ORIGINAL ARTICLE

Hemoperfusion in patients with severe COVID-19 respiratory failure, lifesaving or not?

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Background: The new coronavirus outbreak quickly filled hospital beds and stunned the world. Intensive care is required for 5% of patients, and the mortality rate for critically ill patients is 49%. The "cytokine storm" is considered as the main cause of pathogenesis for coronavirus disease-19 (COVID-19)-related respiratory failure, hemoperfusion may be a modality for treatment of disease. **Materials and Methods:** Thirty-seven an patients with positive real-time polymerase chain reaction for SARStions2 in an upper respiratory tract sample or typical chest computed tomography lesion were eligible for this case–control study. Patients meeting the criteria for hemoperfusion including clinical and laboratory indices, were evaluated for outcomes such as hospitalization length and mortality. Patients were divided into three groups, i.e., patients who received hemoperfusion without a need for mechanical ventilation (MV), patients who received hemoperfusion before MV, and patients who received hemoperfusion after MV. **Results:** Among 37 patients with COVID-19 respiratory failure, 32% were female with a mean age of 55.54 (standard deviation 14.1) years. There was no statistically significant difference between the three groups in terms of length of hospital stay and intensive care unit (ICU) stay (*P*-tayns: 0.593 and 0.243, respectively, confidence interval [CI]: 95%). Heart rate, respiratory rate, PaO_2/FIO_2, high-sensitivity C-reactive protein, and ferritin significantly improved after the application of hemoperfusion in all groups ($P < 0.05$, CI: 95%). **Conclusion:** It seems that applying hemoperfusion in the inflammatory phase of the disease, especially before the intubation, reduce the need for MV. However, hemoperfusion does not have any impacts on the duration of hospital and ICU stay.

Key words: COVID-19, hemoperfusion, respiratory failure

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INTRODUCTION

In late December 2019, the Wuhan Health Commission was notified of a cluster of unknown cases of severe respiratory illness.[1] On January 7, 2020, the new coronavirus species, called 2019 novel coronavirus, was identified as the responsible pathogen.[2] Shortly thereafter, on March 11, the World Health Organization

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declared the coronavirus disease (COVID-19) a pandemic.[3]

The disease mortality rate is 1%, which is close to influenza pandemics in 1918 (2%) and 1957 (0.6%). On the other hand, it is much harder to control than SARS and MERS.[4,5] Although this infection may be a benign disease with fever, cough, and fatigue as presenting symptoms, elderly patients and those with comorbidities are at a higher risk for severe forms of the disease.[6,7]

While most people with COVID-19 present only mild or uncomplicated illness, almost 14% develop a severe disease that requires hospitalization and oxygen support and 5% require admission to an intensive care unit (ICU).[5] Among those with a critical condition, 67% present with additional organ dysfunction syndrome and their mortality rate is 49%.[8-10] This has been thought to be due to a high level of circulatory cytokines in response to the virus itself or a superimposed bacterial infection.[6,9] Cytokine storm can cause consequent complications including acute respiratory distress syndrome (ARDS), shock, acute heart damage, and acute renal failure.[8,11]

In a study in Jin Yin-Tan Hospital (designated for COVID-19) in Wuhan, Huang *et al*. showed that the concentrations of serum inflammatory cytokines were higher in hospitalized patients in both ICU and non-ICU wards than in healthy populations.[6]

Furthermore, the results showed that the higher level of cytokines played a more significant role in the inflammation process, such as interleukin (IL) 2, IL7, IL10, and tumor necrosis factor (TNF)-α, in ICU patients than in non-ICU patients.[6,11] These findings may support the theory of the cytokine storm to explain severe form of the disease.

Since available pharmacological treatments have not yet shown definitive efficient results in critically ill patients with organ dysfunction syndrome, mechanical ventilation (MV) and hemodynamic support are the only available treatment strategies.[12]

However, in a recent spotlight published in *The Lancet Respiratory Medicine*, the possible role of extracorporeal organ support (ECOS) therapies including hemoperfusion and hemoadsorption for those patients at a higher risk for organ dysfunction syndrome in such viral outbreaks has been discussed.[13] Recent findings have provided promising results on the use of ECOS therapies in critical conditions, such as septic shock and ARDS, both in animal and human studies.[14-18] Designing the present study, we sought to evaluate the efficacy and safety of hemoperfusion therapy in critically ill patients with COVID-19 disease.

MATERIALS AND METHODS

This cross-sectional study was conducted from March 1, 2020, to April 29, 2020, in five referral coronavirus hospitals in Isfahan City (the third-largest city of Iran), Isfahan Province, Iran. The study was in accordance with the 1964 Helsinki Declaration, and the local ethics committee approved the study protocol (IR. MUI. RESEARCH. REC.1399.007).

Patients over 18 years old were eligible for inclusion if they had positive real-time polymerase chain reaction for SARS-CoV-2 in an upper respiratory tract sample or typical chest computed tomography lesion[19] and met the necessary criteria for hemoperfusion, for example, a respiratory rate (RP) of more than 25/min, SpO_2 of <90% despite administration of invasive or noninvasive procedures for oxygenation, and having episodes of severe fever T >38.5C) and chills or tachycardia (PR >100/min) with 2 of 4 of the following laboratory parameters: PaO_2 <60 mmHg, PaO_2/FiO_2 <200, high-sensitivity C-reactive protein (HS-CRP) >++, or >50mg/dL, ferritin >1000ug/L, and bicytopenia (platelet <100,000, hemoglobin <9g/dL, and lymphocyte count <1100/mm^3). Patients were excluded if they presented respiratory failure due to a cause other than SARS-CoV-2 or if they presented with severe hypotension so that hemoperfusion would be contraindicated. Other contraindications were obesity (body mass index >40 kg/m^2), pregnancy, heparin-induced thrombocytopenia, sickle cell crisis, severe medical problems with life expectancy <1 month, and severe thrombocytopenia (<200,00/μL).[20] Patients who underwent hemoperfusion received standard treatment according to the National Iranian Guidelines for the Treatment of COVID 19 Infection,[21] and direct hemoperfusion using HA resin hemoperfusion cartridge (Model HA 280, Jafron Biomedical Co., Ltd.). Patients were treated with at least three sessions of direct hemoperfusion: first session for 4 h and then for a longer time in subsequent sessions up to 8 h with 24 h interval. On the 1st day, each patient received only one session of hemoperfusion. Hemoperfusion would stop if the critical condition of a patient improved, including, decreased RP, decreased need to oxygen supplementation, and improvement in consciousness. The blood flow rate was 200–250 mL/min, the patient received heparin 70U/kg, and his/her thrombocytopenia would be reduced according to the discretion of the clinician.

Before the initiation of the treatment, patients' blood samples were sent for laboratory analysis of following parameters: complete blood cells, calcium, magnesium, ferritin, HS-CRP, and erythrocyte sedimentation rate (ESR). At the end of hemoperfusion course of treatment, all the parameters above were checked once again. Patients were monitored every half an hour for blood pressure

measurement, pulse rate, RP, PaO_2/FIO_2 and O_2 saturation, and two times for body temperature during the period of hemoperfusion. In addition, patients were under nursing care for hypotension, hypothermia, and hypocalcemic seizure. All the patients were at the severe phase of COVID-19 disease[21] and received supportive treatments, including corticosteroids, before hemoperfusion sessions. None of the patients received any other treatments, such as interferon or other antiviral therapy.

At the end of the treatment period, patients were evaluated for treatment response criteria as follows: increased O_2 saturation over 90%, normal body temperature, RR <20/min, improved state of consciousness, vital situation, and laboratory variables.

Statistical methods

The descriptive statistics included median and interquartile range for continuous data. The statistics for categorical variables included counts and percentages. Mann–Whitney U-test was performed for continuous variables, and the Chi-square test and Fisher's exact test were used for categorical variables when appropriate. For before–after variable changes, statistical tests including Wilcoxon matched pairs signed-ranks test (nonparametric alternative to the paired t-test) were utilized. The Kaplan–Meier method and log-rank test were used to compare the prognosis of COVID-19 patients in different groups. In addition, multivariable Cox proportional hazards regression model was used to assess the association between age, sex, laboratory findings, underlying comorbidity, and vital symptoms and the dependent variables of time to death from admission and time to death after treatment. The hazard ratio (HR) along with the 95% (confidence interval [CI] was reported. $P < 0.05$ was considered as statistically significant. All statistical analyses were performed using SPSS 25.0 for Windows (SPSS, Inc., Chicago, Ill, USA).

RESULTS

Thirty-seven patients who met the inclusion criteria were included in this study. Twenty-five patients (67.5%) needed MV and 15 patients (40.5%) passed away. Patients' general characteristics and demographic data are summarized in Table 1. No statistically significant difference was observed between age, sex, number of sessions for hemadsorption (HA) treatment, and comorbidities between survived and dead patients ($P > 0.05$).

However, when these variables were compared between groups of patients based on ventilation status [Table 2], the age ($P = 0.036$) and the history of hypertension ($P = 0.002$) were significantly higher in patients who received hemoperfusion before receiving MV.

Hemoperfusion was successfully able to improve part of the vital signs [Table 3]. Body temperature declined after hemoperfusion; however, the reduction was not statistically significant. There was no significant improvement in SpO_2. The systolic and diastolic blood pressures decreased after hemoperfusion; however, the decline was not significant.

As shown in Table 4, when we analyzed posthemoperfusion changes in vital signs in groups of patients based on ventilation status, RP was the only variable significantly improved among all groups of patients. Although we could not prove a significant recovery in SpO_2, oxygenation, which was defined as the PaO_2/FiO_2 ratio, had a significant increase after hemoperfusion. Moreover, all groups of patients showed this improvement in the PaO_2/FiO_2 ratio.

Although HS-CPR, ferritin, and ESR decreased after hemoperfusion, this decline was only significant in HS-CRP and ferritin ($P < 0.05$). However, with further analysis of the groups of patients, none of these inflammatory markers show significant changes between the groups.

Although white blood cells (WBCs) and lymphocytic count showed an increase after hemoperfusion, it was not significant for the lymphocytic count ($P > 0.05$. P- Value 0.044, 0.281 respectively).

As shown in Table 5, the mortality rate was significantly higher in patients who had hemoperfusion after undergoing MV (60%, $P = 0.002$). All patients survived the period of study in the group of hemoperfusion without receiving MV. In addition, among those who underwent MV, patients who received hemoperfusion before MV were weaned significantly earlier from the ventilator group ($P = 0.03$). Nevertheless, the analysis did not confirm any statistically significant difference in hospital and ICU length of stay between the patient groups. The main causes of patients' mortality were respiratory failure and sepsis. Moreover, one patient died due to pneumothorax as a complication of access insertion, while one patient died due to hypotension with unknown cause and cardiac arrest.

The Kaplan–Meier method and log-rank test were used in our study to investigate the relationship between study groups and COVID-19 prognosis. The results indicated that the group of hemoperfusion without receiving MV had a significantly higher overall survival rate than other groups ($P < 0.05$). There was no statistically significant difference between patients who had hemoperfusion before or after MV ($P = 0.063$) [Figure 1].

The multivariate-adjusted Cox proportional hazards model after being adjusted for age and gender was used along with the unadjusted approach to analyze the risk

Table 1: General characteristics of 37 patients who admitted in COVID-19 referral hospitals under hemoperfusion treatment (Chi-square statistic)

Patients characteristics	Total (*n*=37), *n* (%)	Death events, *n* (%)		*P*
		Yes (*n*=15)	No (*n*=22)	
Age, years	55.54±14.10	60±15.20	52.5±12.76	0.113
Sex (female)	12 (32)	3 (20)	9 (41)	0.165
HP treatment number	3.05±1.31	2.93±1.53	3.13±1.16	0.650
Ventilation duration (days)	11.24±15.75	11.26±9.9	11.22±18.96	0.996
Comorbidities (yes)				
Hypertension	13 (35)	8 (53)	5 (23)	0.059
Congestive heart failure	4 (11)	3 (20)	1 (3)	0.172
Respiratory disease	1 (2)	0	1 (3)	0.595
Diabetes	10 (27)	5 (33)	5 (23)	0.364

P<0.05 is significant

Table 2: General characteristics of 37 patients who admitted in COVID-19 referral hospitals under hemoperfusion treatment based on ventilation status (Chi-square static)

Patients characteristics	Hemoperfusion Without MV (*n*=12), *n* (%)	Hemoperfusion before MV (*n*=10), *n* (%)	Hemoperfusion after MV (*n*=15), *n* (%)	*P*
Age, years	53.01±11.02	65.01±13.18	51.02±14.06	0.036
Sex (female)	6 (50)	4 (40)	2 (13)	0.108
HP treatment number	3.2±1.05	2.30±1.03	3.40±1.29	0.097
Comorbidities (yes)				
Hypertension	3 (25)	8 (80)	2 (13)	0.002
Congestive heart failure	1 (8)	2 (20)	1 (6)	0.552
Respiratory disease	0 (0)	0 (0)	1 (6)	0.471
Diabetes	3 (25)	5 (50)	2 (12)	0.127

P<0.05 is significant

Table 3: Vital symptoms and laboratory findings changes before first session and after last session of hemoperfusion (ANOVA and Chi-square static)

Variables	Before hemoperfusion	After hemoperfusion	*P*
Vital symptoms (baseline)			
Temperature (°C)	37.82±0.77	37.51±0.78	0.133
Heart rate,/min	111.62±22.17	92.24±19.44	0.030
Respiratory rate,/min	32.62±7.76	19.59±10.42	<0.001
SpO_2, %	76.23±2.46	75.69±3.54	0.910
PaO_2/FiO_2, mmHg	134.75±14.91	187.01±18.21	0.001
Systolic blood pressure (mmHg)	127.20±20.64	118.62±23.39	0.116
Diastolic blood pressure (mmHg)	78.13±2.71	68.65±4.37	0.066
Laboratory findings (baseline)			
White blood cell count, $\times 10^9$/L	9.18±5.01	13.89±7.18	0.002
Lymphocyte count	854.50±86.59	974.29±113.47	0.231
ESR (mm/H)	75.64±4.68	59.01±10.89	0.080
HS-CRP (mg/dL)	88.06±17.87	58.06±13.16	0.016
Ferritin (ng/mL)	1015.07±164.51	579.79±133.26	0.039
Calcium (mg/dL)	9.64±1.64	8.20±1.30	0.524
Magnesium (mg/dL)	1.94±0.059	2.10±0.045	0.022
Creatinine (mg/dL)	1.42±0.18	1.27±0.83	0.194
Hemoglobin (g/dL)	12.05±3.06	10.89±2.83	0.001
Platelet (/μL)	213,969±16,259	220,545±19,786	0.648

P<0.05 is significant. ESR=Erythrocyte sedimentation rate; HS-CRP=Highly Sensitive C- reactive protein

factors for mortality in patients with COVID-19 who underwent hemoperfusion. The (HR) and 95% (CI) are presented in Table 6. RP (HR: 0.87, CI 95%, $P = 0.028$) was a significant predictor for better outcomes. In both adjusted and unadjusted Cox proportional hazards models, there were no statistically significant differences in other vital signs or laboratory findings for predicting mortality ($P > 0.05$).

Table 4: Vital symptoms and laboratory findings changes during treatment base on ventilation status

Variables	Hemoperfusion without MV (*n*=12)		*P*	Hemoperfusion before MV (*n*=10)		*P*	Hemoperfusion after MV (*n*=15)		*P*
	Before	After		Before	After		Before	After	
Temperature (°C)	37.73±0.25	37.34±0.67	0.373	38.09±0.27	37.84±0.26	0.838	37.71±0.14	37.44±0.21	0.279
Heart rate,/min	111.91±6.71	79.08±3.20	0.002	120.90±5.02	102.60±7.08	0.011	105.20±6.17	95.86±4.57	0.083
Respiratory rate,/min	34.25±2.19	16.66±0.96	0.002	35.40±2.31	26.01±3.70	0.020	29.46±1.88	17.66±3.34	0.005
SpO_2, %	67.89±5.38	79.67±10.68	0.109	74.40±5.18	72.50±5.12	0.779	87.70±2.20	75.05±4.04	0.112
PaO_2/FiO_2	110.55±10.25	175.09±26.92	0.017	136.90±24.90	192.60±34.48	0.037	151.07±31.03	192.01±29.62	0.047
Systolic blood pressure (mmHg)	127.75±12.81	119.25±19.44	0.482	133.77±27.91	110.88±33.32	0.120	121.91±18.64	124.11±16.24	0.723
Diastolic blood pressure (mmHg)	83.37±8.50	69.5±4.50	0.314	76.34±6.22	61.66±12.45	0.333	76.25±4.25	73.33±4.36	0.610
White blood cell count, $\times 10^9$/L	9.37±0.97	13.10±1.5	0.005	7.24±0.87	12.96±1.5	0.008	10.68±1.75	14.59±2.5	0.044
Lymphocyte count	954.45±205.54	949.63±192.37	0.159	752.80±129.64	833.30±112.21	0.575	849.02±120.98	1086.20±224.96	0.281
ESR (mm/H)	80.80±9.69	54.60±19.67	0.223	85.67±4.05	95.01±10.41	0.285	66.33±6.86	44.67±16.32	0.116
HS-CRP (mg/dL)	55.50±12.33	22.25±11.75	0.068	126.02±42.21	98.83±25.46	0.463	71.83±15.22	41.17±11.05	0.249
Ferritin (ng/mL)	906.71±236.44	519.43±230.66	0.116	1650±987.33	587.01±260.94	0.180	912.78±286.09	661.40±200.79	0.500
Calcium (mg/dL)	12.53±4.04	8.64±0.27	0.838	8.53±0.25	8.14±0.19	0.286	7.77±0.28	7.85±14	0.937
Magnesium (mg/dL)	2.02±0.094	2.12±0.102	0.399	2.08±0.129	2.21±0.080	0.497	1.79±0.081	2.03±0.043	0.037
Creatinine (mg/dL)	1.21±0.27	1.11±0.20	0.023	1.68±0.42	1.57±0.38	0.662	1.41±0.28	1.18±0.18	0.262
Hemoglobin (g/dL)	12.96±0.76	11.85±0.63	0.49	10.55±1.52	9.20±1.37	0.071	12.5±2.17	11.29±1.89	0.001
Platelet (/μL)	211,400±21,947.5	257,100±25,416.2	0.277	238,222.22±4552.10	237,000±48,032	0.039	200,214.8±77,664	160,714.2±2193.3	0.092

P<0.05 is significant. ESR=Erythrocyte sedimentation rate; HS-CRP=Highly sensitive C-reactive protein

Table 5: Different outcome distribution totally and based on ventilation status

Patients characteristics	Total	Hemoperfusion without MV (*n*=12)	Hemoperfusion before MV (*n*=10)	Hemoperfusion after MV (*n*=15)	*P*
ICU length of stay (days)	19.35±14.03	14.75±6.07	25.60±16.18	18.86±16.22	0.593
Hospital length of stay (days)	22.37±13.62	20.33±7.90	26.30±15.69	21.40±15.95	0.243
Duration of ventilation (days)	6 (0-13.5)	-	9 (0-28.70)	11 (5-20)	0.030
Mortality rate (yes), *n* (%)	15 (40.5)	0 (0)	6 (60)	9 (60)	0.002

P<0.05 is significant. ICU=Intensive care unit; MV=Mechanical ventilation

DISCUSSION

This study was conducted to investigate the efficacy of hemoperfusion as a hemoadsorption treatment for the removal of poisons[22] and circulatory cytokines in critically-ill patients with COVID-19 infection. Xu *et al.* previously showed that HA330 cartridge by the same manufactures successfully improved ARDS in a porcine model.[15] HA280 resin cartridge was designed to absorb molecules from a weight of 500 Da to 65,000 Da. Since the weight of most cytokines' influential in the inflammatory process, such as ILs and TNF, ranges from 6 kDa to 26 kDa, this procedure can be useful for the elimination of cytokines.

Unfortunately, due to a lack of resources and laboratory kits for measurement of cytokines' level in the bloodstream during the outbreak, we could not directly measure the cytokines before and after HA treatment administration in all participants. Most studies chose IL-6 as a removable key cytokine in inflammation progression, and it is considered as the cartridge adequacy index.[14,23-25] On the other hand, with an interesting pattern, C- reactive protein (HS-CRP)

Table 6: The results of Cox regression for prognostic factors between patients under hemoperfusion

Variables	Unadjusted HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Vital symptoms (changes)						
Temperature (°C)	0.72	0.37, 1.41	0.343	0.52	0.16, 1.68	0.279
Heart rate,/min	1.009	0.98, 1.04	0.353	1.039	0.94. 1.15	0.171
Respiratory rate,/min	0.970	0.92, 1.02	0.292	0.87	0.77, 0.98	0.028
$SpO_{2,}$ %	0.970	0.93, 1.002	0.970	0.95	0.90, 1.01	0.122
PaO_2/FiO_2,%	0.99	0.93, 1.01	0.342	1.04	097, 1.11	0.230
Systolic blood pressure (mmHg)	1.003	0.96, 1.04	0.887	1.023		
Diastolic blood pressure (mmHg)	0.998	0.97, 1.01	0.867	0.992		
Laboratory findings (changes)						
White blood cell count, $\times 10^9$/L	1.001	0.989, 1.002	0.902	1.002	0.999, 1.002	0.789
Lymphocyte count, $\times 10^9$/L	1.024	0.99, 1.078	0.498	0.98	0.96, 1.02	0.336
ESR (mm/H)	1.001	0.95, 1.05	0.988	1.052	0.81, 1.36	0.702
HS-CRP (mg/dL)	1.008	0.98, 1.032	0.468	1.004	0.94, 1.067	0.908
Ferritin (ng/mL)	1.014	0.97, 1.056	0.496	1.025	0.94, 1.11	0.547
Calcium (mg/dL)	1.043	0.52, 2.08	0.905	0.99	0.43, 2.28	0.989
Magnesium (mg/dL)	2.94	0.14, 6.67	0.487	2.32	0.081, 6.31	0.622
Creatinine (mg/dL)	0.686	0.08, 5.84	0.730	0.773	0.007, 8.35	0.914
Hemoglobin (g/dL)	0.866	0.32, 2.36	0.778	1.02	0.96, 1.08	0.497
Platelet (/μL)	0.990	0.96, 1.101	0.508	1.001	0.99, 1.08	0.414

P<0.05 is significant. ESR=Erythrocyte sedimentation rate; Hs-CRP=Highly sensitive C- reactive protein; HR=Hazard ratio; CI=Confidence interval

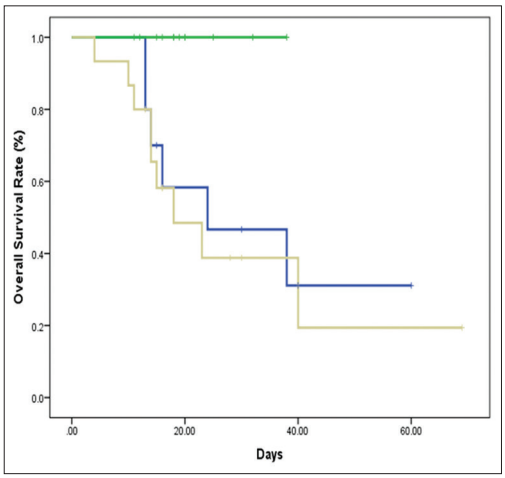

Figure 1: Kaplan–Meier survival curve of COVID-19 patients in different study groups (Blue line: HP before intubation; Yellow line: HP after intubation; Green line: HP without intubation)

and ferritin, as two major acute-phase proteins, had a good correlation with IL-6 and IL-18, respectively, and both increase during inflammation due to a bacterial or viral infection.[26] Therefore, we chose HS-CRP and ferritin as the representative molecules for verification of the ability of HA280 resin cartridge to eliminate cytokines.

In this study, HS-CRP and ferritin showed a significant drop in concentration post hemoperfusion. However, no statistically significant difference was observed in the reduction of HS-CRP and ferritin between patients who received hemoperfusion before, after, and without MV. This finding might indicate that regardless of the need for MV and the time for initiation of HA treatment, it is possible that HA280 resin was successfully able to remove cytokines from the bloodstream. In a study by Shimizu *et al*., a significant decline was reported in the level of cytokines including IL-6, IL-8, IL-10, (IL)-1β, and IL-1 receptor antagonist as the key mediators of inflammatory reaction after hemoperfusion compared to the baseline.[27] Their findings support the effect of hemoperfusion on blunting the cytokines storm to improve organ preservation and patient outcome in severely critical conditions, such as sepsis. Although we did not directly measure cytokines, our findings are in good agreement with what was proposed by Shimizu *et al*. However, further studies are necessary to confirm that hemoperfusion can directly decline the level of inflammatory cytokines in critically ill patients suffering from COVID-19.

We classified patients into three groups, i.e., those who received hemoperfusion without, before, and after MV. The rationale for this type of classification is based on the timing of the hemoperfusion initiation relative to the stage of pulmonary involvement in each patient. Therefore, those patients who received hemoperfusion without indication for MV were speculated to have lower pulmonary involvement than those indicated for MV. Similarly, patients who received hemoperfusion before MV seem to have lower respiratory problems at the time of hemoperfusion compared to those who received it after the initiation of MV. Based on what we found, the mortality rate was significantly lower in patients who received hemoperfusion without having MV. There was no statistically significant difference between those with HA treatment before and after MV in terms of mortality rate. Moreover, the duration of MV was

lower when hemoperfusion was initiated before MV. This can highlight the importance of the issue of time in initiating hemoperfusion and suggests that this treatment has the optimal effect on mortality rate and shortening the MV duration when the lungs have not been severely damaged and MV is not yet indicated. Our results based on these findings are in line with what Huang *et al*. concluded at the end of their report:[23] "*earlyandnon-delayedhemoperfusionmayeffectivelyimprovetheprognosisofsepticpatients*."

Another promising finding was the improvement in oxygenation after hemoperfusion. The PaO_2/FiO_2 ratio significantly increased in all patients after hemoperfusion, which is consistent with the results of previous animal and human studies.[15,23,24] In addition, this difference is more significant in patients who did not need MV during hospitalization than those who needed it, emphasizing the importance of the issue of time for hemoperfusion administration.

The results from the hematologic laboratory findings showed a significant increase in WBC count after hemoperfusion, which is in contradiction with previous results reported in the literature by Huang *et al*. They reported a significant drop in WBC count on day 7 post hemoperfusion compared to the baseline.[23] We speculate that this contradiction might be due to the administration of corticosteroids in our study, which leads to the de-margination of leukocytes and causes leukocytosis despite other signs for the downregulation of inflammation. However, future studies are required to further elucidate this concept.

Limitations

Hemoperfusion is an expensive treatment around the world. One of the limitations in the current study involved the lack of enough approved cartridges for hemoperfusion. Thus, we could not enroll a larger sample. Moreover, because of financial issues and laboratory kits' availability, some cytokine storm biomarkers, including IL6 and TNF-α, were not measured for almost all patients. In addition, small sample size and lack of power of statistical tests besides the nonstability of the results, especially in multivariate analyses, as well as the lack of generalizability are other limitations

CONCLUSION

It seems that applying hemoperfusion in the inflammatory phase of the disease, especially before the need for MV, reduces the need for MV and the duration of MV along with mortality rate in patients who have undergone MV. However, hemoperfusion does not have any effect on the duration of hospital and ICU stay. Regarding high cost and exist of some dangers, it seems it needs more studies with more sample size.

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Conflicts of interest

There are no conflicts of interest.

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