



Comparison of the Effectiveness of Early and Late Convalescent Plasma Treatment Given in Patients Diagnosed with Coronavirus Disease in Intensive Care Unit

COVID-19 Tanısı ile Yoğun Bakım Ünitesinde Takip Edilen Hastalarda Uygulanan Erken ve Geç Konvalesan Plazma Tedavisinin Etkinliğinin Karşılaştırılması

Yeliz Bilir¹, Akın Bilir², Fulya Ciyiltepe¹, Elif Bombacı¹,
 Ayten Saraçoğlu², Kemal Tolga Saraçoğlu¹

¹Kartal Dr. Lütfi Kırdar City Hospital, Department of Anesthesiology and Reanimation, Istanbul, Turkey.

²Marmara University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Istanbul, Turkey.

ABSTRACT

Objective: Passive vaccination with convalescent plasma (CP) therapy has gained popularity in patients with SARS-CoV-2 infection (COVID-19). However, there is no controlled study that will clearly define the use of this treatment in which the patient group, at what dose, and at what optimal time interval. The present study aimed to compare early and late CP treatments in critically ill patients in the intensive care unit (ICU) for efficacy and mortality.

Method: We retrospectively evaluated 20 patients who were admitted to ICU of Kartal Dr. Lütfi Kırdar City Hospital with the diagnosis of COVID-19 and given CP therapy between April and June 2020 and compared early (Group 1) and late (Group 2) outcomes of therapy.

Results: Of 20 patients, 5 (25.0%) were female and 15 (75.0%) were male. The average age of patients was 61±8.6 years. In Group 1, the mortality rate and the length of stay in ICU were significantly lower compared to Group 2 (p=0.025, p=0.001, respectively). A positive correlation was observed between the day that CP was given after diagnosis and total number of days spent in ICU. As CP administration day was delayed, the length of stay in ICU also increased and this was statistically significant.

Conclusion: The treatment modalities and timing to be selected are very important in COVID-19, which is fast and deadly and competes with time to increase survival. This study showed that CP therapy is well-tolerated, that early treatment options can reduce mortality and length of stay in ICU and it is not a final stage rescue therapy.

Keywords: convalescent plasma, COVID-19, intensive care units, mortality, length of stay in ICU.

ÖZ

Giriş: Konvalesan Plazma (KP) tedavisi ile pasif aşılama, SARS-CoV-2 enfeksiyonu (COVID-19) olan hastalarda popülerlik kazanmıştır, ancak hasta grubunun hangi dozda ve hangi optimal zaman aralığında yapılacağına dair kontrollü bir çalışma yoktur. Bu çalışma, yoğun bakım ünitesindeki (YBÜ) kritik hastalarda erken ve geç KP tedavilerini etkinlik ve mortalite açısından karşılaştırmayı amaçladı.

Yöntem: Kartal Dr. Lütfi Kırdar Şehir Hastanesi Yoğun Bakım Ünitesine COVID-19 tanısıyla başvuran ve Nisan 2020-Haziran 2020 tarihleri arasında KP tedavisi verilen 20 hastayı retrospektif olarak değerlendirdi. Erken KP tedavisi alan (Grup 1) ve geç KP tedavisi alan (Grup 2) hastaların sonuçlarını karşılaştırdık.

Bulgular: 20 hastanın 5'i (% 25.0) kadın, 15'i (% 75.0) erkekti. Hastaların ortalama yaşı 61 ± 8.6 yıldır. Grup 1'de mortalite oranı ve YBÜ'de kalış süresi Grup 2'ye göre anlamlı olarak daha düşüktü (sırasıyla p = 0.025, p = 0.001). Tanı konulduktan sonra KP'nin verildiği gün ile YBÜ'de geçirilen toplam gün sayısı arasında pozitif korelasyon görüldü. KP uygulama günü arttıkça, YBÜ'de kalış süresi de arttı ve bu istatistiksel olarak anlamlıydı.

Sonuç: Hızlı ve ölümcül seyreden, sağkalımı artırmak için zamanla yarıştığımız COVID-19 hastalığında seçilecek tedavi yöntemleri ve zamanlaması çok önemlidir. Bu çalışma, KP ile erken tedavi seçeneklerinin mortaliteyi ve YBÜ'de kalış süresini azaltabileceğini ve KP'nin son aşama kurtarma tedavisi olmadığını gösterdi.

Anahtar Kelimeler: konvalesan plazma, COVID-19, yoğun bakım üniteleri, mortalite, ybü'de kalış süresi.

Başvuru Tarihi: 24.02.2021 **Kabul Tarihi:** 11.10.2021

Correspondence: Yeliz Bilir, Kartal Dr. Lütfi Kırdar City Hospital, Department of Anesthesiology and Reanimation, Istanbul, Turkey.

E-mail: dryelizbilir@yahoo.com

Kocaeli Medical Journal published by Cetus Publishing.



Kocaeli Medical Journal 2021 <https://kocaelimj.org>

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INTRODUCTION

In a group of patients who developed acute respiratory symptoms in Wuhan, China in December 2019, the new coronavirus was identified and this disease was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was named COVID-19. It spread rapidly from person to person and spread to other countries, so it was accepted as the International Public Health Emergency on January 30, 2020 (1).

Passive immunization supported by historical experiences, convalescent plasma (CP) has also been discussed in the treatment of COVID-19. In a study in the Influenza-A 2009 virus outbreak, CP therapy was found to be significantly associated with infection severity, viral load, serum cytokine response, and mortality (2). In another study in the SARS-CoV-1 virus outbreak, CP therapy was associated with a high hospital discharge rate (3). In a limited number of studies on the use of CP in COVID-19, it has been reported that the treatment may be effective (4,5).

After suffering a viral infection, the patient's body creates antibodies to fight the virus. Convalescent plasma, donated by persons who have recovered from COVID-19, is the acellular component of blood that contains antibodies, including those that specifically recognize SARS-CoV-2. These antibodies in the blood of a healed patient are collected as CP and mechanisms of CP include direct binding and neutralizing virus, complement activation, initiation of virus elimination by antibody-dependent cellular cytotoxicity, and/or phagocytosis, thereby increasing that patient's immunity and reducing target organ damage (6) (figure 1). In the report published by the Food and Drug Administration (FDA), it is recommended to use CP preferably in the first 7-14 days in patients who meet certain criteria (7). In their study conducted with 5 patients, it was shown that CP therapy given 10-22 days after admission positively affected the results (4).

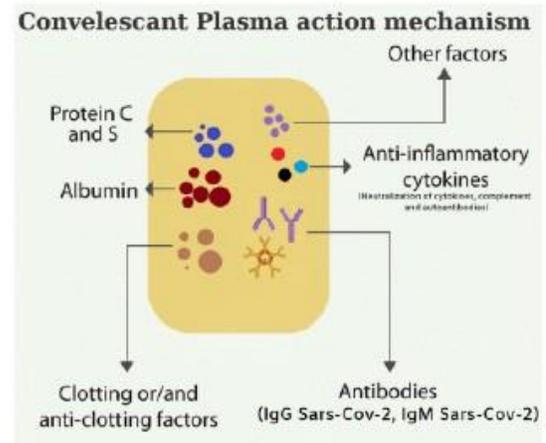


Figure 1.: convalescent plasma mechanism of action

Duan et al. gave CP therapy an average of 16.5 days after the onset of the disease and they stated that new studies were needed for the optimal time point (5). During the pandemic, a guideline for CP treatment was published by the National Scientific Advisory Board of the Ministry of Health in our country and the CP transfusion day in this guideline was periodically updated according to the current literature. In the last guideline, a list of CP treatment indications was created and it was suggested that the most appropriate treatment timing should be within the first 7 days after the onset of symptoms (8). The truth is, the timing of treatment is not yet clear.

Therefore, the present study aimed to compare the results of early and late CP therapy and its potential importance in reducing the disease severity in patients who were followed up intensive care unit(ICU) after being diagnosed with COVID-19.

MATERIAL AND METHODS

The present study was conducted at a university hospital that has been actively operating during the pandemic period with 1100 ward beds and 140 ICU beds. Ethics committee approval with the number [2020/514/177/13] was received from the ethics committee of Kartal Dr Lütfi Kırdar City

Hospital in June 2020 and informed consent was obtained from all the patients or a legally authorized representative. The study was conducted following the ethical principles stated in the Declaration of Helsinki, Good Medical Practice Guidelines, and Good Laboratory Practice Guidelines. Receiving CP treatment.

Study Cohort

In the present research, the inclusion criteria were determined as the following: I-Being over 18 years old II-Being admitted to the ICU for COVID-19 associated with acute respiratory distress syndrome (ARDS) III-Being a patient. The study sample consisted of 20 patients who were admitted to ICU due to COVID-19-related ARDS and received CP therapy between April and June 2020.

Diagnostic Criteria

COVID-19 was diagnosed according to the National Scientific Advisory Board of the Ministry of Health diagnostic criteria (8).

Other potential causes of ARDS were excluded through systemic examinations, laboratory tests, and imaging. Real-time reverse transcriptase-polymerase chain reaction (PCR) assays for SARS-CoV-2 RNA were studied on nasopharyngeal swabs.

CP therapy was applied as per the guidelines for procurement and clinical use of CP for COVID-19 published by the National Scientific Advisory Board of the Ministry of Health. The criteria for clinical use of CP were determined as follows: CT results consistent with COVID-19, bilateral generalized involvement, respiratory rate >30/minutes, PaO₂/FiO₂ <300 mm Hg, oxygen saturation <90% or partial oxygen pressure <70 mmHg despite nasal oxygen support of 5 liters/minutes and higher, need for mechanical ventilation, increased SOFA score (sequential organ failure assessment score), need for vasopressor, expected rapid clinical progression, and poor prognostic parameters (lymphopenia and increased sedimentation, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH) and D-dimer levels (8).

The criteria for being donors for plasma therapy were as follows: being asymptomatic for at least 14 days for patients who have had SARS-CoV-2 infection and treated at the hospital, or for at least 28 days for patients receiving treatment at home, and negative PCR assay results for SARS-CoV-2 infection. After obtaining written informed consent from donors who agreed to donate their recovered plasma and showed negative results for hepatitis B virus, hepatitis C virus, HIV, and other infectious diseases such as syphilis, CP was obtained by the apheresis method. The SARS-CoV-2 Ig test was studied in the plasma obtained and the convalescent plasma of the donors who gave positive results was transferred to the recipients with matching blood type.

Data Collection

The patient's files were retrospectively accessed from the electronic registration system of the hospital. The demographic data (age, gender, and presence of comorbidities), COVID-19 positivity (assessed by PCR), treatments received, clinical course, oxygenation status, regression status according to thoracic tomography and/or chest radiogram, presence of mortality, length of ICU stay and laboratory data (ferritin, D-dimer, CRP, procalcitonin (PCT) and interleukin-6 (IL-6) levels) were recorded. Data on the day of CP application and the data on the fifth day were recorded.

The patients were divided into two groups. Patients who were given CP therapy within the first 5-10 days after diagnosis were included in group 1 (n= 10), while those who received CP therapy after more than 10 days following diagnosis were included in group 2 (n= 10). Two doses of CP therapy with an interval of 48 hours were administered to all patients and received hydroxychloroquine and favipiravir treatment for 5 days. Methylprednisolone treatment was not applied to any of them. Cytokine storm developed in 5 patients in both groups and tocilizumab treatment was administered. Tocilizumab was given to both groups of patients between 10 and 14 days after diagnosis. CP therapy is not recommended in patients with cytokine storm. In our study, tocilizumab was applied after CP treatment.

Statistical Analysis

Statistical analyses were carried out using the IBM SPSS Statistics 25. In a paired comparison of numerical data between groups, we used the Independent Samples T-test for normally distributed data, the Mann Whitney-U test for not normally distributed data, and the Chi-Square test for analyzing discrete variables. Results were tested at a significance level of $p < 0.05$ with a 95% confidence interval.

The study was planned as a retrospective-cohort nature. Pearson’s correlation analysis was used to examine the correlation between the variables (ICU stay (days) - age and the use of plasma). This test was used to reveal whether there is a difference between the groups.

RESULTS

The flow chart of the study is shown in figure 2. Twenty patients aged between 44 and 71 years ($61.10.35 \pm 8.61$ years) were included in the present study. In group 1, two patients were female and eight patients were male, while in the group2, three patients were female and seven patients were male. No significant difference was noted between the groups in terms of the hospitalization SOFA score, APACHE-II score (AcutePhysiologyandChronicHealth Evaluation), presence of comorbidities, age, smoking, received to cilizumab and antiviral treatments (Table 1).

	Group 1 (n=10)		Group 2 (n=10)		p	
	n	%	n	%		
Age,mean (SD),years	60,30±7,62		61,90±9,86		0.689 ^s	
Gender	Male	8	80	7	70	0.604 ^k
	Female	2	20	3	30	
Diabetesmellitus	4	40	4	40	1.000 ^k	
Hypertension	5	50	6	6	0.653 ^k	
SOFA score, mean (SD) (on admission)	5.78±1.37(6)		5.73±1.72(5.5)		0.764	
APACHE-II, mean (SD) (in first 24 hours)	27.28±8.24		26.0±9.16		0.515	
Smoking	No	7	70	8	80	0.606 ^k
	Yes	3	30	2	20	
Tocilizumab treatment	5	50	5	50	1.000 ^k	

^s : Independent Samples, T test: values are given as mean ± stan- dard deviation, ^k : Chi-Square Test: values are given as frequency (percentage), SOFA: Sequential organ failure assessment, APACHE: Acute Physiology and Chronic Health Evaluation

No statistically significant difference was found between the two groups in terms of measured laboratory values. IL-6 levels increased in the rebound in patients who received Tocilizumab treatment due to receptor blockade. However, in the first group with low mortality, the initial IL-6 level was lower than Group 2, but this was not statistically significant. Ferritin value decreased in group 1 compared to the first measurement and increased in group 2. However, this was not statistically significant either. Also, although not statistically significant, SpO₂, PaO₂/FiO₂ ratio values increased and FiO₂ level decreased in Group 1, compared to Group 2, on the 5th day after CP treatment (Table 2).

The mean day of CP administration in group 1 after diagnosis was 8.40 ± 1.27 days, while it was 15.30 ± 2.54 days in group 2. The mortality rate and length of ICU stay were significantly lower in group 1 than in group 2 ($p < 0.05$). In group 1, the time to death of the patients was significantly shorter ($p < 0.021$) (Table 3). IPAP value measured before the treatment was observed to be significantly higher than in group 2 ($p < 0.012$) (Table 2).

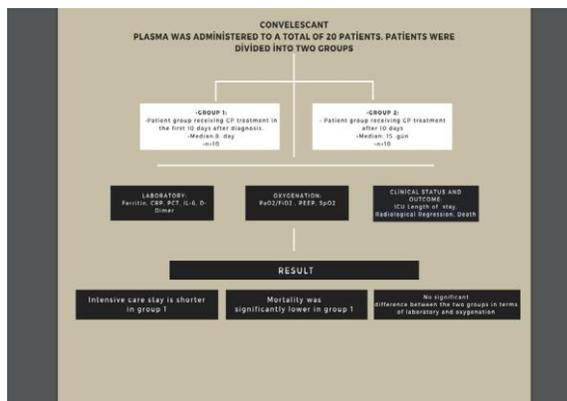


Figure 2.:Flow chart

	Group 1 (n=10)	Group 2 (n=10)	P
PEEP-1,mean(SD), cm H₂O	7.80±5.35	12.0±3,-.89	0.060 ^s
PEEP-2,mean(SD), cm H₂O	9.5±6	8±9	0.591 ^m
IPAP-1, cm H₂O	17±9	22±5	0.012 ^{*m}
IPAP-2 cm H₂O	18±9	20.5±5	0.093 ^m
FiO₂-1, %	74.5±15.36	81.0±17.29	0.386 ^s
FiO₂-2, %	64.50±20.06	76.0±15.78	0.171 ^s
SpO₂-1, %	91.90±3.78	90.90±4.63	1.000 ^s
SpO₂-2, %	92.60±4.27	88.20±5.79	0.152 ^s
PaO₂/FiO₂ -1, mm Hg	92.40±24.22	90.20±31.60	0.988 ^s
PaO₂/FiO₂ -2, mm Hg	103.5±88	72.5±44	0.112 ^m
Ferritin-1,ng/mL	756.49±525.12	381.80±225.72	0.060 ^s
Ferritin-2,ng/mL	670.1±440.98	524.5±447.34	0.473 ^s
D-dimer-1, ng/mL	7196.0±9774.9(2545)	7627.0±10329.5(3115)	0.940 ^m
D-dimer-2, ng/mL	6989.0±9018.5(4325)	6254.0±9333.9(2225)	0.820 ^m
CRP-1,mg/L	74.0±58.85(69.75)	122.74±92.9(88.9)	0.162 ^m
CRP-2,mg/L	75.03±83.7(33.85)	120.89±127.03(94.95)	0.256 ^m
PCT-1,ng/mL	0.71±1.25(0.265)	0.58±0.58(0.405)	0.520 ^m
PCT-2,ng/mL	1.43±1.64(0.76)	3.09±6.05(0.686)	0.623 ^m
IL6 -1, pg/mL	563.03±775.49(195)	774.87±1399.44(193.7)	0.653 ^m
IL6-2, pg/mL	868.02±1202.8(291)	624.17±665.3(340.5)	0.838 ^m

^s : Independent Samples T test : values are given as mean ± standard deviation
^m Mann Whitney U test: values are given as median ± interquartilerange
1: Admission in icu 2: 5th day after CP therapy

IPAP:Inspiratory positive air way pressure, PCT:Procalcitonin, PEEP: Positive end-exporatory pressure, CRP: C-reactive protein, SpO₂:Peripheralcapillary oxygen saturation, IL-6:Interleukin-6 PaO₂:Partial pressure of oxygen, FiO₂:Fraction of Inspired Oxygen

		Group 1 (n=10)		Group 2 (n=10)		P
		n	%	n	%	
Application day, after diagnosis		8.40±1.27		15.30±2.54		0.001 ^{*s}
Death day, after plasma treatment		5.0±0.0(5)		6.38±1.06(6)		0.021 ^{*m}
Death	Survival	7	70	2	20	
	Exitus	3	30	8	80	0.025 ^{*k}
ICU Length of stay, mean (SD), days		11.2±2.53(11)		20.3±12.67(18.5)		0.001 ^{*m}
Radiological regression		6	60	4	40	0.371 ^k

^k : Chi-Square Test: values are given as frequency (percentage),
^m: Mann Whitney U test: values are given as median ± inter quartile range

Table 4: Multivariate Tests Of Between-Subjects Effects						
Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
ICU stay, days	Age	791.467	10	79.147	1.152	0.421
	CP given day after diagnosis	251.217	10	25.122	3.811	0.028
	CP application day in ICU	234.367	10	23.437	30.868	0.000
Pearson correlation is significant at the 0.05 (2-tailed) level						

It was found that there was a positive correlation between the days the CP was given after diagnosis and the total days of ICU stay. It was determined that the late application of CP significantly increased the duration of stay in ICU (Table 4).

DISCUSSION

The study presents a retrospective evaluation of patients who were followed up in ICU after being diagnosed with COVID-19 and received CP therapy. Patients were divided into two groups based on the day they were given CP after diagnosis and their short-term results were compared. Our results have indicated that administering CP therapy within the first ten days after diagnosis has a positive effect on treatment.

CP application has been highlighted as an effective and specific treatment for COVID-19 in several studies published recently (9,10,11). Depending on experience with SARS and severe influenza, it is recommended that CP be administered as early as possible since the production of endogenous Ig M and Ig G antibodies peak respectively in two weeks and four weeks after getting infected (12). Our hospital admitted patients through clinics and emergency services during the pandemic period, and the average time from the onset of the disease to CP therapy was 8 ± 1 days in group 1 and 15 ± 2 days in group 2.

No significant difference was noted between group 1 and group 2 in demographic data, SOFA score, and APACHE-II score. After treatment, no patient developed side effects related to transfusion. There was no evidence of overload in the control chest radiograph and no immune reaction developed during the infusion. It was found that CP therapy given to the appropriate patients was well tolerated.

A retrospective, propensity score-matched case-control study assessed the effectiveness of CP therapy in 39 patients with severe or life-threatening COVID-19 at The Mount Sinai Hospital in New York City. Oxygen requirements on day 14 after transfusion worsened in 17.9% of plasma recipients versus 28.2% of controls who were hospitalized with COVID-19, furthermore, survival also improved in plasma recipients (13). The outcomes of this study are also consistent with our study. Rajendran et al. prepared a systematic review that involved 5 articles covering data of 27 patients and they reported that mortality reduced with CP therapy (14). Similarly, in the present study, CP therapy reduced mortality, and even the mortality rate in group 1 was found to be significantly lower than in group 2 ($p < 0.025$). Unlike other studies, this study demonstrated that CP therapy has a significantly positive effect on mortality and length of ICU stay when it is not used as end-stage rescue therapy, but preferred in the early stage of the viral replication phase.

Zeng et al. compared 6 patients with COVID-19 who received CP therapy with 15 patients who did not receive CP therapy (15). They did not find any significant difference between the two groups in mortality. This was attributed to the late application of CP therapy. On average, the authors applied the therapy at 21.5 days after ICU admission. In that study, the authors underlined that CP therapy applied at the final stage did not decrease mortality in critically ill COVID-19 patients, and therefore, treatment should be started earlier.

In the present study Patients included in the groups also received antiviral and anti cytokines treatments. Therefore, it would not be correct to attribute the low mortality rate to only improving CP therapy. However, when the two groups are compared, it is seen that these intensive care treatments received

were similar in both groups in terms of dose and duration.

In our study, there was no significant regression in the chest radiogram of patients who received early treatment and had lower mortality compared to the other group. Six out of 10 patients in the early treatment group and 4 out of 10 patients in the late treatment group showed regression and clinical improvement in their chest radiography. Furthermore, it was thought that the improvement in radiological results would become more significant in the late period. Similarly, their study demonstrated that a single dose of 200 mL CP therapy was well tolerated and CP provided regression in lung lesions within 7 days on radiological examination by significantly increasing neutralizing antibodies (5). In addition, in this study, was observed out that although not statistically, FiO_2 requirement decreased in both groups after plasma transfusion and that the PaO_2/FiO_2 ratio increased minimally in group 1.

In this study; group 1 patients, it was observed that the time to death was shorter after treatment Although mortality was lower in this group. This may be due to the fact that the patients in group 1 had higher ferritin and sofa score at the time of initiation of treatment compared to the patients in group 2. Izcovich and his colleagues emphasized that these parameters are serious mortality indicators in their study (16). When the biochemical values were examined, it was seen that the response parameters were better in group 1. In patients with an increase in acute phase reactants, empiric antibiotic therapy was started, with secondary infection in mind. In group 1, the ferritin and D-dimer levels of the patients decreased. Other inflammatory markers, IL-6, CRP and PCT, increased, but not as much as group 2. In group 2, IL-6, CRP decreased, but ferritin and PCT values increased. The number of patients who started IL-6 receptor antagonist therapy was equal.

Ye M. et al. reported in their study of 6 patients that CP therapy progressed with clinical and imaging improvement without significant changes in inflammatory parameters and even caused a slight increase in some inflammation indicators,

namely CRP and PCT, in some patients, and that the mechanism of action of CP was not exactly known (12). It was hypothesized in this study that CP therapy may indirectly exhibit anti-inflammatory activity in systemic response by neutralizing the virus in the early recovery.

So far, minimal data are available from adequately powered randomized, controlled trials about CP treatment. Results of several randomized, controlled studies published recently have shown that CP therapy does not have a significant effect on outcome in patients with severe COVID-19 (17, 18). Ventura et al. conducted a double-blind, placebo-controlled, multicenter trial of 228 patients; The main hypothesis of this trial was that in patients with severe SARS-CoV-2 pneumonia Treatment with CP would be associated with improved clinical outcomes at 30 days. As a result of the study, no significant differences were observed in clinical status or overall mortality between patients treated with CP and those who received a placebo, and the use of CP did not result in a significant clinical benefit as compared with placebo in patients with severe COVID-19 pneumonia (16).

Conclusion

The timing of the treatment to be chosen in coronavirus disease, which requires race against time, is very important. The present study was concluded that in addition to standard intensive care support treatment and follow-up, CP therapy may be safely preferred for COVID-19 patients early after diagnosis. And it was revealed that mortality and length of ICU stay can be reduced in COVID-19 patients when we were used CP therapy in the first ten days.

Limitations

Before plasma transfusion, total Ig-G SARS-CoV-2 anti-bodies were not measured in The infused convalescent plasma. For this reason, the treatment was planned to assume that donors meeting the appropriate criteria had adequate antibody titers. We did not know the median anti-body titer available in CP.

Passive immunization is targeted with CP therapy. Plasma administration may be appropriate before the patient's antibodies appear but in this study, neutralizing antibody titers specific to SARS-CoV-2 were not measured in patients before plasma transfusion. For this reason, it is not exactly given to suitable patients. Also, the small size of the sample group is considered as another limitation of this study.

Acknowledgments

We thank the Turkish Red Crescent for their help.

Conflict of Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Abbreviations

SARS-CoV-2	Sever acuterespiratory syndrome coronavirus 2
CP	Convelescan plasma
FDA	Food and drug administration
ICU	Intensive care unit
ARDS	Acute respiratory distress syndrome
PCR	Polymerase chain reaction
SOFA	Sequential organ failure assessment
CRP	C-reactive protein
LDH	Lactate dehydrogenase
IL-6	Interleukin-6
PCT	Procalcitonin

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