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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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

Şiddetli ve Kritik COVID-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 coronavirus disease-2019 (COVID-19) patients who have recovered from the infection and whose plasma contains antibodies against severe acute respiratory syndrome-coronavirus-2 (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 immunoglobulin (Ig)G ratio and the time of CP administration following positive SARS-CoV-2 polymerase chain reaction (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, O_2 saturation, fever at the baseline, acute physiologic, chronic health evaluation (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, PO_2/FiO_2 <300, clinically rapid progression, persistent fever, sequential organ failure assessment 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 unit, convalescent plasma, the power of the IgG ratio, SOFA score, the APACHE II score, macrophage activation syndrome

ÖZ *Amaç:* İlgili çalışmalarda, iyileşen ve plazmaları şiddetli akut solunum yolu sendromu-koronavirüs-2'ye (SARS-CoV-2) karşı antikorlar içeren koronavirüs hastalığı-2019 (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 polimeraz zincir reaksiyonu (PZR) takiben uygulanan KP dozlarının sayısının, immünoglobulin (Ig)G 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 PZR testi ile hastaneye yatış arasındaki süre, ilk KP uygulamasının zamanı, laboratuvar sonuçları, solunum desteği ihtiyaçları, O_2 satürasyonu, başlangıçtaki ateş, akut fizyolojik, kronik sağlık değerlendirmesi (APACHE) II skorları ve ardışık organ yetmezliği değerlendirmesi 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, PO_2/FiO_2 <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

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection presents with a wide range of clinical symptoms, ranging from asymptomatic to severe pneumonia, multiple organ failure, and death (1-3). Although 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 SpO_2 in room air <90%, along with clinical signs of pneumonia, have been defined as severe coronavirus disease-2019 (COVID-19) cases, whereas those who have ARDS or respiratory failure requiring ventilation, sepsis, or septic shock are considered critical COVID-19 cases (7).

In the absence of other specific therapies, convalescent plasma (CP) has been used as either a preventive or therapeutic agent 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 patients with COVID-19 who recovered from the infection and whose plasma contains antibodies against SARS-CoV-2, which is safe and may be effective in treating patients with COVID-19 (11-14). Concurrent with these studies, in August 2020, the American Food and Drug Administration (FDA) issued an Emergency Use Authorization for CP for the treatment of hospitalized patients with COVID-19 (15).

Our study aimed to evaluate the use of COVID-19 CP in patients with severe and critically hospitalized COVID-19 who lacked information regarding 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 conducted at Ege University Hospital after receiving approval from the Clinical Research Ethics Committee (number: 20-5T/48).

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

Study Protocol and Data Collection

CP collection and administration were performed according to the COVID-19 Immune (Convalescent) Plasma Supply and Clinical Use Guidelines of the Ministry of Health of Turkey (16).

Clinical and specific laboratory data were obtained from the electronic file records of the patients. The demographics, comorbidities, co-medications, onset of symptoms, time lag between SARS-CoV-2 polymerase chain reaction (PCR) testing and hospitalization, and time of first CP use were recorded. Laboratory assessments associated with the severity of COVID-19, including neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), procalcitonin, ferritin, D-dimer, and platelet values, were performed. Respiratory support needed, O_2 saturation, fever, and relevant laboratory parameters were determined at baseline, 48 and 72 hours, and 5 days after CP administration. Acute physiologic, chronic health evaluation II scores were obtained during hospitalization, and sequential organ failure assessment scores were recorded during hospitalization, baseline, and 5 days after CP administration. Immunoglobulin (Ig)A deficiency was excluded in all patients before CP transfusion. Adverse events occurred within the first 24 hours after 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 confirmed COVID-19 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 approximately 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 exhibited strong IgG positivity in the immunochromatographic fast test for IgM and IgG.

A total of 200-600 cc plasma was collected using 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 25 Gy Gamma irradiation.

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

We 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 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 distributions were summarized as mean ± standard deviation (SD) and median, respectively. Categorical variables are expressed as frequencies or percentages. Differences between the living and deceased groups were analyzed using the chi-square test. Mann-Whitney U test was used for continuous independent variables and the Wilcoxon signed-rank test for continuous dependent variables (in which the values were evaluated relative to the baseline value).

A One-Way ANOVA test was used for the independent evaluation of dependent variables in the CP subgroup analyses. The post hoc test (Tukey) was used to determine differences between the CP subgroups during follow-up.

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

Results

CP donations were made 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 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 demographic information and admission characteristics of the patients are presented in Table 1. The mean age of the patients was 64.219-91) 14.5±) years, and 143 were males. 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, PO_2/FiO_2 <300, clinically rapid progression, persistent fever, SOFA score increase of >2, and increased vasopressor need were detected to be linked to increased mortality. The mean CP administration time after positive SARS-CoV-2 PCR was 5.893.95± days, and after hospitalization was 4.093.39± days. Overall, the mean durations of stay in the ICU was 10.958.5± days, and in the hospital, 17.639.2± days. The APACHE score was 14.08.2± in the deceased group and 8.745.28± in the survivor group, and the difference was statistically significant

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 mm Hg	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
APACHEII (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, SD: standard deviation, CP: convalescent plasma

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
	48h	58.1±52.5	95.1±79.4	
	72h	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
	48h	0.52±0.54	1.47±2.1	
	72h	0.60±0.64 p$^{\gamma}$=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
	48h	2016.7±1557.7 p$^{\gamma}$=0.011	2971.6±1567.2 p$^{\gamma}$=0.001	
	72h	1818.2±1551.3	3313.6±1433.6 p$^{\gamma}$=0.002	
	D5	1824.8±1480.4	3547.0±1432.0 p$^{\gamma}$=0.001	
Ferritin (30-400 µg/L)	Baseline	913.8±1143.3	2119.6±6052.3	p=0.004
	48h	941.2±1138.5	1409.1±1526.5	
	72h	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
	48h	10.3±11.1	19.6±14.1 p$^{\gamma}$=0.019	
	72h	9.2±6.3	22.9±23.4 p$^{\gamma}$=0.006	
	D5	8.55±6.0 p$^{\gamma}$=0.030	25.2±24.2 p$^{\gamma}$<0.001	
Platelet count (150-450 10^3/µL)	Baseline	274.2±104.7	252.2±126.5	p=0.041
	48h	298.2±108.7 p$^{\gamma}$<0.001	237.7±130.4	
	72h	323.2±111.6 p$^{\gamma}$<0.001	243.6±129.1	
	D5	342.5±112.8 p$^{\gamma}$<0.001	242.9±140.3	

p*: Intergroup variation in the baseline values, p$^{\gamma}$: variation in the follow-up results relative to the baseline value, CRP: C-reactive protein, NLR: neutrophil to lymphocyte ratio, COVID-19: coronavirus disease-2019, SD: standard deviation

(p<0.001). The SOFA scores were statistically higher on the day of hospitalization and on 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 in the deceased group than in the survivor group. Comparing the baseline values, significant increases 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 for the platelet value change in high IgG ratios, no consistent changes were observed on those parameters during follow-up between the groups. It was statistically significant that the platelet value increased relative to the basal value during sequential follow-up in the group with a high Euroimmun IgG ratio (Table 3).

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

CP-associated adverse events were observed in 11 (0.5%) patients; the most common complication was fever in eight patients. In addition, two patients had transfusion-related acute lung injury (TRALI) and one patient had transfusion-

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
	48h	63.7±53.2	84.2±57.8	75.2±68.4	0.239
	72h	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
	48h	2398.7±1620.8	2733.2±1696.6	2323.6±1610.5	0.382
	72h	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
	48h	993.6±1139.0	1405.6±2019.1	1113.9±1173.8	0.958
	72h	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
	48h	16.1±14.2	18.0±18.1	12.6±10.3	0.135
	72h	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
	48h	286.5±134.7	280.1±154.3	264.4±107.2	0.631
	72h	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, CP: convalescent plasma, SD: standard deviation, COVID-19: coronavirus disease-2019, NLR: neutrophil to lymphocyte ratio, Ig: immunoglobulin, MAS: macrophage activation syndrome, CRP: C-reactive protein

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 approximately 100 years to prevent and treat outbreaks in which no vaccine or pharmacological intervention is available. The first CP administration was reported during 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 recent years, CP has been used for Middle East respiratory syndrome, SARS caused by SARS-coronavirus-1 and Ebola (26,27).

However, in many large-scale randomized controlled clinical trials, the results indicated that CP treatment does not contribute to disease progression or to mortality in patients with COVID-19 (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 of clinical improvement (33). On the other

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, CP: convalescent plasma, SD: standard deviation, PCR: polymerase chain reaction, Ig: immunoglobulin

hand, Joyner et al. (34) 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 was associated with lower mortality (34). 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 World Health Organization 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 patients with non-severe COVID-19, 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 patients with severe or critical COVID-19. Advanced age and male sex are associated with mortality as the most important risk factors for developing infection and progression to severe disease in COVID-19 patients (38). Other risk factors are cardiovascular disease, obesity, HT, diabetes mellitus (DM), chronic respiratory tract disease, CRF, cancer, and weakened immune status (5,39-41). In our study, male sex was at the forefront, and the mean age was significantly higher in the deceased group. No significant difference was detected between genders regarding respiratory support, whereas the need for invasive and non-invasive respiratory support statistically increased with advanced age. The most common comorbid diseases in patients with critical and severe COVID-19 were HT/CHF, followed by DM.

In a meta-analysis evaluating the administration time of CP, patients who received CP in the first 10 days of hospitalization were compared with those who received it between 10 and 20 days. Mortality was found to be decreased in those who received CP in the first ten days, however this decrease was not statistically significant (42). However, Salazar et al. (43) showed that mortality in patients who received CP within 72 hours of hospital admission was lower than that in those who received it late. In our study, the mean time to CP administration after the first PCR positivity was 5.893.95± days, and no significant difference was detected between the survivor and deceased patient groups. Furthermore, in our cohort, CP administration within 72 hours 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

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
*: The sequential organ failure assessment score, SD: standard deviation, ICU: intensive care unit, CP: convalescent plasma, Ig: immunoglobulin					

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, CP: convalescent plasma				

plasma of recovered donors. The target titer recommendation of the European Commission for the neutralization test in COVID-19 CP is 1:320. Although the ability to demonstrate the neutralization performance of antibodies in SARS-CoV-2 CP is considered the gold standard, it is not easy to routinely perform tests intended for this purpose because they require a laboratory with a high biosafety level 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, administration of CP with a high antibody titer before seven days was associated with low mortality (49). A randomized controlled clinical study conducted with an outpatient elderly population indicated that CP with a high antibody titer administered within 72 hours of the onset of COVID-19 symptoms improves clinical outcomes compared with placebo (50). However, the RECOVERY study involving 11,558 inpatients showed no difference in mortality risk between patients who received high antibody titers and those who received standard CP treatment (30). We did not observe a difference in mortality and the need for respiratory support among patients who received CP with an IgG ratio >4.0. The optimal dose and timing of CP treatment remains unclear (51). On the other hand, although 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 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, which included 117 COVID-19 inpatients, Yang et al. (52) reported that the SOFA score can be an independent risk factor for in-hospital mortality and can be used to evaluate COVID-19 severity and prognosis. However, Raschke et al. (53) showed that the SOFA score has a low mortality predictive accuracy in ventilator triage among patients with COVID-19, and they associated this with the fact that severe single organ dysfunction causes only a minimal change in SOFA scores. 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.

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

Although CP administration is generally considered safe and effective, it can cause some adverse events. Limited information is available regarding the specific side effects of CP therapy. However, the reported symptoms, including fever, chills, allergic reactions, TRALI, and TACO, are similar to those of other types of plasma blood components (61,25). The causes of the highest mortality risk following plasma transfusion are TRALI and TACO, possibly due to the sequelae of pulmonary complications (62). Theoretical concerns regarding the use of CP in patients with COVID-19 include a clinical condition that worsens after plasma transfusion due to antibody-dependent enhancement (ADE) or antibody-mediated pro-inflammatory effects. Joyner et al. (11) evaluated 5,000 patients with severe and critical COVID-19 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 reactions within the first 4 hours. Since the incidences of TRALI and TACO are expected to be approximately 10% in critically ill patients, the authors assessed CP treatment as reassuring due to their cohort's lower TRALI and TACO incidence rates (11). The incidence of TRALI and TACO in our study is in line with the literature, and there was no mortality due to CP-induced complications. However, the presence of many comorbidities in the patient group and vascular and pulmonary involvement caused by COVID-19 made the differential diagnosis of CP-related TRALI and TACO difficult. The 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 was not suspected.

Conclusion

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 patients are limiting factors, which make it difficult to differentiate the laboratory/clinical impact of CP in severe/critical COVID-19 patients.

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

Ethics

Ethics Committee Approval: This single-center retrospective study was conducted at Ege University Hospital after receiving approval from the Clinical Research Ethics Committee (number: 20-5T/48).

Informed Consent: Donors were approximately 18-55 years, and all provided written informed consent at the time of plasmapheresis.

Footnotes

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., H.A.E., K.D., M.U., Y.A., Design: Ö.Ö., İ.Ç., M.S.T., K.D., M.U., Y.A., Data Collection or Processing: 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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