Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1068864
J Health Sci Med 2022; 5(2): 600-606

Our convalescent plasma experiences in COVID-19 patients hospitalized in the intensive care unit

Bülent Barış Güven[1], Tuna Ertürk[1], Egemen Yıldız[2], Esra Durmayüksel[1], Ayşın Ersoy[1], Alpaslan Tanoğlu[3]

[1]University of Health Sciences, Sultan 2. Abdulhamid Han Training and Research Hospital, Department of Anesthesiology and Reanimation, Istanbul, Turkey
[2]University of Health Sciences, Sultan 2. Abdulhamid Han Training and Research Hospital, Department of Emergency Medicine, Istanbul, Turkey
[3]University of Health Sciences, Sancaktepe Training and Research Hospital, Department of Internal Medicine and Gastroenterology, Istanbul, Turkey

Cite this article as: Güven BB, Ertürk T, Yıldız E, Durmayüksel E, Ersoy A, Tanoğlu A. Our convalescent plasma experiences in COVID-19 patients hospitalized in the intensive care unit. J Health Sci Med 2022; 5(2): 600-606.

ABSTRACT

Objective: Despite vaccine and drug studies, convalescent plasma (CP) therapy remains an alternative treatment for coronavirus disease 2019 (COVID-19). In this study, we aimed to reveal the efficacy of CP therapy on mortality and the factors affecting it for the patients diagnosed with COVID-19 and acute respiratory distress syndrome (ARDS) which were followed in our intensive care unit (ICU).

Material and Method: The data (demographic characteristics, the amount of CP used, PaO_2/FiO_2, leukocyte, neutrophil, lymphocyte, D-Dimer, C-reactive protein (CRP), procalcitonin, ferritin values, and the clinical findings) of the patients who were hospitalized in the ICU with the diagnosis of COVID-19 and received CP treatment between 20 March and 20 October 2020 were analyzed retrospectively. Data of deceased patients (n=29) and survivors (n=50) were compared with each other and logistic regression analysis was performed to investigate the relationship with mortality.

Results: 79 patients who received 166 units of CP therapy after a mean of 13.45±3.6 days symptom onset, were identified. 96.2% of the patients had at least one concomitant disease. Mortality was observed in 29 (36.7%) of the patients. Mortality (5.1%) was less common in those receiving CP therapy within the first 14 days after the onset of symptoms. Patient age (p=0.041), neutrophil/lymphocyte ratio (p=0.004), CRP values (p=0.002), the number of comorbidities (p<0.001), PaO_2/FiO_2 ratio before CP (p=0.005), and the period when CP was first infused from symptom onset (p<0.001) had a statistically significant effect on mortality.

Conclusion: CP can be safely used to treat COVID-19. However, its positive effect is less observed in patients with the advanced stage of the disease, progressive deterioration of oxygenation, and a high number of comorbidities. For this reason, starting CP treatment at an early stage may increase its effectiveness.

Keywords: Convalescent (immune) plasma, COVID-19, intensive care unit, SARS-Cov-2

INTRODUCTION

As of December 2019, coronavirus disease 2019 (COVID-19) has spread all around the world, affecting millions of people and drawing attention to its high mortality. In this context, passive immunization practices, which have historical importance, have come to the fore again. Immune plasma therapy is a treatment method based on the transfusion of plasma obtained from donors who have recovered from COVID-19 disease and have no viral load. The terms "convalescent plasma (CP)" or "hyperimmune plasma" can also be used instead of immune plasma.

Immune plasma therapy has also been used in previous outbreaks of influenza virus A (H1N1), Ebola virus, SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus), and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) (1-3). The first randomized study on the use of convalescent plasma in COVID-19 patients was conducted in China (4). The study reported that there was no difference between mortality and hospital discharge rates at the end of 28 days, but a significant decrease in viral load occurred within 72 hours in the group treated with convalescent plasma.

Corresponding Author: Bülent Barış Güven, barguv@gmail.com
Received: 06.02.2022 **Accepted:** 15.02.2022

The US Food and Drug Administration (FDA) had approved the use of convalescent plasma therapy in patients with severe or life-threatening COVID-19 during the initial period of the pandemic but subsequently limited CP therapy to hospitalized and early-stage disease patients (5). A recent systematic review and meta-analysis showed that convalescent plasma treatment was not significantly associated with a decrease in all-cause mortality (6). Since the level of evidence of the studies is low to moderate, more studies are needed on this subject.

In this study, we aimed to reveal the efficacy of convalescent plasma therapy, which we used in patients with COVID-19 infection who developed acute respiratory distress syndrome (ARDS) followed in our intensive care unit (ICU), on mortality and the factors affecting it.

MATERIAL AND METHOD

Ethical approval was obtained from the University of Health Sciences Hamidiye Clinical Researches Ethics Committee (Date: 27.02.2020, Decision No: 2020.02.27-17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data including patients' age, clinical, biochemical parameters were extracted from the institutional database. The data (demographic characteristics, amount of CP used, PaO_2/FiO_2, leukocyte, neutrophil, lymphocyte, D-Dimer, C-reactive protein (CRP), procalcitonin, ferritin values, and clinical findings) of 79 patients who were hospitalized in the Level 3 Anesthesiology and Reanimation ICU between 20 March and 20 October 2020 with the diagnosis of COVID-19 and received CP treatment were analyzed retrospectively. Laboratory data before and 48 hours after CP transfusion were used in the study. Initial transfusion data were based on patients who had more than one transfusion.

Patients with COVID-19 pneumonia between the ages of 18 and 90 who were hospitalized in the Sultan 2. Abdulhamid Han Training and Research Hospital COVID-19 ICU and were diagnosed with COVID-19 by polymerase chain reaction (PCR) were included in the study. Patients who were pregnant or breastfeeding, had immunoglobulin allergy, had a low IgA titer (<70 mg/dl), were diagnosed as immunodeficiency, and had undergone chemotherapy for the last 6 months were excluded from the study.

Donor assessments were carried out in compliance with the Republic of Turkey, Ministry of Health, and Donor Eligibility Criteria for COVID-19 Convalescent Plasma (7). The criteria were as follows: evidence of COVID-19 documented by a laboratory or serology test; resolution of symptoms at least 14 days and maximum 3 months before donation and at least 2 negative PCR test results for COVID-19 or have passed 28 days after clinical improvement. As of May 2020, donors' neutralizing antibody (anti-spike IgG) levels were routinely measured whose neutralizing titer was higher than 1/80 were accepted as immune plasma donors. All of the CPs used were obtained by the apheresis method. CPs were processed for pathogen inactivation after collection and then frozen in 200 ml (1 unit) packages. Informed consent was obtained from both the donor and the patients. An ABO compatible CP request was made for all patients hospitalized in the intensive care unit due to COVID-19 pneumonia, with a PaO_2/FiO_2 ratio < 180, and without pregnancy or selective IgA deficiency. However, due to the shortage of supply in some blood groups, not every CP request could be met. The standard dose used for each patient was calculated as 3-4 ml/kg and was used at doses of 200 or 400 milliliters per day with intervals of 24-48 hours. In total, a maximum of 4 doses (800 milliliters) was used for one patient. The decision regarding the total dose given to the patient was made by considering the patient's clinical status and oxygen needs, and CP treatment was repeated in patients with no decrease in oxygen needs (PaO_2/FiO_2 ratio > 180).

Statistical analyses were performed using IBM SPSS Statistics 26 software (IBM Corp., Armonk, NY). Descriptive statistics of the variables (frequency, percentage, mean, standard deviation, minimum, maximum) were calculated. The effects of age and gender, WBC, neutrophil/lymphocyte ratio, ferritin, CRP, procalcitonin, and D-Dimer variables on mortality were measured by logistic regression analysis. Wilcoxon test was used to determine the difference between the parameters measured before and after CP transfusion. All analyzes were evaluated at the 95% confidence interval, and significance was evaluated at the $p < 0.05$ level.

RESULTS

In this study, records of a total of 79 patients who received CP treatment were analyzed. The mean age of the patients was 66.1±12.8 years. 52 (65.8%) of the patients included in the study were male. The mean duration of ICU stay of the patients was 11.97±7.47. The shortest hospital stay was 5 days and the longest 53 days. There was at least one concomitant chronic disease in 76 (96.2%) of the patients. The most common accompanied comorbidity was hypertension (N:40, 50.6%) and with decreasing frequency diabetes mellitus (N:26, 32.9%), chronic obstructive pulmonary disease (N:16, 20%), cancer (N:14, 17.7%), coronary artery disease (N:11, 13.9%), kidney disease (N:10, 12.7%), cerebrovascular disease (N:6, 7.6%), and liver disease (N:5, 6.3%) (**Table 1**).

Table 1. Demographic data and clinical characteristics of the patients

	N	Mean±SD	Minimum-Maximum	%
Age (years)	----	66.1 ±12.8	36- 89	----
Gender (F/ M)	27/52	----	----	34.2/65.8
Total number of patients receiving CP	79	----	----	----
Total amount of CP used (Units)	166	2.1 (per person)	1- 4	----
The number of days of hospitalization in ICU	----	11.97±7.47	5 -53	----
The interval between COVID-19 symptoms and CP transfusion (days)	----	13.45±3.6	7- 26	----
Patients under invasive-MV (Before CP/ After CP*)	38/40	----	----	48.1/50.6
Mortality (F/M)	29 (9/20)	----	----	36.7 (11.4/25.3)
Coexisting diseases	N:76			96.2%
Hypertension	40			50.6
Cerebrovascular disease	6			7.6
Coronary artery disease	11			13.9
Diabetes	26			32.9
Cancer	14			17.7
Liver disease	5			6.3
Chronic obstructive lung disease	16			20
Kidney disease	10			12.7

P: Convalescent plasma, N: Number, SD: Standard deviation, F: Female, M: Male, ICU: Intensive care unit, MV: Mechanical ventilation, *Values measured 48 hours after transfusion.

A total of 166 units of CP was used during the study period. No CP-related adverse effects were observed in any of the patients. While an average of 2.1 units of CP was used per patient, a maximum of 4 units of CP was used per patient (**Table 1**). CPs were used a mean of 13.45±3.6 days after the onset of symptoms of the disease. CP was used at the earliest 7 days after symptom onset and the latest 26 days later (**Figure 1**). 15.2% discharge and 31.6% death were observed in patients who received the first CP infusion 14 days after the onset of symptoms, while 48.1% discharge and 5.1% death were observed in patients who received CP infusion before 14 days (**Figure 2**). All patients with indications for convalescent plasma therapy were included in the study. While 38 (48.1%) patients were under treatment with invasive mechanical ventilation (MV) before transfusion, 40 (50.6%) patients were under invasive-MV treatment 48 hours after transfusion. Mortality was observed in 29 (36.7%) of the patients who had CP. Mortality by gender was higher in male patients (38.5%) than in female patients (33.3%) (**Figure 3**).

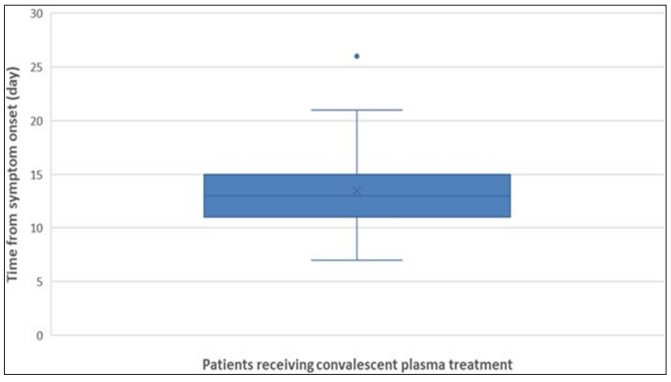

Figure 1. Time interval when patients received first convalescent plasma therapy by symptom onset

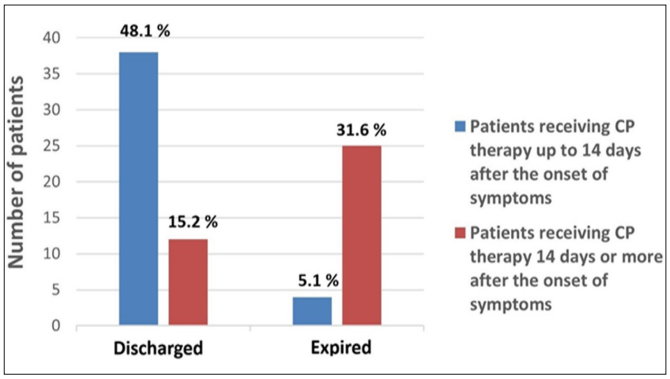

Figure 2. Number of the patients receiving first convalescent plasma therapy by time (day 14) of symptom onset

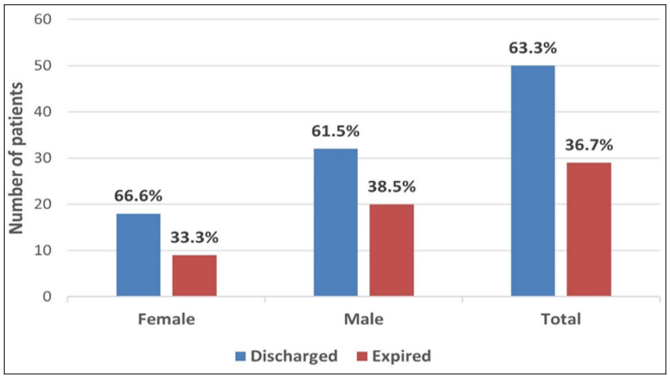

Figure 3. Discharge status of the patients receiving convalescent plasma (CP) therapy.

When the clinical and laboratory characteristics of the patients before and after CP transfusion were compared statistically; No significant difference was detected in terms of oxygenation (PaO_2/FiO_2), Sequential Organ Failure Assessment (SOFA) score, neutrophil, leukocyte, lymphocyte, procalcitonin, D-dimer, ferritin, and CRP values (**Table 2**).

Table 2. Clinical and laboratory characteristics of patients before and after CP transfusion

	Before CP Mean±SD	After CP * Mean±SD	P-value
PaO_2/FiO_2 (NR>300)	139.6±84.9	125.2±82.5	0.850
SOFA score	6.0±3.4	6.2±3.7	0.249
Neutrophil (10^3/mcL) (NR: 1.5 – 8.0)	8.62±4.31	9.23±3.14	0.434
Leukocyte (10^3/mcL) (NR: 4.0- 11.0)	11.15±5.41	11.98±5.04	0.621
Lymphocyte (10^3/mcL) (NR: 1.5- 4.5)	0.76±0.62	0.80±0.64	0.582
Procalcitonin (ng/ml) (NR ≤ 0.05)	0.16±0.23	0.17±0.24	0.357
D-Dimer (ng/ml) (NR ≤ 500)	1520±1955	1552±1385	0.568
Ferritin (ng/ml) (NR: 20-400)	660±454	708±476	0.671
CRP (mg/L) (NR: 0.0- 5.0)	78.6±60.0	65.6±65.4	0.406

SOFA: Sequential Organ Failure Assessment, CRP: C-Reactive Protein, NR: Normal Range, *Values measured 48 hours after transfusion.

The age, gender, number of comorbidities, the first day of CP infusion according to the time of symptom onset, the average amount of CP used, the pre-transfusion PaO_2/FiO_2 ratio, and post-transfusion laboratory data of the deceased and surviving patients were compared with each other and a logistic regression analysis was performed to investigate the relationship with mortality. It was determined that the patient age (p=0.041), neutrophil/lymphocyte ratio (NLR) (p=0.004), CRP value (p=0.002), the number of comorbidities (p<0.001), PaO_2/FiO_2 ratio (p=0.005), and the first day of CP infusion (p<0.001) had a statistically significant effect on mortality. A single unit increase in age, neutrophil/lymphocyte ratio, CRP, the number of comorbidities, PaO_2/FiO_2 ratio, and the first day of CP infusion was found to increase mortality 1.041, 1.071, 1.012, 5.373, 0.990, and 2.064 times, respectively, in a statistically significant manner.

There was no statistically significant effect of gender, mean CP volume used (ml), leukocyte, ferritin, procalcitonin, and D-dimer values on mortality (p>0.05). Although not statistically significant, men had a 0.456 unit higher risk of death than women (**Table 3**).

DISCUSSION

Worldwide, extensive efforts have been made to find effective treatment and prevention agents after facing the SARS-CoV-2 pandemic. Vaccine applications, which are the most important preventive agents, continue rapidly and as of December 2021, 54.5% of the world population has been vaccinated (7). However, despite these efforts, new cases of COVID-19 who are treated in hospital due to new mutagen strains or insufficient antibody response are reported. For this reason, in parallel with the vaccine studies, the search for effective solutions in the treatment continues. One of these treatment modalities is CP treatment, which is a passive immunization, by administering the antibody-rich plasma from recovered patients to the patients after processing. Neutralizing antibodies are the key factor here, preventing the virus from entering cells by binding, regulation of the immune system, phagocytosis, and viral clearance by cells of the immune system, thus shortening the duration of viremia. The history of passive antibody transfer dates back to the 1890s when antibodies were used to protect against bacterial toxins before antimicrobial agents were discovered (8). Since then, CP obtained from recovered

Table 3. Comparison of clinical and laboratory characteristics of the patients according to the outcome

Characteristic	Discharged (n=50)	Expired (n=29)	P value	Logistic regression P value
Age (year)	64.88±13.11	69.07±11.01	0.040*	0.041*
Gender (F/M)	18/32	9/20	0.123	0.456
Neu/Lymph #	31.0±30.3	68.1±49.2	0.007*	0.004*
Leukocyte (10^3/mcL) #	10.52±5.94	15.05±13.49	0.236	0.192
CRP (mg/l) #	86.93±70.58	123.54±62.79	0.006*	0.002*
Procalcitonin (ng/ml) #	2.84±9.13	2.98±4.7	0.463	0.290
Ferritin (ng/ml) #	2422±4631	4105±5837	0.471	0.654
D-Dimer (ng/ml) #	1991±3524	2617±2401	0.169	0.078
The number of comorbidities	1.28±0.73	2.21±0.86	<0.001**	<0.001**
PaO_2/FiO_2 ratio before infusion	162.42±91.1	100.34±55.29	0.01*	0.005*
Mean CP volume (ml)	416±179.98	427.58±237.39	0.81	0.271
Mean day of CP İnfusion (day)	11.7±2.32	16.83±3.35	<0.001**	<0.001**

Neu/Lymph: Neutrophil/Lymphocyte, F: Female, M: Male, CRP: C-reactive protein, CP: Convalescent plasma, # post-transfusion laboratory values, * P < 0.05, **P <0.001

patients has been used as a treatment modality against various infectious pathogens, and varying degrees of clinical efficacy has been achieved, especially in viral infections (9,10).

Based on the experience, the use of CP in the treatment of patients infected with COVID-19 has been suggested at the expert level, and it has been stated that CP therapy will provide potential clinical benefits (11-12). In the Interim Position Paper published by the World Health Organization (WHO) on January 28, 2020, it was stated that immune plasma, serum, or immunoglobulin concentrates could also be used for the SARS-CoV-2 virus, as was applied previously in the MERS epidemic (13).

In our country, CP has started to be obtained from people who have had a COVID-19 infection since April 7, 2020, and 166 units of CP were applied to 79 patients in our ICU until October 2020, and a discharge rate of 63.3% was achieved. In a randomized controlled study conducted by Li et al. (4) in 103 life-threatening COVID-19 patients, CPs with a high neutralizing antibody titer (at least 1:640 and higher) were used in patients on average 14 days after the onset of symptoms, and a mortality rate of 29% in the group receiving CP was found. Similarly, in our patient group, CP was used an average of 13.45±3.6 days after the onset of symptoms, but the mortality rate was higher. We think that this difference is due to the presence of comorbidity in 96.2% of the patients in our study group and the fact that donor plasmas with neutralizing antibody levels of at least 1:80 and above were used in this study.

However, Li et al. (4) did not find a significant difference in 28-day mortality in patients receiving CP therapy added to standard therapy compared with the standard therapy and reported that this may be related to the timing of CP therapy. In a study in which Spironolactone, a potassium-sparing diuretic, was added to the standard treatment of 30 patients hospitalized in the ICU due to COVID-19 and compared with the control group receiving standard treatment, less mortality was observed in the treatment group, and the mortality rate of the treatment group was 46% (14). This rate was found to be higher than the mortality rate of our CP treatment group (36.7%) in this study. In a recent meta-analysis, 7 randomized controlled trials were analyzed. Accordingly, it has been reported that CP therapy reduced mortality when used at an early stage, but did not provide any survival benefits at a stage in which patients required advanced supportive treatments. Only short-term clinical improvements such as a decrease in oxygen demand have been observed (6). In our study, it was also found that the number of comorbidities of patients in the survival group was lower and the oxygenation (PaO_2/FiO_2) values were better than the patients who died. In this case, it will be more useful to start CP therapy before the clinical manifestations of patients deteriorate.

Although CP treatment has been used and researched many times in the past, there is still no standard protocol accepted by all authorities regarding the time and amount of CP use. Chen et al. (9) applied CP treatment to SARS patients (n=80) and observed 6.3% mortality in those receiving CP treatment within the first 14 days after the onset of symptoms, and 21.9% mortality in those receiving treatment after 14 days. In our study, the mortality rate was 5.1% for the early period (first 14 days) and 31.6% for the late period. In addition, in this study, there was a statistical difference between the average time of using CP in expired (mean 16.83±3.35 days) and discharged patients (mean 11.7±2.32 days). Also, there was no difference in terms of the amount of plasma used. Thus, it has been observed that applying early-stage CP treatment shows better clinical results in both diseases.

In an observational study involving 351 patients, it was reported that mortality developed less in individuals who were not intubated and received CP within 72 hours of hospitalization (15). Similarly, another observational study reported that lower mortality was observed when CP was given within three days of diagnosis compared to those given four or more days after diagnosis (16). In our country, according to the newly published guideline after October 2020, CP use is recommended in patients diagnosed with COVID-19 within 7 days at the latest after the onset of symptoms and before the need for intensive care develops (17). In our study, CP treatment was applied to patients an average of 13.45±3.6 days after symptom onset. However, findings showing clinical improvement such as a decrease in MV requirement, increase in oxygenation (PaO_2/FiO_2) value, and decrease in the SOFA score could not be detected. These results also support the current studies in the literature and the CP clinical guide currently applied in our country.

Many researchers have reported that high NLR and CRP levels, which reflect an increased inflammatory process, are effective on prognosis in patients with COVID-19 (18,19). Likewise, studies show that advanced age is a risk factor for mortality in COVID-19 disease (20). In our study, it was determined that the age of the patient, NLR, and CRP values were effective on mortality in the logistic regression analysis using age, gender, and laboratory data (NLR, leukocyte, CRP, procalcitonin, ferritin, D-dimer) measured after CP treatment. Likewise, in a study in which the results of patients who used CP in the ICU were included, it was reported that patient age and lymphocyte count were determining factors in mortality, supporting our results (21).

A large number of articles have been published recently reporting the correlation of biochemical parameters such as NLO, leukocyte, CRP, PaO_2/FiO_2 ratio, procalcitonin, ferritin, D-dimer with the progression of the disease in COVID-19 patients (20-27). Some authors also reported these biomarkers involved in inflammation and coagulation processes as independent risk factors in determining the prognosis (26-29). However, since many of these parameters may cause incorrect assessments in patients with comorbidities that have led to multiple organ dysfunction, they alone may not be sufficient to evaluate the effectiveness of treatment. It is necessary to use parameters that also indicate clinical manifestations while evaluating the effectiveness of treatment. For this purpose, SOFA scores are the most commonly used in critically ill patients. Yang et al. (30) reported that the SOFA score can be used to assess the severity and 60-day mortality of COVID-19.

In this study, the clinical and laboratory characteristics of the patients before and 48 hours after CP transfusion were compared statistically and no significant difference was detected. At the same time, the fact that the SOFA score was higher than 5 before CP treatment was the most important indicator of higher mortality. In a study conducted by Erkurt et al. (21) in 26 COVID-19 patients hospitalized in the ICU, the leukocyte, neutrophil, lymphocyte, platelet, CRP, ferritin, LDH, ALT, AST, spO_2, total bilirubin values of the patients before and 7 days after CP treatment were compared and found no significant difference similar to our study. However, the major limitation here is that the anti-cytokine and anti-inflammatory treatments (steroids, tocilizumab, and cytokine filtration) were given to patients for the treatment of the hyperinflammatory response developing in the course of COVID-19 may have affected this result. For this, there is a need for larger randomized controlled studies comparing the treatments given to the patients.

Some undesirable adverse effects can be seen in CP treatment. These are transfusion-related circulatory overload, infections, acute lung injury, serious allergic reactions, antibody-dependent enhancement (ADE), and coagulation disorders (31). No such adverse effects were observed in the patients in our study.

Our study has some limitations. Firstly; our study didn't have a control group with standard therapy and the patients included in our study received at least one or more of the treatments such as antiviral agents, varying doses of steroids, tocilizumab, and Coupled Plasma Filtration Adsorption (CPFA) before CP transfusion. In conclusion, the possibility that these treatment applications may affect the clinical and laboratory data of the patients cannot be excluded. Second, some patients in the study received up to 800 mL of CP transfusion, and the optimal dose for the disease was not planned.

CONCLUSION

As a result, CP can be safely used to treat COVID-19. However, it has been observed that the positive effect of CP treatment is less in patients in patients with advanced age, advanced stage of the disease, progressive deterioration of oxygenation, and a high number of comorbidities. We believe that the addition of CP treatment with a high neutralizing antibody titer to standard COVID-19 treatment in the early stages of the disease may increase the effectiveness of treatment

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences Hamidiye Clinical Researches Ethics Committee (Date: 27.02.2020, Decision No: 2020.02.27-17).

Informed Consent: All patients signed the free and informed consent form.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015; 211: 80-90.
2. Arabi YM, Hajeer AH, Luke T, et al. Feasibility of using convalescent plasma immunotherapy for MERS-CoV infection. Saudi Arabia. Emerg Infect Dis 2016; 22: 1554-61.
3. Van Griensven J, De Weiggheleire A, Delamou A, et al. The use of ebola convalescent plasma to treat ebola virus disease in resource-constrained settings: a perspective from the field. Clin Infect Dis 2016; 62: 69-74.
4. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020; 324: 460-70.
5. U.S Food & Drug Administration Recommendations for Investigational COVID-19 Convalescent Plasma. Available from: https://www.fda.gov/vaccines-blood-biologics/ investigational-new-drug-applications-inds-cber-regulated-products/ recommendations-investigational-covid-19-convalescent-plasma [accessed 11 September 2021]
6. Janiaud P, Axfors C, Schmitt AM, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. JAMA 2021; 325: 1185-95.
7. Our World in data. Coronavirus (COVID-19) vaccinations. https://ourworldindata.org/covid-vaccinations [accessed 01 December 2021]

8. Casadevall A, Dadachova E, Pirofski LA. Passive antibody therapy for infectious diseases. Nat Rev Microbiol 2004; 2: 695–703.
9. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005; 24: 44–6.
10. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015; 211: 80–90.
11. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest 2020; 130: 1545-8.
12. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest 2020; 130: 2757-65.
13. WHO Blood Regulators Network (BRN), "Interim Position Paper on blood regulatory response to the evolving out-break of the 2019 novel coronavirus SARS-CoV-2." http://www.transfusion.ru/2020/04-03-3.pdf [accessed 19 September 2021]
14. Ersoy A, Güven BB, Ertürk T et al. Assessment of the efficacy of spironolactone for COVID-19 ARDS patients. Aydın Sağlık Dergisi 2021; 7: 191-209
15. Salazar E, Christensen PA, Graviss EA, et al. Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG. Am J Pathol 2021; 191: 90-107.
16. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. Preprint. medRxiv 2020; 2020.08.12.20169359.
17. Covıd-19 İmmün (Konvalesan) Plazma Tedarik ve Klinik Kullanım Rehberi 2020. Available from: https://shgmkanhizmetleridb.saglik.gov.tr/Eklenti/39167/0/covid-19-immun-plazma-rehberi-v5.pdf [accessed 11 September 2021]
18. Lagunas-Rangel FA. Neutrophil-to lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID19): A meta-analysis. J Med Virol 2020; 92: 1733-4.
19. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Maladies Infect 2020; 50: 332-3.
20. Albitar O, Ballouze R, Ooi JP, Sheikh Ghadzi SM. Risk factors for mortality among COVID-19 patients. Diabetes Res Clin Pract 2020; 166: 108293.
21. Erkurt MA, Sarici A, Berber İ, Kuku İ, Kaya E, Özgül M. Life-saving effect of convalescent plasma treatment in covid-19 disease: Clinical trial from eastern Anatolia. Transfus Apher Sci 2020; 59: 102867.
22. Roback JD, Guarner J. Convalescent plasma to treat COVID-19: possibilities and challenges. JAMA 2020; 323: 1561-2.
23. Klassen SA, Senefeld JW, Senese KA, et al. Convalescent plasma therapy for COVID-19: a graphical mosaic of the worldwide evidence. Front Med (Lausanne) 2021; 8: 684151.
24. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci 2020; 57: 389-99.
25. Yufei Y, Mingli L, Xuejiao L, et al. Utility of the neutrophil-to-lymphocyte ratio and C-reactive protein level for coronavirus disease 2019 (COVID-19). Scand J Clin Lab Invest 2020; 80: 536-40.
26. Gu Y, Wang D, Chen C, et al. PaO_2/FiO_2 and IL-6 are risk factors of mortality for intensive care COVID-19 patients. Sci Rep 11, 7334 (2021). https://doi.org/10.1038/s41598-021-86676-3
27. Şahin Özdemirel T, Akkurt ES, Ertan Ö, Gökler ME, Akıncı Özyürek B. Complications with moderate-to-severe COVID-19 during hospital admissions in patients with pneumonia. J Health Sci Med 2021; 4: 766-71.
28. Güngörer B. Baseline demographic, clinical and laboratory risk factors for predicting admission to intensive care unit in patients diagnosed with COVID-19 in the emergency department. Anatolian Curr Med J 2021; 3; 279-83
29. Ertan Ö, Akkurt ES, Şahin Özdemirel T, Akıncı Özyürek B. A rare case: acute ischemic stroke that developed in a case with severe COVID-19 pneumonia. Anatolian Curr Med J 2021; 3; 256-8
30. Yang Z, Hu Q, Huang F, Xiong S, Sun Y. The prognostic value of the SOFA score in patients with COVID-19: A retrospective, observational study. Medicine (Baltimore) 2021; 100:e26900.
31. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest 2020; 130: 4791-7.