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Evaluation of the Effectiveness of Convalescent Plasma Therapy in Severe and Critical COVID-19 Patients

Şiddetli ve Kritik COVİD-19 Hastalarında Konvelesan Plazma Tedavisinin Etkinliğinin Değerlendirilmesi

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ABSTRACT *Objective:* Relevant studies have suggested that the administration of convalescent plasma (CP) collected from COVID-19 patients who have recovered from the infection and whose plasma contains antibodies against SARS-CoV-2 is safe and may be effective in treating COVID-19 patients. The present study aimed to investigate whether the number of CP doses administered, the power of the IgG ratio and the time of CP administration following positive SARS-CoV-2 PCR had an impact on the 30-day in-hospital mortality.

Materials and Methods: This single-center retrospective study was conducted with patients who were hospitalized and met the severe/critical COVID-19 disease criteria and received CP. Demographics, comorbidities, co-medications, onset of symptoms, duration between SARS-CoV-2 PCR testing and hospitalization, the time of the first CP administration, laboratory results, respiratory support needs, O2 saturation, fever at the baseline, APACHE II scores and SOFA scores were recorded.

Results: Of the 224 patients with the mean age of 64.2±14.5 (19-91) years, 143 were male. The most common comorbidities were hypertension and congestive heart failure. Chronic renal failure, mechanical ventilation needs, PO2/FiO2 <300, clinically rapid progression, persistent fever, SOFA score increase and increased vasopressor need were associated with increased mortality. There was a statistically significant difference between the deceased (14.0±8.2) and survivor (8.74±5.28) groups in terms of APACHE II scores (p<0.001). The number of CP units administered, the power of the IgG ratio in the CP units and the timing of CP administration had no effect on the need for respiratory support and mortality rate. CP-associated complications were observed in 11 (0.5%) patients.

Conclusion: In conclusion, CP therapy was not associated with improved survival or other positive clinical outcomes in severe/critical COVID-19 patients.

Keywords: severe/critical COVID-19, intensive care ünit, convalescent plasma, the power of the IgG ratio, SOFA score, The APACHE II score, macrophage activation syndrome

ÖZ *Amaç:* İlgili çalışmalarda, iyileşen ve plazmaları SARS-CoV-2'ye karşı antikorlar içeren COVID-19 hastalarından toplanan konvelesan plazma (KP) uygulanmasının güvenli olduğunu ve COVID-19 hastalarının tedavisinde etkili olabileceğini öne sürülmekte. Bu çalışma, pozitif SARS-CoV-2 PCR'yi takiben uygulanan KP dozlarının sayısının, IgG oranının gücünün ve KP uygulama süresinin 30 günlük hastane içi mortalite üzerinde bir etkisi olup olmadığını araştırmayı amaçladı.

Gereç ve Yöntem: Bu tek merkezli retrospektif çalışma, hastaneye yatırılan ve ciddi/kritik COVID-19 hastalığı kriterlerini karşılayan ve KP alan hastalarla yapılmıştır. Demografi, komorbiditeler, ek ilaçlar, semptomların başlangıcı, SARS-CoV-2 PCR testi ile hastaneye yatış arasındaki süre, ilk KP uygulamasının zamanı, laboratuvar sonuçları, solunum desteği ihtiyaçları, O2 satürasyonu, başlangıçtaki ateş, APACHE II skorları ve SOFA skorları kaydedildi.

Bulgular: Yaş ortalaması 64,2±14,5 (19-91) olan 224 hastanın 143'ü erkekti. En yaygın komorbiditeler hipertansiyon ve konjestif kalp yetmezliği idi. Kronik böbrek yetmezliği, mekanik ventilasyon ihtiyacı, PO2/FiO2 <300, klinik olarak hızlı ilerleme, inatçı ateş, SOFA skorunda artış ve artmış vazopresör ihtiyacı mortalite artışı ile ilişkilendirildi. APACHE II puanları açısından ölen (14,0±8,2) ve yaşayan (8,74±5,28) grupları arasında istatistiksel olarak anlamlı fark vardı (p<0,001). Uygulanan KP ünitesi sayısı, KP ünitelerindeki IgG oranının gücü ve KP uygulama zamanlaması, solunum desteği ihtiyacı ve ölüm oranı üzerinde hiçbir etkiye sahip değildi. 11 (%0,5) hastada KP ile ilişkili komplikasyonlar görüldü.

Sonuç: Sonuç olarak, KP tedavisi, şiddetli/kritik COVID-19 hastalarında sağkalım veya diğer pozitif klinik sonuçlarla ilişkili değildi.

Anahtar Kelimeler: şiddetli/kritik COVID-19, yoğun bakım ünitesi, konvelesan plazma, IgG oranının gücü, SOFA skor, APACHE II skoru, makrofaj aktivasyon sendromu

Introduction

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection is presented with a wide range of clinical spectrum from asymptomatic to severe pneumonia, multiple organ failure, and death (1-3). While 80% of reported cases are estimated to have a mild or asymptomatic course of infection, approximately 5% are admitted to the intensive care unit (ICU) with acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure, or all three (4-6). Patients with a respiratory rate >30/min, or SpO2 in room air <90%, along with clinical signs of pneumonia, have been defined as severe COVID-19 cases, whereas those who have ARDS or respiratory failure requiring ventilation, sepsis, or septic shock as critical COVID-19 cases (7).

In the absence of other specific therapies, convalescent plasma (CP) has been used as either prevention or treatment to provide immediate passive immunity with variable success in various infectious diseases (8-10). In the early period of the COVID-19 pandemic, randomized controlled studies and case series have suggested that the administration of CP was collected from COVID-19 patients who have recovered from the infection and whose plasma contains antibodies against SARS-CoV-2 is safe and may be effective in treating COVID-19 patients (11-14). Concurrently with the studies, in August 2020, the American Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for CP in the treatment of hospitalized COVID-19 patients (15).

Our study aimed to evaluate the application of COVID-19 CP in severe and critically hospitalized COVID-19 patients with a lack of information in terms of hospital mortality and changes in clinical and laboratory markers in the early course of the disease.

Materials and Methods

Patients

This single-center retrospective study was commenced at Ege University Hospital (EUH) after receiving approval from the Clinical Research Ethical Committee (Ethical Committee Number 20-5T/48).

The adult patients admitted to the hospital COVID-19 ICU and services dedicated to treating COVID 19 patients who met the severe/critical disease criteria and received COVID-19 CP between April 2020 and January 2021 were included in the study.

The Study Protocol and Data Collection

The CP collection and administration were performed based on the COVID-19 Immune (Convalescent) Plasma Supply and Clinical Use Guideline of the Ministry of Health of Turkey (16).

We have obtained the clinical and specific laboratory data from the electronic file records of the patients. The demographics, comorbidities, co-medications, onset of symptoms, the time lag between SARS-CoV-2 PCR testing and hospitalization, and the time of the first CP use of the patients were recorded. The laboratory assessments associated with the severity of COVID-19, including neutrophil to lymphocyte ratio (NLR), CRP, procalcitonin, ferritin, D-dimer, and platelet values, were detected. Respiratory support that the patient need, O2 saturation, fever, and the relevant laboratory parameters were determined at the baseline, 48 and 72 hours, and five days after CP administration. APACHE II scores were obtained during hospitalization, and SOFA scores were recorded during hospitalization, baseline, and fifth day of CP administration. IgA deficiency was excluded in all patients before CP transfusion. Adverse events following the first 24 hours of CP infusion were noted.

All patients were transfused with one unit of COVID-19 CP. The 2nd and 3rd units of CP, at least 24 hours apart, were transfused based on the physician's judgment of worsening the patients' respiratory, hemodynamic, and laboratory parameters due to COVID-19.

The patients received corticosteroids, antiviral agents, anticytokines and antiplatelet/anticoagulants by considering the current treatment protocols for COVID-19 (17-24) within the scope of the recommended basic treatments specific to the patient.

Production and Storage Conditions of COVID-19 CP:

All plasma donors had COVID-19 confirmed by SARS–CoV-2 PCR test positivity and were donated at least 14 days after complete resolution of COVID-19 symptoms and negative PCR testing, or 28 days after well-being. Donors were between 18-55 years, and all provided written informed consent at the time of plasmapheresis. All donors met the standard blood donor criteria and were documented to be negative for hepatitis B, hepatitis C, HIV, and syphilis, per standards in Turkish regulations, and a strong IgG positivity in the immunochromatographic fast test for IgM and IgG.

A total of 200-600 cc plasma was collected with the apheresis method using the Trima Accel® Automated

Blood Collection System (Terumo BCT) and divided into two or three bags of 200 ml each. CPs to be used in the first six hours were kept unfrozen, while the others were stored frozen. Those used as liquid plasma in the first six hours of the collection were subjected to gamma irradiation of 25 Gy.

Following the donation, all donor serum samples were tested with Euroimmune SARS-CoV-2 IgG ELISA (Euroimmun, Lübeck, Germany) test against the SARS-CoV-2 spike protein subunit 1 (S1). The results were expressed as a ratio of the optical density of the sample to the optical density of the internal calibrator supplied with the kit. The threshold value for positive results was ≥ 1.1, and the values between 0.8 and 1.0 were considered borderline positive.

We have evaluated whether the number of CP doses administered (i.e. 1-3 units), power of the IgG ratio (i.e. low (1.1-2.0), moderate (2.1-4.0), and high (>4.1)), or the time of CP administration following positive SARS-CoV-2 PCR (i.e. very early (0-3 days), early (4-7 days) and late (> 7 days)) had an impact on the 30-day in-hospital mortality.

Statistical Analysis

The statistical analyses were performed using IBM SPSS Statistics 26 software (IBM Corp., Armonk, NY). Continuous variables with normal and non-normal distribution were summarized as mean ± standard deviation and median, respectively. Categorical variables were expressed as frequencies or percentages. Differences between living and deceased groups were analyzed using the chi-square test. Mann-Whitney U test was used for continuous independent variables and the Wilcoxon Sign Test for continuous dependent variables (in which the values were evaluated relative to the baseline value).

A one-way ANOVA test was employed for the independent evaluation of dependent variables in the CP subgroups analyses. The post hoc test (Tukey) was used to determine the difference between the CP subgroups in the patient follow-up.

All analyses were evaluated at the 95% confidence interval, and significance was assessed at the $p < 0.05$ level.

Results

CP donations were performed from the donors between 24 and 188 days (Median: 80 days, SD: ± 44.5 days) after the onset of their first symptoms. A total of 417 CP doses were used in 224 patients. Out of these 417 doses, 407 (97.6%) were found IgG positive, and strong positivity (IgG ratio > 4) was detected in 58.3% of those.

When CP treatment was commenced, 173 of 224 patients (77%) were in the ICU. The patients' demographic information and admission characteristics are given in Table 1. The mean age of the patients was 64.2 ± 14.5 (19-91) years, and 143 were male. The most common comorbidities were hypertension (HT) and congestive heart failure (CHF), whereas the presence of chronic renal failure (CRF) was found to be associated with increased mortality. MV needs, PO2/FİO2 < 300, clinically rapid progression, persistent fever, SOFA score increase of > 2, and increased vasopressor need were detected to be linked with increased mortality. The mean CP administration time after positive SARS-CoV-2 PCR was 5.89 ± 3.95 days, and after hospitalization was 4.09 ± 3.39 days. Overall the mean duration of stay in the ICU was 10.95 ± 8.5 days, and in the hospital, 17.63 ± 9.2 days. The APACHE score was 14.0 ± 8.2 in the deceased group and 8.74 ± 5.28 in the survivor group, and the difference was statistically significant ($p<0.001$). SOFA score was statistically higher on the day of hospitalization, the first and the 5th day of CP administration in the deceased group ($p<0.001$). (Table 1)

The macrophage activation syndrome (MAS)-like inflammation indicators, including baseline CRP, procalcitonin, D-dimer, ferritin, and NLR values, were significantly higher, while the platelet count was lower in the deceased group than in the survivor group. Comparing the baseline values, a significant increase in the D-dimer and NLR values in the deceased group and the platelet count in the survivor group were observed during the sequential follow-up (Table 2). Although there was no significant difference between the baseline levels of the inflammation indicators between the groups that received low, moderate, and high IgG ratios in CPs, except the platelet value change in high IgG ratios and also no consistent changes were observed on those parameters during follow-up between the groups. It was statistically significant that the platelet value increased compared to the basal value in the sequential follow-up in the group with a high Euroimmun IgG ratio (Table 3).

The number of CP units, the power of the IgG ratio in the CP units, and the timing of CP administration did not impact the need for respiratory support and mortality rate (Table 4). SOFA score has not significantly differed between the groups receiving different power of IgG ratio (Table 5)

Table 1. Demographic information and clinical data of the patients receiving CP					
		Survivor group (n=123)	Deceased group (n=101)	Total (n=224)	p-value
Age (mean ± SD) (years)		60.85±14.796	68.31±13.029	64.21±14.5	<0.001
Gender	Female	48 (59.3)	33 (40.7)	81 (36.2)	0.325
	Male	75 (52.4)	68 (47.6)	143 (63.8)	
Comorbidity (%)	Hypertension/congestive heart failure	58 (50)	58 (50)	116	0.126
	Diabetes mellitus	39 (52)	36 (48)	75	0.535
	Coronary artery disease	11 (39.3)	17 (60.7)	28	0.076
	Chronic renal failure	10 (32.3)	21 (67.7)	31	0.006
	Chronic obstructive pulmonary disease	9 (52.9)	8 (47.1)	17	0.865
	Malignancy	7 (41.2)	10 (58.8)	17	0.236
	Hyperlipidemia	2 (50)	2 (50)	4	1.000
CP indications (%)	Invasive mechanical ventilator need	28 (22.8)	77 (76.2)	105	<0.001
	PaO_2/FiO_2 <300	35 (28.5)	59 (58.4)	94	<0.001
	SpO_2 sat <90	44 (35.8)	38 (37.6)	82	0.775
	Respiratory rate >30/min	38 (30.9)	43 (42.6)	81	0.070
	PaO_2 <70 mmHg	38 (30.9)	28 (27.7)	66	0.604
	Rapid progression	21 (17.1)	30 (29.7)	51	0.025
	Persistent fever	32 (26.0)	15 (14.9)	47	0.041
	SOFA score increase >2	5 (4.1)	41 (40.6)	46	<0.001
	Increased CT infiltration	22 (17.9)	13 (12.9)	36	0.304
	Vasopressor need	1 (0.8)	18 (17.8)	19	<0.001
CP time (day) (mean ± SD)	After PCR positivity	6.00±3.737	5.76±4.203	5.89±3.947	0.43
	After hospitalization	3.93±3.147	4.30±3.66	4.09±3.386	0.93
APACHE-II (mean ± SD)		n=72 8.74±5.28 (1-24)	n=93 14.0±8.19 (2-39)	n=165 11.70±7.52 (1-39)	<0.001
SOFA (mean ± SD)	Hospitalization day	n=73 3.25±1.89 (0-9)	n=91 4.59±2.59 (1-14)	n=164 3.99 (0-14)	<0.001
	CP baseline	n=73 3.49±1.90 (0-9)	n=92 6.14±2.64 (1-14)	n=165 4.97 (0-14)	<0.001
	Day 5	n=73 2.86±1.96 (0-8)	n=70 6.66±2.60 (0-14)	n=143 4.76 (0-14)	<0.001
Respiratory support (at the first CP) (%)	MV/NIV/HFNC ()	37 (32.4)	77 (67.5)	114	<0.001
	Mask and nasal O_2/room air ()	86 (78.1)	24 (21.8)	110	<0.001
Stay duration (day) (mean ± SD)	Intensive care unit (mean)	8.27±8.7	14.17±7.02	10.95±8.5	<0.001
	Hospital (mean)	17.93±9.06	17.26±8.82	17.63±9.2	0.686

MV: Mechanical ventilator, NIV: Non-invasive mechanical ventilator, HFNC: High flow nasal cannula, SOFA: The sequential organ failure assessment score

CP-associated adverse events were observed in 11 (0.5%) patients; the most common complication was fever in eight patients. In addition, there were two patients with transfusion-related acute lung injury (TRALI) and one patient with transfusion-associated circulatory overload (TACO); no mortality caused by complications was determined (Table 6).

Discussion

CP serum and immunoglobulin is a passive immunization method that has been used for about 100 years preventing and treating of outbreaks in which no vaccine or pharmacological intervention is available. The first CP administration was reported in the pandemic period of Spanish influenza A (H1N1) pneumonia (1918–1920); the meta-analysis of studies conducted during this pandemic revealed that CP reduces mortality (25). In the ensuing years, CP has been used for Middle East respiratory syndrome, severe acute respiratory syndrome (SARS) caused by SARS–coronavirus 1 (SARS-CoV-1), and Ebola (26, 27).

However, in many large-scale randomized controlled clinical trials, results indicate that CP treatment does not contribute to disease progression or reduction in mortality in COVID-19 patients (28-32). Further, in May 2021, it was reported in the Cochrane Review that there is a high degree of certainty in the evidence that CP for the treatment of individuals with moderate to severe COVID-19 does not reduce mortality and has little or no effect on measurements

Table 2. Survival analysis of laboratory parameters related to COVID-19 severity

		Survivor group (n=123) (mean ± SD)	Deceased group (n=101) (mean ± SD)	p*-value
CRP (0-5 mg/L)	Baseline	88.2±67.7	119.7±95.1	0.015
	48 h	58.1±52.5	95.1±79.4	
	72 h	45.6±52.4	98.7±72.2	
	D5	28.5±34.1	78.6±50.4	
Procalcitonin (<0.05 µg/L)	Baseline	1.47±2.0	2.41±3.9	<0.001
	48 h	0.52±0.54	1.47±2.1	
	72 h	0.60±0.64 p^{γ}=0.043	1.40±1.6	
	D5	0.28±0.26	1.54±2.5	
D-dimer (<550 µg/L FEU)	Baseline	1504.8±1312.6	2592.0±1613.5	p<0.001
	48 h	2016.7±1557.7 p^{γ}=0.011	2971.6±1567.2 p^{γ}=0.001	
	72 h	1818.2±1551.3	3313.6±1433.6 p^{γ}=0.002	
	D5	1824.8±1480.4	3547.0±1432.0 p^{γ}=0.001	
Ferritin (30-400 µg/L)	Baseline	913.8±1143.3	2119.6±6052.3	p=0.004
	48 h	941.2±1138.5	1409.1±1526.5	
	72 h	969.2±1048.4	1463.5±3182.5	
	D5	753.7±761.3	2645.0±8799.2	
NLR	Baseline	10.6±14.1	18.1±13.4	p < 0.001
	48 h	10.3±11.1	19.6±14.1 p^{γ}=0.019	
	72 h	9.2±6.3	22.9±23.4 p^{γ}=0.006	
	D5	8.55±6.0 p^{γ}=0.030	25.2±24.2 p^{γ}<0.001	
Platelet count (150-450 10^3/µL)	Baseline	274.2±104.7	252.2±126.5	p=0.041
	48 h	298.2±108.7 p^{γ}<0.001	237.7±130.4	
	72 h	323.2±111.6 p^{γ}<0.001	243.6±129.1	
	D5	342.5±112.8 p^{γ}<0.001	242.9±140.3	

p^{*}: Intergroup variation in the baseline values; p^{γ}: Variation in the follow-up results relative to the baseline value
CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio

of clinical improvement (33). On the other hand, Joyner et al. reported in a retrospective analysis of 3,082 COVID-19 patients who were hospitalized and needed no mechanical ventilation that the transfusion of CP containing high anti-SARS-CoV-2 IgG antibody levels is associated with lower mortality (34). Some other studies also support the use of CP to reduce in-hospital mortality and emphasize the need for relevant studies (35, 36). In December 2021, although WHO revised the survival guide on COVID-19 treatments as "in addition to its high costs, CP does not improve survival or reduce the need for mechanical ventilation," citing evidence that CP does not provide benefit to non-severe COVID-19 patients, it recommends that randomized clinical trials should continue in severe and critically ill patients (37). In this retrospective cohort study, we evaluated the impact of CP use on survival in severe/critical COVID-19 patients.

Advanced age and male gender have been associated with mortality as the most important risk factors in terms of developing infection and progression to severe disease in COVID-19 patients (38). Other risk factors are cardiovascular disease, obesity, hypertension, diabetes mellitus (DM), chronic respiratory tract disease, chronic renal failure, cancer and weakened immune status (5, 39-41). In our study, male gender was at the forefront, and the mean age was statistically significantly higher in the deceased group. No significant difference was detected between genders

Table 3. Evaluation of laboratory parameters related to COVID-19 severity and MAS based on the Euroimmun IgG ratio in the first administered CP

		Low IgG ratio 1.1-2.0 (mean ± SD)	Moderate IgG ratio 2.1-4.0 (mean ± SD)	High IgG ratio >4.1 (mean ± SD)	p*-value
CRP (0-5 mg/L)	Baseline	91.8±73.3	103.1±84.4	105.5±85.4	0.846
	48 h	63.7±53.2	84.2±57.8	75.2±68.4	0.239
	72 h	63.8±88.9	73.4±61.8	70.6±80.7	0.276
	D5	35.6±61.8	66.9±65.8	46.6±59.3	0.015
	p$^{\gamma}$	<0.001	0.140	<0.001	
D-dimer (<550 µg/L FEU)	Baseline	1998.7±1480.2	2235.4±1636.8	1907.4±1523.1	0.499
	48 h	2398.7±1620.8	2733.2±1696.6	2323.6±1610.5	0.382
	72 h	2085.9±1644.2	2574.1±1795.4	2382.9±1643.2	0.620
	D5	2055.2±1697.9	2671.9±1695.6	2498.2±1690.9	0.364
	p$^{\gamma}$	0.410	0.007	0.252	
Ferritin (30-400 µg/L)	Baseline	3271.9±10982.0	1365.1±2420.7	1120.5±1260.0	0.569
	48 h	993.6±1139.0	1405.6±2019.1	1113.9±1173.8	0.958
	72 h	1887.9±4930.2	647.5±734.8	1106.3±1008.8	0.061
	D5	699.3±675.5	813.9±828.2	1829.3±6727.1	0.182
	p$^{\gamma}$	0.228	0.960	0.638	
NLR	Baseline	16.7±15.8	15.3±13.3	13.3±13.9	0.295
	48 h	16.1±14.2	18.0±18.1	12.6±10.3	0.135
	72 h	15.1±13.1	21.3±32.4	12.9±10.3	0.327
	D5	13.6±12.4	20.2±28.3	14.3±14.9	0.457
	p$^{\gamma}$	0.465	0.544	0.205	
Platelet count (150-450 10^3/µL)	Baseline	281.2±113.9	276.0±131.9	256.0±110.7	0.229
	48 h	286.5±134.7	280.1±154.3	264.4±107.2	0.631
	72 h	309.0±127.0	301.6±147.2	276.5±119.1	0.405
	D5	319.3±130.2	316.3±148.9	299.5±129.6	0.621
	p$^{\gamma}$	0.670	0.383	< 0.001	

p*: Intergroup variation; p$^{\gamma}$: Variation in follow-up results

Table 4. Age, gender, respiratory support need and 30-day in-hospital mortality assessment in the groups

	CP doses administered (Unit)				Power of the EI IgG ELISA				The time of CP administration following PCR+			
	1	2	3	p-value	1.1-2.0 Low	2.1-4.0 Moderate	> 4.1 High	p-value	0-3 day Very early	4-7 day Early	>7.0 day Late	p-value
Frequency, n	88	78	58	-	30	51	134	-	74	85	65	-
Age (mean ± SD) (years)	63.5±15.6	64.5±12.5	64.8±15.2	0.83	62.2±18.2	66.2±11.9	63.5±14.6	0.48	65.8±13.6	64.9±15.1	61.5±14.4	0.18
Gender, F, n (%)	33 (37.5)	28 (35.9)	20 (34.5)	0.93	12 (41.4)	17 (33.3)	46 (34.3)	0.43	28 (37.8)	29 (34.1)	24 (36.9)	0.88
MV/NIV/HFNC (%)*	41 (46.6)	41 (52.6)	32 (55.2)	0.56	14 (48.3)	29 (56.9)	66 (49.3)	0.92	39 (52.7)	40 (47.1)	35 (53.8)	0.67
30-day in-hospital mortality n (%)	38 (43.2)	35 (44.9)	28 (48.3)	0.83	11 (37.9)	27 (52.9)	57 (42.5)	0.45	37 (50)	34 (40)	30 (46.2)	0.44

MV: Mechanical ventilator, NIV: Non-invasive mechanical ventilator, HFNC: High flow nasal cannula

regarding respiratory support, whereas it was observed that the need for invasive and non-invasive respiratory support statistically increased with advanced age. The most common comorbid diseases in critical and severe COVID-19 patients were hypertension/CHF, followed by DM.

In a meta-analysis evaluating the administration time of CP, patients who received CP in the first ten days of hospitalization have been compared with those who received it between 10 and 20 days, mortality was found to be decreased in those received CP in the first ten days, however this decrease was not statistically significant (42). However, in the study by Salazar et al. mortality in patients who were given CP within 72 hours of hospital admission was lower than those who were given late (43). In our study, the mean CP administration time after the first PCR positivity was 5.89 ± 3.95 days, and no significant difference was detected between the survivor and deceased patient groups. Further, in our cohort, CP administration within 72 hours or later of PCR positivity had no impact on mortality and the need for respiratory support.

The efficacy of passive antibody therapy was associated with the concentration of neutralizing antibodies in the plasma of recovered donors. The target titer recommendation of the European Commission for the neutralization test in COVID-19 convalescent plasma is 1:320 and above. Although the ability to demonstrate the neutralization performance of antibodies in SARS-CoV-2 CP is considered the gold standard, it isn't easy to routinely perform tests intended for this purpose because they require a laboratory with a high biosafety level

Table 5. SOFA scores of the ICU patients in the groups created based on the power of the EI IgG ELISA of the first administered CP

		Low 1.1-2.0	Moderate 2.1-4.0	High >4.10	p-value
SOFA* score (Mean ± SD)	Hospitalization day	n=19 3.68±2.0	n=39 4.41±2.78	n=98 3.98±2.36	0.645
	CP baseline	n=19 4.84±2.71	n=39 5.67±3.1	n=99 4.83±2.5	0.351
	Day 5	n=16 3.75±3.06	n=27 5.41±3.21	n=91 4.79±2.88	0.223

SOFA: The sequential organ failure assessment score

Table 6. Distribution of CP induced complications

Complication	Survivor group (n=123)	Deceased group (n=101)	Total (n=224) (%)	p-value
Fever (baseline >1 °C)	1	7	8 (3.5)	
Allergic reaction	0	0	0	
TRALI	1	1	2 (0.8)	
TACO	0	1	1 (0.4)	
ADE	0	0	0	
Total	2	9	11 (4.9)	0.061

TRALI: Transfusion-related acute lung injury, TACO: Transfusion-associated circulatory overload, ADE: Antibody-dependent enhancement

and experienced staff. Euroimmun IgG has been shown to correlate with neutralization assays (44-46). The FDA has stated that CP with a Euroimmun sample to the cutoff of ≥3.5 can be used to treat hospitalized patients (47).

It has been determined in many studies that the efficacy of CP treatment is linked to the SARS-CoV-2 antibody titer it contains (34, 48). In a multicenter study, the administration of CP with high antibody titer before seven days has been associated with low mortality (49). A randomized controlled clinical study conducted with outpatient elderly population has indicated that CP with high antibody titer administered within 72 hours of the onset of COVID-19 symptoms improves clinical outcomes compared to placebo (50). However, the RECOVERY study involving 11,558 inpatients showed no difference in mortality risk between patients who were administered CP with high antibody titer and those who received standard CP treatment (30). We have not observed a difference in mortality and the need for respiratory support in patients who received CP with an IgG ratio above 4.0 or lower.

The optimal dose and timing of CP treatment are still unclear (51). On the other hand, even though it is observed that the dosage is not standardized in CP administration in clinical practice, administering 200-500 ml CP in one or two regimens is generally accepted approach (42). In our study, there was no significant difference between the patients administered 1, 2 and 3 units of CP (200-400-600 ml) regarding mortality and the need for respiratory support.

In their retrospective study, including 117 COVID-19 inpatients, Yang et al reported that the SOFA score can be an independent risk factor for in-hospital mortality and that it can be used to evaluate COVID-19 severity and prognosis (52). However, Raschke et al. showed that the SOFA score has a low mortality predictive accuracy in ventilator triage of COVID-19 patients, and they associated this with the fact that severe single organ dysfunction cause an only a minimal change in SOFA scores (53). In our study, the SOFA scores were significantly higher in the deceased group than in the survivor group. Nonetheless, there were no significant differences in SOFA scores at baseline and day 5 of CP administration between the groups based on the antibody ratio of CPs administered.

Hyperinflammation associated with COVID-19 are similar to symptoms of macrophage activation syndrome (MAS), whose clinical features have been previously reported. Increased serum ferritin, CRP, and D-dimer levels and decreased fibrinogen and platelet counts in COVID-19 patients indicate the development of severe MAS-like inflammation and fibrinolysis (41, 54). Inflammatory cascade, complement activation, and proinflammatory cytokines determine the course of the disease in COVID-19 patients. It has been stated that specific hematological, inflammatory biochemical laboratory parameters correlate with the severity of COVID-19 (55-57). Among inflammatory markers, CRP has been found to increase significantly in the initial stages of infection for COVID-19 patients and is considered an early marker for severe COVID-19 (58, 59). In a prospective study evaluating 267 severe COVID-19 patients who received CP, a decrease in CRP, ferritin, and IL-6 levels was determined (60). The higher and the persistent inflammation markers and lower platelet counts were also associated with a dismal prognosis in our cohort. Nevertheless, a consistent effect of CP administration in hyper inflammation markers during follow-up was not observed. No similar studies in which the relationship between the changes in the laboratory parameters evaluated in our study and power of the IgG ratio is investigated come across in the literature. For this reason, our study presents importance.

Although CP administration is generally considered a safe and well-tolerated treatment, it can also cause some adverse events. Limited information is available about specific side effects of CP treatment. However, the reported symptoms including fever, chills, allergic reactions, TRALI, and TACO, are similar to those of other types of plasma blood components (61, 62). The cause of the highest mortality risk following plasma transfusion is TRALI and TACO, possibly due to the sequelae of pulmonary complications (63). A theoretical concern regarding the use of CP in COVID-19 patients is a clinical condition that worsens after plasma transfusion due to antibody-dependent enhancement (ADE) or antibody-mediated proinflammatory effects. Joyner et al. evaluated 5,000 severe and critical COVID-19 patients regarding side effects after CP, considering that respiratory problems due to COVID-19 may increase CP-associated complications. They detected less than 1% serious adverse events, 0.22% TRALI, 0.1% TACO, and 0.06% severe allergic reaction in the first 4 hours. Since the incidences of TRALI and TACO are expected to be approximately 10% in critically ill patients, they assessed CP treatment as reassuring due to their cohort's lower TRALI and TACO incidence rates (11). The incidence of TRALI and TACO found in our study is in line with the literature, and no mortality because of CP-induced

complications was observed. However, the presence of many comorbidities in the patient group in our study and vascular and pulmonary involvement caused by COVID-19 made the differential diagnosis of CP-related TRALI and TACO difficult. Specific signs and symptoms of COVID-19-induced ADE are unknown, and clinical deterioration and worse outcomes following CP administration can be associated with ADE. In our study, ADE has not been suspected.

The retrospective nature of our study and the use of multiple drugs (antibiotic, antiviral, corticosteroid, anti-cytokines, low molecular weight heparin) in the individualized treatment of the patients are limiting factors, which make it difficult to differentiate the laboratory/clinical impact of CP in severe/critical COVID-19 patients.

Conclusion

In conclusion, under the conditions of this retrospective cohort study, CP treatment was not associated with improved survival or other positive clinical outcomes in severe/critical COVID-19 patients. There is a need for more comprehensive and prospective controlled studies that can demonstrate the efficacy of CP administration for COVID-19 patients.

Ethics

Ethics Committee Approval: Approval was obtained from the Ege University Hospital (EUH) Clinical Research Ethics Committee (Ethics Committee No 20-5T/48).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Ö., İ.Ç., A.T., M.S.T., H.A.E., K.D., M.U., Y.A., Concept: Ö.Ö., İ.Ç., M.S.T., K.D., M.U., Y.A., Design: Ö.Ö., İ.Ç., M.S.T., K.D., M.U., Y.A., Data Collection and Process: Ö.Ö., İ.Ç., A.T., H.A.E., Y.A., Analysis or Interpretation: Ö.Ö., İ.Ç., A.T., M.S.T., H.A.E., P.K., K.D., M.U., T.Y., Y.A., Literature Search: Ö.Ö., İ.Ç., A.T., M.S.T., K.D., M.U., Y.A., Writing: Ö.Ö., İ.Ç., A.T., M.S.T., H.A.E., P.K., K.D., M.U., T.Y., Y.A.

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