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The Effect of Convalescent Plasma Infusion in the Intensive Care Unit on Mortality of COVID-19 Patients: A Retrospective Cohort Study

Yoğun Bakım Ünitesinde Konvelesan Plazma İnfüzyonunun COVİD-19 Hastalarının Mortalitesi Üzerinde Etkisi: Retrospektif Bir Kohort Çalışması

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ABSTRACT *Objective:* This study investigates the effect of convalescent plasma (CP) addition to the standard treatment on mortality in critical coronavirus disease-2019 (COVID-19) patients.
Materials and Methods: This retrospective cohort study was conducted by evaluating the data of 255 critical COVID-19 patients in Marmara University Medical Faculty Hospital, Pandemic Intensive Care Unit (ICU), between April and November 2020.
Results: The patients were divided into two groups, a control group that received standard treatment (153; 60.0%) versus a second group that received CP in addition to standard treatment (102; 40.0%). The ICU mortality rate was found to be lower (p<0.05) in patients receiving CP (38; 37.3%) compared to patients not receiving CP (79; 51.6%). The use of CP was found to reduce the probability of ICU mortality in patients with Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score ≤10 [odds ratio (OR): 0.251; confidence interval (CI) 95%: 0.063-0.994, p=0.049) and APACHE-II score 11-14 (OR: 0.237; CI 95%: 0.066-0.844, p=0.026). CP transfusion, however, did not reduce the mortality in patients with an APACHE-II score of 15 and above. Furthermore, each day of delay in CP transfusion was found to increase the probability of mortality by 1.3 times (OR: 1.369; CI 95%: 1.155-1.622, p<0.001).
Conclusion: The addition of CP to standard treatment in COVID-19 patients followed in ICU reduces mortality.
Keywords: Convalescent plasma, COVID-19, SARS-CoV-2, intensive care unit, mortality

ÖZ *Amaç:* Bu çalışmada yoğun bakım ünitesinde (YBÜ) kritik koronavirüs hastalığı-2019 (COVİD-19) hastalarında standart tedaviye eklenen konvelesan plazma (CP) uygulamasının mortaliteye olan etkisi araştırıldı.
Gereç ve Yöntem: Retrospektif kohort şeklinde planlanan bu çalışma 1 Nisan 2020-1 Kasım 2020 tarihleri arasında Marmara Üniversitesi Tıp Fakültesi Hastanesi, Pandemi YBÜ'de, 255 kritik COVİD-19 hastasının verileri değerlendirilerek gerçekleştirildi.
Bulgular: Hastalar standart tedavi alan hastalar (153; %60,0) ve CP alan hastalar (102; %40,0) olarak 2 gruba ayrıldılar. YBÜ mortalite oranı CP alan hastalarda (38; %37,3), almayanlara göre (79; %51,6) daha düşük bulundu (p<0,05). Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II (APACHE-II) skoru ≤10 olan [olasılık oranı (OR): 0,251; güven aralığı (CI) %95: 0,063-0,994, p=0,049)] ve APACHE-II skoru 11-14 olan (OR): 0,237; %95: 0,066-0,844, p=0,026 hastalarda CP tedavisinin YBÜ mortalite olasılığını düşürdüğü belirlendi. APACHE-II skoru 15 ve üzerinde olan hastalarda CP transfüzyonunun mortaliteyi düşürmediği saptandı. Ayrıca CP transfüzyonundaki her bir günlük gecikmenin mortalite olasılığını 1,3 kat arttırdığı (OR: 1,369; CI %95: 1,155-1,622, p<0,001) belirlendi.
Sonuç: YBÜ'de takip edilen COVİD-19 hastalarında standart tedaviye ek olarak CP kullanımı mortaliteyi düşürmektedir.
Anahtar Kelimeler: Konvelesan plazma, COVİD-19, SARS-CoV-2, yoğun bakım ünitesi, mortalite

1. Introduction

Severe acute respiratory syndrome, coronavirus disease-2019 (COVID-19) pandemic caused by coronavirus 2 [severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)] infection, continues to affect global public health and related healthcare services seriously. More than 376 million confirmed cases and 5,666,064 deaths over 220 countries/regions worldwide reported COVID-19 cases as of February 2022 (1). This number continues to increase rapidly and is expected to threaten more people's daily life, mental and physical health (2).

COVID-19 infection symptoms range from asymptomatic infection, mild to moderate self-limiting respiratory disease to severe progressive pneumonia, multi-organ failure, and death (3,4). Previous studies reported that intensive care unit (ICU) follow-up is required in approximately 14% to 29% of patients who develop COVID-19 pneumonia (5,6). Standard supportive care and various therapeutic strategies ranging from oxygen supplementation and steroid therapy in mild pneumonia to extracorporeal membrane oxygenation (ECMO) in critically ill patients were investigated (4,7). One of the treatment strategies available in this complex and chaotic environment is the infusion of specific antibodies found in recovering patients' plasma to COVID-19 patients (8-12). The use of convalescent plasma in the treatment of other infectious diseases has proven effective; however, it is still under investigation in the context of COVID-19 (13).

The use of CP in the treatment of SARS, Middle East respiratory syndrome (MERS), and H1N1 (2009) patients were reported satisfactory efficacy and safety in the past two decades (13,14). CP transfusion can be a promising treatment for COVID-19 due to the similarities between SARS, MERS, and COVID-19 regarding virological and clinical features (15). Preliminary data from COVID-19 patients reported positive results of CP transfusion (16-18). The United States Food and Drug Administration (FDA) has approved the emergency use of CP for patients with severe or life-threatening COVID-19 (19). CP has a significant potential in the fight against COVID-19, although finding suitable donors, the timing of treatment, and logistical difficulties restrict its use (18,20). Studies investigating the results of CP transfusion in COVID-19 patients have emphasized that its use is beneficial, especially in the early period in hospitalized patients (8,11). However, some have found that it is not effective (9,10,16). Thereby the use of CP in patients followed up in ICU has become controversial. The inability to report the efficacy of CP use can be attributed to the fact that some patients receive it before being admitted to the ICU or patients are admitted to the ICU after the viral replication period has ended. Therefore, studies on the use of CP in COVID-19 patients in ICU are limited (12,17,18).

Complex results and timing of studies investigating the relationship between CP transfusion and the mortality of COVID-19 patients create uncertainty regarding CP's use in treating patients diagnosed with COVID-19 in ICU. Thereby, this study evaluates the effect of CP transfusion in critical COVID-19 patients in the ICU using a standardized approach in a large health center, donor selection, and CP preparation to eliminate this uncertainty.

2. Materials and Methods

2.1. Data Extract Center

This retrospective cohort study was conducted by evaluating the data of COVID-19 patients treated in Marmara University Training and Research Hospital, Pandemic ICU between April 1, 2020, and November 1, 2020.

2.2. Data Collection

The data of patients diagnosed with COVID-19 admitted to the ICU during the study period were collected by scanning the hospital electronic database and patient files.

ICU admission and CP administration, ICU and length of hospital stay, clinical parameters observed during ICU admission, and laboratory results of the patients were screened based on the age, gender, comorbidities, onset of symptoms, and time to hospital admission. The development and stage of acute kidney injury (AKI) according to the AKI criteria determined by Kidney Disease: Improving Global Outcomes, ARDS development, and severity according to the Berlin criteria, Acute Physiology and Chronic Health Evaluation-II (APACHE-II), Sequential Organ Failure Assessment (SOFA) score values calculated in the ICU, treatments (vasoactive drug, antibiotic) and interventions [mechanical ventilation (MV), hemodialysis, plasmapheresis, ECMO], developing secondary infections, duration of MV, and mortality data were evaluated during the ICU follow-up.

2.3. Study Population

The treatment of patients diagnosed with COVID-19 and admitted to the ICU during the study period was planned according to the guidelines published and updated by the Ministry of Health (21).

Requirements for obtaining CP from a recovering patient per guidelines published by the Ministry of Health are as follows: The diagnosis of COVID-19 infection via laboratory test results [polymerase chain reaction (PCR) test positivity studied from nasopharynx swab sample, or serological SARS-CoV-2 antibody positivity]. Clinically (cough, fever, shortness of breath, weakness, etc.) being at least 14 days after recovery, and at least two negative PCR tests studied from nasopharynx swab samples (one of the tests should have been performed within the last 48 hours of the other). Immune plasma donation is accepted from persons with neutralizing anti-SARS-CoV-2 titers 1:80 and above. It is separately labeled and applied as 200 mL divided components by apheresis procedure (22). In patients with expected rapid clinical progression and in patients with poor prognostic parameters, in the presence of tachypnea (respiratory rate >30/min), if the computed tomography findings are compatible with COVID-19 and there is a >50% increase in lung infiltration within 24-48 hours, if SaO_2<90% or PaO_2<70 mmHg was measured despite nasal oxygen support for 5 L/min. or more, if there was a need for vasopressor support, a need for MV, or an increase of at least 2 points in the SOFA score, CP was planned to be performed. Intubation was planned if hypoxemia, dyspnea-tachypnea (>30 breaths/min) continued despite oxygen therapy if accessory respiratory muscles were used (especially sternocleidomastoid) if there was a paradoxical breathing pattern if respiratory alkalosis ($PaCO_2$ <35 mmHg, pH>7.45) was present.

All patients admitted to the ICU with the diagnosis of COVID-19 during the study's planned period were planned to constitute the study sample. Twenty-five thousand one hundred and eighty patients applied to our hospital with the preliminary diagnosis of COVID-19 during the study period. One thousand nine hundred and forty patients diagnosed with COVID-19 were hospitalized. Three hundred and fifty-three patients diagnosed with COVID-19 were admitted to the ICU. It was calculated that at least 116 patients were required for our study with a 95% confidence interval (CI), 80% power, and a planned sample structure of 1/1. A total of 255 patients were included in the study, 102 patients who were followed up in the ICU after the exclusion criteria were applied and CP was transfused, and 153 patients received standard treatment (Figure 1).

2.3.1. Acceptance Criteria

All patients over the age of 18 years who were followed up in the ICU with the diagnosis of COVID-19 were planned to be included in the study.

2.3.2. Exclusion Criteria

Patients whose COVID-19 diagnosis could not be confirmed, ones with multiple ICU admissions, patients referred to an external center, and patients with missing data were excluded from the study.

2.4. Primary Conclusion

The primary objective of the study was to evaluate the effect of CP transfusion added to standard treatment in COVID-19 patients followed in ICU on mortality. The secondary objectives of the study were to evaluate the effect of timing of CP transfusion on mortality in criticaly ill COVID-19 patients and to determine the association of CP use with mortality in patient groups with different disease severity scores.

2.5. Ethical Issues

Institutional permission and ethics committee approval (protocol code: 09.2020.1159, date: 21.01.2021) were obtained from Marmara University Faculty of Medicine Clinical Research Ethics Committee before the research started. The study conforms to the provisions of the 1995 Declaration of Helsinki (as revised in Brazil, 2013).

2.6. Statistical Analysis

The data collected in the study were evaluated with SPSS 22.00 software. Shapiro-Wilk test was used to test the normal distribution of data. Categorical variables were given as frequency (n) and percentage (%), numerical variables as mean ± standard deviation or median and interquartile ranges. Independent samples t-test was used to compare numerical data and the Mann-Whitney U test was used when assumptions of this test could not be met. The chi-square test was used to compare categorical variables and Fisher's Exact test was used when the conditions of the chi-square test could not be met. In patients who underwent CP transfusion, plasma administration day was divided into 4 quarters (4, 5-6, 7-8, ≥9) to determine the relationship between the number of days from the onset of the disease to the administration of convalescent plasma and mortality. In addition, APACHE-II score was divided into 4 quarters (10, 11-14, 15-18, ≥19) to determine the relationship between disease severity and mortality. Logistic regression analysis was used to determine the relationship between the groups and mortality. The significance level was considered as $p<0.05$.

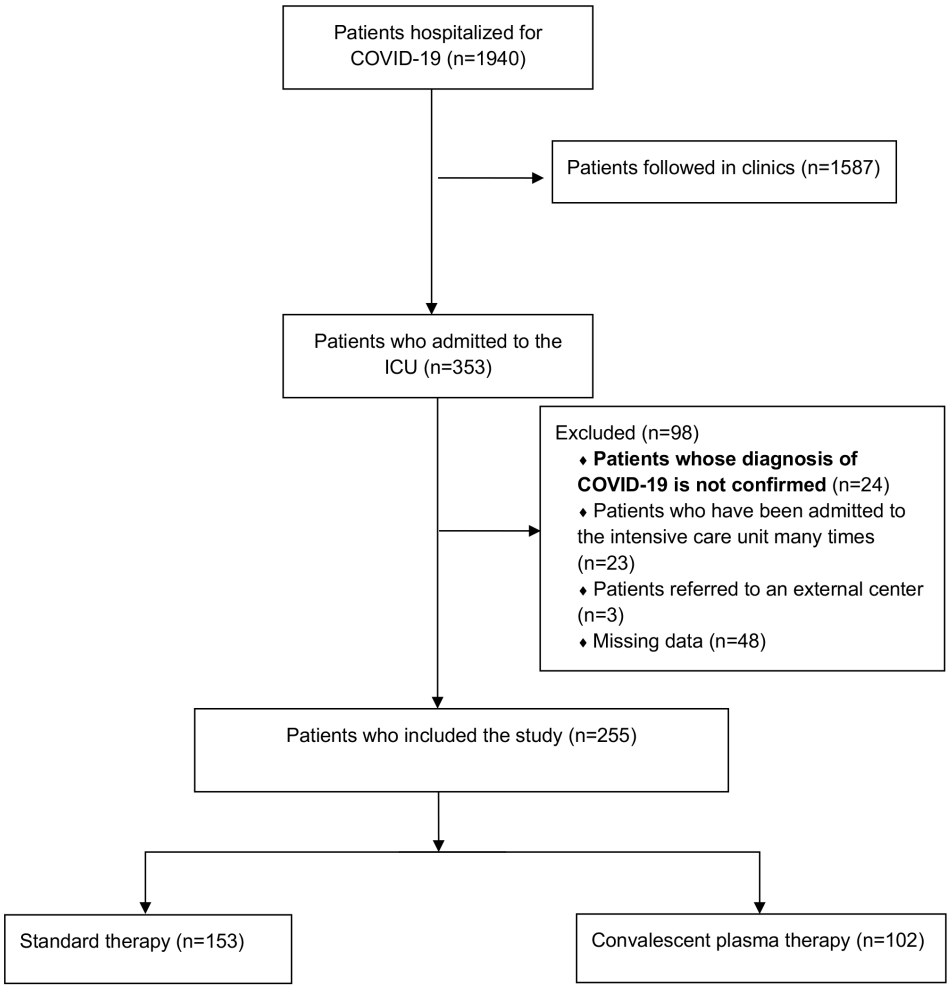

Figure 1. Flow diagram of patients selection
COVID-19: Coronavirus disease-2019, ICU: intensive care unit

3. Results

The general characteristics of the patients are provided in Table 1. The ICU patients were divided into two groups, one that received standard treatment (153; 60.0%) and another that received CP transfusion in addition to the standard treatment (102; 40.0%). Male gender was found to be more common in both groups; gender and age distribution between the two groups were found to be similar. The time from onset of symptoms to hospital admission and admission into ICU were similar in both groups. The prevalence of comorbidities was found to be similar between the two groups. The most common comorbidity was hypertension (HT) in both groups. HT frequency was more common in the group not receiving CP (79; 51.6%) compared to those receiving CP (39; 38.2%) ($p<0.05$). The vast majority of patients in both groups were diagnosed with acute respiratory distress syndrome (ARDS), which was seen in 95.1% (97) of CP receiving patients and 92.8% (142) of non-CP patients. The frequency of mild, moderate, severe ARDS, and PaO_2/FiO_2 ratio of the patients were found to be alike between the groups.

APACHE-II and SOFA scores were found to be alike between the two groups at ICU admission. Heart peak rate and minute respiration rate were higher, while oxygen saturation was lower in the group receiving CP ($p<0.05$). Ferritin, lactate dehydrogenase, and alanine aminotransferase were higher in patients receiving CP. On the other hand, D-dimer, troponin, brain natriuretic peptide, and creatinine were higher in the group not receiving CP when the patients' first laboratory parameters after ICU admission

Table 1. Demographic characteristics and admission symptoms of the patients			
Parameter	**Plasma- 153 (60) n (%) Median (IQR)**	**Plasma+ 102 (40) n (%) Median (IQR)**	**p-value**
Age (years), mean ± SD	64.27±15.21	61.59±14.22	0.158
Gender			0.168
Male	100 (65.4)	75 (73.5)	
Female	53 (36.4)	27 (26.5)	
Duration between symptom-hospital (day)	4 (2-7)	4 (3-6)	0.147
Duration between hospital-ICU (day)	4 (3-8)	4 (2-6)	0.141
Comorbidity	121 (79.1)	70 (68.6)	0.059
Hypertension	79 (51.6)	39 (38.2)	0.036
Diabetes	59 (38.6)	31 (30.4)	0.181
Cardiovascular disease	50 (32.7)	33 (32.4)	0.956
COPD	26 (17.0)	13 (12.7)	0.356
Malignancy	19 (12.4)	8 (7.8)	0.245
CRF	17 (11.1)	5 (4.9)	0.084
Cerebrovascular disease	23 (15.0)	9 (8.8)	0.143
Other	4 (2.6)	6 (5.9)	0.162*
Admission symptom			
Fever	59 (38.6)	54 (52.9)	0.024
Shortness of breath	103 (66.7)	80 (78.4)	0.042
Cough	53 (34.6)	46 (45.1)	0.093
Myalgia-arthralgia	25 (16.3)	23 (22.5)	0.214
Diarrhea	15 (9.8)	16 (15.7)	0.159
Nausea-vomiting	8 (5.2)	10 (9.8)	0.162
Headache	5 (3.3)	9 (8.8)	0.056
Other	9 (5.9)	10 (9.8)	0.243
ARDS	142 (92.8)	97 (95.1)	0.461
Mild ARDS	25 (16.3)	12 (11.8)	0.310
Moderate ARDS	52 (34.0)	39 (38.2)	0.488
Severe ARDS	65 (42.5)	46 (45.1)	0.680
PaO_2/FiO_2	110 (78-182)	120 (80-180)	0.752

IQR: Interquartile range, ICU: intensive care unit, COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, ARDS: acute respiratory distress syndrome, PaO_2: partial pressure of oxygen, FiO_2: fraction of inspired oxygen, *Fisher's Exact test

were examined (p<0.05). Procalcitonin, C-reactive protein, lymphocyte count, lymphocyte percentage, neutrophil/lymphocyte ratio, fibrinogen, and aspartate aminotransferase levels were found to be homogeneous between the two groups (Table 2).

Fifty-two (51.0%) patients who received CP during ICU follow-up and 108 (70.6%) patients who did not receive CP were mechanically ventilated (p<0.05). There were no differences between the two groups in terms of the duration of MV. High flow nasal cannula, non-invasive MV, and awake prone position frequency were higher in patients receiving CP. On the other hand, intubation prone position frequency was lower in patients not receiving convalescent plasma (p<0.05). Hemodialysis, cytokine filter, ECMO, and stem cell applications were alike in both groups. The drugs administered to the patients were similar in both

Table 2. Clinical and laboratory characteristics of the patients			
Parameter	**Plasma- 153 (60)**	**Plasma+ 102 (40)**	**p-value**
APACHE-II	15 (8-19)	15 (10-18)	0.774
SOFA	6 (4-8)	5 (3-7)	0.053
HR (per min)	97±24	107±23	<0.001
Systolic tension (mmHg)	121 (105-140)	120 (108-139)	0.429
Diastolic tension (mmHg)	68 (60-75)	70 (60-76)	0.761
Respiratory rate (per min)	32 (27-38)	36 (32-40)	<0.001
SpO_2 (%)	92 (88-95)	88 (84-90)	<0.001
Laboratory parameters			
Lymphocyte count (10^3 µL)	0.7 (0.5-1.1)	0.6 (0.4-0.8)	0.055
Lymphocyte (%)	7.0 (3.8-11.1)	6.4 (4.2-11.0)	0.579
Neutrophil/Lymphocyte ratio	12.0 (7.0-22.5)	13.8 (8.0-21.0)	0.333
Procalcitonin (ng/mL)	0.55 (0.16-1.76)	0.31 (0.14-1.30)	0.088
CRP (mg/L)	150 (89-224)	128 (96-195)	0.273
Ferritin (ng/mL)	527 (215-936)	647 (404-1137)	0.024
LDH (U/L)	478 (333-643)	573 (414-711)	<0.001
D-dimer (µg/mL)	1.97 (1.05-3.70)	1.24 (0.69-2.10)	<0.001
Fibrinogen (mg/dL)	591±187	574±171	0.470
Troponin (pg/mL)	33 (14-80)	17 (9-35)	<0.001
proBNP (pg/mL)	1284 (390-5605)	729 (178-1789)	0.002
Creatinine (mg/dL)	1.02 (0.71-1.72)	0.81 (0.63-1.31)	0.017
AST (U/L)	51 (35-81)	56 (37-77)	0.826
ALT (U/L)	33 (18-50)	39 (21-63)	0.021

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, HR: heart rate, SpO_2: Peripheral capillary oxygen saturation, CRP: C-reactive protein, LDH: lactate dehydrogenase, proBNP: brain natriuretic peptide, AST: aspartate transaminase, ALT: alanine transaminase

groups, with no significant differences between them. The most commonly administered drug was favipiravir in both groups. Other commonly administered agents were steroids, antibiotics, and tocilizumab (Table 3).

Forty-eight percent of the group receiving CP during ICU follow-up and 49% of the group not receiving CP developed AKI. The proportion of patients who developed AKI and its stages were found to be similar between the two groups. The incidence of secondary infection was 48.0% (49) in the CP group and 59.5% (91) in the non-CP group (p>0.05). The prevalence of pneumothorax, another complication, did not differ significantly between the two groups. Pneumothorax was detected in 4 (3.9%) patients and 13 (8.5%) patients who did not receive CP (Table 3). Rash and redness were reported in 2 (1.96%) patients who underwent CP transfusion. No other adverse effects and no severe complications were observed.

Mortality differed significantly between groups (Table 3). The 28-day mortality rate was lower in patients receiving CP (35; 34.3%) compared to those not receiving CP (73; 47.7%) (p<0.05). Furthermore, the ICU mortality rate was found to be lower (p<0.05) in patients receiving CP (38; 37.3%) compared to those not receiving CP (79; 51.6%). Length of ICU stay did not differ significantly between groups, although the length of hospital stay was longer in patients receiving CP [19 days; (14-17)] compared to patients not receiving CP [16 days (10-24)]. CP treatment was found to reduce the risk of ICU mortality in patients with APACHE-II score ≤10 [odds ratio (OR): 0.251; CI 95%: 0.063-0.994, p=0.049] and APACHE-II score 11-14 (OR: 0.237; CI 95%: 0.066-0.844, p=0.026) as a result of subgroup analyses conducted by dividing the patients into quarters according to APACHE-II score. CP transfusion did not significantly affect mortality probability in patients with APACHE-II score of 15 and above (Table 4).

Table 3. Interventions and treatments administered to the patients, developing complications and mortality			
Parameter	**Plasma- 153 (60) n (%) Median (IQR)**	**Plasma+ 102 (40) n (%) Median (IQR)**	**p-value**
Treatment			
Favipiravir	149 (97.4)	102 (100.0)	0.128*
Steroid	123 (80.4)	87 (85.3)	0.314
Tocilizumab	59 (38.6)	38 (37.3)	0.833
Cytokine hemoadsorption	23 (15.0)	18 (17.6)	0.578
Stem cell	6 (3.9)	1 (1.0)	0.159
Antibiotic	116 (75.8)	71 (69.6)	0.272
Vasopressor	104 (68.0)	51 (50.0)	0.004
Ventilation			
HFNC	31 (20.3)	62 (60.8)	<0.001
Awake prone positioning	34 (22.2)	59 (57.8)	<0.001
NIMV	5 (3.3)	26 (25.5)	<0.001
MV-intubation	108 (70.6)	52 (51.0)	0.002
Prone intubated	21 (13.7)	30 (29.4)	0.002
ECMO	6 (3.9)	6 (5.9)	0.469
Complication			
Seconder infection	91 (59.5)	49 (48.0)	0.072
AKI	75 (49.0)	49 (48.0)	0.878
AKI 1	21 (13.7)	19 (18.6)	0.292
AKI 2	12 (7.8)	12 (11.8)	0.094
AKI 3	42 (27.5)	18 (17.6)	0.071
Hemodialysis	38 (24.8)	19 (18.6)	0.244
Mortality			
Mortality ICU	79 (51.6)	38 (37.3)	0.024
28-day mortality	73 (47.7)	35 (34.3)	0.034
Duration of MV	6 (4-13)	6 (4-11)	0.877
Length of stay in the ICU	8 (5-14)	10 (6-14)	0.116
Length of stay in the hospital	16 (10-24)	19 (14-27)	0.015

IQR: Interquartile range, HFNC: high flow nasal cannula, NIMV: non-invasive mechanical ventilation, MV: mechanic ventilation, ECMO: extracorporeal membrane oxygenation, AKI: acute kidney injury, ICU: intensive care unit, *Fisher's Exact test

A significant relationship was determined between the time from onset of symptoms to plasma therapy and ICU mortality from subgroup analysis of patients receiving CP treatment. It was determined that CP transfusion was performed later in patients with mortality [8 days (6-9)] compared to patients without mortality [6 days (4-7)] (p<0.001). Each day of delay in CP transfusion increases the probability of mortality by 1.3 times according to the analysis obtained (OR: 1.369; CI 95%: 1.155-1.622, p<0.001). It was determined that there was no difference in mortality in the first four days between the patients who received CP treatment (OR: 0.410; CI 95%: 0.094-1.789). The probability of mortality increased approximately 3.5-fold in patients receiving treatment in 7-8 days (OR: 3.492; CI 95%: 1.012-12.051, p=0.048), and the increase in the probability of mortality was 5.6-fold (OR: 5.657, CI 95%: 1.792-17.854, p=0.003) in patients receiving CP treatment in 9 or more days as a result of the subgroup analyses conducted by

Table 4. Relationship between APACHE-II score and transfusion timing with mortality in patients receiving convalescent plasma therapy			
Parameter	**OR**	**CI %95**	**p-value**
APACHE-II score			
APACHE-II ≤10	0.251	0.063-0.994	0.049
APACHE-II 11-14	0.237	0.066-0.844	0.026
APACHE-II 15-18	0.500	0.191-1.310	0.500
APACHE-II ≥19	2.857	0.712-11.462	0.139
CP therapy			
CP therapy day	1.369	1.155-1.622	<0.001
CP subgroups			
CP ≤4 day	References		
CP 5-6 day	0.410	0.094-1.789	0.236
CP 7-8 day	3.492	1.012-12.051	0.048
CP ≥9 day	5.65	1.79-17.85	0.003
OR: Odds ratio, CI: confidence interval, APACHE-II: Acute Physiology and Chronic Health Evaluation-II; CP: convalescent plasma			

dividing the day data starting CP transfusion into quarters (Table 4).

4. Discussion

It was found that CP treatment in COVID-19 patients followed up in ICU reduced mortality in patients with low APACHE-II score (≤10) and had no effect on mortality in critical patients with a high APACHE-II score (≥15). Besides, CP transfusion timing was associated with mortality. It was found to increase in the patients who underwent CP transfusion on the 7th day and after compared to the patients who underwent CP transfusion within the first four days.

The mechanism of action of CP transfusion is well defined. The specific antibodies present in CP bind to the virus and neutralize its virulent activity. The use of virus-neutralizing antibodies reduces viral load and prevents SARS-CoV-2 from entering uninfected cells (23). Thus, CP can suppress the peak viremia within seven days of infection, followed by virus cleansing with the onset of patients' immune response (24). This theoretical basis explains why CP transfusion in the early period of COVID-19 is more effective than late transfusion. Another critical issue in CP activity is the amount of neutralizing antibodies it contains. The use of CP with low antibody levels may cause a weaker response than desired in humoral immunity. US-FDA recommends the measurement of neutralizing antibody titers in CP. A titer of 1:160 is recommended if the measurement is possible. An antibody titer of 1:80 is also indicated to be acceptable if the measurement cannot be performed according to US-FDA. In addition, it is recommended that appropriate donors are selected to obtain effective CP, and CP is collected in licensed blood institutions under standard procedures and regulations for plasma collection (25).

The results of previous studies investigating the relationship between the use of CP and mortality in COVID-19 patients are contradictory (8-12,16,26-28). Some studies have reported a decrease in mortality similar to our results (8,11,16,27), whereas others have reported that CP transfusion is ineffective on mortality (9,10,12). The mortality rate of CP transfused patients was found to decrease by 51% compared to standard treatment in a systematic analysis of CP transfusion in COVID-19 (27). Mortality after 7 and 30 days of CP transfusion was analyzed; it was found that CP transfusion reduced mortality in a large study evaluating the data of patients with severe or life-threatening COVID-19 who received at least one unit of CP transfusion at hospitalization (16). These results support CP efficacy as a therapeutic tool in COVID-19. However, a Cochrane analysis including 20 studies concluded that the effect of CP transfusion on mortality is uncertain contrary to the above results (28). CP transfusion was not found to be superior to placebo in patients diagnosed with COVID-19 pneumonia when the 30-day clinical results were examined in a multicenter study excluding mild and moderate pneumonia cases (10). CP transfusion was not associated with 28-day mortality in another multicenter study involving patients with severe COVID-19 pneumonia (9). These complex results may

have been caused by the lack of standardization and control procedures regarding the donor selection process, the level of antibodies in CP units, the different timing of transfusion, and the severity of the disease in patients. This may even explain the different outcomes seen in similar patient groups.

The optimal timing of CP treatment is unknown (29). It is known to have higher efficacy when transfused early in the course of an infectious disease in the past (30). In agreement with our results, previous results show that each one day delay for CP transfusion increases the probability of mortality in patients by 36%. In agreement with our results, previous results show that each one day delay for CP transfusion increases the probability of mortality in patients by 36%. A meta-analysis study found that COVID-19 patients treated with early CP transfusion were more likely to survive (31). It was concluded in another study that CP reduced mortality in patients who underwent transfusion within 72 hours (11). Another recent study established that CP transfusion within 72 hours in the early stages of COVID-19 reduced the risk of progression to severe respiratory disease by 48% in elderly adult patients (8). A multicenter study conducted in the USA determined that the mortality of patients who received CP transfusion within the first 72 hours was lower than that of patients who underwent later CP transfusion (32). These results indicate that the therapeutic effect of CP transfusion is associated with transfusion timing.

Another parameter affecting the results in patients undergoing CP transfusion is disease severity. The fact that CP transfusion was found to reduce mortality in patients with low APACHE-II scores and not associated with mortality in patients with high scores supports this hypothesis. The results of our study are consistent with previous studies. CP use was associated with clinical improvement in severe cases in a similar study; however, it was not associated with critical patients' mortality (12). A meta-analysis study concluded that mild COVID-19 cases benefited more from CP transfusion when compared to critical cases (31). The advanced pathological process accounts for the lack of CP efficacy in critical cases with high APACHE-II scores (26). The mortality estimation obtained with the APACHE-II score is found to be lower when applied to COVID-19 patients compared to normal ICU patients (33). This can be explained by the fact that Glasgow coma score, an important component of the APACHE-II score, remains high in COVID-19 infection. In COVID-19 patients, the nervous system is typically less affected than the respiratory system (33). Additionally, a study established that neutralizing immunoglobulin G autoantibodies against interferon was not detected in asymptomatic or mild COVID-19 cases but was in 10.2% of critical COVID-19 cases, emphasizing the possibility of potential harm related to CP (34). These autoantibodies may cause a defective type I interferon response, contributing to the severity of the disease. Transfer from donor to critical COVID-19 patient with CP may lead to the exacerbation of the case. The longer ICU stay in patients undergoing CP can be explained by the lower mortality in patients undergoing CP. Low CP mortality may have caused more living patients to stay in the ICU and the ICU stay to be longer in patients who underwent CP.

The study has some limitations such as the implementation of standardized treatment protocols according to the recommendations of the current guidelines published by the Ministry of Health of all patients, the evaluation of factors such as secondary infection that may have an effect on the prognosis, AKI development, and the absence of data loss in the patients included in the study due to the completion of the entire treatment process in our hospital in addition to the strengths of our study. First, it lacks dynamic clinical and laboratory data due to its retrospective design. Furthermore, this retrospective design can inevitably result in some confounding factors (for example, biased patient selection). The data were collected from the electronic health record database. This prevented the possible level of detail with manual medical record review. All of our patients were treated in a single health center from a single geographical region. Therefore, the factors associated with the results may vary in other geographical regions despite the diversity in our patient population. The relationship between the quality of donor plasma and the efficacy of CP treatment could not be evaluated due to the lack of detailed data on neutralizing antibody titer in CP units. The significant difference between the groups in prone positioning, both awake and after intubation, may have affected mortality. The possibility of obesity contributing to death in COVID-19 patients was excluded from the study due to a lack of data on body mass index.

5. Conclusion

The inclusion of CP to the standard treatment in COVID-19 patients with similar demographic and clinical features followed in ICU resulted in reduced mortality compared to

only standard treatment. The use of CP is reliable, and the rate of complications is low. CP efficacy is influenced by the timing of transfusion and the severity of the case. This study concludes that early CP transfusion reduces mortality in critically ill COVID-19 patients.

Ethics

Ethics Committee Approval: Institutional permission and ethics committee approval (protocol code: 09.2020.1159, date: 21.01.2021) were obtained from Marmara University Faculty of Medicine Clinical Research Ethics Committee before the research started.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Concept: M.S.S., F.G., B.B., S.T.K., B.D.O., İ.C., Design: M.S.S., F.G., B.B., S.T.K., B.D.O., İ.C., Data Collection or Processing: M.S.S., F.G., B.B., S.T.K., B.D.O., İ.C., Analysis or Interpretation: M.S.S., F.G., B.D.O., İ.C., Literature Search: M.S.S., F.G., B.D.O., İ.C., Writing: M.S.S., F.G., B.D.O., İ.C.

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