Blood Purification

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# Efficacy of Hemoperfusion in Severe and Critical Cases of COVID-19

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**Keywords**
COVID-19 · SARS-CoV-2 · Hemoperfusion · Acute respiratory distress syndrome · Cytokine storm

**Abstract**

***Introduction:*** Uncontrolled overproduction of inflammatory mediators is predominantly observed in patients with severe COVID-19. The excessive immune response gives rise to multiple organ dysfunction. Implementing extracorporeal therapies may be useful in omitting inflammatory mediators and supporting different organ systems. We aimed to investigate the effectiveness of hemoperfusion in combination with standard therapy in critically ill COVID-19 patients. ***Method:*** We conducted a single-center, matched control retrospective study on patients with confirmed SARS-CoV-2 infection. Patients were treated with hemoperfusion in combination with standard therapy (hemoperfusion group) or standard treatment (matched group). Hemoperfusion or hemoperfusion and continuous renal replacement therapies were initiated in the hemoperfusion group. The patients in the matched group were matched one by one with the hemoperfusion group for age, sex, oxygen saturation (SPO2) at the admission, and the frequency of using invasive mechanical ventilation during hospitalization. Two types of hemoperfusion cartridges used in this study were Jafron© (HA330) and CytoSorb® 300. ***Result:*** A total of 128 COVID-19-confirmed patients were enrolled in this study; 73 patients were allotted to the matched group and 55 patients received hemoperfusion. The median SPO2 at the admission day in the control and hemoperfusion groups was 80% and 75%, respectively ($p$ value = 0.113). The mortality rate was significantly lower in the hemoperfusion group compared to the matched group (67.3% vs. 89%; $p$ value = 0.002). The median

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length of ICU stay was statistically different in studied groups (median, 12 days for hemoperfusion group vs. 8 days for the matched group; $p < 0.001$). The median final SPO2 was statistically higher in the hemoperfusion group than in the matched group, and the median PaCO2 was lower. ***Conclusion:*** Among critically ill COVID-19 patients, based on our study, the use of hemoperfusion may reduce the mortality rate and improve SPO2 and PaCO2. 

## Introduction

On March 11, 2020, the World Health Organization declared COVID-19 a pandemic. Infected cases with COVID-19 represent a wide spectrum of symptoms ranging from mild to severe forms. Although the number of infected cases with mild or no symptoms is significant, COVID-19 leads to critical illness in some cases. Multiple organ failure can be expected among severe forms of infection with COVID-19. Therefore, extracorporeal organ support may be required [1, 2].

In some patients, the excessive immune response against SARS-CoV-2 results in a cytokine storm characterized by uncontrolled overproduction of proinflammatory cytokines (e.g., interferon γ, interleukin [IL-] 1B, IL-6, IL-12) [3]. Increased circulating levels of proinflammatory cytokines and chemokines may be associated with endothelial dysfunction and microvascular and macrovascular thrombosis [4]. Therefore, a cytokine storm may result in multiple organ failures, including acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI). Multiple organ failure is responsible for high mortality among at least severe cases of COVID-19 [5]. It has been shown that there is a positive association between mortality rate and levels of pro- and anti-inflammatory cytokines [6].

Based on the pathophysiology of COVID-19, implementing sequential extracorporeal therapies may have some beneficial effects on eliminating extra inflammatory mediators [7]. Hemoperfusion is an extracorporeal blood purification modality. Throughout the hemoperfusion process, anticoagulated blood is circulated through a sorbent containing cartridge (or column), and large endogenous and exogenous molecules including targeting cytokines, endotoxin, and virus particles are removed depending on the type of sorbent (e.g., pure resins, polymyxin-coated resins, or heparin-coated resins) [1, 8]. Hemoperfusion devices adsorb and remove both proinflammatory and anti-inflammatory cytokines nonselectively. Therefore, the other side of the coin is excessive immunosuppression or removing anti-inflammatory mediators [7]. A study by De Vriese et al. [9] showed that levels of proinflammatory and anti-inflammatory cytokines decreased significantly after performing continuous venovenous hemofiltration in patients with septic shock and AKI. However, based on a recent expert review, information regarding the fact that implementing hemoperfusion provides beneficial effects on quenching cytokine storm products is limited and sporadic.

The Emergency Use Authorization authority allowed FDA to grant temporary authorization for four hemoperfusion devices for treatment of severe COVID-19 with cytokine storm [10]. To date, there is no effective and promising treatment; hence, extracorporeal therapies may be a treatment option for improving COVID-19 outcomes and preventing organ dysfunction. We performed a matched control retrospective study to investigate the efficacy of hemoperfusion in combination with standard therapy in critically ill COVID-19 patients.

## Material and Methods

*Study Design*

We conducted a single-center, matched control retrospective study on cases with confirmed SARS-CoV-2 infection (positive reverse transcriptase polymerase-chain-reaction (RT-PCR) and positive computed tomography scan (CT scan) findings). The study's participants were selected by purposive sampling from those who were hospitalized between October 17, 2020 and January 17, 2021 at our hospital (a major referral medical center for COVID-19 outbreak). Inclusion criteria for selecting the patients for the hemoperfusion group were (1) adults ≥18 years old, (2) SPO2 ≤86% or respiratory rate ≥30, (3) diffuse bilateral pulmonary opacities without effusions in chest CT scan, (4) respiratory failure not fully explained by cardiac failure or fluid overload, (5) within 1 week of a known clinical insult or new/worsening respiratory symptom, and (6) hospitalization days ≤14 from the sign and symptom onset. The manifestations were including at least one of the radiation contactless body temperature ≥37.8, cough, shortness of breath, nasal congestion/discharge, myalgia/arthralgia, diarrhea/vomiting, headache, or fatigue on admission. Patients in the matched group also met the same criteria defined for the hemoperfusion group and were selected from the same patients within a similar time period. Patients in the matched group were also matched one by one with the hemoperfusion group for age (with a 3-year age difference or less), sex, SPO2 at the admission, and the frequency of using invasive mechanical ventilation during hospitalization. The study was approved by the Medical Research Committee for Research Ethics and signed informed consents were obtained from all patients or their legally authorized representatives. This study is registered with Iranian registry of clinical trials (IRCT), IR.SBMU.RETECH.REC.1399.582.

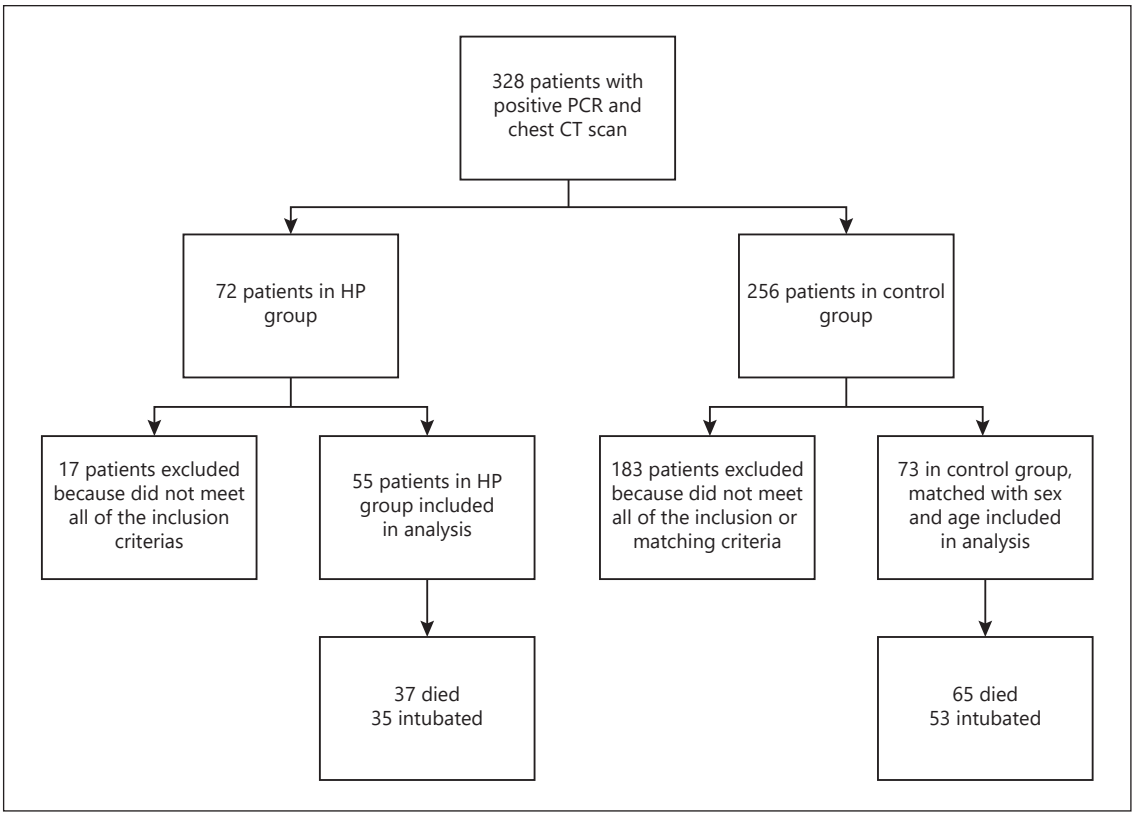


**Fig. 1.** Study flow diagram.

*Treatment*

Hemoperfusion and matched groups received IFN-β1a (Recigen) (subcutaneous injections of 44 μg (24,000 IU) on days 1, 3, 6) + remdesivir (200 mg first dose then 100 mg daily dose for 5 days) + methylprednisolone pulse therapy (1,000 mg for 3 days then 1 mg/kg twice daily) and standards of care including the necessary oxygen support, noninvasive, or invasive mechanical ventilation. In addition, Hemoperfusion or hemoperfusion and continuous renal replacement (CRRT) therapies were initiated in the hemoperfusion group.

Hemoperfusion treatment: The patients were administered hemoperfusion through femoral venous catheters at a blood flow rate of 250–300 mL/min. Two types of hemoperfusion cartridges used in this study were Jafron© (HA330) for 4 h or CytoSorb® 300 for 8–12 h.

Hemoperfusion + CRRT: Blood was filtered and returned to the patient with replacement fluid. The modality of CRRT was predilution continuous venovenous hemofiltration. The volume of the CRRT dose was adjusted according to individual patient requirements, nevertheless, the CRRT dose was usually 20–25 mL/kg per hour and access was achieved through a central venous catheter placed in one of the large central veins. The cartridges used in this method were Jafron© (HA330) for 8 h or CytoSorb® 300 for 12–24 h. Based on the improvement in patient's clinical status after hemoperfusion, including being able to reduce mechanical ventilation support in the intubated patients or improve SPO2 in nonintubated patients, the medical team decided to perform a second or third course of hemoperfusion.

Sodium heparin was used as an anticoagulant and administered as a bolus dose. Activated partial thromboplastin time ratio was tried to be maintained equal or less than 2. The loading dose of heparin in hemoperfusion therapy was 3,000–1,000 IU and the maintenance dose was between 1,000 and 2,000 IU per hour. The loading dose of heparin in hemoperfusion plus CRRT therapy was between 2,000 and 5,000 IU and the maintenance dose was between 500 and 1,000 IU per hour [11]. In patients with coagulopathy and patients treated with other anticoagulants, the heparin was not used.

*Outcome Measures*

We studied the clinical progression of two groups during their hospital admission. The mortality rate (if the patient died due to Covid-19 complications) in the late phase of admission (including the survival time), duration of hospitalization, intubation length, SP02, arterial blood gas findings, complete blood count findings, and, C-reactive protein (CRP) were compared between two groups.

*Statistical Analysis*

Frequencies and percentages were used for categorical variables, and interquartile ranges (IQRs) and median were used for

**Table 1.** Characteristics of the patients at baseline

| Parameters | Total (*n* = 128) | Hemoperfusion (*n* = 55) | Matched (*n* = 73) | *p* value |
|---|---|---|---|---|
| Characteristics | | | | |
| Age, mean (SD), year | 59.6 (10.9) | 57.5 (10.9) | 61.2 (11.2) | 0.052 |
| Male sex, *n* (%) | 82 (64.1) | 40 (72.7) | 42 (57.5) | 0.076 |
| Underlying conditions, *n* (%) | | | | |
| Diabetes | 45 (36.0) | 17 (31.5) | 28 (39.4) | 0.359 |
| Hypertension | 54 (43.9) | 17 (31.5) | 37 (53.6) | 0.014 |
| CVA | 4 (3.3) | 2 (3.7) | 2 (2.9) | 0.803 |
| CKD | 7 (5.7) | 1 (1.9) | 6 (8.7) | 0.134 |
| Ischemic heart disease | 22 (17.9) | 3 (5.6) | 19 (27.5) | 0.002 |
| Respiratory factors | | | | |
| SPO2, median (IQR) | 79 (68–84) | 75 (66.0–82.25) | 80 (70–85) | 0.113 |
| pH, median (IQR) | 7.4 (7.3–7.44) | 7.4 (7.33–7.43) | 7.4 (7.35–7.46) | 0.031 |
| PaCO2, median (IQR) | 38.2 (29.8–45.2) | 40.3 (33.8–47.05) | 36 (27.2–42) | 0.020 |
| HCO3(DISS), median (IQR) | 23.6 (21.1–27) | 23.8 (21.4–27.1) | 23 (20.2–26.9) | 0.561 |
| White blood cell count ($\times10^{-9}$/L), median (IQR) | 7.9 (5.5–11.0) | 7.3 (5.3.-11) | 7.9 (5.6–10.6) | 0.868 |
| <4, *n* (%) | 9 (7.5) | 4 (7.4) | 5 (7.6) | |
| 4–10, *n* (%) | 72 (61.7) | 31 (57.4) | 43 (65.2) | 0.64 |
| >10, *n* (%) | 37 (30.8) | 19 (35.2) | 18 (27.3) | |
| Lymphocyte count ($\times10^{-9}$/L), median (IQR) | 9.5 (5.5–14) | 10.4 (7.5–17.4) | 7.3 (4.9–12) | 0.001 |
| ≥1.0, *n* (%) | 35 (29.2) | 21 (38.9) | 14 (21.2) | 0.034 |
| <1.0, *n* (%) | 85 (70.8) | 33 (61.1) | 52 (78.8) | |
| Platelet count ($\times10^{-9}$/L), median (IQR) | 172 (125–233.5) | 184 (141–238) | 157 (120–231) | 0.083 |
| ≥100, *n* (%) | 102 (87.2) | 50 (94.3) | 52 (81.3) | 0.035 |
| <100, *n* (%) | 15 (12.8) | 3 (5.7) | 12 (18.8) | |
| CPK, median (IQR) | 1.43 (0.86–2.96) | 1.17 (0.73–2.66) | 1.65 (1.03–3.03) | 0.077 |
| ≤1.33 μmol/L, *n* (%) | 47 (44.8) | 24 (57.1) | 23 (36.5) | 0.037 |
| >1.33 μmol/L, *n* (%) | 58 (55.2) | 18 (42.9) | 40 (63.5) | |
| AST, U/L, median (IQR) | 61.5 (46.2–88) | 61 (46.2–88.7) | 61.5 (45.5–88) | 0.966 |
| ≤40, *n* (%) | 19 (15.8) | 9 (17.3) | 10 (14.7) | 0.699 |
| >40, *n* (%) | 101 (84.2) | 43 (82.7) | 58 (85.3) | |
| ALT, U/L, median (IQR) | 44.5 (28–66) | 45 (28–64.2) | 42 (27.7–66.7) | 0.870 |
| ≤50, *n* (%) | 73 (60.8) | 34 (65.4) | 39 (57.4) | 0.372 |
| >50, *n* (%) | 47 (39.2) | 18 (34.6) | 29 (42.6) | |
| LDH, U/L, median (IQR) | 747 (516–926) | 842 (556–1,035) | 700 (513–895) | 0.089 |
| ≤245, *n* (%) | 6 (5.5) | 4 (8.2) | 2 (3.3) | 0.262 |
| >245, *n* (%) | 104 (94.5) | 45 (91.8) | 59 (96.7) | |
| CRP, median (IQR) | 42 (27.3–56) | 42.3 (31–56) | 40.3 (22–56.4) | 0.488 |
| CRP <6, *n* (%) | 3 (3.5) | 1 (2.1) | 2 (5.3) | 0.436 |
| CRP >6, *n* (%) | 82 (96.5) | 46 (97.9) | 36 (94.7) | |
| ESR, median (IQR) | 48.5 (31.7–60.2) | 48.5 (33–61.5) | 47.5 (28.2–58.2) | 0.383 |
| Ferritin, median (IQR) | 622 (502–774) | 614 (513–656) | 668 (500–809) | 0.074 |

CVA, cerebrovascular accident; CKD, chronic kidney disease; CPK, creatine phosphokinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate.

continuous variables. For comparison of the non-normal continuous variables, Mann-Whitney U test was used. The $\chi^2$ test was used for comparing the frequency of categorical variables. Cox proportional hazard regression model and Kaplan-Meier curve (with log-rank test) were also applied to calculate the hazard rate (HR) with 95% confidence intervals (CIs). STATA software version 14.0 was used to perform the statistical analyses and 0.05 was considered a statistically significant level.

## Results

### *Patients*

Of all recruited patients (*n* = 128), 55 patients received hemoperfusion (3 of these patients received hemoperfusion and CRRT) and 73 patients were allotted to the control group who were matched for age, gender, SPO2, and

**Table 2.** Clinical outcomes of patients in the matched group and patients in the hemoperfusion group

| Parameters | Total (*n* = 129) | Hemoperfusion (*n* = 55) | Matched (*n* = 74) | *p* value |
|---|---|---|---|---|
| Mortality, *n* (%) | 102 (79.7) | 37 (67.3) | 65 (89.0) | 0.002 |
| ICU stay, median no. of days (IQR) | 10 (6–13) | 12 (9–17) | 8 (4.5–10.5) | <0.001 |
| Intubation | 88 (69.3) | 35 (64.8) | 53 (72.6) | 0.347 |
| Intubation length, median no. of days (IQR) | 6 (3–8) | 8 (5.7–14) | 4 (2–7) | <0.001 |
| Sepsis | 38 (34.9) | 15 (40.5) | 23 (31.9) | 0.373 |
| Respiratory factors | | | | |
| SPO2, median (IQR) | 70 (60.7–80.2) | 80 (73–85) | 64 (60–70) | <0.001 |
| pH, median (IQR) | 7.3 (7.2–7.4) | 7.4 (7.3–7.4) | 7.3 (7.2–7.4) | 0.105 |
| PaCO2, median (IQR) | 46.7 (36.2–61.2) | 42.9 (33.1–50.3) | 53 (39.5–65) | 0.006 |
| HCO3, median (IQR) | 23.1 (19.8–26.8) | 23.4 (20.3–27) | 22.3 (17.1–26) | 0.207 |
| White blood cell count ($\times 10^{-9}$/L), median (IQR) | 10.9 (8.3–14.6) | 12.2 (9–15.6) | 10.5 (7.9–14.5) | 0.382 |
| <4, *n* (%) | 9 (7.3) | 5 (9.3) | 4 (5.7) | |
| 4–10, *n* (%) | 41 (33.1) | 15 (27.8) | 26 (37.1) | 0.47 |
| >10, *n* (%) | 74 (59.7) | 34 (63.0) | 40 (57.1) | |
| Lymphocyte count ($\times 10^{-9}$/L), median (IQR) | 7.7 (4.5–12.6) | 5.8 (3.8–11.3) | 10 (5.7–13) | 0.024 |
| ≥1.0, *n* (%) | 51 (42.9) | 19 (35.2) | 32 (49.2) | 0.123 |
| <1.0, *n* (%) | 68 (57.1) | 35 (64.8) | 33 (50.8) | |
| Platelet count ($\times 10^{-9}$/L), median (IQR) | 182 (128–250) | 170 (104–231) | 196 (147–235) | 0.101 |
| ≥100, *n* (%) | 101 (82.1) | 41 (75.9) | 60 (87.0) | 0.113 |
| <100, *n* (%) | 22 (17.9) | 13 (24.1) | 9 (13.0) | |
| CRP, median (IQR) | 44 (19.5–62.2) | 19.9 (7.7–38.5) | 59 (42.9–87.7) | <0.001 |
| CRP <6, *n* (%) | 12 (12.2) | 9 (22.0) | 3 (5.3) | 0.013 |
| CRP >6, *n* (%) | 86 (87.8) | 32 (78.0) | 54 (94.7) | |

incubation rate with the hemoperfusion group. The flowchart for the study was depicted in Figure 1. The mean (SD) age of the total participants was 59.6 (10.92). The distribution of male and female gender was 64.1% and 35.9%, respectively. No significant difference was observed in terms of age and gender between the hemoperfusion and matched control group. Table 1 outlines demographic and baseline clinical factors in two studied groups. Although the majority of clinical factors did not reach a significant difference between the two groups, hypertension rate, ischemic heart disease as the underlying conditions, pH, PaCO2, lymphocyte count, platelet count, and creatine phosphokinase were significantly different between the two studied groups (Table 1). Fifty-one patients (92%) in the hemoperfusion group and 27 patients (37%) in the controls received tocilizumab (*p* value <0.001). Other treatments were not significantly different between the two studied groups.

*Outcomes Finding*

The total number of deaths in our study was 102 (70.9%). In the hemoperfusion group, the mortality rate was significantly lower as opposed to the matched control group (67.3% vs. 89%; *p* value = 0.002). Although the percentage of receiving tocilizumab treatment was significantly different between the two groups, subgroup analysis indicated no significant association between tocilizumab and mortality in both groups. In the hemoperfusion group, the mortality rate for recipients of tocilizumab (68.8%) and other patients not treated with tocilizumab (50%) was not significantly different (*p* value = 0.59). Similar to the hemoperfusion group, in the control group, the mortality rate could not hold a significant difference between patients treated with tocilizumab (92.6%) and those who did not receive tocilizumab (87%).

As outlined in Table 2, the median length of ICU stay and duration of incubation was significantly higher in the hemoperfusion group. Final SPO2 was significantly higher in the hemoperfusion group whilst PaCO2 was found to be lower in this group compared to the control group. In addition, CRP was also different between the two groups (Table 2).To evaluate the effect of hemoperfusion on survival of severe COVID-19 patients, the log-rank test was conducted on the survival time of hospitalized patients which was statistically different between two groups (median, 12 days for the hemoperfusion group vs. 8 days for the control group; $p < 0.001$), and the Kaplan-

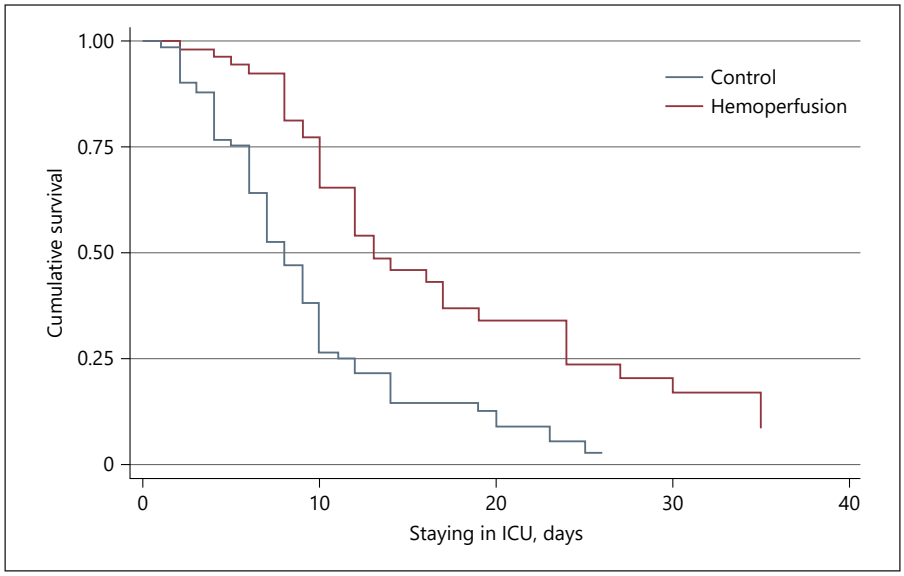


**Fig. 2.** Kaplan-Meier curve for cumulative survival of patients in the control group versus patients in the hemoperfusion group.

Meier curve indicated that the cumulative survival was higher for patients in the hemoperfusion group compared to their matches (Fig. 2).

*Treatment*

Of 55 patients in the hemoperfusion group, the number of patients who received one, two, and three or four courses of hemoperfusion was 18 (32.7%), 14 (25.4%), and 23 (41.9%), respectively. The number of patients who received hemoperfusion with cartridges 300 and 330 was 9 and 46, respectively. The number of deaths among patients who had cartridge 300 was 4 (44.4%) and the respective number for patients who had cartridge 330 was 14 (30.4%). No significant association was found between cartridge type and mortality rate in the hemoperfusion group.

The Cox regression model was employed to calculate the hazard of death for patients in the matched group compared to the hemoperfusion group. Analyses were done in crude and adjusted models. Two significant underlying diseases (hypertension and ischemic heart disease) were not included in the multivariate model since the Cochran's Mantel-Haenszel test indicated conditional independence across these two underlying diseases for both hypertension ($p$ value = 0.646) and ischemic heart disease ($p$ value = 0.400), but age, sex, SPO2, and lymphocyte count at the baseline were included as the adjusting factors. According to the analysis in the crude model, the HR of death in matched groups compared to the hemoperfusion group was 2.54 (95% CI: 0.1.67–3.87, $p < 0.001$) and the adjusted HR was 2.39 (95% CI: 1.49–3.83, $p < 0.001$). Both crude and adjusted analyses revealed that patients who were treated in the matched group were at a higher risk of death compared to patients who were treated in the hemoperfusion group.

## Discussion

Hemoperfusion has been suggested as an effective treatment for COVID-19 patients in conjunction with other conventional remedies. In this study, the hemoperfusion group exhibited higher SP02 but lower PaCO2 and CRP levels compared to the matched control group. An interesting finding of this study was that a lower mortality rate was observed among the patients in the hemoperfusion group. Jafron® and CytoSorb® are two different models of hemoperfusion cartridges. Although they employ a different methodology for performing hemoperfusion, their cartridge efficacy has not been compared so far in a study.

Cytokine storm and intensive immune responses have been addressed as the root causes of a severe form of COVID-19 infection [12]. It has been observed that cytokine storm plays a crucial role in exerting end-organ damage and increased mortality rate among patients with COVID-19. Of all series of cytokines, IL-1, IL-6, IL-10, and TNF-β are the most remarkable inflammatory factors through the cytokine storm phenomenon [13–15]. In addition, IL6 has been shown to play the most important

role in cytokine storms, patient mortality, and disease severity [16]. In the early stages of COVID-19, increased levels of CRP may be associated with severe pulmonary complication like ARDS [17]. Therefore, timely clearance of cytokines and inflammatory factors may decrease patients' complications and mortality in COVID-19 infection [18].

Hemoperfusion, an extracorporeal blood purification modality, is used for circulating patients' anticoagulated blood through a circuit containing an absorbent filter that reduces toxic agents and inflammatory factors like inflammatory cytokines [1, 19]. The absorbent system in hemoperfusion is usually a cartridge that has been loaded with absorbent ingredients including charcoal (for water-soluble materials) and resins (for lipid-soluble materials) [20]. HA 330 and HA 380 cartridges are two types of hemoperfusion cartridges that are used in inflammatory conditions. These cartridges have the capability of inflammatory cytokines absorption [21]. In addition, HA 280 cartridges are capable to absorb smaller particle size [22]. In the current study, Jafron® (HA 330) and CytoSorb® 300 cartridges were used for hemoperfusion. In a systematic review in 2013 by Borthwick et al. [23], it has been suggested that hemoperfusion may have significant effects on ICU stay and mortality rate in sepsis patients. In addition, in the pandemic era, there are some studies that have suggested the positive effects of hemoperfusion in COVID-19 patients [24, 25]. In a study by Vardanjani et al. [26], hemoperfusion and CRRT therapies were effective in ceasing ARDS progression, decreasing patient intubation and patient's oxygen dependency in addition to their preventive effects on AKI and septic shock. Moreover, they reduced mortality and length of hospital stay [26]. In the study by De Rosa et al. [27], hemoperfusion with polymyxin in COVID-19 patients with endotoxic shock was associated with organ function recovery and hemodynamic improvement.

This study was in the same line as the results of previous studies. In the current study, the mortality rate was significantly lower in the hemoperfusion group compared to the matched group. Furthermore, it was observed that SPO2 may be improved significantly after performing hemoperfusion in COVID-19 patients. In this study, the median length of hospital stay was lower in the matched group. However, based on the Kaplan model, we could find that the cumulative survival of patients in the hemoperfusion group was associated with the median length of hospital stay.

Our study's major strength was the high sample size of the hemoperfusion group. A study by Asgharpour et al. [28] was conducted on 10 patients, whereas the current study was conducted on 55 patients which is the highest sample size in the literature. In addition, considering the high costs of hemoperfusion for the patients, we could not implement this treatment option for every patient due to ethical considerations, and this may be the reason for the lack of a high-sample clinical trial in this regard.

This treatment option was used in this study as a salvage treatment option in the accompaniment of the final-stage treatments. The hemoperfusion group and matched group in this study were not homogeneous. Some patients in this study received tocilizumab which can affect the mortality of patients [29]. Moreover, patients in this study received different courses of hemoperfusion (not the same in the number and length of sessions) by two different cartridges. As shown in this study, hemoperfusion by Jafron® 330 cartridge had lower mortality compared to CytoSorb® cartridge; however, it failed to reach a significant difference. The results may be changed in future studies with homogeneous and higher sample sizes.

*Limitation*

Our data collection depended on physicians' completion because our study was a retrospective study. This study was not a randomized clinical trial; therefore, there were no exact inclusion and exclusion criteria. It was not possible to analyze arterial blood gas for some patients because of technical procedures and trained staff limitations. In this study, two types of hemoperfusion cartridges were used due to lack of access to a certain type of hemoperfusion cartridge at various times. In this study, the level of IL-6 was not evaluated.

## Conclusion

Among critically ill COVID-19 patients, we found a significant reduction in mortality rate and improvement of SPO2 and PCO2 in the hemoperfusion group. Future randomized controlled clinical trials are needed to evaluate the efficacy of hemoperfusion.

## Acknowledgments

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, for their help and support in conducting this study.

## Statement of Ethics

The study was confirmed by the Ethics in Medical Research Committee of the Shahid Beheshti University of Medical Sciences. This study is registered with IRCT (Iranian registry of clinical trial), IR. SBMU.RETECH.REC.1399.582. Signed informed consents were obtained from all the participants or their legally authorized representatives. The research was conducted ethically in accordance with the World Medical Association and Declaration of Helsinki.

## Conflict of Interest Statement

We declare no competing interests.


## Funding Sources

Not applicable.


## Author Contributions

Ilad Alavi Darazam, Firouze Hatami, Mohammad Mahdi Rabiei, Muhanna Kazempour, Davoud Rangraz, Hassan Falahaty, Hosein Syami, Yaghoob Irannejad, and Maryam Fallah contributed to the acquisition of data; Ilad Alavi Darazam and Mohamad Amin Pourhoseingholi contributed to the analysis of data; Farid Javandoust Gharehbagh, Mahdi Amirdosara, Mohammadreza Hajiesmaeili, Minoosh Shabani, Shervin Shokouhi, Masoud Mardani, Maryam Haghighi-Morad, Masoud Zangi, Amir Ahmad Nassiri, and Navid Shafigh contributed to the drafting of the article and/or critical revision; and Ilad Alavi Darazam, Mohammad Mahdi Rabiei, Firouze Hatami, and Legha Lotfollahi contributed to the final approval of manuscript.

## Data Availability Statement

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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