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Factors Affecting Clinical Course and Mortality among COVID-19 Patients Receiving Convalescent Plasma Treatment

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ABSTRACT: In this study, our research objectives are; to evaluate death risk covariates and the clinical course of the COVID-19 patients who had received convalescent plasma treatment. This study was performed between April 2020 -April 2021, retrospectively. The study was conducted at two centers in Izmir, Turkey. Demographic characteristics, number of plasma given, the time between the onset of the symptoms and the first plasma treatment, and laboratory results(C-reactive protein, white blood cell, thrombocyte, lymphocyte counts, D-dimer, alanine aminotransferase, aspartate aminotransferase, and procalcitonin) are recorded. Biochemical parameters and the necessity of oxygen support for the patients were evaluated on days 0, 3, and 7 of the first plasma treatment. Death risk covariates were analyzed. Described as moderate, severe, and critical, 199 patients were included in this study. The patients' mean age of the patients was63.7±14.2 (min:24-max:93). Most patients were in the severe group (41.7%). The frequency of necessity of non-invasive mechanical ventilation/mechanical ventilation (NIMV/MV) support on day three and day seven was lower than on day 0 (p:0.004). C-reactive protein and procalcitonin levels were progressively decreased on day three and day 7 (p<0.001, p<0.001).Multivariate analysis showed that; ≥65 years of age (HR:1.62 [1.06–2.49]),critical disease severity(HR:2.64 [1.10–6.30]), necessity of corticosteroid treatment (HR:2.22 [1.29–3.82]), leukocyte counts of ≤4.23x103/UL (HR:2.10 [1.19–3.69]), lymphocyte levels of ≤0.80 x103/UL (HR:1.74 [1.06–2.86]), AST levels of ≥ 50 U/L (HR:2.18[1.42–3.34]), and procalcitonin levels of ≥0.5 ng/ml (HR:1.91 [1.26–2.91]) on day 3 were found independently associated with mortality. As a result, being older than 65 years old, having acute disease, receiving corticosteroids, having low lymphocyte-leucocyte counts, and having high ALT and procalcitonin levels are associated with mortality. Considering our findings, we think that more studies are needed in the patient groups.

Keywords: Convalescent plasma; mortality; SARS-CoV-2

INTRODUCTION

In late 2019, a different type of coronavirus was identified in a cluster of patients with acute respiratory tract infection symptoms in Wuhan, Hubei Province, China[1]. The disease was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was later identified as coronavirus disease 2019 (COVID-19)[2,3]. It rapidly spread in China, causing a worldwide pandemic. Over 500 a million confirmed

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cases of COVID-19 have been reported globally[4]. Before the COVID-19 pandemic, convalescent plasma (CP) or immune plasma therapies had been involved in the treatment of SARS-CoV-1 (2003) and MERS-CoV(2012)[5]. In this context, passive immunization has come to the fore again. The Food and Drug Administration (FDA) stated that using CP obtained from people who have recovered from COVID-19 may be effective in treating COVID-19 patients in March 2020[6].

Convalescent plasma treatment is based on forming passive immunity in a patient with an infectious disease by giving plasma obtained from donors who had previously recovered from the same infection. Immune plasma contains neutralizing antibodies against the relevant pathogen. According to the Turkish COVID-19 Immune Plasma Procurement and Clinical Use Guidelines, people with at least 1:80 neutralizing anti- SARS-CoV-2 antibodies agreed to donate plasma[7]. FDA recommended that CP for COVID-19 treatment should contain neutralizing antibody titer of ≥1:160[6]. According to both FDA and Turkish Guidelines, it was recommended that CP treatment should be given in the early stages of COVID-19 and cases of immuno-compromising conditions[8]. There were studies on overall mortality, but due to the lack of detailed analysis in patients receiving CP treatment, this study aimed to analyze death risk covariates and evaluate the clinical course of the patients who had received convalescent plasma treatment.

MATERIALS AND METHODS

Patients and Demographic Characteristics

This two-centered (Bozyaka and Tepecik Training and Research Hospitals, Izmir, Turkey) retrospective study included hospitalized adult COVID-19 patients who had received convalescent plasma treatment between April 2020 and April 2021. Demographic characteristics such as; age, gender, co-morbid conditions, and other treatment modalities of the patients were recorded. Approval was obtained from the Ethics Committee of Izmir Bozyaka Training and Research Hospital on 28/05/2021 with the decision number 2021/88.

Donor Selection

According to the Turkish Guidelines, donors meet the necessary conditions for the whole blood donation. Besides, the donation was made between 14 days and three months after clinical recovery. Before the donation, microbiological screening tests (serologically HBsAg, anti-HCV, anti-HIV 1-2, and anti-syphilis antibody tests) were done. Immune plasma donors were preferably selected from men or women who did not become pregnant and those who had not received blood transfusions.

Convalescent Plasma Storage and Clinical Use

Immune plasma donation was accepted from those with neutralizing anti-SARS-CoV-2 titers of ≥1:80. Plasma was obtained by apheresis, from two hundred to six hundred milliliters of plasma were collected from a donor. It was either administered immediately to the patient or was frozen for later use. Convalescent plasma administration is recommended in the early stages of the disease (within the first week)[8]. The Turkish Guidelines published in April 2020 recommended that patients in the range of 7-14 days after the onset of symptoms might receive plasma treatment[9]. However, in the last published guideline, updated in October 2020, it was recommended that the administration of immune plasma should be within the first week after the onset of symptoms[7]. According to the Turkish guideline, a minimum of 200 ml CP treatment per day was administered for an adult patient. This dose could be repeated up to a maximum of 3 times within 24-48 hour intervals, according to clinical and laboratory responses.

Clinical Conditions

At hospitalization, the patients were described as moderate, severe, and critical[10]. Severe patients had an oxygen saturation of ≤93%, respiratory frequency of ≥30, and lung infiltrates of more than 50%. Critical patients had respiratory failure, sepsis, and multi-organ failure. The day the first plasma treatment was administered was described as day 0. The third and seventh days after the first plasma treatment was described as day three and day 7, respectively. On days 0,3 and 7, clinical conditions such as; body temperature, oxygen saturations, the necessity of oxygen support, non-invasive mechanical ventilation (NIMV) or invasive mechanical ventilation(MV), any side effects during/after the administration of CP, and any proven secondary bacterial infections, The total length of hospital stay of the patients and the number of patients who had recovered/died were also recorded.

Laboratory Findings

On day 0, day three, and day 7; the laboratory findings such as; C-reactive protein (CRP), white blood cell, thrombocyte, lymphocyte counts, D-dimer, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and procalcitonin levels were analyzed.

Radiological Assessment

Computerized chest tomography (CT) was performed on all patients before hospitalization. A semi-quantitative scoring system was used according to pulmonary involvement[11]. Percentage of the involvement of the lungs was described as <5%, 5-25%, 26-49%, 50-75%, and >75%.

Other Treatment Applications

The patients had received favipiravir 2x1600 mg as a loading dose and 2x600 mg as a maintenance dose for a total of 5 days, and hydroxychloroquine 2x200 mg for a total of 5 days. They were recorded whether they had corticosteroids (0.5-1 mg/kg i.v. methylprednisolone up to 10 days or pulse steroid, ≥ 250 mg i.v.) or not before the CP treatment.

Outcome and covariates:

In our study, analyzed death risk covariates were; sociodemographic characteristics, co-existing conditions, disease severity, lung involvement in CT, number of plasma given, the time between the onset of the symptoms and the first plasma treatment, anti-viral/ corticosteroid treatment, secondary bacterial infections and laboratory results (white blood cell counts, lymphocyte counts, thrombocyte counts, C-reactive protein, procalcitonin, D-Dimer, AST, ALT levels).

Statistical Analysis

Descriptive statistics were given as numbers and percentages for categorical variables. Visual (histogram and probability graphics) and statistical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests) examined the conformity of continuous variables to normal distribution. If continuous variables fit the normal distribution, the mean and standard deviation was used, but if not, median and 25th-75th percentile (IQR)were used. Survival analyses were given as mean and standard error. McNemar's test was used for two dependent groups, and Cochran's Q test was used for more than two groups to compare categorical variables. Analysis of not normally distributed continuous variables was performed using the Wilcoxon test for two dependent groups and the Friedman test for more than two groups. Bonferroni correction was used when the result was statistically significant in Cochran’s Quest and Friedman test by making a pairwise comparison of groups. The log-rank test first tested the possible association between covariates and outcome. Variables potentially associated with the outcome in univariate comparisons ($p<0.05$) and significant

variables in the literature were included in the Cox regression multivariate model with the backward elimination method to determine independent predictors controlling correlated factors. Analysis was performed using computer application, and a two-way p-value of < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Sociodemographic Characteristics

Described as moderate, severe, and critical, 199 patients were included in this study, 70 (35.2%) of them were female, and 129 (64.8%) were male. The mean age of the patients was63.7±14.2 (min:24-max:93). At least one co-morbid condition (mostly hypertension) was detected in 153 (76.9%) of the patients, while any co-morbid conditions were not detected in 46 (23.1%) of them. The patients' demographic/baseline clinical characteristics, the necessity of oxygen support, treatment modalities before the first plasma, the total number of plasma given, and the day between the onset of the sypmtoms and first plasma treatment are presented in Table 1.

Table 1. Demographic/Baseline Clinical Characteristics of the Patients, the Necessity of Oxygen Support, Treatment Modalities Before the First Plasma, the Total Number of Plasma Given, and the Day Between the Onset of the Symptoms and First Plasma Treatment

Characteristics	N (%)
Age groups	
<65 years	95(47.7)
≥65 years	104 (52.3)
Gender	
Female	70 (35.2)
Male	129 (64.8)
Co-morbidity status	
One disease	76 (38.2)
≥2 diseases	77 (38.2)
None	46 (23.1)
Co-existing conditions*	
Hypertension	83 (31)
Diabetes mellitus	67 (25)
Chronic heart disease	47 (17.5)
Hematological disease	16 (6)
End-stage renal disease	14 (5.2)
Chronic obstructive pulmonary disease	14(5.2)
Solid malignancy	10(3.7)
Cerebrovascular disease	7 (2.6)
Organ transplantation	4 (1.5)
Rheumatological disease	4 (1.5)
Asthma	1 (0.3)
Disease Severity	
Moderate	41 (20,6)
Severe	83 (41,7)
Critical	75 (37,7)

Computerized tomography; lung involvement	
None	7 (3,5)
<5%	7 (3,5)
5-25%	24 (12,1)
25-50%	67 (33,7)
50-75%	58 (29,1)
75-100%	36 (18,1)
Use of oxygen supplementation devices	
None	27 (13,6)
Nasal cannula	31 (15,6)
Reservoir oxygen mask	62 (31,2)
NAME	40 (20,1)
MV	39 (19,6)
Anti-viral treatment	
Only favipiravir	170 (85.4)
Favipiravir+ hydroxychloroquine	27 (13.6)
Only hydroxychloroquine	2 (1)
Corticosteroid treatment	
Received	135 (67.8)
Not received	64 (32.2)
Time from onset of the symptoms to the first plasma treatment	
0-7 days	123 (61.8)
≥8 days	76 (38.2)
Total number of plasma	
1	97 (48,7)
2	56 (28,1)
3	43 (21,6)
4	3 (1,5)

*The frequency of existing co-morbidities is given

Initial Clinical Findings and Treatment Modalities

While receiving plasma treatment, 64 (32.2%) of the patients were being followed up in the inpatient clinic, and 135 (67.8%) were being followed up in the intensive care unit (ICU). The mean time between the onset of the symptoms and the day of the first plasma treatment was 7±4 days (min:1-max:25 days). Among the cases in which glucocorticoid treatment was started (n:135), methylprednisolone was given to 129(64.8%) patients at a dose of 0.5-1 mg/kg i.v. And six patients (3%) at a dose of ≥ 250 mg i.v.

Clinical and Laboratory Findings During/After the Plasma Treatment

Biochemical parameters, body temperature, and necessity of oxygen support for the patients were evaluated on days 0, day three, and 7. A comparison of clinical and laboratory findings of patients on days 0, day three, and seven is given in Table 2.

Table 2. Comparison of Clinical and Laboratory Findings of Patients on Day 0, Day 3, and Day 7.

Parameter-Normal range	Day 0	Day 3	Day 7	p-value
Clinical Findings				

Body Temperature				
≥37.8°C	30 (15.1%)	9 (4.9%)	6 (3.7%)	
<37.8°C	168 (84.8%)	175 (95.1%)	155 (96.3%)	**p:<0.001[a]**
The necessity of Oxygen Support None-Cannula-Mask NIMV-MV	120 (60.3%) 79 (39.7%)	119 (59.8%) 80 (40.2%)	130 (68.1%) 61 (31.9%)	**p:0.004[b]**
Laboratory Findings	Median (IQR)	Median (IQR)	Median (IQR)	
White blood cell count 4.23-9.07 x10^3 /UL	n:199 9.10 (5.90-12.30)	n:186 9.03 (6.40-12.52)	n:154 10.35 (7.20-15.22)	**p:<0.001[1]**
Lymphocyte count 1.32-3.57 x10^3 /UL	n:199 0.60 (0.40-0.97)	n:186 0.80 (0.50-1.10)	n:154 0.50 (1.00-1.60)	**p:<0.001[2]**
Thrombocyte count 160-340 x10^3 /UL	n:199 232.000 (154.000-323.000)	n:186 281.500 (180.250-379.500)	n:154 308.000 (202.000-392.000)	**p:<0.001[3]**
C-reactive protein 0-5 mg/L	n:199 113.2 (72-180.5)	n:182 89.7 (39.6-142.1)	n:154 51.9 (14.7-107.1)	**p:<0.001[4]**
Procalcitonin <0.5 ng/ml	n:170 0.21 (0.12-0.86)	n:165 0.18 (0.10-1.30)	n:137 0.15 (0.07-0.49)	**p:<0.001[5]**
Alanine aminotransferase 0-50 U/L	n:198 33 (23-51)	n:186 39 (26-63)	n:154 44 (26-68)	**p:0.005[6]**
Aspartate aminotransferase 0-50 U/L	n:198 44 (30-69)	n:186 42 (27-71.2)	n:154 38 (26-55)	**p:0.002[7]**
D-Dimer 0-240 ng/mL	n:191 759 (436-1968)	n:172 1060 (500-2943)	n:143 1107 (560-2320)	p:0.116

[a]Between day 0-3 and day 0-7 groups
[b]Between day 3-7 groups
[1]Between day 0-7 and day 3-7 groups,
[2]Between day 0-3-7 groups,
[3]Between day 0-3 and day 0-7 groups,
[4,5]Between day 0-3-7groups,
[6,7]Between day 0-3 and day 0-7 groups.

No side effects were observed in any patient during/after the plasma treatment. Frequencies of clinical findings were compared using Cochran's Q test, and data regarding laboratory findings were analyzed using the Friedman test followed by Bonferroni's multiple comparisons.

Follow-up Results

The median follow-up period of the patients was 15 days (min:2-max:142 days). Ninety-four(47.2%) of the patients died. The median survival time was 25±2.5 (95%

CI:20-30) days. The mean time of discharge from the hospital was 18.3±9.6 days. The cumulative survival rate was 90%±2.1% on day 7, 75%±3.2% on day 14, and 43.5%±4.8% on day 30. Survival time according to demographic and clinical covariates is given in Table 3.

Table 3. Survival Time According to Demographic and Clinical Covariates

	Median for survival time (day) (95%CI)	Mean for survival time (day) (95%CI)	p-value
Age groups			
<65 years	31±7.7 (15.8-46.1)	32.3±2.5 (27.3-37.3)	**p:0.01**
≥65 years	23±3.4 (16.3-29.6)	31.7±7.1 (17.7-45.7)	
Gender			
Female	27±7.1 (12.9-41)	45.7±9.8 (26.4-65)	p:0.09
Male	22±2.9 (16.2-27.7)	25.1±1.5 (22.1-28.1)	
Total number of plasma			
1	27±4.5 (18-35.9)	29.1±2.6 (24-34.2)	p:0.97
2	21±3.7 (13.5-28.4)	28.3±2.9 (22.5-34)	
3 or 4	24±4.7 (14.6-33.3)	34.3±7.4 (19.8-48.9)	
Time from onset of the symptoms to the first plasma treatment			p:0.60
0-7 days	24±3.5 (17.1-30.8)	28.3±2.1 (24.1-32.5)	
≥8 days	25±2.9 (19.1-30.8)	39.5±8.5 (22.8-56.3)	
Anti-viral treatment			
Only favipiravir	45±8.8 (27.7-62.2)	32.6±5.9 (20.9-44.3)	
Favipiravir+ hydroxychloroquine	23±1.9 (19.1-26.8)	32.5±3.9 (24.7-40.4)	p:0.32
Corticosteroid treatment			
Received	22±1.9 (18-25.9)	23.3±1.5(20.4-26.3)	**p<0.001**
Not received	45±8.9 (27.5-62.4)	56.4±12.5 (31.8-81)	
Co-morbid conditions			
At least one	24±2.4(19.1-28.8)	27.4±1.8 (23.8-30.9)	p:0.42
None	45±17.1 (11.3-78.6)	47.1±15 (17.7-76.5)	
Secondary bacterial infections			
Yes	23±2.2(18.5-27.4)	32.8±5. (22.5-43.1)	p:0.26
No	32±4.5 (23-40.9)	33.6±2.7 (28.2-39.1)	
Disease Severity			
Moderate	55(-/-)	44.8±4.4(36.1-53.6)	
Severe	25±3.9(17.2-32.7)	53.1±11.3(30.9-75.3)	**p:0.001**
Critical	19±2.2(14.5-23.4)	23.2±2.1 (19-27.4)	
Computerized tomography; lung involvement			

0-5%	19±18.3 (0-54.8)	34.8±8.2 (18.7-51)	p:0.12
5-25%	53 (-/-)	37.1±6 (25.2-49.1)	
25-50%	25±5.8 (13.5-36.4)	36.1±9.1 (18.1-54.1)	
50-75%	23±3.1 (16.7-29.2)	24.5±2.2 (20.1-28.9)	
>75%	16±2.9 (10.1-21.8)	24±3.2 (17.5-30.4)	
Oxygen Support			
None-cannula-mask	32±7.5 (17.2-46.7)	58±16.4 (25.7-90.3)	**p<0.001**
NIMV-MV	16±2.5 (11-20.9)	21.2±1.8 (17.6-24.9)	

*Log-rank test was used.

The mean and median survival time according to laboratory findings on days 0 and 3 is given in Table 4.

Table 4. Survival Time According to Laboratory Findings by Days 0 and 3

	Median for survival time (day) (95%CI)	Mean for survival time (day) (95% CI)	p-value
Day 0			
White blood cell count			
≤4.23 x10^3/UL	20±2.5 (15-24.9)	31±5.7 (19.8-42.2)	
>4.23 x10^3/UL	25±2.2 (20.6-29.3)	35.2±5.5 (24.2-46.1)	p:0.87
Lymphocyte count			
≤0.80 x10^3/UL	23±2.9 (17.2-28.7)	31.1±4.8 (21.6-40.6)	
>0.80x10^3/UL	31±6.9 (17.3-44.6)	31.4±3.9 (23.7-39.1)	p:0.08
Thrombocyte count			
≤ 160 x10^3/UL	20±2.6 (14.8-25.1)	24.9±3.1 (18.7-31.1)	
> 160 x10^3/UL	27±4 (19-34.9)	38.8±6.7 (25.6-52)	p:0.07
D-Dimer			
≤1000 ng/ml	21±2.2 (16.6-25.3)	25.4±2.2 (21-29.8)	p:0.11
>1000 ng/ml	28±4.9 (18.3-37.6)	38.8±8.1 (22.8-54.8)	
AST			
≤50 U/L	35±7.5 (20.2-49.7)	43.3±10.1 (23.4-63.3)	**p:0.02**
>50 U/L	22±2 (18-25.9)	23.9±1.9 (20.1-27.7)	
ALT			
≤50 U/L	28±5 (18-37.9)	35.5±6 (23.6-47.3)	p:0.40
>50 U/L	22±1.7 (18.5-25.4)	24.1±2.4 (19.3-28.9)	
C-Reactive Protein			
≤50 mg/L	25±10.2 (4.9-45)	33.9±5.1 (23.8-44.1)	
>50 mg/L	24±2.6 (18.8-29.1)	31.9±5.2 (21.6-42.2)	p:0.09
Procalcitonin			
≤0.5ng/mL	35±5.8 (23.5-46.4)	32±2.1 (27.8-36.3)	**p:0.001**
>0.5ng/mL	17±1.6 (13.7-20.2)	36.5±8.5 (19.7-53.3)	
Day 3			
White blood cell count			
≤4.23 x10^3/UL	15±5.1(4.8-25.1)	21.5±4.7 (12.3-30.8)	
>4.23 x10^3/UL	27±2.9(21.2-32.7)	37±6 (25.6-49.4)	**p:0.02**
Lymphocyte count			
≤0.80 x10^3/UL >0.80 x10^3/UL	21±2.1 (16.7-25.2) 32±6.5 (19.1-44.8)	25.2±1.8 (21.5-28.9) 48.6±14.1 (20.9-76.2)	**p:0.02**
Thrombocyte count			

≤ 160 x10^3/UL	16±2.7(10.6-21.3)	23.8±3.4 (17-30.6)	
> 160 x10^3/UL	25±3.8(17.4-32.5)	38.3±6.3 (25.9-50.8)	**p:0.005**
D-Dimer			
≤1000 ng/ml	23±3.6 (15.8-30.1)	27.5±2 (23.5-31.5)	p:0.44
>1000 ng/ml	25±3.4 (18.1-31.8)	41.4±10.7 (20.4-62.4)	
AST			
≤50 U/L	35±5.1 (24.8-45.1)	43±10.1 (23.2-62.8)	**p:0.002**
>50 U/L	19±2.3 (14.4-23.5)	22.9±2 (18.9-26.9)	
ALT			
≤50 U/L	24±4.8 (14.4-33.5)	29.1±2.1 (24.9-33.2)	p:0.87
>50 U/L	40.3±8.4 (23.7-56.9)	23.9±1.9 (20.1-27.7)	
C-Reactive Protein			
≤50 mg/L	38±10.8 (16.8-59.1)	34.4±3.6 (27.2-41.5)	
>50 mg/L	23±2.1 (18.8-27.1)	31.4±4.9 (21.6-41.1)	p:0.29
Procalcitonin ≤0.5 ng/mL	36±5.7 (24.7-47.2)	39.6±7.2 (25.4-53.8)	**p<0.001**
>0.5 ng/mL	17±1.2 (14.5-19.4)	21.6±2 (17.5-25.6)	

*Log-rank test was used.

Predictors of mortality among patients by multivariate Cox regression analysis are given in Table 5.Multivariate analysis showed that; ≥65 years of age (Hazard Ratio[HR]:1.62 [1.06–2.49]),critical disease severity(HR:2.64 [1.10–6.30]), necessity of corticosteroid treatment (HR:2.22 [1.29–3.82]), leukocyte counts of ≤4.23x103/UL (HR:2.10 [1.19–3.69]), lymphocyte levels of ≤0.80 x103/UL (HR:1.74 [1.06–2.86]), AST levels of ≥ 50 U/L (HR:2.18[1.42–3.34]), and procalcitonin levels of ≥0.5 ng/ml (HR:1.91 [1.26–2.91]) on day 3 were found independently associated with mortality.

Table 5. Predictors of Mortality among Patients by Multivariate Cox Regression Analysis

	Model 1** Multivariate HR (95% CI) p value		Model 2*** Multivariate HR (95% CI) p value	
Clinical Features*				
Over 65 years old (vs. Under 65 years old)	1.62 (1.06-2.49)	**0.02**		
Critical (vs. Moderate)	2.64 (1.10-6.30)	**0.02**		
Received corticosteroid (vs. Not received)	2.22 (1.29-3.82)	**0.004**		
Laboratory Findings*				
Day 3-leukocyte count ≤4.23 x10^3/UL (vs. >4.23 x10^3/UL)			2.10 (1.19-3.69)	**0.01**
Day 3-lymphocyte count≤0.80 x10^3/UL (vs.>0.80 x10^3/UL)			1.74 (1.06-2.86)	**0.02**
Day 3-AST level ≥50 U/L (vs.<50 U/L)			2.18 (1.42-3.34)	**<0.001**
Day 3-procalcitonin level≥0.5ng/mL (vs.<0.5 ng/mL)			1.91 (1.26-2.91)	**0.002**

*Only results for variables retained in the final multivariate model are presented.
**Variables included in the model: age, disease severity, corticosteroid treatment, co-existing conditions, secondary bacterial infections, the time between the onset of the symptoms and the first plasma treatment
*** Variables included in the model: AST and procalcitonin levels on day 0, white blood cell, lymphocyte, and thrombocyte counts, and AST and procalcitonin levels on day 3.

At least one secondary bacterial infection developed in 77 (38.9%) patients during the follow-up. The most common infection was found to be bacterial pneumonia (n:56, 28.1%), also bloodstream infection (n:16, 8%),urinary tract infection (n:10, 5%),central catheter-related infection(n:8, 4%) and other infections (n:3, 1.5%) were seen, respectively. Convalescent plasma has been used for treatment in previous viral pandemics. Experiences in using convalescent plasma against coronavirus were obtained from the Severe Acute Respiratory Syndrome 1 (SARS-COV-1) outbreak in 2003 and showed some beneficial effects[12]. Recently published systematic review and meta-analysis investigating the association of CP treatment with clinical outcomes in patients with COVID-19, 10 published randomized clinical trials showed no significant associations or benefits for mortality, hospital length of stay, MV use, clinical improvement, or clinical deterioration[13]. In addition, in the latest guideline released in July 2021, the WHO recommended administering CP for the treatment of COVID-19 because of having no evidence of beneficial effect and noted that CP use is associated with significant resource requirements[14].

However, since the vaccine was not developed against the SARS-CoV-2 virus at the beginning of the pandemic and the abovementioned previous beneficial effects, CP treatment was started to provide an antibody response with passive immunity. This treatment opportunity has also been widely used in our hospital, mostly in patients with severe or critical diseases. In our study, mortality predictors were found as; being over 65 years of age, having acute disease, receiving corticosteroid treatment, being leucopenic, lymphopenic, having AST levels of ≥50 U/L, and having procalcitonin levels of ≥0.5ng/mL on day 3. In a study by Muhammad et al, mortality predictors were found as; age >65, elevated markers of inflammation as CRP >20 mg/dl, procalcitonin>2.5 ng/ml, ferritin >2000 ng/ml and D-Dimer> 3.0 µg/ml[15]. In another study, decreased lymphocyte and platelet counts and increased D-dimer levels of>3.0 µg/ml at admission were found to be significantly associated with mortality[16].

Our study reduced the necessity of NIMV/MV after day 3. Similarly, in a study by Liu et al. that found that overall survival probability was greater in convalescent plasma recipients than in non-recipient control patients, the recipient group showed a reduction in the ratio of patients with worsened oxygenation status. However, the difference between day one and day seven was not statistically significant[17]. Duan et al., in 10 adult cases, showed that one dose (200 mL) of CPwas well tolerated and could significantly increase or maintain neutralizing antibodies at a high level, leading to the disappearance of viremia on day 7. Also, clinical symptoms and oxyhemoglobin saturation rapidly improved within day three, and radiological examination showed varying degrees of absorption of lung lesions at the end of day 7 in all patients. In this study, all patients had severe diseases, needed NIMV/MV, and were treated in the ICU[18].

As mentioned above, the WHO recommended convalescent plasma treatment in the latest COVID-19 guidelines but also stated that clinical studies should continue in severe and critical patients. Considering our findings, we also think more studies are needed in the patient groups, such as severe and critical patients. There are some

limitations of our study. Firstly, the study was conducted at only two centers with a small number of patients, and no probability sampling method was used. In this respect, it is not possible to generalize our results. Secondly, measurement bias should be considered, as there are minor differences in test kits between the two centers, even though the reference values are the same.

CONCLUSION

As a result, being older than 65 years old, having acute disease, receiving corticosteroids, having low lymphocyte-leucocyte counts, and having high ALT and procalcitonin levels are associated with mortality. Considering our findings, we think that more studies are needed in the patient groups.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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