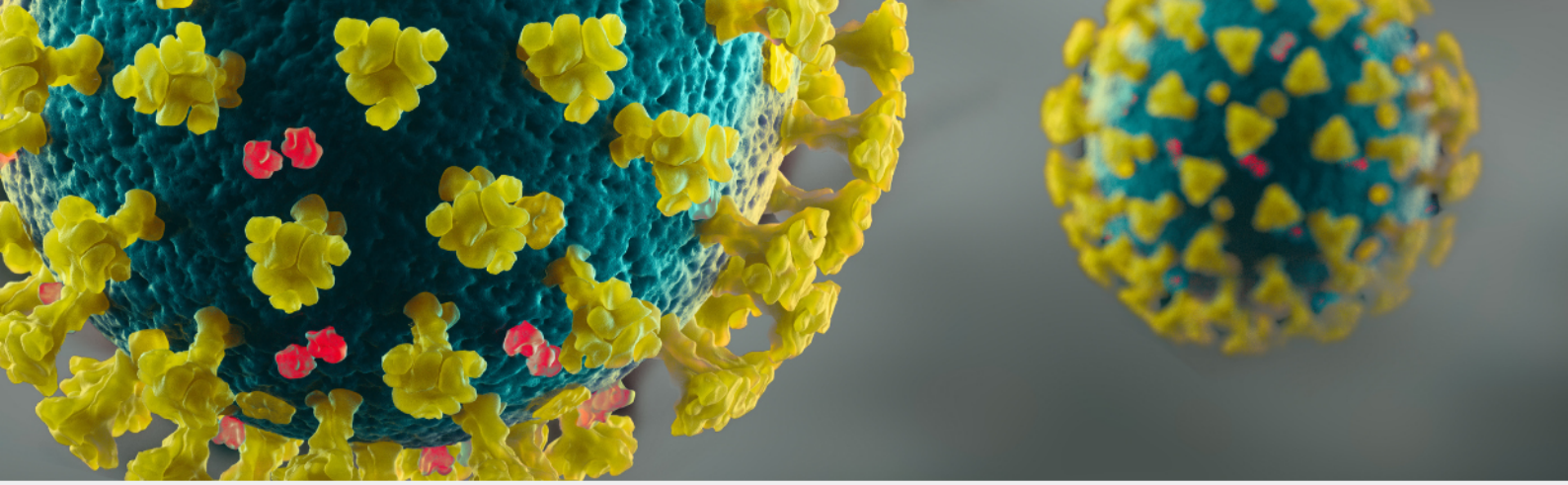

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REVIEW

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Investigation of plasma exchange and hemoperfusion effects and complications for the treatment of patients with severe COVID-19 (SARS-CoV-2) disease: A systematic scoping review

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Abstract

Some previous studies suggested that the plasma exchange (PE) and hemoperfusion (HP) played a cardinal role in the treatment of severe coronavirus disease 2019 (COVID-19) cases by diminishing the cytokine storm. This study aimed to assess the effects of PE and HP on cytokine storms in patients with severe COVID-19 through a systematic scoping review. Four Electronic databases (Medline [accessed from PubMed], Scopus, Science Direct, and Cochrane library) were searched systematically on February 2, 2021, using MESH terms and related keywords in the English language. Considering the titles and abstracts, unrelated studies were excluded. The full texts of the remained studies were evaluated by authors, independently. Then, their findings were assessed and reported. A total of 755 articles were obtained within the first step of searching, and 518 remained after removing the duplications. Through the title and abstract screening, 438 were removed. Of the rest, 59 papers were excluded. Finally, after reading the full text of the remained articles, 21 were included in data extraction. Most of the previously reported evidence were case reports and case series. Findings were summarized in two categories. The first category encompassed nine studies regarding HP and continuous renal replacement therapy, and the second category included twelve studies about PE. The results revealed that HP and PE within the cytokine storm phase would be beneficial with a high probability in the treatment of severely ill COVID-19 patients.

Highlights Some studies showed that plasma exchange (PE) and hemoperfusion (HP) played an important role in the treatment of patients with severe COVID-19 disease. The results of this systematic scoping review revealed that HP and PE within the cytokine storm phase would be beneficial with a high probability in the treatment of severely ill COVID-19 patients.

KEYWORDS

coronavirus, COVID-19, hemoperfusion, plasma exchange, plasmapheresis, renal replacement therapy

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is caused by a new variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The current outbreak was first reported in Wuhan, China in December 2019. The infection has since spread rapidly worldwide. According to a recent World Health Organization report, 110,749,023 definite cases of COVID-19, including 2,455,131 deaths, were observed until February 21, 2021. Currently, the mortality rate of COVID-19 is estimated from 1.36% to 15%.[1–3] Individuals can be infected with SARS-COV-2 for the second time as well.[4] COVID-19 has no definitive treatment. Remdesivir, favipiravir, and corticosteroids have been suggested for moderate to severe cases to date.[5]

Recent evidence suggests that an immune response in severely ill individuals is responsible for acute respiratory distress syndrome and multiple organ failures.[6,7] A cytokine surge, also called hypercytokinemia is also the main cause of death in SARS, MERS, H5N1, and H7N9 infections.[6–8] Cytokine release syndrome (CRS) is increasingly being diagnosed in a variety of conditions, including COVID-19, and can cause severe symptoms of systemic inflammation. CRS can create hematological complications and affect different parts of the coagulation pathway, including the endothelial cells, platelets, coagulation cascade, and fibrinolytic system. Various underlying causes of CRS like primary hemophagocytic lymphohistocytosis, chimeric antigen receptor T-cell therapy, and COVID-19, have different cytokine profiles and coagulopathy presentations, with microvascular thrombosis and superficial microcoagulation known as the most common pathologies, respectively. Therefore, timely control of cytokine storms and decreasing inflammatory cell infiltration in the lungs is key to reducing COVID-19-associated mortality.[9]

Treatment strategies with antibodies, such as tocilizumab, sarilumab, siltuximab, and blood-purification techniques, including therapeutic plasma exchange (PE), absorption, perfusion, and blood plasma filtration, are likely to be more beneficial for COVID-19.[10–13] PE replaces patient's plasma with another fluid, such as allogeneic plasma maintaining homeostasis by eliminating excess cytokines and modifying the coagulation factors. This is a standard treatment for a subtype of thrombotic microangiopathy, thrombocytopenic purpura, through the elimination of ADAMTS-13 inhibitors.[14] PE has also shown some degrees of success in disseminated intravascular coagulation (DIC),[15,16] which can occur as a complication of COVID-19. It has been reported that PE can prevent the progression of the disease.[17]

Although there are vaccines available in many countries, there are some limitations in other regions due to some issues.[18] Hence, physicians are still dealing with severe COVID-19 patients who need more complex treatments. Based on a preliminary search in PubMed and Cochrane Database of Systematic Reviews, there is no systematic review regarding the treatment of COVID-19 with "hemoperfusion," or "plasma exchange," or "plasmapheresis." Hence, this review was aimed to evaluate the effects of PE and hemoperfusion (HP) on cytokine storm in patients with severe COVID-19. The findings would help physicians to find guidance in the appropriate COVID-19 treatment strategy in the cytokine storm phase.

2 | MATERIALS AND METHODS

The present systematic scoping review was conducted based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews statement.[19]

As shown in Figure 1, a multi-step search strategy was performed. The electronic literature searches were conducted to identify all studies in the field of treatment of COVID-19 with "hemoperfusion" or "plasma exchange," or "plasmapheresis." Hence, Medline (accessed from PubMed), Scopus, Science Direct, and Cochrane
library were four databases taken into account for systematic searching till February 2, 2021, by two authors (RSM, MR). Google search engine was also reviewed manually to explore the gray literature (RSM). Table 1 shows the search strategy for PubMed, Scopus, Science Direct, and Cochrane library. To ensure literature saturation, the reference lists of the included studies or relevant reviews identified through the search were scanned. No time restriction was considered for the searching, and all searching was done in English.

Studies, which were not relevant to the study's aim, written in non-English language, or considered other coronaviruses except COVID-19, studies without any specific patient's data, as well as not available full-text were excluded, through reading the title and the abstract (MR, AF, FH). Also, we excluded the studies that evaluated renal replacement therapy in patients with raised creatinine or acute kidney injury.

Then, two authors evaluated the full texts of the obtained studies, independently, and they decided whether these papers met the inclusion criteria or not (MR, AF). Disagreements were resolved by discussion between all authors, and eventually, the articles were selected based on consensus. None of the authors was blind to the titles of the journals or to the authors or institutions of the studies. Then, the level of evidence of each study was determined.[20] The following data were extracted from the included studies: study authors, time of publishing, study designs, population and sample size, treatment, main findings, complications, and limitations. A data extraction form was designed in a Microsoft Excel sheet 2013, and two authors extracted the data, independently (AF, FH, DK). The discrepancies were resolved, and then the obtained results were summarized (RSM).

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

3 | RESULTS

A total of 755 articles (160 from Medline, 242 from Scopus, 336 from Science Direct, and 17 from Cochrane Database of Systematic Reviews, as well as 21 from gray literature) were selected through the first step of searching. Then, 518 articles were assessed after duplications deletion. In the title and abstract screening, 438 studies were removed. Of the rest, 59 papers were excluded in the next

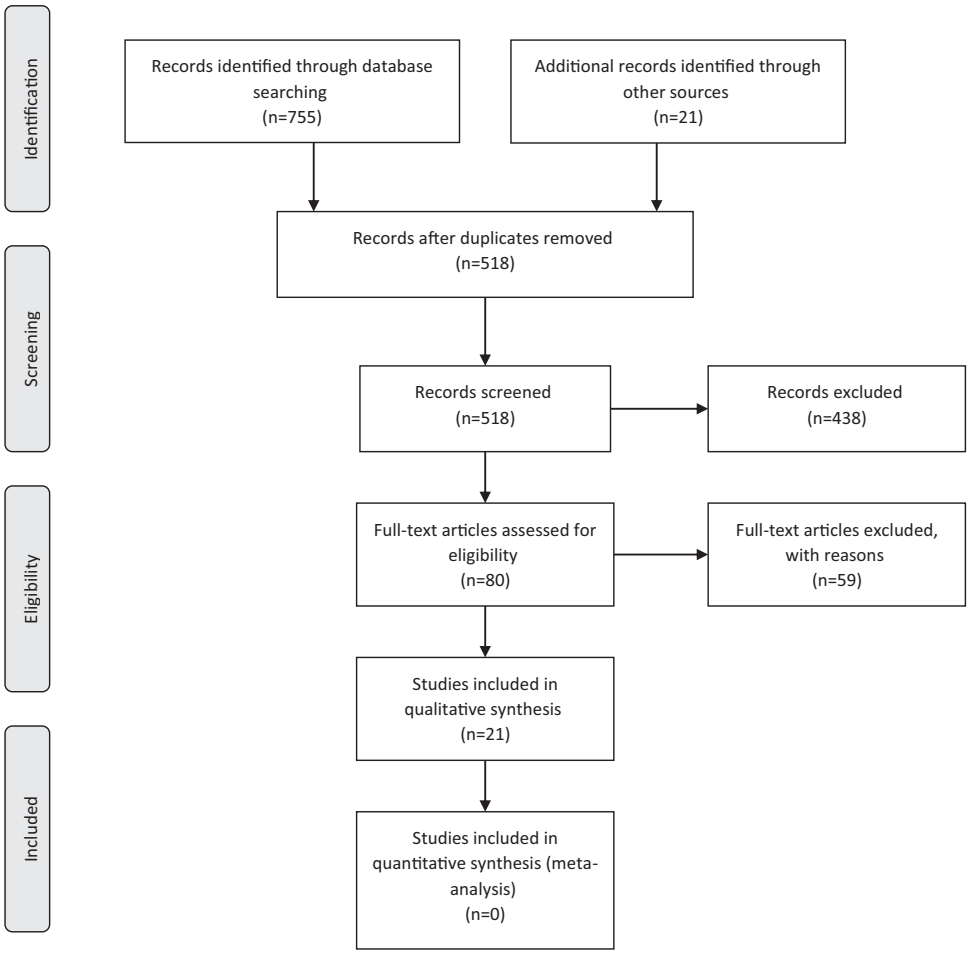

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the study

TABLE 1 Search strategy used in the present study

Database	Search strategy	Results
PubMed	([hemoperfusion] OR ["Plasma exchange"] OR ["Plasmapheresis"]) AND (COVID) ("haemoperfusion" [All Fields] OR "hemoperfusion" [MeSH Terms] OR "hemoperfusion" [All Fields] OR "haemoperfusions" [All Fields] OR "hemoperfusions" [All Fields] OR "Plasma exchange" [All Fields] OR "Plasmapheresis" [All Fields]) AND ("sars cov 2" [MeSH Terms] OR "sars cov 2" [All Fields] OR "covid" [All Fields] OR "covid 19" [MeSH Terms] OR "covid 19" [All Fields]) Translationshemoperfusion: "haemoperfusion" [All Fields] OR "hemoperfusion" [MeSH Terms] OR "hemoperfusion" [All Fields] OR "haemoperfusions" [All Fields] OR "hemoperfusions" [All Fields]COVID: "sars-cov-2" [MeSH Terms] OR "sars-cov-2" [All Fields] OR "covid" [All Fields] OR "covid-19" [MeSH Terms] OR "covid-19" [All Fields]	160
Scopus	(TITLE-ABS-KEY (haemoperfusion) OR TITLE-ABS-KEY ("Plasma exchange") OR TITLE-ABS-KEY (plasmapheresis) AND TITLE-ABS-KEY (covid))	242
Science Direct	hemoperfusion covid "Plasma exchange" covidPlasmapheresis covidTotal	17183136336
Cochrane	hemoperfusion covid "Plasma exchange" covidPlasmapheresis covid	17

level. Eventually, after reading the full text of these articles, 21 articles were included for the final data extraction.[13,21–40] Inter-rater agreement following the first round of screening between the two investigators was 94.26% (Cohen's $k = 0.55$). Within the second round of screening, inter-rater agreement rose to 100%. Our investigation illustrated that the most of available reported evidence was basically case reports and case series, and they did not have high quality. Also, the studies used various methods and did not have enough data homogeneity for meta-analysis. For instance, the number of sessions and hours per session for each of both treatments were different in available studies. Furthermore, the filters used in the HP treatments were also different.

Results were summarized in two categories: (1) HP and continuous renal replacement therapy (CRRT); (2) PE.

3.1 | Hemoperfusion and continuous renal replacement therapy

With respect to HP and CRRT treatments for COVID-19 patients with severe conditions, nine studies were enrolled, in which 1/8 was a controlled trial,[21] 4/8 were case series,[27,29,34,36] and 4/8 were case reports[13,32,35,39] (Table 2).

Asgharpour et al.[21] conducted a study on ten confirmed critically ill COVID-19 patients (5/10 men and 5/10 women) through a non-randomized and non-blinded controlled trial study. Three sessions (14–18 h per day) of resin-directed HP using CRRT with a mode of continuous venovenous hemofiltration were administered for all of them. A resin-directed hemoadsorption cartridge (HA-280 and HA-230) was applied. Peripheral capillary oxygen saturation (SpO_2) increased significantly following the intervention (from 89.6% ± 3.94% to 92.13% ± 3.28%), but the mode of oxygen therapy was not effective. In addition, C-reactive protein (CRP) decreased significantly but the reduction of serum interleukin-6 (IL-6) was not significant. Finally, 6/10 patients improved after the intervention. The authors concluded that extracorporeal hemoadsorption might improve the general condition in most of the patients with severe COVID-19.

Rampino et al.[36] reported nine (5 individuals as cases vs. 4 ones as control) critically ill patients with severe COVID-19 treated with and without HP for 4 h sessions in 2 consecutive days. It was performed before the occurrence of renal failure, in adjunction to standard antiviral and supportive therapies. HP was started 6–7 days after hospital admission in all patients. The level of CRP decreased in both groups, but to a greater extent after HP. Lymphocytopenia and procalcitonin worsened in control groups. Respiratory function remained stable in both groups. No complications (such as clotting, vascular access problems, and bleeding) were detected. The level of serum pro-inflammatory cytokines (IL-6, tumor necrosis factor α [TNF-α], and IL-8) were reduced in all survived patients in the treatment group. IL-10 did not change in both groups. All patients survived, except 1/9. Two of nine patients needed to be intubated. After 2 months, all treated and survived patients were discharged with good clinical conditions.

De Rosa et al.[29] used extracorporeal endotoxin removal by polymyxin B HP (2 sessions, every 24 h which was lasted 120 min) for 12 patients. But, 1/12 patients died and could not receive the second session. Heparin 2500 IU (0–4250) as intravenous bolus and 19.25 (14.5–20) IU/kg/h as continuous infusion was administrated. Septic shock was diagnosed in 9/12 patients, in whom Gram-negative bacteria were found in most of the microbiological cultures. Nine out of 12 patients needed CRRT due to acute kidney injury. The sequential organ failure assessment (SOFA) score and hemodynamic conditions improved over the next 120 h. Furthermore, lung injury score and endotoxin activity assay decreased showing the recovery of organ function. No related complications, such as bleedings and cartridge clotting, were reported.

In another case series by Shadvar et al.,[27] eight critically ill COVID-19 patients fulfilled at least two items of the criteria for the cytokine storm phase, 4/8 patients were intubated. HP with Jafron hemoabsorber (HA380 Disposable HP Cartridge) (6–8 h daily for 3 consecutive days) was applied in the first 48 h after intensive care unit (ICU) admission with different sessions. Although 3/8 patients died, improvements in the levels of inflammatory, respiratory, and perfusion parameters were observed. Incremental dosage of anticoagulation both to maintain circuit patency and to manage the thrombophilia, as well as low molecular heparin 10 IU/kg/h were administrated, but in some patients, a higher dosage of up to 20 IU/kg/h may be required.

Twelve confirmed severe acute COVID-19 patients, who received polymyxin B-immobilized polystyrene column with Toraymyxin PMX-20R at a blood flow rate of 100 ml/min (3 h on two consecutive days for each patient), reported in a case series by Katagiri et al.[34] Anticoagulation therapy was performed by Nafamostat mesylate (30 mg/h) or 50 U/kg/h of low molecular-weight heparin (LMWH). Eight of the 12 patients did not receive systemic LMWH; 4/12 patients received systemic LMWH therapeutic dose, without any stated reason by authors. Circuit coagulation occurred for the 2/4 patients who received LMWH, and both of them had high levels of D-dimer. Although 1/12 patients died, it was reported that PMX-DHP could be completed without any serious problem. HP could increase the P/F ratio and decrease the levels of urine β2MG, urinary L-FABP l, PDGF-BB, RANTES, VEGF, and IL-6 levels. However, the levels of IL-8 and IL-10 remained almost unchanged or tended to decrease.

Four other case reports described patients, who were treated with HP, and all of them were discharged from the hospital with good conditions.[13,32,35,39]

3.2 | Plasma exchange

Twelve studies were enrolled in this category and PE was introduced as a therapeutic strategy for critically ill patients with COVID-19. This category included 1/12 clinical trial,[24] 1/12 cohort,[26] 1/12 case-control,[22] 5/12 case series,[23,25,28,38,40] and 4/12 case reports[30,31,33,37] (Table 3).

Plasmapheresis was performed by Hashemian et al. for fifteen critically ill adult patients with confirmed COVID-19, whose clinical condition did not improve.[24] Plasmapheresis (6 h per day, three times overall) was administrated for the patients via femoral venous catheters using a hemodialysis machine. The lymphocyte level was increased and the clinical course improved one week after plasmapheresis. Also, the levels of TNF-α and IL-6 as an inflammatory cytokine, as well as acute-phase reaction proteins, such as ferritin and CRP levels, PaO_2/FiO_2, liver enzymes, and bilirubin were significantly diminished. Although the number of T helper cells decreased immediately after the intervention, they increased after 1

TABLE 2 An overview of studies on hemoperfusion (HP) and continues renal replacement therapy (CRRT) for treatment of patients with coronavirus disease 2019 (COVID-19)

Study authors (year)	Title	Country	Type of study	Population and sample size	Treatment	Main results	Death	Complication	Level of evidence
Asgharpour M, et al. (2020) [21]	Effectiveness of extracorporeal blood purification (hemoadsorption) in patients with severe coronavirus disease 2019 (COVID-19).	Iran	Nonrandomized and non-blinded controlled trial	Ten critically ill COVID-19 patients (5 men and 5 women)	HP of resin-directed for three sessions (14–18 h per day) using CRRT with a mode of CVVH, resin-directed hemoadsorption cartridge (HA-280 and HA-230)	Increasing the peripheral capillary oxygen saturation (SpO_2) (from 89.6%±3.94% to 92.13% ±3.28%). Reduction in CRP. Reduction of serum IL-6 was not significant.6/10 patients have improved after the intervention.	0/10	NR	III
Rampino T, et al. (2020) [36]	Hp with Cytosorb as adjuvant therapy in critically ill patients with SARS-COV2 pneumonia,	Italy	Case series	Nine critically ill patients with severe COVID-19, who were treated with and without HP (5 as case vs. 4 as control)	HP using multiFiltrate machine and CytoSorb cartridge for 4 h sessions in 2 consecutive days, before the occurrence of renal failure.	Reduction in the level of CRP in both groups, but to a greater extent after HP. Worsening of lymphocytopenia and procalcitonin in control groups. Respiratory function remained stable in both groups. Reduction in the level of serum pro-	1/9	No complications (clotting, vascular access problems, bleeding) were detected.	VI

TABLE 2 (Continued)

Study authors (year)	Title	Country	Type of study	Population and sample size	Treatment	Main results	Death	Complication	Level of evidence
						inflammatory cytokines (IL-6, TNF-α, and IL-8) in all survived patients in treatment group.			
De Rosa S, et al. (2020) [29]	Polymyxin B HP in coronavirus disease 2019 patients with endotoxic shock: case series from EUPHAS2 registry	Japan	Case series	Twenty patients with COVID-19	Polymyxin B HP (2 sessions, every 24 h and last 120 min)	Improvement in SOFA score and hemodynamic over the next 120 h. Decreasing in Lung Injury Score (LIS) and endotoxin activity assay (EAA).	1/12	Septic shock in 9/12 patients, which Gram-negative bacteria. 9/12 patients needed CRRT due to acute kidney injury. Bleedings and cartridge clotting were not observed.	VI
Shadvar K, et al. (2020) [27]	HP as a potential treatment for critically ill COVID-19 patients with cytokine storm.	Iran	Case series	Eight critically ill COVID-19 patients with at least two of the criteria of cytokine storm	HP with Jafron hemoabsorber (HA380 Disposable HP Cartridge) (6–8 h daily for 3 consecutive days) in the first 48 h after ICU admission. It was combined with RRT in 2/8 patients.	Improvement in levels of inflammatory, respiratory, and perfusion parameters	3/8	NR	VI
Katagiri D, et al. (2020) [34]	Direct HP using a polymyxin B-immobilized polystyrene	Japan	Case series	Twelve confirmed severe acute COVID-19 patients with	Polymyxin B-immobilized polystyrene column with	Increasing the P/F ratio. Reduction in the levels of	1/12	NR	VI

(Continues)

TABLE 2 (Continued)

Study authors (year)	Title	Country	Type of study	Population and sample size	Treatment	Main results	Death	Complication	Level of evidence
	column for COVID-19.			a partial pressure of arterial oxygen/ percentage of inspired oxygen (P/F) ratio <300	Toraymyxin PMX-20R at a blood flow rate of 100 ml/min (3 h on two consecutive days for each patient)	urine β2MG, urinary L-FABP I, PDGF-BB, RANTES, VEGF, and IL-6 levels. The levels of IL-8 and IL-10 remained almost unchanged or trended downward.			
Esmaeili VA, et al. (2021) [13]	Early HP for cytokine removal may contribute to the prevention of intubation in patients infected with COVID-19.	Iran	Case report	One critically ill COVID-19 patient	HP with HA280 cartridge (Jafron Biomedical) in combination with CRRT for four sessions.	Increasing O_2 saturation reached to 95%. Reduction in the serum levels of creatinine and BUN.	0/1	NR	VI
Moradi H, et al. (2020) [35]	HP as a supportive treatment in a COVID-19 patient with late pulmonary thromboembolism: A case report	Iran	Case report	One critically ill COVID-19 patient	HP (HA230 cartridge, Jafron) for 4.5 h.	Improvement of the symptoms and SOFA score. Reduction need of oxygen therapy.	0/1	NR	VI
Dastan F, et al. (2020) [32]	CRRT with disposable HP cartridge: A promising option for	NR	Case report	One critically ill COVID-19 patient	CRRT with CVVH plus HP for three sessions.	Improvement in patient's clinical condition and chest X-ray. Improvement	0/1	NR	VI

TABLE 2 (Continued)

Study authors (year)	Title	Country	Type of study	Population and sample size	Treatment	Main results	Death	Complication	Level of evidence
	severe COVID-19.					in the O_2 saturation of 95%. Reduction in serum creatinine, IL-1, IL-6, IL-8, and tumor necrosis factor alpha. No laboratory abnormality was seen during the CRRT.			
Ishiwari M, et al. (2020) [39]	Polymyxin B HP treatment for respiratory failure and hyperferriti-naemia due to COVID-19.	Japan	Case report	One critically ill COVID-19 patient with a history of type 2 diabetes and high blood pressure, hyperferriti-naemia, and respiratory failure	Polymyxin B-immobilized fiber column direct HP for 5 h.	Improvement in serum ferritin and bilateral infiltration in chest X-ray. Reduction in ARDS progression, and the need for intubation and mechanical ventilation. No requirement for supplemen-tary oxygen.	0/1	NR	VI

Abbreviations: ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; CRP, C-reactive protein; CVVH, continuous venovenous hemofiltration; ICU, intensive care unit; IL, interleukin; NR, not reported; RRT, renal replacement therapy; SOFA, the sequential organ failure assessment score.

TABLE 3 An overview of studies on plasma exchange (PE) for treatment of patients with COVID-19

Study authors (year)	Title	Country	Type of study	Population and sample size	Treatment	Main results	Death	Complication	Level of evidence
Hashemian SM et al. (2020) [24]	Plasmapheresis reduces cytokine and immune cell levels in COVID-19 patients with acute respiratory distress syndrome (ARDS)	Iran	Clinical trial	Fifteen critically ill adult patients with confirmed COVID-19	Plasmapheresis (6 h per day, three times) was administrated via femoral venous catheters at a blood flow rate of 50-120 ml/min based on the patient's blood pressure using an HD Machine. A volume of 40 ml/kg bodyweight of the patient's plasma was exchanged with an equal volume of 5% human albumin solution and 0.9% saline during each session. Fresh plasma from donors with positive detection of anti-COVID-19 IgG and IgM in their whole blood based on patients' ABO blood group matching were administered.	Improvements in clinical outcomes, oxygenation status, and hepatic function. Reduction in inflammatory mediators (TNF-α and IL-6) and acute phase reactant levels (ferritin and CRP), PaO_2/FiO_2, liver enzymes, and bilirubin.	6/15	NR	III
Gluck WL, et al. (2020) [26]	Efficacy of therapeutic plasma exchange in the treatment of Penn class 3 and 4 cytokine release syndrome complicating COVID-19	USA	Cohort	Ten critically ill patients with confirmed COVID-19 and Penn class 3 and 4 CRS, who needed supplemental oxygen or mechanical ventilation	Five single volume PE (one plasma volume exchange daily for 2 consecutive days, then three times every other day) using the Spectra Optia Apheresis System, applying centrifugal blood component separation	Reduction in oxygenation requirement, CRP, IL-6, IL-10, and TNF-α. Improvement in oxygenation by a 78% average in the P/F ratio and a 43% in OI in mechanically ventilated patients.	0/10	NR	IV
		UK					0/14	NR	VI

TABLE 3 (Continued)

Study authors (year)	Title	Country	Type of study	Population and sample size	Treatment	Main results	Death	Complication	Level of evidence
Arulkumaran N, et al. (2020) [22]	Plasma exchange for COVID-19 thrombo-inflammatory disease.		Case-control	Fourteen critically ill adults patients with severe COVID-19 respiratory failure (seven patients as case group and seven matched patients as control group)	PE daily, for at least 5 days with 3L single volume daily, using a Spectra Optia Apheresis system in case group.	Reduction in prothrombotic factors [von Willebrand Factor (VWF) antigen and activity, VWF antigen/ADAMTS13 ratio, Factor VIII levels], D-dimer, acute phase response markers (ferritin, fibrinogen, and CRP). Improvement the lymphocyte count, PaO_2:FiO_2 ratio from 11.6% kPa to 18.1 kPa in the case group. Acute kidney injury in 5/7 patients in the control group.			
Zhang L, et al. (2020) [25]	Efficacy of therapeutic plasma exchange in severe COVID-19 patients.	China	Case series	Three critically ill COVID-19 patients	PE for with a plasma separator multi-filtration system	Reduction in circulating cytokines and inflammatory mediators, neutrophil-to-lymphocyte ratio (NLR). Improvement in the PaO2/FiO_2 (mmHg).	0/3	NR	VI
Morath C, et al. (2020) [28]	Plasma exchange in critically ill COVID-19 patients.	Germany	Case series	Five critically ill COVID-19 patient	Single PE with FFP	Reduction in inflammatory markers (CRP and LI-6), ferritin, LDH, and D-dimer. Improvement microcirculatory clot formation, hypotension, and clinical outcomes.	2/5	NR	VI
Fernandez J, et al. (2020) [23]	Plasma exchange: An effective rescue therapy in critically Ill patients with coronavirus disease 2019 infection.	Spain	Case series	Five critically ill adults COVID-19 patients	PE for 2–6 sessions (1.2 plasma volumes) in company with five percent human albumin	Dramatic reduction in inflammatory markers, including the main cytokines, and improved severity scores after PE were observed in all patients and all of them were survived.	0/5	NR	VI
Dogan L, et al. (2020) [38]	Plasmapheresis treatment in COVID-19-related autoimmune	Turkey	Case series	Six critically ill COVID-19 patients	Plasmapheresis with albumin	Improvement in clinical condition and MRI neurological findings. Reduction in serum ferritin.	1/6	NR	VI

(Continues)

TABLE 3 (Continued)

Study authors (year)	Title	Country	Type of study	Population and sample size	Treatment	Main results	Death	Complication	Level of evidence
	meningoencephalitis: case series.								
Ma J, et al. (2020) [40]	Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19.	China	Case series	Three critically ill COVID-19 patients	PE (3 sessions for 1 patient) and CRRT with a modified AN69 surface-treated membrane with adsorption capacity (for 2 patients)	Reduction in the titers of antiphospholipid antibodies and inflammatory markers.	1/3	1/3 patients died suddenly, who received CRRT after experiencing multiple complications, such as refractory DIC and right lung pneumothorax	VI
Lin JH, et al. (2020) [31]	Application of plasma exchange in association with higher dose CVVH in Cytokine Storm Complicating COVID-19.	Taiwan	Case report	Three critically ill COVID-19 patient	PE (three times for about 120 min per session) and CVVH with an effluent rate of 35 ml/kg per hour	Improvement in clinical manifestations, radiography, and laboratory findings.	0/1	Not fully removed cytokines in the immune system.	VI
Ragab D, et al. (2020) [30]	A case of COVID-19, with cytokine storm, treated by consecutive use of therapeutic plasma exchange followed by convalescent plasma transfusion: A case report.	Egypt	Case report	One critically ill COVID-19 patient	PE with plasma replacement with FFP (1 session)	Improvement in clinical condition, oxygen saturation, and laboratory findings, in spite of having bad prognostic risk factors (age and comorbidities, such as diabetes and hypertension). Reduction in CRP.	0/1	NR	VI
Nihei Y, et al. (2020) [33]	Continuous extracorporeal treatments in a dialysis patient with COVID-19.	Japan	Case report	One critically ill COVID-19 patient	PE with replacement by 2880 ml of FFP (5 sessions: 3 consecutive days from day 17 to day19, with two subsequent on days 20 and 22)	Reduction in serum IL-6 levels, thrombocytopenia and hyperferritinemia. Improvement in thePaO2/FiO2 ratio from 95 to 200.	1/1	The patient developed respiratory failure and died 30 days after admission due to an uncontrolled immune response and hypercoagulability.	VI
Logan D, et al. (2020) [37]	Plasma exchange in the treatment of thrombotic microangiopathy associated with COVID-19 infection: a case report.	NR	Case report	One critically ill COVID-19 patient	Direct HE using a polymyxin B-immobilized fiber column and continuous hemodiafiltration (totally 18 sessions)	Normalization of the complement pathway with a resolution of hemolysis, and improvement of renal function and mental status	0/1	NR	VI

Abbreviations: ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; COVID-19, coronavirus diease 2019; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; HD, hemodialysis; HP, hemoperfusion; IL, interleukin; MRI, magnetic resonance imaging; NR, not reported; PE, plasma exchange; TNF, tumor necrosis factor.

week. Totally, 6/15 patients undergoing invasive mechanical ventilation (IMV) did not survived. The authors stated that plasmapheresis might improve systemic cytokine and immune responses in patients with severe COVID-19 who did not undergo IMV.

In a cohort pilot study by Gluck et al.,[26] ten critically ill patients with confirmed COVID-19 and Penn class 3 and 4 CRS, who needed supplemental oxygen or mechanical ventilation, were enrolled. Five single volume therapeutic PE (one plasma volume exchange daily for two consecutive days, then every other day times three) were administrated. None of the patients received previous or concurrent convalescent plasma, remdesivir, corticosteroids, or IL-6 inhibitors, although 2/10 patients received a short course (less than 4 days) of hydroxychloroquine before study's enrollment. All 9/10 patients completed all five planned TPE, but 1/10 patients completed 4/5 sessions and stopped early due to intercurrent staphylococcal pneumonia. Five percent human albumin as replacement fluid was administrated for all patients, except for 1/10 patients who received fresh frozen plasma (FFP) for 2/5 PEs. The results showed that the oxygenation requirement was reduced. The average reduction of oxygenation requirements was reported at 87%, following the second PE. Oxygenation was improved by a 78% average in the PaO_2/FiO_2 (P/F) ratio and a 43% in oxygenation index (OI) for mechanically ventilated patients. All CRP, IL-6, IL-10, and TNF-α were decreased, significantly without compromising patient safety. But this change was not observed for IL-8. No 14-day mortality was observed, and no adverse effects were stated, especially hypofibrinogenemia.

In another study with a case-control design, Arulkumaran et al.[22] assessed seven critically ill adults patients with severe COVID-19 respiratory failure, who needed invasive or noninvasive ventilatory support and elevated thrombo inflammatory markers (LDH > 800 IU/L and D-dimer >1000 μg/L (or doubling from baseline). The matched control group consisted of seven matched patients admitted at the same time and met the inclusion criteria for PE. The case group was administered PE daily, for at least five days with a three-liter single volume daily, using a Spectra Optia Apheresis system. No other immunomodulatory medications were initiated during the study period. The results showed that PE could reduce prothrombotic factors, such as Von Willebrand factor (VWF) antigen and activity, VWF antigen/ADAMTS13 ratio, Factor VIII levels, D-dimer, as well as acute phase response markers, such as ferritin, fibrinogen, and CRP, significantly. The lymphocyte count was normalized, and PaO_2:FiO_2 ratio significantly increased from 11.6% kPa to 18.1 kPa. Similar improvements were not seen in the control group. Acute kidney injury occurred among 5/7 patients in the control but not for the receivers of PE.

Zhang et al.[25] applied one session of PE for three patients with a plasma separator multi-filtration system, and about 3000 ml of normal FFP was exchanged for one person. PE could decrease circulating cytokines and inflammatory mediators, neutrophil-to-lymphocyte ratio, as well as improve the PaO_2/FiO_2 (mmHg). Also, Morath et al.[28] reported five patients taking single PE with FFP. Inflammatory markers (CRP and LI-6), ferritin, LDH, and D-dimer decreased significantly. Finally, 3/5 were alive. The authors concluded that this intervention improved inflammation, microcirculatory clot formation, and hypotension, thereby improving clinical outcomes.

In another case series by Fernandez et al.,[23] five critically ill adult patients with COVID-19 received 2–6 sessions of PE (1.2 plasma volumes) combined with five percent human albumin. Dramatic reduction in inflammatory markers, including the main cytokines and improvement of severity scores after PE, were observed in all patients and all of them were survived. Thus, it was recommended that PE might attenuate cytokine storm, reverse organ failure, and promote survival rate. Dogan et al.[38] reported six severely ill patients with COVID-19-related autoimmune meningoencephalitis. They found that although 1/6 patients died, plasmapheresis with albumin could develop a better clinical condition, decrease serum ferritin, as well as reverse the MRI neurological findings.

Moreover, in Ma et al.'s study,[40] three sessions of PE were applied for one patient, which dramatically reduced the titers of antiphospholipid antibodies and inflammatory markers. CRRT with a modified AN69 surface-treated membrane with adsorption capacity was used for two other patients. One of them died suddenly, who received CRRT after experiencing multiple complications, such as refractory DIC and right lung pneumothorax.

In each other of four case reports,[30,31,33,37] PE was administered with different protocols for the patients. All patients improved, as seen in clinical and laboratory findings and also survived,[30,31,37] except one of them,[33] who received several extracorporeal treatment approaches, including PE, direct HP using a polymyxin B-immobilized fiber column, and continuous hemodiafiltration.

4 | DISCUSSION

As it was confirmed through previous evaluations, the cytokine storm phase can play an important role in severe COVID-19. Scientists tried to find therapeutic protocols for the purification of the blood from harmful cytokines, and if they control it, many lives can be saved.[13,24,32] Invasive therapeutic strategies are categorized into two, including PE and HP. Because of the lack of available clinical and analytical investigations on PE and HP, we decided to evaluate these two invasive treatments by a systematic scoping review.

Studies have shown that the use of PE can be effective for patients having very poor general conditions and experiencing decreased oxygen saturation due to severe lung involvement. Investigations showed that PE could increase the lymphocyte level and decrease the levels of TNF-α, IL-6, ferritin, D-dimer, and CRP. This therapeutic manner could also improve clinical features like PaO_2/FiO_2 ratio, oxygen demand, and length of admission, especially in ICU. Plasmapheresis was able also to lessen noninvasive or ventilator demand. Studies that have used PE did not report any life-threatening side effects, especially severe thrombosis.[22–26,28,35]

HP also was known as a method for removing harmful interleukins and acute phase reactants. In some studies, this manner

caused improving P/F, and the patients announced better condition after administrating it. For more safety, using heparin was advised by different protocols.[21,27,29,34,36]

As was mentioned above, using either HP or plasmapheresis is a good way to reduce cytokines and improve oxygenation in patients with severe COVID-19. For more safety and decreasing the chance of thrombosis, using heparin was recommended in HP, while FFP or immunoglobulins were recommended in some PEs.

It is worthy to mention that according to the current findings, PE and HP should be planned when the patient with COVID-19 is in the cytokine storm phase, which means the presence of high levels of ferritin, CRP, and IL-6 in the bloodstream, as well as severe hypoxic condition (P/E < 100).

Due to the insufficient high-quality studies, it is recommended that more controlled clinical trials be done, and a specific therapeutic protocol, as well as its advantages and disadvantages, be defined.

It was concluded that HP and PE would be helpful methods in the treatment of severely ill COVID-19 patients, especially within the cytokine storm phase. But, it was not conclusive that HP prefers PE or vice versa because the available studies used various methods and had no enough data homogeneity. For example, the number of sessions and hours per session for each of both treatments were different in various studies. Also, in HP treatment, the used filters were different, too. A probable reason was that both treatments may not available at the same time in most health centers, so the studies described the treatment used. On the other hand, as the patients within the cytokine storm phase are severely ill and critical patients, urgent treatment should begin so that the physicians start the treatment with a more available setup. Although studies show that thrombosis was more observed after HP, to better compare both treatments, it is recommended to perform clinical trials with specified controlled setup and matching methods.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Mohammad Rezaeisadrabadi and Hamidreza Dehghan completed study concept and design. Razieh Sadat Mousavi-Roknabadi, Fatemeh Haddad, Aylar Fazlzadeh, Dorna Kheirabadi, Hamidreza Dehghan, and Mohammad Rezaeisadrabadi completed acquisition of data. Razieh Sadat Mousavi-Roknabadi, Fatemeh Haddad, Aylar Fazlzadeh, Dorna Kheirabadi, Hamidreza Dehghan, and Mohammad Rezaeisadrabadi finished drafting the manuscript. All authors completed the final approval of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the references.

SYSTEMATIC REVIEW REGISTRATION NUMBER

The review protocol was not previously registered.

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