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Research article

The comparison of the mortality rates of plasmapheresis/hemoperfusion therapy with current treatment among Covid-19 patients

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ABSTRACT

Background: There is no definitive treatment for COVID-19. Hemoperfusion and plasmapheresis have only been studied in a few cases of COVID-19. In this study, plasmapheresis-hemoperfusion and current treatment for COVID-19 patients were compared for mortality.

Methods: In this cross-sectional study, 103 patients with COVID-19 underwent hemoperfusion, plasmapheresis, and conventional medical treatment in educational hospitals in Ahvaz, Iran. A census method was used to include the patients in the study. The data from the hospital file were used to complete a checklist containing demographic information, clinical findings, and paraclinical findings for all patients.

Results: There was not a statistically significant difference (P-value = 0.051) between the plasmapheresis group (78.8%), the hemoperfusion group (71.9%), and the current treatment group (52.6%) in mortality rates. Hemoperfusion had a median survival time of 18.9 days, plasmapheresis had a median survival time of 16.9 days, and current treatment had a median survival time of 13.5 days. In terms of patient survival time, there was no significant difference (P-value = 0.181). Multiple regression results showed that death rates in the hemoperfusion (P = 0.393) and plasmapheresis (P = 0.073) groups were not statistically different from those in the current treatment group.

Conclusion: As a result of this study, there were no differences between the treatment groups in regard to death rates or patient survival times.

1. Introduction

A severe acute respiratory infection (SARI) is caused by Coronavirus disease 2019 (COVID-19), which is an infectious viral disease caused by the Severe Acute Respiratory Virus 2. Acute Respiratory Distress Syndrome (ARDS) and Multi-Organ Dysfunction Syndrome (MODS) can result in death [1]. The development of ARDS can occur shortly after the onset of dyspnea in patients with severe disease. Among Chinese patients with COVID-19-induced pneumonia, 23% were admitted to the intensive care unit (ICU), 17% had ARDS, and 11% died [2]. A sepsis-like syndrome caused by high levels of circulating cytokines may cause organ failure in 67% of patients with severe COVID-19 disease. Many vital organs can be affected, including the lungs, kidneys, heart, and liver [3]. Indirectly caused by sepsis or directly caused by the virus, cytokine storms can be caused by high levels of cytokines released. By binding to alveolar epithelial cells, SARS-CoV-2 activates the innate and acquired immune systems, releasing large amounts of cytokines. These inflammatory events also increase vascular permeability, causing large amounts of fluid and blood cells to enter the alveoli, causing dyspnea and respiratory failure [4].

Previous experiences with viruses, such as the H1N1 influenza virus, SARS-CoV, and Middle East Respiratory Syndrome coronavirus (MERS-CoV), indicate that the severity of the illness depends on the patient's immune system and some signs and symptoms. The only treatment options for patients with severe hypoxia and COVID-19-induced septic shock appear to be mechanical ventilation and hemodynamic support [5]. It has been shown that cytokine storms are associated with the development and progression of ARDS, septic shock, and multiple organ failure (MOF). Cytokines can potentially be removed from the circulation at an early stage and their associated adverse effects reduced by early detection of the storm and timely removal from the circulation of cytokines [6]. Since the start of the COVID-19 pandemic, several treatment

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strategies have been introduced and implemented. In SARS-CoV2, antiviral agents such as remdesivir, sofosbuvir, and favipiravir, antiinflammatory agents, such as corticosteroids and interleukin-6 inhibitors, and convalescent plasma have potential effects [7, 8]. There are still a number of newer strategies to investigate, such as plasma exchange. Multiple toxic mediators can be removed through therapeutic plasma replacement, including endotoxins, proinflammatory cytokines, and precoagulation factors [9].

A hemoperfusion treatment involves transferring a large amount of the patient's blood to an absorbent to remove toxins. Septic shock caused by H1N1 influenza was treated with hemoperfusion cartridges designed to destroy cytokines [10]. By absorbing cytokines, the hemoperfusion cartridge prevents them from attaching to alveoli and endothelium. As a result, ARDS may progress more slowly and mortality may be reduced [11]. Various vital organs can be supported and dysfunction prevented via hemofiltration or hemoperfusion. Direct hemoperfusion with fully bioavailable resin cartridges can yield promising results. This method seems to be quite beneficial for eliminating circulating cytokines and supporting hemodynamic and organ functions [12].

In plasma exchange therapy (PET), many plasma proteins and immunoglobulins (IgG, IgM, and IgA), along with cytokines and storm-induced cytokines are destroyed. As a result, the immune system is weakened and the body is more susceptible to pathogens. Furthermore, the patient's hemodynamics and blood pressure drop when consuming two to three liters of plasma per day [13]. The primary effect of hemoperfusion (HP) is to destroy cytokines and other inflammatory mediators. In the meantime, plasma proteins are restored. Furthermore, HP has little effect on hemodynamics because no plasma volume is removed from the patient. A second consideration is the contraindication of PET in hypotensive patients or those with hemodynamic disorders, such as those receiving hemodialysis [9, 13]. Unlike PET, HP does not need to replace the volume with a solution, which is a significant advantage. Approximately 1–1.5 L of plasma should be replaced with crystalloid or colloidal solution (400 cc of 20% albumin, gelatin product) or 3–4 units of fresh frozen plasma (FFP). Each of these liquid replacement options has its own disadvantages. During the disease, we experience severe shortages of blood products, especially FFP and albumin [13]. Compared with PET, hemoperfusion provides these products more efficiently. A shortage of centrifuges and a lack of tools and trained staff make plasma exchange therapy difficult in Iran [14]. Most hospitals have trained dialysis staff who can perform HP on a dialysis machine. Insurance covers PET costs, but not HP. During the time of this research, HP cartridges cost 3–4 times as much as PET filters. There are significant side effects associated with both treatments. As an example, HP may lead to thrombocytopenia (usually within 24–48 h), hypocalcaemia, hypoglycemia, hypothermia, neutropenia, hypophosphatemia, and rarely hypotension (usually mild) [14]. Furthermore, PET reduces hemoglobin, fibrinogen, and antibodies. Additionally, it can cause seizures, urticaria, chest pain, hypertension, and coagulation disorders [9]. HP and PET both have the disadvantage of removing both harmful and beneficial cytokines and interleukins [14, 15, 16].

In fact, COVID-19 has no definitive treatment; plasmapheresis and hemoperfusion have been performed in some patients. However, few studies have been conducted so far on the effectiveness of these treatments. This study was designed to compare the mortality rate of COVID-19 patients treated with plasmapheresis-hemoperfusion and those managed with conventional therapies.

2. Patients and methods

This is a cross-sectional descriptive-analytical study. The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical Code: IR. AJUMS.REC.1399.798). We used the census method to include all patients who underwent hemoperfusion in hospitals under the supervision of Ahvaz Jundishapur University of Medical Sciences (Iran). There was a similar sample size in the plasmapheresis, hemoperfusion, and current treatment groups. COVID-19 patients admitted to ICUs with PaO2/FIO2 less than 300 and multiple pulmonary segments involved on chest CT scan between April 2020 and March 2021 underwent hemoperfusion, plasmapheresis, and current treatment. It is noteworthy that patients in the hemoperfusion and plasmapheresis groups received current therapy based on the national protocol.

Inclusion criteria were COVID-19 patients undergoing hemoperfusion, plasmapheresis, and current treatment according to the national protocol, who had the required information in the hospital files. Hemoperfusion and plasmapheresis were administered for those COVID-19 patients who were in the second weeks of their illness (inflammatory phase) and had elevated inflammatory markers such as C-reactive protein (CRP) greater than 20 mg/l, lactate dehydrogenase (LDH) greater than 600 IU/l, persistent lymphopenia (defined as lymphocyte counts less than 1200/ml), ferritin greater than three times above the upper limit of normal, or interleukin 6 (IL-6) above 12 pg/ml. Patients with active infection, sepsis or coagulation disorders (INR greater than 2 or platelet counts less than 50,000 cells/μl) were excluded.

For plasmapheresis, a dose of 50cc/kg was considered and FFP and normal saline were replaced in equal proportions. Instead of using normal slain, albumin was used if the patient's albumin was lower than 3.5 g/dL. In case of hypocalcaemia (calcium level less than 8 mg/dl), a vial of 10% calcium gluconate was prescribed. Filters No. 330 were used for hemoperfusion. A 4-h first session was followed by a 6-h second session. Hemoperfusion and plasmapheresis sessions were scheduled according to the patient's condition and tolerance and the absence of contraindications. Laboratory parameters recorded in the file were daily checked and imaging were requested based on the patient's condition. No allergic reaction, fever, and systemic adverse events were reported in any groups.

3. Statistical analysis

We used descriptive statistics such as frequency distribution, frequency percentage, mean, and standard deviation. Data validity was evaluated using the Shapiro-Wilk test. In order to compare the frequency distributions of qualitative variables between the groups under study, the Chi-square test was used. A one-way analysis of variance and non-parametric Kruskal-Wallis test were used to compare the mean distribution of quantitative study variables among the study groups (plasmapheresis, hemoperfusion, and current treatment). The relationship between independent variables and the final outcome variable (death and survival) was assessed using multiple logistic regression by controlling for confounding factors. Median survival time was estimated using the Kaplan-Meyer test. SPSS version 22 was used for the analysis. A significance level of less than 0.05 was considered significant.

4. Results

The number of patients was 32 in the hemoperfusion (31.1%), 33 (32.0%) in the plasmapheresis, and 38 (36.9%) in the current treatment group. Males consisted 78.1% of the hemoperfusion, 60.6% of the plasmapheresis, and 44.7% of the current treatment group. Twenty five percent of the hemoperfusion group, 15.2% of the plasmapheresis group, and 36.8% of the current treatment group had diabetes. Twenty five percent of the hemoperfusion group, 18.2% of the plasmapheresis group, and 44.7% of the current treatment group had hypertension. In addition, 9.4% of the hemoperfusion group, 12.1% of the plasmapheresis group and 21.1% of the current treatment group had coronary artery disease (CAD). According to the Chi-square test, sex and hypertension distributions differed between study groups according to sex. However, the frequency distributions of other variables, including diabetes, heart failure, coronary artery disease, asthma, stroke and chronic kidney disease were homogeneous according to the study groups (Table 1).

Table 1. Frequency distribution of demographic variables, underlying diseases, clinical findings and final outcome according to the studied groups.

Variable		Group			P-value
		Hemoperfusion N (%)	Plasmapheresis N (%)	Current treatment N (%)	
Sex	Female	7 (21.9)	13 (39.4)	21 (55.3)	0.018
	Male	25 (78.1)	20 (60.6)	17 (44.7)	
Diabetes mellitus	No	24 (75.0)	28 (84.8)	24 (63.2)	0.115
	Yes	8 (25.0)	5 (15.2)	14 (36.8)	
Heart failure	No	31 (96.9)	33 (100.0)	36 (94.7)	0.419
	Yes	1 (3.1)	0 (0.0)	2 (5.3)	
Hypertension	No	24 (75.0)	27 (81.8)	21 (55.3)	0.039
	Yes	8 (25.0)	6 (18.2)	17 (44.7)	
Coronary artery disease	No	29 (90.6)	29 (87.9)	30 (78.9)	0.344
	Yes	3 (9.4)	4 (12.1)	8 (21.1)	
Asthma	No	31 (96.9)	32 (97.0)	37 (97.4)	0.991
	Yes	1 (3.1)	1 (3.0)	1 (2.6)	
Stroke	No	31 (96.9)	33 (100.0)	36 (94.7)	0.419
	Yes	1 (3.1)	0 (0.0)	2 (5.3)	
Chronic kidney disease	No	31 (96.9)	33 (100.0)	37 (97.4)	0.611
	Yes	1 (3.1)	0 (0.0)	1 (2.6)	
Need for Oxygen mask	No	32 (100.0)	29 (87.9)	37 (97.4)	0.055
	Yes	0 (0.0)	4 (12.1)	1 (2.6)	
Need for reserve bag mask	No	8 (25.0)	15 (45.5)	12 (31.6)	0.203
	Yes	24 (75.0)	18 (54.5)	26 (68.4)	
Severity of lung involvement	Mild	2 (6.3)	2 (6.1)	2 (5.3)	0.041
	Moderate	9 (28.1)	1 (3.0)	12 (31.6)	
	Sever	21 (65.6)	30 (90.9)	24 (63.2)	
Final outcome	Survival	9 (28.1)	7 (21.2)	18 (47.4)	0.051
	Death	23 (71.9)	26 (78.8)	20 (52.6)	

Sixty-five-point six percent of the hemoperfusion group, 90.9% of the plasmapheresis group, and 63.2% of the current treatment group were involved with severe SARS-CoV-2 infection. The results show that the frequency distribution of the severity of lung involvement was statistically different among the groups. The most severe involvement was related to the plasmapheresis group and then the hemoperfusion group. Moreover, 71.9% of the hemoperfusion group, 78.8% of the plasmapheresis group, and 52.6% of the current treatment group passed away. The frequency distribution of death was not statistically significant among the groups (Table 1).

Compared to the hemoperfusion group and current treatment group, the plasmapheresis group had a lower mean age (45.9 years). In terms of the groups under study, mean ages were not evenly distributed. Hemoperfusion patients stayed 16 days in the hospital, plasmapheresis patients stayed 14.6 days, and current treatment patients stayed 9.1 days.

Although the mean duration of hospital stay was statistically different among the following groups, there was no statistical difference in mean distributions for respiratory rate, oxygen saturation, diastolic blood pressure, systolic blood pressure, heart rate, lymphocyte count, LDH, D-dimer, CRP, non-invasive ventilation, and mechanical ventilation (Table 2).

Considering the confounding effects of other important variables, the results of multiple logistic regression show that there is no statistically significant relationship between the variables of the studied groups (hemoperfusion, plasmapheresis, and current treatments) and the final outcome variables (death and survival). In other words, the frequency distribution of deaths in the hemoperfusion group was not statistically different from that of the current treatment group ($P = 0.393$) and the frequency distribution of death in the plasmapheresis group was not statistically different from the current treatment group (Table 3) ($P = 0.073$).

Among the hemoperfusion, plasmapheresis, and current treatment groups, the median survival time was 18.9 days. According to the log-rank test, median patient survival time did not differ significantly between the three groups (Figure 1) (P-value = 0.181).

5. Discussion

Cytokine storm is one of the most important events in COVID-19, which could lead to multi-organ failure, ARDS, and eventually death. It is believed that strategies to remove the pro-inflammatory mediators from the circulation, including TPE and HP, could prevent disease progression and decrease mortality [17]. Studies on the effectiveness of TPE and HP in COVID-19 patients are scarce [18]. Some studies even state that these interventions can be beneficial only in COVID-19 induced macrophage activation syndrome, or MODS [19]. Therefore, we aimed to compare the mortality rates in the plasmapheresis, hemoperfusion, and current treatments groups.

The numbers of deaths were 71.9% in the hemoperfusion group, 78.8% in the plasmapheresis group, and 52.6% in the current treatment group. The highest numbers of deaths belonged to the plasmapheresis and hemoperfusion groups, while the current treatment group had the lowest mortality rate, which was not statistically significant. In a study by Khamis F et al., those COVID-19 patients who underwent therapeutic plasma exchange (TPE) had a lower 14-day and 28-day mortality rate, compared with the non-TPE group (0 vs. 35%, $P = 0.033$). In spite of this, TPE group mortality was significantly lower than non-TPE group mortality [20]. In a study by Adeli et al., only one of the eight patients undergoing TPE died [21]. One explanation for the higher rate of mortality in the TPE and HP groups could be the higher male-to-female ratio in these groups in our study. It is well documented that COVID-19 severity and mortality are independent risk factors for males [22]. Therefore, we should have matched all the three groups according to sex ratio.

As a result of hemoperfusion, the median survival time was 18.9 days, plasmapheresis, 16.9 days, and current treatment, 13.5 days. Patient survival did not differ significantly between the three groups. In a study

Table 2. Mean distribution of age, clinical, laboratory parameters and number of hospitalization days of patients in each group.

Variable	Group	N	Mean	SD	Min	Max	F	P-value
Age (n)	Hemoperfusion	32	56.6	13.6	24	83	5.7	0.004
	Plasmapheresis	33	45.9	14.5	17	73		
	Current treatment	38	56.6	16.2	17	94		
Duration of hospitalization (days)	Hemoperfusion	32	16.0	8.2	1	36	20.0	<0.001
	Plasmapheresis	33	14.6	7.9	5	43		
	Current treatment	38	9.1	5.8	2	28		
Respiratory rate (n)	Hemoperfusion	32	31.8	5.5	22	44	3.0	0.224
	Plasmapheresis	33	33.2	13.0	18	79		
	Current treatment	38	29.4	6.5	18	48		
Oxygen saturation (%)	Hemoperfusion	32	81.7	8.0	60	95	4.2	0.122
	Plasmapheresis	33	81.9	12.0	43	98		
	Current treatment	38	84.0	13.8	30	99		
Diastolic blood pressure (mmHg)	Hemoperfusion	32	73.2	19.6	0	100	0.7	0.696
	Plasmapheresis	33	76.3	11.9	53	100		
	Current treatment	38	76.1	12.3	50	110		
Systolic blood pressure (mmHg)	Hemoperfusion	32	125.3	17.9	90	170	0.2	0.839
	Plasmapheresis	33	123.7	16.1	100	170		
	Current treatment	38	126.5	23.4	80	190		
Heart rate (n)	Hemoperfusion	32	89.4	21.6	0	120	3.2	0.196
	Plasmapheresis	33	97.2	15.3	62	134		
	Current treatment	38	92.0	17.9	59	150		
Lymphocyte count (n/ml)	Hemoperfusion	32	1130.5	959.8	190	6120	4.3	0.119
	Plasmapheresis	33	1131.4	519.3	200	2470		
	Current treatment	38	1363.6	1048.1	25	6000		
Lactate dehydrogenase (IU/l)	Hemoperfusion	32	882.0	279.2	402	1590	4.8	0.089
	Plasmapheresis	33	917.5	420.2	221	2214		
	Current treatment	38	727.1	271.8	300	1373		
D Dimer (ng/mL)	Hemoperfusion	32	1470.1	1319.9	130	5700	4.0	0.135
	Plasmapheresis	33	3797.8	11849.7	8	69000		
	Current treatment	38	1706.1	942.8	195	4000		
CRP (mg/L)	Hemoperfusion	32	66.4	39.1	3	222	0.4	0.813
	Plasmapheresis	33	140.5	428.0	2	2511		
	Current treatment	38	55.8	27.4	2	104		
Non-invasive ventilation (days)	Hemoperfusion	32	6.0	5.7	1	24	1.2	0.537
	Plasmapheresis	33	4.2	3.3	1	13		
	Current treatment	38	3.6	2.7	1	11		
Mechanical ventilation (days)	Hemoperfusion	32	9.4	8.0	1	32	4.0	0.135
	Plasmapheresis	33	9.6	7.7	1	29		
	Current treatment	38	5.7	5.2	1	21		

Table 3. The relationship between groups' (hemoperfusion, plasmapheresis, and current treatments) variables and mortality, by modulating the confounding effect of age, sex, diabetes mellitus, hypertension, LDH levels and severity of lung involvement (multiple logistic regression model).

Variable	B	S.E	P-value	OR	95% C.I.for OR	
					Lower	Upper
Hemoperfusion	0.533	0.625	0.393	1.704	0.501	5.796
Plasmapheresis	1.204	0.672	0.073	3.332	0.893	12.434
Current treatment (base group)	—	—	—	—	—	—
Age	0.033	0.022	0.129	1.033	0.990	1.078
Sex	0.146	0.527	0.782	1.157	0.412	3.251
Diabetes mellitus	1.285	0.733	0.079	3.616	0.860	15.196
Hypertension	-0.290	0.684	0.672	0.748	0.196	2.861
LDH levels	0.003	0.001	0.003	1.003	1.001	1.005
Severity of lung involvement						
Severe	1.087	1.153	.346	2.966	0.309	28.445
Moderate	0.010	1.217	0.993	1.010	0.093	10.979
Mild (base group)	—	—	—	—	—	—

by Zhang et al., all three COVID-19 patients with ARDS were discharged after 10 days of plasma replacement therapy [23]. In the study of Adeli et al., the condition of 7 out of the 8 patients improved following plasmapheresis [21]. Hemoperfusion in combination with standard treatment was studied by Alavi Darazm et al. in patients with severe COVID-19. Their study showed an overall mortality rate of 9.70%, with hemoperfusion having the lowest death rate [24]. Asgharpour et al. studied the effect of study recovered after being treated with hemoperfusion [18]. The results of these two studies are in contrast with the present study. The conflict between our study and other trials could be that the decision of TPE and HP has been made in more severe patients.

There was no statistically significant difference between the mean lymphocyte counts of the three groups. According to Zhang et al., despite antiviral therapy and other therapeutic interventions, all three patients' conditions progressed to respiratory failure. Nutrophils to lymphocytes ratio decreased after plasma exchange treatment [23]. A study by Alavi Darazm et al. found that patients treated with hemoperfusion had significantly higher lymphocyte counts than other patients [24]. In spite of this, Asgharpour et al. found no improvement in lymphocyte counts in patients after hemoperfusion [18].

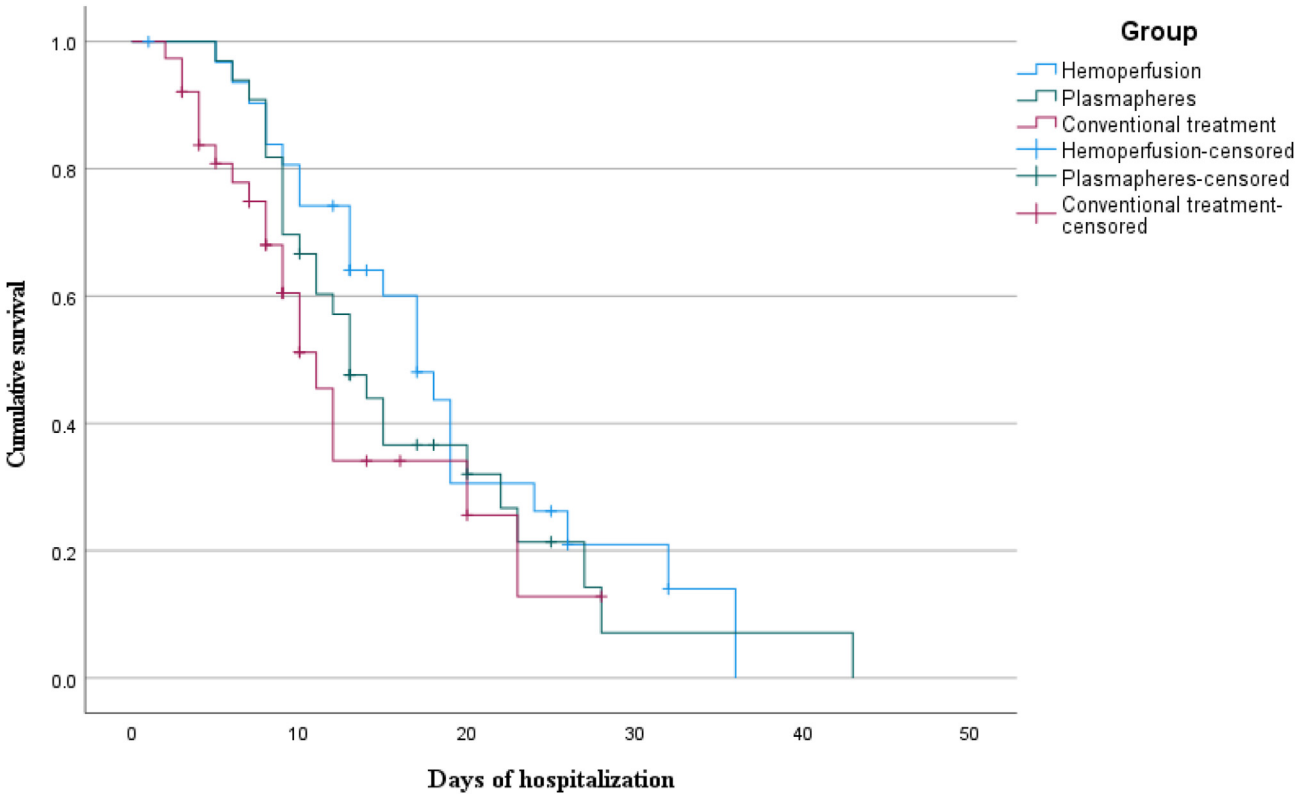

Figure 1. Cumulative survival probability according to different groups.

Among the hemoperfusion, plasmapheresis, and current treatment groups, there was no statistically significant difference in CRP levels between the groups. After treatment, CRP levels decreased by more than 70% and IL-6 levels decreased by more than 70% in the study by Zhang et al. [23]. According to Alavi Darazm et al., CRP levels were significantly different between the two groups [24]. Moreover, in the study by Asgharpour et al., CRP level decreased significantly after hemoperfusion therapy [18].

There was severe pulmonary involvement in 65.6% of the hemoperfusion group, 90.9% of the plasmapheresis group, and 63.2% of the current treatment group in the present study. In spite of this, there was no statistically significant difference between the three groups. Plasmapheresis had the most severe involvement, followed by hemoperfusion. Hence, the high mortality rate in the TPE and HP groups could be the result of more severely SARS-CoV-2 infected patients in these groups. Probably, decision about TPE and HP had been made in more severe patients.

Among the three groups, there was no statistically significant difference in oxygen saturation, reserve bag mask usage, and oxygen mask use. In the study by Zhang et al., the Pao2/Fio2 ratio significantly increased within 24 h after TPE. Moreover, the patients were switched from high flow to low flow oxygenation within approximately 4–5 days after TPE treatment [23]. The study by Khamis F et al. also showed more extubation rate in the group that underwent TPE, compared with the non-TPE group (73% vs. 20%, $P = 0.0018$) [20]. In addition, the hemoperfusion group had significantly higher blood oxygen saturations than the other patients in the study by Alavi Darazm et al. [24].

The mean hospitalization duration in this study was 16 days for the hemoperfusion group, 14.6 days for the plasmapheresis group, and 9.1 days for the current treatment group. In the study of Adeli et al., the average duration of hospitalization was 14.6 days in patients undergoing plasmapheresis [21]. In addition, the study of Alavi Darazm et al. showed a significantly higher mean length of ICU admission and intubation period in the hemoperfusion group, compared with other patients.

Khamis F et al. reported an improvement in laboratory and ventilatory parameters in COVID-19 patients who underwent TPE [20]. Tabibi et al. also came to the same conclusion that TPE can be an invaluable means of stabilizing critically ill COVID-19 patients and reducing mortality. TPE is therefore potentially useful in managing respiratory viral infections resulting in ARDS and multiorgan dysfunction [25]. Accordingly, Keith et al. found that TPE is promising, and have suggested that randomized trials be designed for further investigations [26]. Lu et al. in a review study stated that there is no published data to support the claim that TPE can reduce the viral load of SARS-CoV-2 and its suppressing effect on the cytokine-mediated inflammation still remains unclear [27]. Adele et al. stated that TPE helps reduce the patient's inflammatory status by restoring the anti-inflammatory mediators, suppressing the pro-inflammatory cytokines, and compensating the organ damage due to a hyperactivation of the host defense [21]. Patients with COVID-19 may benefit from direct hemoperfusion using polymyxin B-immobilized fiber columns (PMX-DHP), according to Katagiri et al. [28].

The limitations of our study was the cross sectional retrospective nature of our investigation, which led to some missing data in the files and lack of similarity of all three groups. TPE and HP were chosen in the present study for more severe patients. Thus, a higher severity of the disease could result in a higher mortality rate. In addition, limited sample size could be among the reasons why our study results were inconsistent with others.

It requires high-quality randomized controlled clinical trials because there are only a limited number of studies related to this field.

6. Conclusion

As a result of this study, little evidence was found that plasmapheresis and hemoperfusion improved the conditions of patients with severe COVID-19, and the death and survival rates did not differ between any of the treatment modality groups.

Declarations

Author contribution statement

Seyede Mahboobeh Raoofi Kelachayeh and Hanieh Raji: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Maryam Haddadzadeh Shoushtari, Zahra Mehraban; Mehrdad Dargahi-Malamir, Gholamreza Alizadehattar: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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