case of having an evidence for that CP is for patients in critical condition, and then, the trial will be terminated, and all the patients admitted to ICU will receive CP therapy. REMAP-CAP and RECOVERY trails will give us very important information about CP therapy in critically ill patients. If CP therapy showed promising improvements in the outcomes of COVID-19, hyperimmunoglobulin production may be ensured by fractionation of CP containing considerable but diminished titers of anti-SARS-CoV-2 antibody.[5]

Benefit harm ratio of CP therapy should be considered. We should not forget that we transfuse blood products

to patients. Therefore, transfusion-related adverse reaction such as TRALI, TACO, anaphylactic reactions, hemolysis, chills, fever, transfusion-transmitted infections, etc., can be seen during CP therapy should be monitored closely.[7,10] CP therapy was reported by several studies as safe and not associated with major adverse outcomes in COVID-19.[6] After CP therapy, fever (P = 0.031), arrhythmia (P = 0.024), vasopressor support (P = 0.000), oliguria (P = 0.013), and TACO (P = 0.008) were observed more frequently in the group with mortality. Only two cases were reported to have adverse events related with transfusion including non-severe allergic/febrile transfusion reaction and severe dyspnea.[11] Transfer of the coagulation factors during the CP therapy may be harmful for the COVID-19 patients who are at risk of thromboembolic events. TACO and TRALI should be considered seriously as COVID-19 patients with comorbidities, who are potentially eligible for experimental CP transfusion, are at elevated risk of these adverse events.[1] Blood or plasma collection from only male individuals or from females who have never been pregnant (including miscarriages and abortions) is recommended to prevent TRALI.[11] Administration of promethazine hydrochloride or dexamethasone to the patients before CP therapy is required to decrease the risk of adverse reaction of the transfusion and enhance the clinical outcomes.[17] Ahn *et al*. indicated that CP transfusion may bear both pros and cons of corticosteroid administration when systemic corticosteroids were used. It is possible that corticosteroids not only decrease excessive inflammatory response but also promote the reduction of viral loads by CP therapy in concert.[14]

As Epstein stated,[11] COVID-10 CP preparation and transfusion must be carefully performed in especially in the countries with low and middle incomes. Major ethical, quality, and safety guidance must be followed during the donor selection, blood collection, and processing and CP transfusion.[13]

We used the CP therapy as a salvage treatment in critically ill COVID-19 patients. Mean APACHE-2 score of our patients was 27.8 ± 4.2. The predicted mortality rate was calculated as 55%. However, the mortality rate of our critically ill COVID-19 patients was 70.73% in CP therapy. Of course, the reason of this is multifactorial. Most importantly, mean SOFA scores of our patients are 5.4 ± 2.0 points. The SOFA score is used for the quantification of organ dysfunction, and it is a reliable discriminative tool for hospital mortality. SOFA score is still a very important tool in other various settings including in the detection of sepsis and the evaluation of the patient condition.[29] Various studies revealed that significant reduction in the viral load and mortality rate by CP therapy while treating COV infections, including SARS-CoV and MERS-CoV, especially when it was performed early after symptom onset.[12] A consensus among experts about volume and dosage of the CP has not been present yet. A volume between 200 and 600 mL of CP that is approximately 8-10 mL/kg and a maximum of 600 mL once per day with a duration of three consecutive days is recommended. This administration schedule could then be reperformed once more.[30] However, in our protocol, we only administered one unit of CP. In the mortality group, on the other hand, only four patients were transfused with two units of CP. Higher volumes could be contraindicated due to the risk of TACO.[30] Higher volumes of CP could be contraindicated because of the TACO risk.[30] However, TACO diagnosis was made in 18 of 29 patients (62.1%) in the mortality group. Higher pro-BNP levels were associated with higher mortality of patients with pneumonia.[31] The ADHERE study showed that BNP levels > 1730 pg/ml were associated with in-hospital mortality of 6%, versus 1.9% for BNP levels > 430 pg/ml.[32] In our recent study, pro-PNP levels in mortality group higher than recovery group (6076.0 ± 9157.8 > 436.0 ± 707.8 pg/ml, $P < 0.05$) were observed in mortality group compared to recovery group. Moreover, one patient were bearing four of six known risk factors for TACO as renal impairment, hypoalbuminemia, cardiac impairment and old age, plasma transfusion (received 1,400 mL of FFP), and fluid overload are the other risk factors.[15] However, the etiology of TACO likely has much more complexity than an abnormal blood volumes.[16] TACO may also arise even after transfusion with small volumes such as one unit or less.[30] TACO is a pulmonary oedema and that is mainly related to circulatory overload caused by three or more of the six factors including acute respiratory distress, radiographic pulmonary enema, increased central venous pressure, evidence of left heart failure, increased BNP, and a positive fluid balance.[20] Moreover, either BNP or NT-pro-BNP advises as a biomarker to diagnose TACO. But, in critically ill patients pro-BNP cannot used to diagnose TACO or differentiate it from TRALI.[19] We only measured once post-transfusion pro-BNP level in our patients. We cannot diagnose and distinguish neither TACO nor TRALI without pre/post-transfusion ratios of pro-BNP. Unfortunately, it was not possible to easily distinguish between TRALI and TACO in critically ill COVID-19 patients with ARDS.

Several limitations were present in this study. First, the sample size of this retrospective study was small. Second, we do not have any data regarding the time between the symptom onset and transfusion time.

Third, all patients received other accompanying medications including antiviral and anti-inflammatory drugs. Therefore, we cannot conclude on that the outcomes of the patients are the results of CP therapy alone. Fourth, standard CP transfusion therapy was allowed for the patients in both groups. Lastly, we did not have any data regarding the characteristics of the CP donors.

As a result, there are still questions that remain to be answered: (1) For which critically ill COVID-19 patients we need to start CP therapy? (2) How should the CP therapy be used in critically ill COVID-19 patients? (3) What is the optimal timing for CP administration in critically ill COVID-19 patients? (4) Is CP therapy efficient in critically ill COVID-19 patients? (5) What is the amount of CP unit required to be administered in critically ill COVID-19 patients? We have one answer for all: "we still don't know." Duan *et al*. stated in their studies regarding the outcomes as the optimal time points and dosage and the exact clinical benefits of CP therapy need to be investigated more in the randomized clinical trials.[18] A treatment may be not beneficial but should not be harmful. Clinicians working in intensive care units should/must notify the health authorities and evaluate the safety and necessity of CP therapy in ICU. We also recommend our colleagues to continue randomized clinical studies regarding this subject.

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Conflicts of interest

There are no conflicts of interest.

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