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Effectiveness of Plasmapheresis Treatment in the Treatment of Patients with COVID-19 Disease

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Abstract

Background: According to the World Health Organization, COVID-19 management focuses primarily on infection prevention, case management, case monitoring, and supportive care. However, due to the lack of evidence, no specific anti-SARS-CoV-2 treatment is recommended. This study aimed to evaluate the effectiveness of plasmapheresis treatment in COVID-19 patients with symptoms of pulmonary involvement on the computed tomography (CT) of the lung.

Methods: In 2021, an experimental study in critically ill patients admitted to the COVID-19 ward in the Hazrat-e Rasool hospital diagnosed with COVID-19 was conducted in the second phase (pilot study). The diagnosis was confirmed according to clinical signs, CT scan of the lung, and the Polymerase chain reaction (PCR) test. All patients received the usual treatments for COVID-19 disease and underwent plasmapheresis at a dose of 40 cc/kg daily up to 4 doses. All patients were observed for 24 hours for complications of plasmapheresis treatment and simultaneously for symptoms of COVID-19, after which only routine care measures were performed. The next day and 2 weeks after resumption of the treatment, patients experienced COVID-19 symptoms, including shortness of breath, cough, and fever. Blood oxygen saturation, and treatment results were evaluated. Qualitative and rank variables were described using absolute and relative frequencies and quantitative parametric variables were used using mean and confidence interval. Frequencies were compared in groups using the chi-square test. All tests were performed in 2 directions and $P > 0.05$ was considered statistically significant.

Results: Of the 120 patients studied, 79 (65.8%) were men and 41 (34.2%) were women. The mean age was 60.30 ± 15.61 years (22-95 years). The mean hospital stay was 12.89 days ± 7.25 days (2-38 days). Increased blood oxygen saturation levels in patients had an increasing trend. Inflammatory indices had a downward trend in patients. The frequency of plasmapheresis had no significant effect on reducing the downward trend of inflammatory markers. The greatest reduction occurred in the first plasmapheresis.

Conclusion: Finally, according to the findings, plasmapheresis is one of the appropriate treatments to improve patients' symptoms and reduce cytokine storm. Recovered patients had lower levels of inflammatory markers than those who died.

Keywords: Plasmapheresis, COVID-19, Blood Oxygen Saturation, PCR

Conflicts of Interest: *None declared*
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Introduction

The main target of coronaviruses in humans is the respiratory system. There have been cases of coronavirus

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↑What is "already known" in this topic:
There is currently no effective and complete treatment in patients with coronavirus disease 2019 (COVID-19). Plasmapheresis is a new COVID-19 treatment that is still under research. Standard research can help determine the effectiveness of this treatment.

→What this article adds:
Plasmapheresis is an appropriate treatment to improve COVID-19 patients' symptoms and reduce cytokine storms. If plasmapheresis is used, especially in the early stages of the disease and the onset of the severe phase of the disease, the mortality rate may be effectively reduced.

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outbreaks in the past, including Mid dle East Respiratory Syndrome (MERS) and acute respiratory syndrome (SARS). The previous outbreaks of coronaviruses included (SARS) -CoV and (MERS) -CoV, previously identified as risk factors for community health. A group of patients with a primary diagnosis of pneumonia with unknown cause were hospitalized, in December 2019. These patients have attended a market of marine and wet animals in Wuhan, Hubei Province, China (1, 2). Early reports predicted the onset of a possible coronavirus outbreak. In February 2020, the World Health Organization (WHO) named the coronavirus COVID-19 (3).

COVID-19 management focuses primarily on infection prevention, case management, case monitoring, and supportive care. However, due to the lack of evidence, no specific anti-SARS-CoV-2 treatment is recommended (4). Importantly, guidelines emphasize that systemic corticosteroids should not be routinely recommended to treat COVID-19 (5). In addition, several studies have shown that patients treated with plasmapheresis have a shorter hospital stay and lower mortality than patients not treated with plasmapheresis (6, 7).

COVID-19 disease has different degrees of disease. On the one hand, it is asymptomatic and may progress to a complete and fatal conflict. The WHO estimates that the serious disease enters a critical phase in 6.1% of cases (4). In this case, patients may develop sepsis, acute respiratory distress syndrome (ARDS), or multiple organ failures that are not specific to the coronavirus. While treatment for the virus is certainly desirable, systemic response therapy is probably the most important aspect of patient management and should be treated promptly. This response to infection involves a complex interaction of inflammation, cytokine storm, endothelial dysfunction, and pathological coagulation (8). This route is common in critical situations and has been the goal of treatment for many years. Plasmapheresis is used to treat this condition by eliminating inflammatory cytokines, stabilizing endothelium membranes, and resetting hypercoagulation (9, 10). This study aimed to evaluate the effectiveness of plasmapheresis in COVID-19 patients with symptoms of pulmonary involvement on a CT scan of the lung.

Methods

Setting

The study was performed as a second phase clinical trial (IRCT20180316039112N3).

Participants

Critically ill patients with a Covid-19 disease were admitted to the intensive care unit of Hazrat-e Rasoul Hospital in Tehran, Iran, in 2020. Inclusion criteria included age over 18 years, no diseases requiring special treatment protocol, and no pregnancy. In case of severe plasmapheresis, the treatment was discontinued and necessary measures were taken to improve the complications. The diagnosis was confirmed according to clinical signs, lung CT scan, and PCR test.

All patients underwent clinical and paraclinical examinations after providing consent to participate in the study. All patients received the usual treatments for COVID-19 disease and underwent plasmapheresis at a dose of 40 mL/kg/d for up to 4 doses.

Plasmapheresis is similar to dialysis in that blood is delivered to a patient via a Shaldon catheter, which filters the plasma and replaces it with albumin in the plasmapheresis equipment. A Spectra Optia plasmapheresis apparatus was used in this study (Spectra Optia).

All patients were followed up for 24 hours for complications of plasmapheresis treatment and simultaneously for symptoms of COVID-19, after which only routine care measures were performed in COVID-19. The next day and 2 weeks after resumption of treatment, patients experienced COVID-19 symptoms, including shortness of breath, cough, and fever. Lactate Dehydrogenase (LDH), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), blood oxygen saturation and treatment results were evaluated. Possible side effects of plasmapheresis treatment include flashing, sudden shortness of breath, increased heart rate, and shortness of breath. Patients are monitored throughout the plasmapheresis treatment for up to 24 hours and the medical team, including a physician specializing in hematology and oncology, an internal assistant, a specialist in pulmonology, and a trained nurse, were present at the patient's bedside and all clinical signs and possible complications were managed and, if necessary, the procedure was discontinued and treatment of the patient's complications was started. The primary result was a rise in arterial blood oxygen saturation levels, with improvement in shortness of breath, fever, and cough as a secondary outcome. All patients were under constant medical care and vital signs monitoring throughout the hospital stay.

Statistical Analysis

Qualitative and rank variables were described using absolute and relative frequencies and quantitative parametric variables were used using mean and confidence interval and quantitative nonparametric variables were performed in the middle and range of a quarter. Frequencies were compared in groups using the chi-square test.

All tests were performed in 2 directions and $P > .05$ was considered statistically significant.

Ethical Considerations

This study with the code IR.IUMS.REC.1399.550 was approved by the ethics committee of Iran University of Medical Sciences and data collection and follow-up of patients were performed. Information obtained from patients (through case files or face-to-face interviews) was considered confidential and was used only for research purposes.

Results

In the present study, 120 patients underwent plasmapheresis. Patient characteristics are listed in Table 1. The mean frequency of plasmapheresis was 2.36 ± 1.24 (1-10 times). More than 98% of patients received 1 to 4 plasmapheresis sessions. One patient received 7 sessions, which was effective, and was discharged from the hospital. The

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Table 1. Characteristics of participants and clinical manifestations

Variable		N=120
Age (years), mean (SD)	60.30 (15.61)	
Sex, n (%)	Male	41 (34.2)
	Female	79 (65.8)
Hospital stay (days), mean (SD)	12.89 (7.25)	
Clinical symptoms and sign, n (%)	Fever	67 (55.8)
	Cough	90 (75)
	Dyspnea	75 (62.5)
	Mialgia	60 (50)
	GI distrubance	35 (29.2)
Background diseases, n (%)	Diabetes	40 (33.3)
	Hypertention	39 (32.5)
	Cardiac disease	21 (17.5)
	Kidney disease	8 (6.7)
	Respiratory disease	5 (4.2)
	Nourologic disease	6 (5.0)
	Malignancy	4 (3.3)
	Kidnystone	1 (0.8)
Blood groups, n (%)	A+	38 (31.7)
	B+	25 (20.8)
	O+	36 (30.0)
	A-	5 (4.2)
	B-	3 (2.5)
	O-	9 (7.5)
	AB+	4 (3.3)
PCR, n (%)	Positive	42 (35)
	Negative	78 (65)
IgG, n (%)	Positive	30 (25)
	Negative	90 (75)
IgM, n (%)	Positive	30 (25)
	Negative	90 (75)
Outcome, n (%)	Dead	38 (31.7)
	Alive	82 (68.3)

SD= Standard deviation

mean hospital stay was 12.89 ± 7.25 days (2-38 days). One patient died after partial recovery after the tenth round of plasmapheresis. The oxygen saturation in the patients in the state of with or without oxygen uptake was evaluated separately. It was found that during the hospitalization, oxygen intake plays an important role in increasing oxygen saturation (Fig. 1). Examination of blood oxygen in the studied patients showed that increased blood oxygen saturation (with or without oxygen uptake) is one of the variables that play a role in predicting a patient's survival. The results showed that the discharged patients had higher mean blood oxygen saturation than the deceased patients on all days of hospitalization (Figs. 2 and 3). The role of patients' gender, clinical signs, and underlying diseases as independent factors in patient survival were investigated. The results showed these factors do not play an important role in a patient's survival (Table 2). More than 70% of patients (85 of 120) received 2 to 4 rounds of plasmapheresis. Of them, 77% (69 of 85) were discharged in good general condition, with decreased levels of inflammatory cytokines (Table 3). A decreasing trend in inflammatory factors was observed in most patients. The deceased patients had higher levels of CRP, ESR, and LDH in the second and third rounds than the discharged patients (Table 4). Decreasing inflammatory factors appear to play the main role in the survival of patients treated with plasmapheresis.

Discussion

The SARS-CoV-2 virus is a human infectious virus. Structural analysis of the virus shows that spike glycoproteins are the immunogenic part of SARS-CoV-2 and may use the angiotensin-converting enzyme (ACE-2) receptor to enter host cells. The distribution of ACE-2 receptors on the epithelial surface, cardiac, renal, intestinal, and endothelial cells of type 2 alveoli (AT2) leads to the involve-

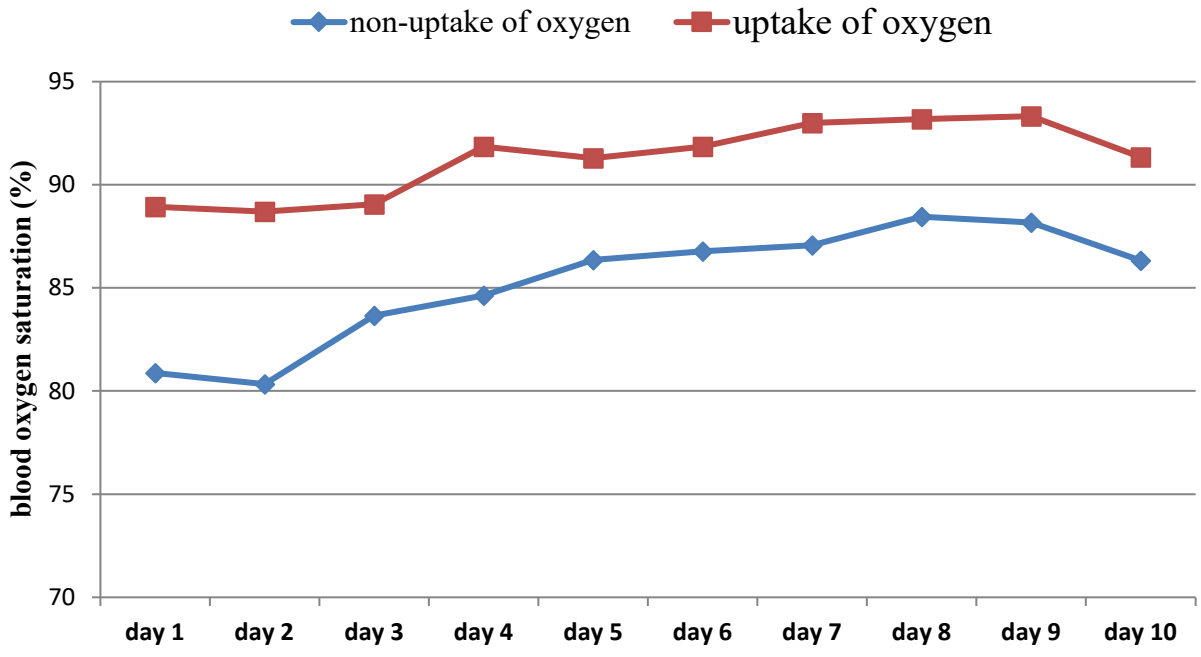

Fig.1. Distribution of mean blood oxygen saturation level of patients in terms of uptake or non-uptake of oxygen

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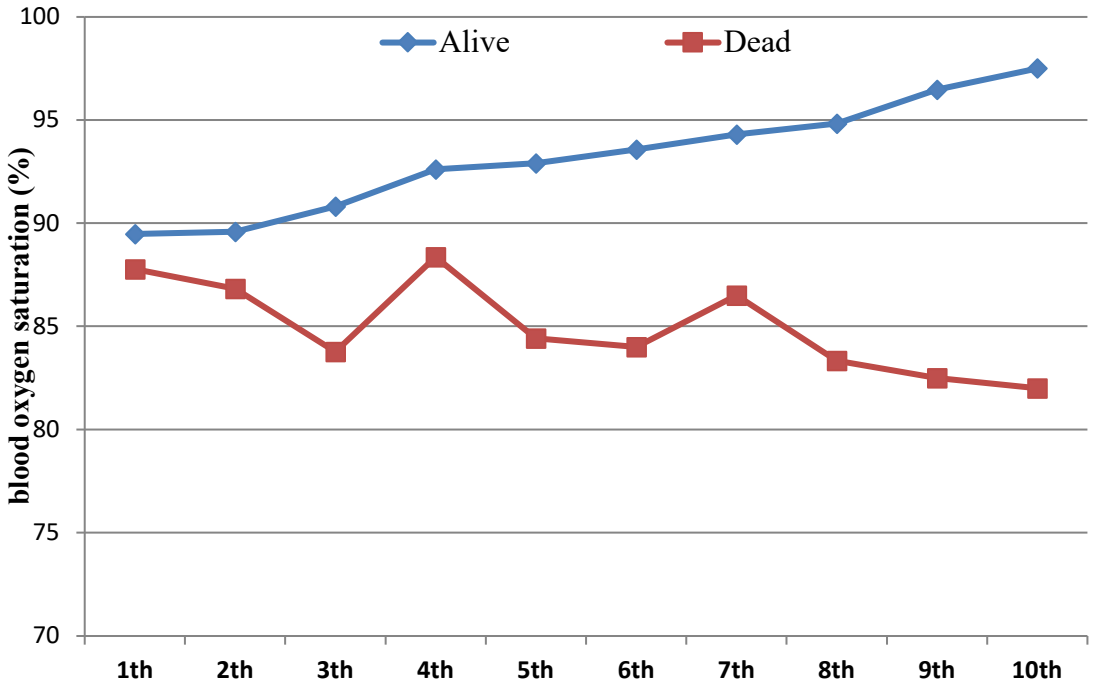

Fig. 2. Distribution of mean blood oxygen saturation level with oxygen uptake in lived and deceased patients

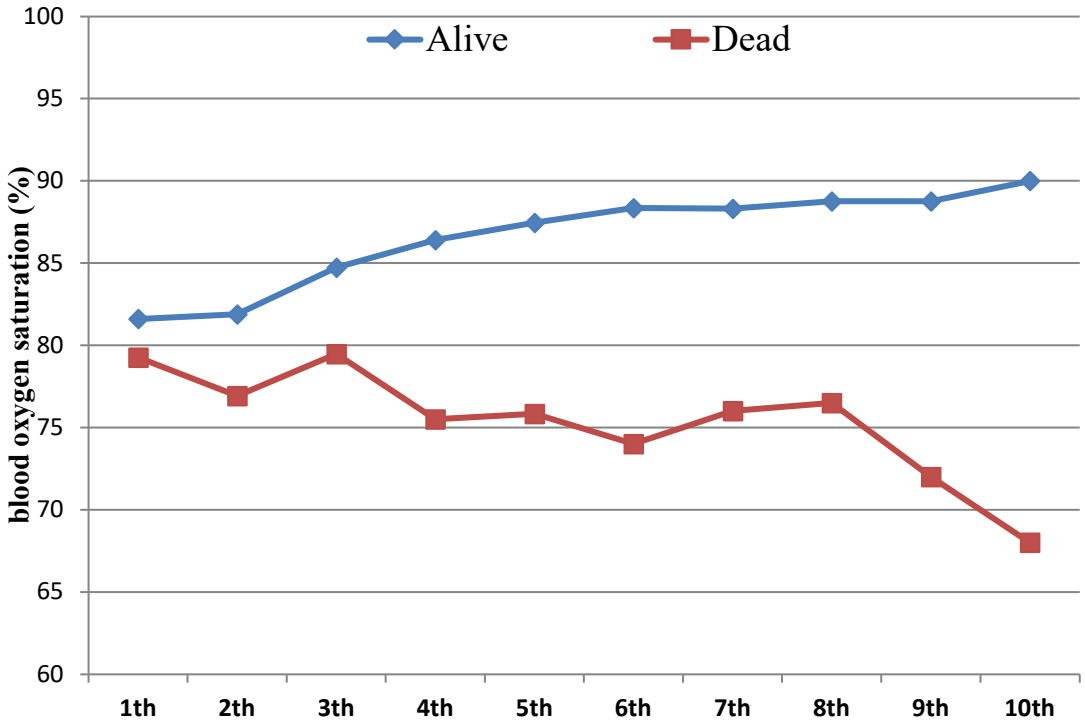

Fig. 3. Distribution of mean blood oxygen saturation level without oxygen uptake in lived and deceased patients

ment of target organs and clinical signs of COVID-19. Control of cytokine storm in its early stages through tools such as immune modulators and cytokine antagonists as well as reducing cytokine load is the key to successful treatment and reduction of mortality in patients with COVID-19 (11-13).

The importance of anti-glycoprotein (anti-S IgG) antibodies as a stimulant of preinflammatory monocyte and macrophage accumulation was assessed (14-16). The study by Golonka et al suggested that the specific antibodies' response against the virus is associated with the glycoprotein S protein pathological changes on the corona-

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Table 2. Distribution of individual variables between lived and deceased patients

Variable		Lived 82 (%100)	Deceased 38 (%100)	*P*-value*
Sex	Female	26 (31.7)	15 (39.5)	0.404
	Male	56 (68.3)	23 (60.5)	
clinical symptoms and sign	fever	44 (65.7)	23 (34.3)	0.401
	Cough	51 (68.0)	24 (32.0)	0.919
	Dyspnea	59 (65.5)	31 (34.4)	0.257
	Mialgia	43 (71.7)	17 (28.3)	0.432
	GI distrubance	22 (62.9)	13 (37.1)	0.408
Background diseases	Diabetes	30 (75)	10 (25)	0.267
	Hypertention	25 (64.1)	14 (35.9)	0.489
	Cardiac disease	14 (66.7)	7 (33.3)	0.857
	Kidney disease	6 (75)	2 (25)	0.675
	Respiratory disease	2 (40)	3 (60)	0.164
	Nourologic disease	3 (50)	3 (50)	0.322
	Malignancy	2 (50)	2 (50)	0.423
	Kidnystone	1 (100)	0 (0)	0.494

*Pearson Chi-Square, *P* <0.05 was significant.

Table 3. Distribution of plasmapheresis repeats between lived and deceased patients

Plasmapheresis repeat	Lived (n=82)	Deceased (n=38)	Total (n=120)	*P*-value*
1	15 (45.5)	18 (54.5)	33 (100)	0.008
2	20 (69.0)	9 (31.0)	29 (100)	
3	40 (81.6)	9 (18.4)	49 (100)	
4	6 (85.7)	1 (14.3)	7 (100)	
7	1 (100)	0 (0)	1 (100)	
10	0 (0)	1 (100)	1 (100)	

*Pearson Chi-Square; P < .05 was significant.

Table 4. Distribution of lab tests between lived and deceased patients

Variables	Times	Lived (n=82)	Deceased (n=38)	*P*-value*
CRP, mean (SD)	1th	43.76(10.25)	44.3(9.73)	0.739
	2th	12.30 (9.66)	26.14 (11.89)	0.001
	3th	8.59 (5.54)	25.33 (11.56)	0.001
ESR, mean (SD)	1th	60.90 (8.41)	61.46 (9.05)	0.751
	2th	30.06 (2.88)	42.76 (7.78)	0.001
	3th	21.39 (4.68)	31.16(8.88)	0.001
LDH, mean (SD)	1th	722.43 (141.18)	811.17 (148.84)	0.006
	2th	392.06 (38.11)	584.72 (231.24)	0.001
	3th	170.10 (15.23)	427.90 (206.23)	0.001

*Pearson Chi-Square, Pvalue <0.05 was significant.

virus. In other words, they proposed a mechanism for the virus to enter antibody-dependent host cells (17).

The research implies that underlying conditions such as diabetes, hypertension, and renal disease as well as systemic cytokine flexibility and tolerance have an impact on vascular health (18-20). This situation creates the cytokine storm conditions, which is considered as the sudden production of IL-1, IL-6, IL-2, IL-7, IL-10, G-CSF, MCP 1, MIP-1a, and TNF-α and one ARDS are the main causes of disease exacerbation (21).

Inflammatory factor levels must be significantly higher in patients in an intensive care unit (ICU) than in non-ICU patients, which means that cytokine storms may be the main cause of disease severity (22). ICU patients also had more laboratory disorders than non-ICU patients. Elevated aspartate aminotransferase, creatine kinase (CK), creatinine, and C-reactive protein levels, serum ferritin levels, diffuse intravascular coagulation (DIC), and macrophage activation syndrome were found in some of these patients (15, 23).

One method identified for reducing cytokine loads, as well as inappropriate coagulation factors and virus loads in COVID-19, is their physical removal using plasmapheresis with or without plasma exchange. Plasmapheresis therapy is used to remove improperly present substances in plasma, such as cytokines or autoimmune antibodies, which can be beneficial in some circumstances. This capacity has led to plasma switching as an adjunct therapy for storm cytokine management and coagulopathy in the COVID-19 pandemic (10, 16, 19).

Plasmapheresis is performed in 2 completely different ways: filtration and centrifugation. A main advantage of the centrifuge is that there is no limit to the size of the substance removed. In the filtration method, the size of the removed substance is limited by the size of the filter pores (24).

Continuous hemofiltration and dual filtration plasmapheresis methods in improving COVID-19 have been investigated in some studies. It has been reported that the use of medium/large pore membranes (50/100 KD) with albumin replacement may be effective in removing IL-6 and Il-23 molecules from plasma (25). In some studies on patients with SARS-CoV2 associated with ARDS and MOD, cytokine storm therapy has been suggested to treat

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severe pulmonary insufficiency secondary to severe inflammatory cytokine. In these cases, plasmapheresis causes cytokine clearance (26).

In the present study, in all patients after the third or fourth plasmapheresis session, a relative improvement in clinical status and reduction of cytokines was shown. On the other hand, oxygen saturation increased when consuming or not consuming oxygen. According to the findings of the present study, it seems that decreasing the level of cytokines and increasing oxygen saturation is associated with improving patients and increasing their survival. Of course, such a conclusion needs further investigation.

In a study by Shi et al (27), after 3 periods of plasmapheresis for a patient, symptoms of improvement were identified and the oxygen delivery index improved, oxygen saturation increased to 96%, and the patient's hypertension improved on day 16. Simultaneously, serum transaminase and creatinine levels improved. However, diarrhea persisted on day 16 and the patient was prescribed intravenous anisodamine (10 mg daily). The patient experienced immediate recovery without diarrhea after the fourth plasma exchange followed by Intravenous immune globulin (IVIG) on day 17. Simultaneously with the improvement of radiographic evidence on day 18, the patient received the sixth IVIG treatment; swab throat samples on days 16, 18, and 20 were negative for the patient. The patient was discharged from the hospital after 15 days of hospitalization with a significant improvement in chest radiographic evidence. This study showed that timely initiation of plasmapheresis treatment followed by IVIG protects the patient from progression to ARDS.

In the present study, plasmapheresis was performed with delay and for critically ill patients admitted to the ICU. The fact that around 70% of these patients were treated successfully demonstrates the method's usefulness to a great extent. In another study (28) evaluating the plasmapheresis effectiveness in patients with COVID-19, a total of 31 patients admitted to the ICU were evaluated. The mean age was 51 years, 90% (n = 28) were men, and 35% (n = 11) underwent plasmapheresis. Almost all patients in the plasma group (10.11) had moderate/severe dyspnea, while the control group had severe dyspnea. The results showed that the plasmapheresis group was associated with a higher extubation rate than the control group (73% vs 20%; p = .018). Patients undergoing plasmapheresis had 14 days less discharge time than the control group. They also had lower mortality in the 28 days after admission than the control group (9.1% vs 45%; p = .001).

The mean age of the patients in this study was 60.30 years. After plasmapheresis, inflammatory indicators such as ESR, CRP, and LDH showed a considerable decrease. It appears that lowering the level of inflammatory indicators has lowered the number of deaths. Other factors, such as the severity of the dispute, the time of referral, the extent of lung involvement, and the exacerbation of inflammatory factors, all had a part in patients' deaths.

Conclusion

Finally, according to the findings, plasmapheresis is one of the appropriate treatments to improve patients' symptoms and reduce cytokine storm. Recovered patients had lower levels of inflammatory markers than those who died. This could indicate the role of reducing inflammatory factors in the survival of patients treated with plasmapheresis.

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Conflict of Interests

The authors declare that they have no competing interests.

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