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A retrospective cross-sectional study on the efficacy of immune plasma in critical COVID-19 patients under intensive care follow-up

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Abstract

Many methods have been attempted for the treatment of severe acute respiratory failure caused by COVID-19. One of these methods is immune plasma therapy. In this study, we aimed to evaluate the efficacy of immune plasma therapy using laboratory parameters and the effect of the time of initiation of immune plasma therapy on mortality in patients with COVID-19 who developed severe acute respiratory failure. 74 patients who were diagnosed with COVID-19 during hospitalization and given immune plasma in the intensive care unit were included in our study. Demographic data, comorbid diseases, time of immune plasma administration (first 4 days and after the 4th day), and laboratory and mortality data before and 1 and 2 days after plasma administration were recorded retrospectively. Analysis of the data we obtained in our study showed no difference in mortality between immune plasma administration within the first 4 days and after 4 days. In the group that received immune plasma transfusions in the first 4 days, glucose was lower, while creatinine and AST values were higher. The urea, leukocyte, neutrophil, PO_2, PCO_2, PCT, and D-dimer values of the patients 1 day and 2 days after immune plasma transfusion was higher than the pre-transfusion values, while CK, albumin and CRP values were lower. Immune plasma transfusion therapy improved laboratory parameters supporting clinical improvement due to decreased viral load in patients with COVID-19 who developed severe acute respiratory failure; however, it did not affect mortality and the number of patients discharged was higher in the group given early treatment (first 4 days). We suggest that early immune plasma administration may be an adjunctive treatment option to improve clinical recovery and reduce mortality until a definitive and permanent cure is found under pandemic conditions.

Keywords: COVID-19, intensive care unit, mortality, immune plasma therapy

Introduction

First emerging in Wuhan province of China, Coronavirus 2 (SARS-CoV-2) spread rapidly within three months and was classified as an epidemic by the World Health Organization (WHO) on March 11, 2020 [1]. Many methods have been attempted for the treatment of severe acute respiratory failure caused by COVID-19. Immune plasma transfusion, one of these methods, is a passive antibody therapy that has been shown to be effective in epidemic periods in history [2]. It was used for therapeutic purposes in the recent outbreaks of SARS-1 in 2003, H1N1 in 2009, and MERS in 2012 [3,4]. It was reported that immune plasma treatment for COVID-19 was first applied in China on February 9, 2020, considering the positive results obtained in the past [5]. Despite the lack of randomized studies, the use of immune plasma has been included in treatment algorithms with positive results. The US Food and Drug Administration (FDA) approved the use of immune plasma therapy in critically ill patients on March 24, 2020 [6]. A guideline has been provided for the preparation and clinical use of immune plasma containing SARS-CoV-2 antibody to be used in patients in need during the COVID-19 pandemic, which is also affecting our country [7].

Many methods have been attempted for the treatment of severe acute respiratory failure caused by COVID-19. One of these methods is immune plasma therapy. In this study, we aimed to

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evaluate the efficacy of immune plasma therapy using laboratory parameters and the effect of the time of initiation of immune plasma therapy on mortality in patients with COVID-19 who developed severe acute respiratory failure.

Material and Methods

Our retrospective cross-sectional study was conducted in accordance with the Declaration of Helsinki and Strobe Checklist after the approval of Malatya Turgut Ozal University Clinical Research Ethics Committee dated 25.04.2023 and with no. 27. In the study, 74 patients who had a positive COVID-19 PCR (polymerase chain reaction) test during hospitalization between May 2020 and April 2022 and who received immune plasma treatment followed in the intensive care units of our hospital were included. The antibody titres in the donor Immune plasma we gave to the patients were confirmed and all our patients showed clinical symptoms of ARDS. All patients included in our study received concurrent other standard care and antiviral drugs. Our patients were given 0.5-1 mg/kg methylprednisolone (2x1), 40 mg pantoprazole (1x1), 300 mg acetylcysteine (3x1) intravenous infusion, 0.5 mg/kg enoxaparin (2x1) subcutaneously. In addition, standard maintenance treatment was applied by administering 2x1600 mg/day loading on the first day as an anti-viral agent and favipiravir per-oral or nasogastric tube as a maintenance 2x600 mg/day. Pediatric patients, pregnant patients, and patients diagnosed with COVID-19 with PCR tests after hospitalization were excluded from the study group. Immune plasma therapy was administered as a single daily dose of 200 ml. A second dose was administered to approximately 25% of the patients 48 hours later.

Data on the patients included in the study were obtained from patient files and the automation system of the hospital. Demographic characteristics of the patients (age, sex), concomitant congestive heart failure (CHF), neurologic disease, asthma, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, stroke, obesity, obstructive sleep apnea syndrome (OSAS), Comorbid diseases such as chronic renal failure (CRF), blood saturation oxygen value (SpO_2), the number of days and doses of immune plasma treatment, intubation status, length of hospital and intensive care unit (ICU) stay, non-survival and discharge status were recorded. In our study, the duration of immune plasma administration was calculated based on the length of stay in the intensive care unit (first 4 days and after the 4th day). Glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), albumin, C-reactive protein (CRP), leukocytes (WBC), platelets (PLT), haemoglobin, neutrophils, Lymphocyte, partial arterial oxygen pressure (PO_2), partial arterial carbon dioxide pressure (PCO_2), procalcitonin (PCT), troponin, pro-brain natriuretic peptide (pro-BNP) and D-dimer values of the patients before, and 1 day and 2 days after immune plasma transfusion were recorded. In our study, short-term laboratory parameters such as before the immune plasma transfusion, 1 day and 2 days after the immune plasma transfusion were used.

Statistical analysis

Number (n) and percentage (%) values were used to show the distribution of demographic information such as sex, disease status, obesity status, intubation status, etc. The Shapiro-Wilk test was used to evaluate whether the variables in the study conformed to a normal distribution. It was determined that continuous variables did not conform to the normal distribution except albumin and PLT. Mean±Standard deviation and median (interquartile range, IQR) values were used to represent the descriptive statistics of the variables.

In order to examine whether the parameters in the study differed at the measurement times (before immune plasma transfusion, 1 day and 2 days after immune plasma transfusion), repeated measures ANOVA was used for normally distributed parameters, and dependent sample Friedman's test was used for non-normally distributed parameters. In pairwise comparisons, the results of the analysis are given with the Bonferroni correction.

In the comparison of the values before immune plasma transfusion, 1 day after immune plasma transfusion, and 2 days after immune plasma transfusion according to the non-survivor-discharge group, the Independent Sample t-test was used for normally distributed parameters, and Mann- Whitney U test was used for non-normally distributed parameters.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 programs were used for statistical analyses and calculations. The statistical significance level was regarded as $p<0.05$.

Results

The mean age of the patients was 65.07±12.66 years and the number of male patients was more common, with a rate of 85.1% (n=63). The most common comorbidities were hypertension, CHF, and diabetes. The mean SpO_2 of the patients was 86.90±9.58. 74.3% (n=55) of the patients were intubated; the mean hospitalization was 15.85±8.44 days, and the mean intensive care unit stay was 9.20±7.11 days. Of the patients, 37.8% (n=28) were discharged and 62.2% (n=46) did not survive. Of the patients, 78.4% (n=58) received 1 dose, 21.6% (n=16) received 2 doses, 51.4% (n=38) received immune plasma transfusion in the first 4 days, and 48.6% (n=36) received immune plasma transfusion after the 4th day. Immune plasma administration doses were similar in both groups. (Table 1).

When the laboratory parameters before the immune plasma transfusion and 1 day and 2 days after the immune plasma transfusion were evaluated between the non-survival and discharge groups, glucose, urea, creatinine, LDH, CK, CRP, leukocyte, neutrophil, PCT, D-dimer and troponin values were lower in the discharge group than in the non-survival group, while albumin and platelet values were higher and statistically significant ($p<0.005$). However, AST, ALT, lymphocyte, haemoglobin, PO_2, PCO_2, and pro-BNP values in the discharge

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group were similar to those in the non-survival group and not statistically significant (p>0.05) (Table 2).

Co-morbid diseases were similar among patients who received Immune plasma transfusions within the first 4 days and after Day 4. Evaluation of the patients who received immune plasma transfusion in the first 4 days and after the 4th day revealed that glucose was lower and creatinine and AST values were higher and statistically significant (p<0.05) in the group who received immune plasma transfusion in the first 4 days. However, urea, ALT, LDH, CK, albumin, CRP, WBC, PLT, neutrophil, lymphocyte, PO_2, PCO_2, PCT, D-dimer, troponin, and pro-BNP values were similar and not statistically significant (p>0.05). Evaluation of time-based laboratory parameters (before, 1 day, and 2 days after immune plasma transfusion) showed that urea and PaO_2 values increased in the group that received immune plasma transfusion in the first 4 days, while albumin values decreased in the group that received immune plasma transfusion after the 4th day. In addition, CK and CRP values tended to decrease in both groups and were statistically significant (p<0.005). Other time-based laboratory parameters were similar in both groups and were not statistically significant (p>0.05) (Table 3).

The number of patients discharged was higher and mortality rate was lower in the group that received immune plasma transfusion within the first 4 days. However, it was not statistically significant (p>0.05) (Table 4).

Table 1. Demographic data

		n (%) or mean±SD
Age (year)		65.07±12.66
Gender (male)		63 (85.1)
Congestive hart failure		29 (39.2)
Asthma		3 (4.1)
Chronic obstructive pulmonary disease		8 (10.8)
Diabetes mellitus		19 (25.7)
Hypertension		39 (52.7)
Neurological disease		3 (4.1)
Obesity		2 (2.7)
Obstructive sleep apnea,		2 (2.7)
SpO_2		86.90±9.58
Intubation		55 (74.3)
Length of stay in hospitalization		15.85±8.44
Length of stay in intensive care		9.20±7.11
Discharge		28 (38.7)
Non-survival		46 (62.2)
Plasma delivery time,	**First 4 days**	38 (51.4)
	After day 4	36 (48.6)
Given plasma dose	**1 dose**	58 (78.4)
	2 dose	16 (21.6)

Data are given as n (%) and mean±SD (standart deviation). SpO_2: oxygen saturation in the arterial blood

Table 2. Comparison of laboratory values among mortality and discharge of patients groups

		Non-survival	Discharge	p-value (between groups)
Glucose, mg/dl	**Before**	183 (100)	164 (100)	0.385
	1st day	196.50 (79)	171 (77)	**0.021**
	2nd day	198 (117)	131 (89)	**0.002**
Urea mg/dl	**Before**	72.5 (43.5)	46 (28.5)	**<0.001**
	1st day	96 (59)	50.5 (29)	**<0.001**
	2nd day	102 (61)	58.5 (31)	**0.001**
Creatinine mg/dl	**Before**	0.93 (0.71)	0.81 (0.41)	0.089
	1st day	1.04 (0.6)	0.8 (0.32)	**0.002**
	2nd day	1.13 (1.09)	0.8 (0.3)	**0.001**
AST, U/L	**Before**	44.5 (34)	48.5 (31)	0.973
	1st day	46 (55)	39.5 (41)	0.394
	2nd day	42.5 (51)	46.5 (31)	0.364
ALT, U/L	**Before**	35.5 (45)	40.5 (24)	0.705
	1st day	39.5 (52)	42 (39)	0.991
	2nd day	34.5 (67)	52.5 (48)	0.385
LDH, U/L	**Before**	660 (394)	391 (249)	**<0.001**
	1st day	684 (411)	458 (201)	**<0.001**
	2nd day	686.5 (480.8)	455.5 (205.6)	**<0.001**

Independent sample t-test, Mann-Whitney U test statistics were used as statistical tests. AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, CRP: C-reactive protein, WBC: white blood cells, Hb: hemoglobin, BNP: brain natriuretic peptide, PO_2: blood pressures of oxygen, PCO_2: blood pressures of carbon dioxide. The results of our study were given as median (interquartile range-IQR) values

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Table 2. Comparison of laboratory values among mortality and discharge of patients groups

	Before	108.1 (256.7)	113.8 (136.9)	0.841
CK, U/L	**1st day**	138.6 (208.8)	60.4 (81.2)	**0.006**
	2nd day	94.8 (285.4)	53 (41.3)	**0.002**
	Before	2.6 (0.5)	2.95 (0.4)	**<0.001**
Albumin, g/dL	**1st day**	2.4 (0.5)	2.7 (0.6)	**0.012**
	2nd day	2.3 (0.63)	2.7 (0.65)	**<0.001**
	Before	13.34 (14.47)	8.05 (6.79)	**0.022**
CRP, mg/dL	**1 st day**	8.96 (13.81)	6.23 (9.16)	**0.032**
	2nd day	9.98 (9.30)	2.80 (9.97)	**0.001**
	Before	12.24 (6.15)	10.15 (6.37)	0.101
Wbc, 10^3/µL	**1st day**	12.91 (7.12)	10.78 (4.83)	**0.038**
	2nd day	14.22 (8.96)	10.98 (5.31)	**0.008**
	Before	11.09 (6.28)	8.41 (5.91)	**0.035**
Neutrophils, 10^3/µL	**1st day**	11.92 (5.81)	9.63 (5.25)	**0.022**
	2nd day	13.17 (8.27)	10.36 (6.28)	**0.011**
	Before	0.53 (0.47)	0.65 (0.28)	0.063
Lymphocytes, 10^3/µL	**1st day**	0.5 (0.51)	0.66 (0.5)	0.228
	2nd day	0.45 (0.56)	0.69 (0.51)	0.094
	Before	248 (132)	251.5 (129)	0.571
Platelet, 10^3/µL	**1st day**	253 (152.3)	306 (129)	**0.023**
	2nd day	231.5 (183.8)	325 (165)	**0.025**
	Before	13.15 (3.80)	13 (2.2)	0.529
Hb, g/dL	**1st day**	12 (3.1)	12.8 (1.3)	0.121
	2nd day	12.2 (3.13)	13.2 (1.6)	0.074
	Before	49 (36.5)	63 (41)	0.423
PO_2, mmHg	**1st day**	57.85 (30.6)	55.6 (22.1)	0.823
	2nd day	57.1 (30.5)	69.1 (29.8)	0.123
	Before	42.55 (21)	39. (6.5)	0.614
PCO_2, mmHg	**1st day**	45.95 (22.5)	40.2 (11.4)	0.059
	2nd day	46.4 (29.1)	40.9 (14)	0.096
	Before	0.58 (1.18)	0.14 (0.2)	**<0.001**
Procalcitonin ng/ml	**1st day**	0.77 (3.55)	0.12 (0.16)	**<0.001**
	2st day	0.86 (2.68)	0.08 (0.13)	**<0.001**
	Before	1.96 (3.57)	0.57 (2.02)	**0.002**
D-dimer, µg/mL	**1st day**	2.55 (4.00)	0.68 (1.64)	**0.004**
	2nd day	3.12 (3.63)	0.85 (3.33)	**0.030**
	Before	0.1 (0.17)	0.1 (0)	**0.011**
Troponin, ng/mL	**1st day**	0.11 (0.16)	0.1 (0)	**0.005**
	2nd day	0.13 (0.23)	0.1 (0)	**<0.001**
	Before	1346 (3317.1)	445 (775.75)	0.484
proBNP, pg/mL	**1st day**	3256 (9120.3)	379.50 (618.95)	0.589
	2nd day	2881 (7525.7)	303.8 (504.05)	0.190

Independent sample t-test, Mann-Whitney U test statistics were used as statistical tests. AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, CRP: C-reactive protein, WBC: white blood cells, Hb: hemoglobin, BNP: brain natriuretic peptide, PO_2: blood pressures of oxygen, PCO_2: blood pressures of carbon dioxide. The results of our study were given as median (interquartile range-IQR) values

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Table 3. Comparison of laboratory parameters over time between plasma administration day groups

		First 4. day	After day 4	p-value (between groups)
Glucose, mg/dl	**Before**	167.5 (69)	205 (107)	0.314
	1st day	182.5 (97)	186 (74)	0.570
	2nd day	151.5 (116)	198 (121)	**0.048**
		p(t)=0.421	p(t)=0.820	
Urea mg/dl	**Before**	61.25 (48.3)	64.00 (28.00)	0.829
	1st day	79 (59)	65.50 (59.00)	0.114
	2nd day	84.5 (57)	75.50 (83.00)	0.611
		p(t)<**0.001**	p(t)=0.051	
Creatinine mg/dl	**Before**	1.01 (0.56)	0.75 (0.41)	0.059
	1st day	0.98 (0.39)	0.79 (0.38)	**0.031**
	2nd day	0.91 (0.65)	0.77 (0.86)	0.124
		p(t)=0.421	p(t)=0.820	
AST, U/L	**Before**	50.5 (31)	40 (34)	0.147
	1st day	43.5 (58)	45.5 (38)	0.214
	2nd day	53 (47)	38.5 (38)	**0.044**
		p(t)=0.405	p(t)=0.920	
ALT, U/L	**Before**	34 (31)	44 (37)	0.209
	1st day	38.5 (52)	43 (44)	0.999
	2nd day	50 (65)	36 (54)	0.650
		p(t)=0.368	p(t)=0.671	
LDH, U/L	**Before**	559 (425)	579 (379)	0.916
	1st day	617 (370)	590.5 (322)	0.864
	2nd day	620 (549)	549.5 (298.5)	0.642
		p(t)=0.413	p(t)=0.358	
CK, U/L	**Before**	146.95 (261.36)	82.76 (120.8)	0.097
	1st day	132.41 (222.20)	70.96 (112.7)	0.068
	2nd day	86.45 (284.93)	57.96 (75.31)	0.300
		p(t)=**0.016**	p(t)=**0.004**	
Albumin, g/dL	**Before**	2.7 (0.4)	2.55 (0.8)	0.084
	1st day	2.6 (0.6)	2.45 (0.5)	0.095
	2nd day	2.6 (0.5)	2.3 (0.7)	0.019
		p(t)=0.078	p(t)=**0.004**	
CRP, mg/dL	**Before**	12.90 (12.41)	10.87 (9.58)	0.661
	1 st day	7.62 (8.92)	9.73 (13.69)	0.333
	2nd day	5.31 (9.6)	8.58 (10.38)	0.222
		p(t)<**0.001**	p(t)=**0.017**	
Wbc, $10^3/\mu L$	**Before**	10.47 (6.67)	11.18 (5.57)	0.948
	1st day	11.93 (6.54)	12.84 (8.86)	0.456
	2nd day	12.13 (8.34)	12.98 (6.81)	0.433
		p(t)=0.139	p(t)=0.097	

Independent sample t-test, Mann-Whitney U test statistics, repeated measures ANOVA test statistics and Friedman test statistics were used as statistical tests. AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, CRP: C-reactive protein, WBC: white blood cells, Hb: hemoglobin, BNP: brain natriuretic peptide, PaO_2: blood pressures of oxygen, PCO_2: blood pressures of carbon dioxide, P(t): time comparison of groups. $p<0.05$ was considered statistically significant. The results of our study were given as median (interquartile range-IQR) values

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Table 3. Comparison of laboratory parameters over time between plasma administration day groups

Neutrophils, 10^3/µL	**Before**	9.17 (7)	9.95 (5.8)	0.693
	1st day	10.88 (6.16)	11.83 (7.8)	0.369
	2nd day	10.83 (8.4)	12.55 (6.73)	0.210
		p(t)=0.118	p(t)=0.080	
Lymphocytes, 10^3/µL	**Before**	0.64 (0.47)	0.59 (0.33)	0.677
	1st day	0.53 (0.52)	0.56 (0.5)	0.903
	2nd day	0.62 (0.58)	0.53 (0.51)	0.643
		p(t)=0.993	p(t)=0.717	
Platelet, 10^3/µL	**Before**	243.5 (124)	255.00 (126)	0.241
	1st day	253 (172.5)	282.00 (123.5)	0.289
	2nd day	248 (206)	279.5 (193.3)	0.381
		p(t)=0.491	p(t)=0.524	
Hb, g/dL	**Before**	12.95 (3.40)	13.05 (2.7)	0.953
	1st day	12.90 (2.50)	12.40 (2.)	0.623
	2nd day	12.70 (3.30)	12.30 (2.45)	0.414
		p(t)=0.558	p(t)=0.074	
PO_2, mmHg	**Before**	49.2 (40.2)	52 (35.1)	0.969
	1st day	55.7 (29.5)	57.85 (25.2)	0.778
	2nd day	60.4 (33.7)	59.45 (24.6)	0.906
		p(t)=0.035	p(t)=0.101	
PCO_2, mmHg	**Before**	42 (15.5)	40.1 (17.6)	0.550
	1st day	43.1 (20)	45.95 (19.7)	0.246
	2nd day	44 (19.4)	44.35 (23)	0.979
		p(t)=0.227	p(t)=0.074	
Procalcitonin ng/ml	**Before**	0.34 (0.88)	0.26 (0.52)	0.182
	1st day	0.28 (1.8)	0.24 (1.07)	0.459
	2st day	0.23 (1.26)	0.33 (1.29)	0.679
		p(t)=0.051	p(t)=0.123	
D-dimer, µg/mL	**Before**	1.21 (2.98)	1.03 (2.79)	0.957
	1st day	1.51 (3.39)	1.50 (4.84)	0.960
	2nd day	1.48 (3.54)	2.07 (4.24)	0.510
		p(t)=0.520	p(t)=0.662	
Troponin, ng/mL	**Before**	0.1 (0.15)	0.1 (0.06)	0.201
	1st day	0.1 (0.11)	0.1 (0.13)	0.701
	2nd day	0.13 (0.24)	0.1 (0.06)	0.115
		p(t)0.520	p(t)=0.662	
proBNP, pg/mL	**Before**	990.7 (3587.9)	625.65 (1585.4)	0.484
	1st day	2669.5 (6220.1)	786.2 (3087.6)	0.589
	2nd day	2881 (5541)	614.3 (1335.4)	0.190
		p(t)=0.126	p(t)=0.846	

Independent sample t-test, Mann-Whitney U test statistics, repeated measures ANOVA test statistics and Friedman test statistics were used as statistical tests. AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, CRP: C-reactive protein, WBC: white blood cells, Hb: hemoglobin, BNP: brain natriuretic peptide, PaO_2: blood pressures of oxygen, PCO_2: blood pressures of carbon dioxide, P(t): time comparison of groups. $p<0.05$ was considered statistically significant. The results of our study were given as median (interquartile range-IQR) values

Table 4. Mortality rates in groups receiving immune plasma transfusion in the first 4 days and after the 4th day

	First 4. day n (%)	After day 4 n (%)	p value	x^2 value
Non-survival	23 (60.5)	23 (63.9)	0.766	0.089
Discharge	15 (39.5)	13 (36.1)		

x^2 Chi-square test

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Discussion

Analysis of the data we obtained in our study showed while the mortality rate was 60.5% in the group given immune plasma within the first 4 days, it was 63.9% in the group given immune plasma after four days. Mortality rates were similar between groups. In the group that received immune plasma transfusions in the first 4 days, glucose was lower, while creatinine and AST values were higher. The urea, leukocyte, neutrophil, PO_2, PCO_2, PCT, and D-dimer values of the patients 1 day and 2 days after immune plasma transfusion were higher than the pre-transfusion values, while CK, albumin and CRP values were lower.

There is no specific therapeutic agent for COVID-19 disease. The efficacy and side effects of most of the treatment options used in the treatment of the disease have been the subject of debate. In our retrospective study with a group of intensive care unit patients, most of whom were intubated, there was an improvement in laboratory parameters supporting clinical improvement due to decreased viral load with immune plasma transfusion, however, the mortality rates were high. This is attributed to the high number of intubated patients and comorbid diseases that increase COVID-19 mortality, such as diabetes, viral load, and age. No serious side effects related to immune plasma transfusion therapy were observed in our patients.

In their study on 10 patients, Duan et al. reported that immune plasma treatment was well tolerated and could potentially improve clinical outcomes by neutralizing viremia in severe COVID-19 cases [8]. Ye et al. observed regression in clinical symptoms and improvement in laboratory parameters due to immune plasma transfusion in six COVID-19 patients and claimed that immune plasma transfusion was effective in the treatment of COVID-19 [9]. Similarly, an improvement in clinical and laboratory parameters was observed in our study. Zhang et al. achieved clinical improvement in all patients in their study on four patients, one of whom was pregnant, in whom immune plasma transfusion was administered [10]. In their multicenter study, Abolghasemi et al. administered immune plasma therapy in addition to standard treatment to 115 patients, while 74 patients in the control group received only standard treatment. Hospital stay and mortality rates were lower in the group receiving immune plasma transfusion [11]. Mortality rates in both studies were lower than ours. We attribute this to our intensive care unit patients with a high viral load, most of whom were intubated. In their study of five critically ill COVID-19 patients, Shen et al. observed improvement in laboratory parameters related to immune plasma transfusion [12]. Only 2 of 5 patients could be discharged; mortality rates were high and similar to our study. In their study on 7 patients with intensive care follow-up, Yektas et al. showed an improvement in laboratory parameters due to immune plasma transfusion; however, mortality rates were high and were compatible with the results in our study [13].

In their multicenter study conducted across India, Agarwal et al. administered immune plasma therapy in addition to standard treatment to 235 patients and only standard treatment to 229 patients in the control group. There was no difference between the groups in terms of progression to severe disease or mortality [14]. In a multicenter randomized controlled study by Li et al. 52 patients received immune plasma in addition to standard treatment and 51 patients received only standard treatment, and no difference was found in terms of mortality [15]. Both studies showed that immune plasma transfusion therapy did not affect mortality and were consistent with our study. In their comprehensive study, Simonovich et al. gave immune plasma transfusion therapy to a total of 228 patients and placebo to 105 patients [16]. Similar to our study, the patient groups had severe COVID-19 pneumonia and high-dose O_2 needs. Nevertheless, no significant difference was observed in terms of ICU admission, clinical status, or overall mortality in both groups.

It has been observed that hospitalizations with a diagnosis of mild to moderate COVID-19 are generally between the 4th-5th days, clinical and laboratory values worsen between the 7th-10th days, and intensive care is needed [17]. In the guideline published in October 2020 in Türkiye, it is recommended to use immune plasma transfusion therapy within 7 days at the latest after the onset of symptoms in patients diagnosed with COVID-19 [7]. Bilir et al. emphasized that early immune plasma transfusion treatment may decrease mortality and length of stay in the intensive care unit in their study on 20 patients [18]. They also observed that it provides a decrease in laboratory parameters such as glucose, which is known to have an effect on mortality. Erkurt et al. showed that intubation and intensive care unit hospitalization rates decreased and mortality rates were low in COVID-19 patients due to early immune plasma transfusion treatment in their study conducted in our region, in which 26 patients were included [19]. In a large multicenter study by Joyner et al. in which 35,322 patients with a high critical patient population were evaluated, it was shown that administration of immune plasma transfusion therapy within 4 days significantly reduced the mortality rate [20]. Similar to our study, the number of patients discharged was higher in the group given immune plasma within the first 4 days.

Limitations of study

Our study is a single-center study and our number of patients is limited since only patients hospitalized in intensive care unit were included in the study. Therefore, our data was more limited and radiological changes due to immune plasma therapy were not considered. In addition, the effect of immune plasma on the development of acute respiratory failure is unknown due to the lack of patients who received immune plasma in the ward.

Conclusion

Immune plasma transfusion therapy improved laboratory parameters supporting clinical improvement due to decreased viral load in patients with COVID-19 who developed severe acute respiratory failure; however, it did not affect mortality and the number of patients discharged was higher in the group given

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early treatment (first 4 days). We suggest that early immune plasma administration may be an adjunctive treatment option to improve clinical recovery and reduce mortality until a definitive and permanent cure is found under pandemic conditions. However, we believe that its place in standard treatment should be re-evaluated. We also consider that further studies are needed to administer immune plasma before the development of acute respiratory failure. Multicenter, comprehensive studies are necessary in this regard.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

Malatya Turgut Ozal University Clinical Research Ethics Committee dated 25.04.2023 and with no. 27.

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