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## Effects on mortality of early vs late administration of convalescent plasma in the treatment of Covid-19

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### ABSTRACT

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first seen in the city of Wuhan, China, in December 2019 and then spread worldwide. On 24 March 2020, the U.S. Food and Drug Administration reported that the use of convalescent plasma (CP) containing antibodies against COVID-19 could be effective against infection. The aim of this study is to retrospectively investigate whether early CP transfusion treatment has an effect on recovery of clinical and laboratory parameters in patients diagnosed with severe COVID-19 who were admitted to the intensive care unit (ICU). The study included 141 consecutive patients who had laboratory confirmation of COVID-19 and were admitted to the ICU between 1 May and 30 September 2020. Of the 141 patients, 84 received CP in the first five days of hospitalization in the ICU (early group), and 57 received CP after the fifth day of hospitalization in the ICU (late group). There were no significant differences between the two groups in terms of age, gender, comorbidities and the severity of the disease (according to the evaluation of lung tomography). There was no difference between the two groups in terms of mechanical ventilator needed, inotrope support, and tracheostomy procedure during the ICU admission ( $p = 0.962$ ,  $p = 0.680$ , and  $p = 0.927$ , respectively). Despite these limitations, the overriding result of our study is that it suggests that administration of CP either early or late in the treatment of COVID-19, had no effect on mortality.

### 1. Introduction

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first seen in the city of Wuhan, China, in December 2019 and then spread worldwide [1]. The pneumonia caused by SARS-CoV-2 was designated coronavirus disease-2019 (COVID-19). By 10 October 2020, this pandemic had affected more than a hundred million people worldwide and caused more than 2.3 million deaths.

Although various treatment methods are being investigated to combat this disease, no specific treatment and no vaccine had been approved by the end of 2020. Agents such as remdesivir, favipiravir, hydroxychloroquine, and lopinavir/ritonavir are included in treatment protocols, but their antiviral efficacies are unclear [2–4]. Therefore, current treatment practices are often directed towards supportive care,

lung protective mechanical ventilation strategies, and prevention of secondary infections. While research for treatment continues, the concept of passive immunization has come up. It is believed that the administration of plasma, serum, or immunoglobulin concentrates obtained from individuals who have survived the disease may be effective in preventing or treating COVID-19 infection. CP use was successfully applied in the 2009–2010 H1N1 influenza virus outbreak, the 2003 SARS-CoV-1 outbreak, and the 2012 MERS-CoV outbreak. Administration of CP to inpatients for therapeutic purposes in cases of active virus infection is defined as “passive immune transfer.” Passive immune antibodies can reduce damage to target organs and directly neutralize pathogens that cause disease. On 28 January 2020, the World Health Organization stated that CP, serum, or immunoglobulin concentrates can be used for the SARS-CoV-2 outbreak [5]. On 24 March 2020, the U.

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S. Food and Drug Administration reported that the use of CP containing antibodies against COVID-19 could be effective against infection [6].

The aim of this study is to investigate whether early CP transfusion treatment has an effect on recovery of clinical and laboratory parameters in patients diagnosed with severe COVID-19 who were admitted to the ICU.

## 2. Materials and Methods

### 2.1. Study design and population

This study was conducted at the ICU of Sakarya University Training and Research Hospital, Sakarya, Turkey, from 21 March to 30 September 2020. Ethical committee approval was obtained for this study from Sakarya University Ethical Committee. Written informed consent was obtained from all patients and donors. The study included 141 consecutive patients who had laboratory confirmation of COVID-19 and were admitted to the ICU between 1 May and 30 August 2020. Follow-up continued through 17 September 2020 when the last patients included in the study were discharged.

Clinical data for the patients before CP transfusion were obtained from the hospital computer system or patient follow-up charts and include clinical data, such as demographic characteristics, comorbid diseases, ABO blood type, days from ICU hospitalization to CP transfusion, number of CP transfusions, ICU supportive therapies (inotropic agents, renal replacement therapy, invasive or non-invasive mechanical ventilation) and laboratory data (white blood cell count, lymphocyte count, neutrophil count, C-reactive protein (CRP), procalcitonin, D-dimer, high-sensitive (hs) troponin, ferritin, erythrocyte sedimentation rate, and lactate).

The first PCR positive test date was accepted as the beginning of the symptoms in the study. If the patient has several PCR tests in the hospital and intensive care period, the first PCR test is taken as basis. For the study, the designation of “convalescent plasma administration day,” the time between the positive PCR test and the day of CP administration day, was taken as the basis.

### 2.2. Patients

Patients with respiratory distress (>30 breaths/min), oxygen saturation <90 at rest under nasal oxygenation with 5–6 L/min, arterial partial pressure of oxygen (PaO<sub>2</sub>) fraction of inspired oxygen (FiO<sub>2</sub>) <300 mmHg were admitted to the ICU. All patients received favipiravir (200 mg tablet; Haizheng Pharmaceutical Co., Shenzhen, China) as an antiviral treatment with a loading dose of 1600 mg followed by a daily 600 mg dose. Steroid treatment (methylprednisolone 1 mg / kg daily) was administered to the patients who were intubated.

CP treatment was administered to patients with a definitive or strongly likely diagnosis of COVID-19, over the age of 18, in the first 14 days of the disease, and 7–10 days after the onset of symptoms and pneumonic infiltrations due to COVID-19. If the clinical condition of the patient was appropriate, CP transfusion was given at 48-h intervals with a maximum of three doses after the first CP transfusion. Each CP given to a patient who received multiple CP transfusions was obtained from different donors. Each CP transfusion volume was 200 mL, and the infusion duration was 45–60 min.

### 2.3. Donors

Donors for CP were selected from patients who survived SARS-CoV-2 infection and whose SARS-CoV-2 antibody test was positive. After treatment, at least two PCR tests of nasopharyngeal swab samples were negative. At least 14 days had passed since clinical recovery after negative PCR tests. If the donor completed COVID-19 recovery or a quarantine period at home, at least 28 days had passed since clinical recovery, and the PCR test (nasopharyngeal swab) for SARS-CoV-2 was

negative. Hepatitis B, hepatitis C, syphilis, HIV, and indirect Coomb's tests were negative for all donors. Plasma was obtained using a single-arm plasmapheresis device and kit (MCS® + 9000 mobile platelet collection system, Haemonetics, Massachusetts, USA) from donors who had been positive for COVID-19 according to combo IgG/IgM rapid antibody test. Pathogen inactivation processes were not routinely performed. Clearance of SARS-CoV-2 was defined as at least 2 consecutive negative RT-PCR test results.

### 2.4. Statistical analysis

Descriptive values of the variables are expressed as mean ± SD in normal distribution, and parameters with abnormal distribution are expressed as the median of the 25th–75th percentile. Categorical data are expressed as proportions. The chi-square and student's *t*-test were used for categorical and continuous variables, respectively. Fisher's exact test was applied in analysing small samples. For continuous variables, differences between the two groups were evaluated using the student's *t*-test when the data were normally distributed and the Mann–Whitney *U* test when the assumption of normality was not met. A *p*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using statistical software (SPSS 20.0, Chicago, IL, USA).

## 3. Results

Of the 148 consecutive patients with COVID-19 who were admitted to the ICU between 1 May and 30 September 2020, seven were excluded because they died within the first 24 h. Thus, 141 patients were included in this study. The mean age of the patients was 66.0 ± 13.3 years. Thirty-nine patients were female (27.5 %). Seventy-eight of the patients (54.9 %) had a history of hypertension, 44 (31.0 %) had diabetes mellitus, 35 (24.6 %) had coronary artery disease, 19 (13.4 %) had chronic obstructive pulmonary disease, three (2.1 %) had cerebrovascular disease, nine (6.3 %) had chronic renal disease, 13 (9.2 %) had congestive heart failure, and ten (7.0 %) had malignancies (Table 1). Of the 141 patients, 84 received CP in the first five days of hospitalization in the ICU (early group), and 57 received CP after the fifth day of hospitalization in the ICU (late group). There were no significant differences between the two groups in terms of age, gender, and comorbidities.

One hundred thirty-seven patients underwent computed tomographic assessment of the chest before admission to the ICU and all 137 (100 %) had typical findings compatible with COVID-19 pneumonia. In the evaluation of lung tomography, the two groups were found similar as to classification according to the severity of the disease (*p* = 0.691) (Table 1).

Table 2 presents the laboratory findings of the patients upon ICU admission. The white blood cell count was in normal range in both groups (9.0 [6.4–12.1] vs 8.7 [6.3–13.8], *p* = 0.565). Although neutrophil count increased in both groups, it was found to have increased more in the early group than in the late group (7.6 [5.1–10.5] vs 7.5 [5.0–12.5], *p* = 0.024). Lymphocyte counts and high-sensitive troponin levels were similar and within normal limits in both the early and late groups (0.6 [0.5–1.0] vs 0.5 [0.4–1.0], *p* = 0.530 and 16 [6.4–44.5] vs 16.5 [5.3–60.5], *p* = 0.753, respectively). In both groups, C-reactive protein and procalcitonin levels were elevated (144 ± 84 vs 130 ± 72, *p* = 0.333 and 0.3 [0.1–1.0] vs 0.4 [0.1–1.0], *p* = 0.812, respectively). Serum ferritin levels were found to have increased approximately three-fold in both groups, and there was no significant difference between the two groups (*p* = 0.791). Although the level of d-dimer increased in both groups, it was found to have increased more in the late group (955 [551–1847] vs 1130 [754–2820], *p* = 0.052). Ferritin and ESR levels also increased in both groups, with no significant difference between the two (*p* = 0.791 and *p* = 0.429, respectively) (Table 2).

The amount of CP given to both groups was similar. The CP

**Table 1**  
Clinical and demographic characteristics of the patients.

	All Patients (n = 141)	Early Group (n = 84)	Late Group (n = 57)	P
Age (years)	66.0 ± 13.3	64.8 ± 13.6	67.7 ± 12.6	0.690
Gender (n, %)				
Female	39 (28.2 %)	24 (28.6 %)	15 (26.3 %)	0.769
Male	102 (71.8 %)	60 (71.4 %)	42 (73.7 %)	
Comorbidities				
Hypertension (n, %)	78 (54.9 %)	43 (51.2 %)	35 (61.4 %)	0.231
Diabetes mellitus (n, %)	44 (31.0 %)	26 (31.0 %)	18 (31.6 %)	0.937
Coronary artery disease (n, %)	35 (24.6 %)	22 (26.2 %)	13 (22.8 %)	0.648
Cerebrovascular disease (n, %)	3 (2.1 %)	2 (2.4 %)	1 (1.8 %)	0.800
Congestive heart failure (n, %)	13 (9.2 %)	9 (10.7 %)	4 (7.0 %)	0.457
Chronic renal disease (n, %)	9 (6.3 %)	6 (7.1 %)	3 (5.3 %)	0.654
Chronic obstructive pulmonary disease (n, %)	19 (13.4 %)	10 (11.9 %)	9 (15.8 %)	0.507
Malignancy (n, %)	10 (7.0 %)	8 (9.5 %)	2 (3.5 %)	0.172
Computed tomography				
1	25 (17.7 %)	13 (15.5 %)	12 (22.2 %)	0.691
2	44 (31.2 %)	29 (34.5 %)	15 (27.8 %)	
3	30 (21.3 %)	17 (20.2 %)	13 (24.1 %)	
4	38 (27.0 %)	24 (28.6 %)	14 (25.9 %)	
Missing	4 (2.8 %)			

Computed Tomography classification: 0 = No involvement, 1 = minimal involvement below 25 %, 2 = mild involvement 25 %–50 %, 3 = moderate involvement 50 %–75 %, 4 = severe involvement above 75 %.

**Table 2**  
Laboratory findings of patients at admission to the ICU.

	All Patients (n = 141)	Early Group (n = 84)	Late Group (n = 57)	P
White blood cells, ×10 <sup>9</sup> /mL	9.0 (6.4–12.4)	9.3 (6.4–12.1)	8.7 (6.3–13.8)	0.565
Neutrophils, ×10 <sup>9</sup> /mL	7.6 (5.2–11.0)	7.7 (5.1–10.5)	7.5 (5.0–12.5)	0.024*
Lymphocytes, ×10 <sup>9</sup> /mL	0.6 (0.4–1.0)	0.6 (0.5–1.0)	0.5 (0.4–1.0)	0.530
C-reactive protein, mg/L	138 ± 79	144 ± 84	130 ± 72	0.333
Procalcitonin, ng/L	0.3 (0.1–1.0)	0.3 (0.1–1.0)	0.4 (0.1–1.0)	0.812
High-sensitive troponin, ng/L	16 (6–55)	16.0 (6.4–44.5)	16.5 (5.3–60.5)	0.753
D-dimer, ugFEU/L	1020 (649–2065)	955 (551–1847)	1130 (754–2820)	0.052
Ferritin, µg/L	716 (440–1617)	684 (391–1651)	733 (463–1267)	0.791
ESR (mm/h)	40 (22–61)	39.5 ± 22.5	42.8 ± 25.5	0.429

ERS: erythrocyte sedimentation rate. median [IQR (25–75)], Mean ± SD.

\* p < 0.05.

administration day for the early group was determined as 3 [2–4], and the time of giving immune plasma to the late group was 8.5 days [7–11] ( $p = 0.00$ ). There was no difference between the two groups in terms of mechanical ventilator needed, inotrope support, and tracheostomy procedure during the ICU admission ( $p = 0.962$ ,  $p = 0.680$ , and  $p = 0.927$ , respectively). Renal replacement therapy needed for acute renal failure was statistically higher in the late group compared to the early group (20 (35.1 %) vs 14 (16.7 %),  $p = 0.012$ ) (Table 3).

When days of hospitalization were examined, in terms of patients who were discharged or died, there was no significant difference between the two groups ( $p = 0.264$  and  $p = 0.363$ , respectively). In

**Table 3**  
Treatment, complications, and clinical outcomes of the patients.

	All Patients (n = 141)	Early Group (n = 84)	Late Group (n = 57)	P
Immune plasma	2 (1–3)	2 (1–3)	2 (2–3)	0.737
Immune plasma administration day	5 (2–8)	3 (2–4)	8.5 (7–11)	0.00*
Oxygen inhalation, n (%)	67 (47.2 %)	40 (47.6 %)	27 (47.4 %)	0.962
Invasive mechanic ventilation, n (%)	74 (52.1 %)	44 (52.4 %)	30 (52.7 %)	
Vasopressor, n (%)	54 (38.0 %)	31 (36.9 %)	23 (40.4 %)	0.680
Renal replacement therapy, n (%)	34 (23.9 %)	14 (16.7 %)	20 (35.1 %)	0.012*
Tracheostomy, n (%)	12 (8.4 %)	7 (8.3 %)	5 (8.8 %)	0.927
Median stay (days) in ICU (IQR)				
All patients	10 (7–14)	9 (6–14)	11 (7.3–14.8)	0.124
Died	11 (8–14)	10 (7–14)	11 (9–13.5)	0.264
Discharged	8.5 (6–14)	8 (6–14)	10 (5–16)	0.363
Discharged from ICU, n (%)	69 (49.3 %)	41 (48.8 %)	28 (49.1 %)	0.971
Died, n (%)	72 (50.7 %)	43 (51.2 %)	29 (50.9 %)	

\* p < 0.05.

addition, early group and late group mortality rates were similar (43 (51.2 %) and 29 (50.9 %), respectively,  $p = 0.971$ ) (Table 3).

#### 4. Discussion

By the end of 2020, management of COVID-19 is mainly focused on infection prevention by vaccination. All countries started protocols to vaccinate their citizens with different vaccines all over the world [6], but the COVID-19 pandemic is not over yet, and people are still becoming infected with COVID, being hospitalized, and dying. As a result of research conducted all over the world on the treatment of COVID, no consensus has been reached, and there is still no 100 %-effective antiviral treatment for COVID-19.

Previous studies have reported the use of convalescent plasma transfusion in the treatment of Ebola, H1N1, and SARS-CoV-1 infections [7–9]. There is evidence of reductions in mortality, especially when convalescent plasma is administered early after symptom onset, and a statistically significant reduction of mortality following treatment, compared with a placebo or no therapy in SARS-CoV-1 infection and severe influenza [10]. The use of convalescent plasma in the treatment of Middle East respiratory syndrome coronavirus as a protocol was established in 2015 [11]. Although the effectiveness of CP in COVID-19 treatment remains controversial, it is still recommended in some indications [12]. This study investigated whether early CP treatment reduces mortality in the treatment of COVID-19.

There were no significant differences in mean age, gender ratio, and comorbidities between the early and late groups into which patients were separated according to the lapse between ICU admission and CP administration date. In addition, the evaluation of the patients according to involvement rates reflected by computed tomography was found to be similar. In this respect, it can be said that the early and late groups were comparable. When the two groups were evaluated in terms of mortality and hospitalization days, there was no significant difference between the early and late groups.

Previous studies showed reductions in mortality when CP was administered early after symptom onset of SARS-CoV-1 and H1N1 infections [11]. Hung et al. performed a prospective cohort study in which patients received a single 500-mL dose of convalescent plasma for H1N1 infections and showed a significant reduction in the relative risk of mortality [9]. Based on this, declines in mortality and hospital stay were expected in the treatment of COVID-19. In articles published in the early days of the pandemic, it was stated that CP treatment shortened both

mortality rate and hospital stay. A case series from China suggested clinical benefits, including radiological resolution, reduction in viral loads, and improved oxygenation with CP treatment for COVID-19 [13]. Perotti et al. showed that the infusion of highly qualified hyperimmune plasma in COVID-19 patients with severe respiratory failure reduced short-term mortality by 2.5 times [14]. In a meta-analysis that included 40 studies, it was concluded that the studies included were mostly of low or very low quality with a moderate or high risk of bias. Nevertheless, in July 2020, the study reported that CP therapy had fewer side effects in the treatment of COVID-19 and was a potentially effective treatment [15].

The accuracy of this hypothesis was later questioned. In a study conducted by Omrani et al. among intensive care patients, those who received CP were compared to those receiving standard supportive treatment, and no significant difference was found in respiratory improvement or mortality between the two groups [16]. In a randomized controlled study involving 228 patients, no difference was found between the placebo group and the CP group in mortality and clinical improvement in the treatment of COVID-19 [17]. A Cochrane analysis including 20 studies concluded that the efficacy of CP therapy on mortality and clinical improvement in the treatment of COVID-19 disease remains inconclusive [18].

In articles published subsequently, the importance of the application time of CP treatment started to be emphasized. Altuntaş et al. divided patients into five groups according to the day of CP administration—in the first 5 days, 6–10 days, 11–15 days, 16–20 days, and after 20 days—and found a decrease in the need for mechanical ventilation and vasopressor support, and the case fatality rate declined in line with decreasing time before CP application [19]. In another randomized controlled trial, it was reported that giving CP treatment within the first three days from the onset of symptoms decreased the 7- and 30-day mortality rates in the treatment of COVID-19 [20]. In our study, the median CP administration day was 3 (2–4) days in the early group and 8.5 (7–11) days in the late group. However, we found no effect of early or late application of CP treatment on hospital stay and mortality. We think the reason we did not observe an effect of early CP application on mortality was that our study was conducted on severely ill COVID-19 patients.

The doses of CP treatment described in the different studies vary. In a COVID-19 CP treatment study by Duan et al., the dosage was 200 mL CP, antibody titre >1:640 [21]. In another study, 400 mL of CP was administered in two doses on the same day, antibody titre >1:1000 [13]. Because of the variability of CPT doses in previous reports, the optimal dose of CP treatment for COVID-19 has not been determined. In our study, a mean of 400 mL CP was administered.

#### 4.1. Limitations

The pertinent limitations in this study are two: 1) randomization among patients could not be performed because the study design was retrospective, and 2) there was no control group. Despite these limitations, the overriding result of our study is that it suggests that whether administration of CP is early or late in treatment of COVID-19 has no effect on mortality.

#### Author Statement

##### Category 1

Havva Kocayigit, Kezban Özmen Süner, Selçuk Yaylacı, Yakup Tomak: Conception and design of study.

Gürkan Demir, Alper Karacan, Selçuk Yaylacı, Yasin Kalpakci: Acquisition of data.

Havva Kocayigit, Hamad Dheir, Yakup Tomak, Ali Fuat Erdem: Analysis and/or interpretation of data.

##### Category 2

Havva Kocayigit, Kezban Özmen Süner, Selçuk Yaylacı, Hamad

Dheir: Drafting the manuscript.

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##### Category 3

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#### Declaration of Competing Interest

The authors report no declarations of interest.

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