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MAIN TEXT

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Blood purification with CytoSorb in critically ill COVID-19 patients: A case series of 26 patients

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Abstract

Severe forms of the coronavirus disease 2019 (COVID-19) can progress to sepsis-like complications accompanied by "cytokine storm" for which the most effective treatment has not yet been established. Our study describes the results of CytoSorb hemoadsorption in COVID-19 patients treated on the intensive care unit (ICU). In this retrospective study, 26 patients with COVID-19 and acute respiratory distress syndrome (ARDS) were treated with hemoadsorption therapy. Pre-, and post-treatment values (clinical and laboratory) were compared. Data are expressed as mean (confidence intervals, CI), or median [interquartile ranges, IQR], as appropriate. Patients received 2 hemoadsorption treatments. This resulted in a significant decrease in norepinephrine requirements, and inflammatory marker plasma concentrations (procalcitonin, C-reactive protein, ferritin) when comparing pre versus post treatment levels. The PaO_2/FiO_2 and overall organ function (ie, Sequential Organ Failure Assessment—SOFA score) also improved significantly. Patients stayed on the ICU for 9 days and 21 of them survived. To the best of our knowledge, this is one of the largest case series to date reporting early experiences on extracorporeal hemoadsorption therapy in SARS-CoV-2 positive patients with hyperinflammation and moderate ARDS. Treatment proved to be effective, technically feasible and well-tolerated.

KEYWORDS

COVID-19, CytoSorb, hemoadsorption, hemodynamic, hyperinflammation, lung function

1 | INTRODUCTION

In December 2019, China became the center of an outbreak of the novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], which has since spread globally, resulting in the ongoing pandemic coronavirus disease 2019 (COVID-19). Clinical symptoms of the disease include fever, myalgia, fatigue, headache, dry cough, expectoration, hemoptysis and diarrhea, while some patients go on to develop severe sepsis-like complications such as acute respiratory distress syndrome (ARDS) (40.3%), acute renal failure (18.3%), cardiac injury (59.6%) and shock (11.9%).[1]

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BMI, body mass index; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; CRS, cytokine release syndrome; CRRT, continuous renal replacement therapy; CVVHD, continuous veno-venous hemodialysis/hemofiltration; ICU, intensive care unit; IL, interleukin; PaO2/FiO2, ratio of partial pressure arterial oxygen and fraction of inspired oxygen; PCT, procalcitonin; RT-PCR, Real-Time-Polymerase-Chain-Reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, Sequential Organ Failure Assessment.

Moreover, there is good evidence that age, presence of underlying diseases or secondary infections, as well as elevated plasma levels of inflammatory mediators represent major predictors of poor outcome.[2] The current management of COVID-19 largely comprises of supportive measures and the focus has since been on the development of novel therapeutics, including antivirals and vaccines, where results are eagerly awaited. Given these facts, the world faces a serious disease with significant need for intensive care unit (ICU) admissions and mortality, causing severe burdens on the health care system, families and the economy, in general.

Hyperinflammation accompanied by an uncontrolled release of inflammatory mediators represents a common feature in critically ill patients. This so called "cytokine release syndrome" (CRS) can have serious adverse cytotoxic but also systemic effects that are primarily driven by a massive release of vasoactive substances which in turn cause severe vasodilatation and hemodynamic instability, provoke damage to the endothelium and the glycocalyx, and ultimately result in capillary leakage and interstitial fluid accumulation with potential consecutive impairment of vital organ functions.[3] Interestingly, the cytokines interleukin (IL)-6 and IL-10 have been shown to predict disease severity, eg in patients with pneumonia and sepsis,[4] while a virus-activated CRS can also be frequently observed in COVID-19 patients so that recent studies have suggested a similar prognostic value of these two cytokines.[5]

Given that, treatment options focusing on immunomodulation and mitigation of systemic hyperinflammation, in particular by means of clinically established and approved therapy options with proven safety profiles, open a new window for therapeutic intervention. For example, IL-6 is supposed to play a key role in the cytokine release syndrome that occurs during COVID-19 and the recombinant humanized monoclonal antibody against human IL-6 receptor (tocilizumab), has undergone extensive testing in severe cases of the disease.[6] However, in the past, most treatment approaches that targeted single cytokines have been unsuccessful, if not detrimental.[7,8] A recent article addresses this aspect and highlights the role of extracorporeal organ support therapies for the treatment of the sepsis-like syndrome in COVID-19 patients.[9] Different approaches using extracorporeal therapies have been applied in COVID-19 that range from elimination of the virus by a biomimetic adsorbent device[10] over replenishment of ADAMTS-13 and removal of vWF antigen by plasma exchange[11] to cytokine removal.[12] The latter, specifically CytoSorb hemoadsorption therapy, has gained importance in the field of critical care medicine as it represents a broad-spectrum treatment approach in contrast to single-mediator strategies with proven effectiveness to reduce excess levels of various inflammatory cytokines from blood (ie IL-1, IL-6, and TNF-α) in conditions such as septic shock and other hyperinflammatory states.[13,14] Moreover, there are first promising results, mainly from single case reports but also medium sized case series, that point towards a potential benefit in patients with severe COVID-19.[12,15] We therefore conclude that critically ill COVID-19 patients might benefit from adjuvant CytoSorb treatment and herein describe the clinical experience of 26 patients admitted to our ICU with COVID-19 and moderate ARDS.

2 | PATIENTS AND METHODS

This case series was carried out in the ICU of Shahid Beheshti University of Medical Sciences, Teheran, Iran. The study protocol was approved by the local Ethics Committee and was carried out in line with the principles of the Declaration of Helsinki. Included were 26 consecutive patients with the diagnosis of severe COVID-19 in combination with moderate ARDS who were admitted to our ICU between April 3 and September 23, 2020.

Baseline characteristics as well as symptoms and clinical status on admission are outlined in Table 1. SARS-CoV-2 diagnostics was performed by means of Real-Time-Polymerase-Chain-Reaction (RT-PCR) nasopharyngeal swab assay. Initial therapy consisted of an anti-infective regimen including antivirals (lopinavir/ritonavir, remdesivir, and favipiravir), which were all given prior to the need for ventilation, as well as hemodynamic management with catecholamines (ie, norepinephrine) and volume therapy according to the standard of care protocol. Mean arterial pressure (MAP) target was 65 mm Hg and if higher values were sustained, vasopressor support was reduced accordingly. The protocol was based on national recommendations and provided guidance in regard to pharmaceutical approaches and proper organ support depending on the severity of the disease.[16]

All patients received corticosteroids (dexamethasone, 4 mg twice a day) or methylprednisolone (125 mg twice a day) or hydrocortisone (50-100 mg every 8 hours).

2.1 | Inclusion criteria

Patients were eligible for inclusion if they had a positive RT-PCR test for COVID-19, evidence of ARDS (PaO_2/FiO_2 ratio <200 mm Hg), a CT scan compatible with the diagnosis of COVID-19, an elevated serum ferritin level (>1500 µg/L), and an elevated C-Reactive Protein (CRP) (>50 mg/L) according to the "First Guideline of Hemoperfusion in COVID-19 Patients" released by the Ministry of Health and Medical Education of Iran.[17]

2.2 | Exclusion criteria

Patients excluded from analysis were those who were older than 80 or younger than 18-years of age, body mass index (BMI) > 40, pregnant women, and severe thrombocytopenia (<20 000/µL).

TABLE 1 Baseline characteristics

Variable	All ($n = 26$)	Survivors ($n = 21$)	Non-survivors ($n = 5$)	*P* value
Age [y]	53.7 (47.5-59.8)	52.7 (45-60.3)	57.8 (53.0-62.6)	.51
Females [%]	23.1 (10.3-43.1)	19.0 (6.9-42.9)	40 (5-89.4)	.32
BMI	28.9 (26.6-30.7)	28.1 (26.1-30.1)	32.2 (27.8-36.6)	.07
APACHE pre [points]	29.9 (28.9-30.8)	29.5 (28.4-30.7)	31.4 (30.7-32.1)	.11
SOFA pre [points]	15.4 (14.2-16.6)	14.7 (13.6-15.7)	18.4 (13.2-23.6)	<.01
PCT [ng/mL]	9.3 [5-13.3]	9.7 [6.4-12.9]	9 [3.6-13.3]	.90
Ferritin [μg/L]	1082.3 (909-1255.5)	908.8 (690.5-1127.2)	1543.2 (1235.1-1851.3)	<.01
Norepinephrine [μg/kg/min]	0.19 (0.16-0.21)	0.19 (0.16-21.5)	0.19 (0.11-0.27)	.83
CRP [mg/L]	82 [64-92]	84.2 [60.3-93.8]	67.4 [64-83]	.90
PaO_2/FiO_2 ratio [mm Hg]	180.3 [150-202.9]	180.6 [150-202.9]	180 [148.7-192.3]	1
Lactate [mg/dL]	12.24 (10.3-14.2)	11.2 (3.9-9.4)	16.8 (6.4-8.8)	.02
D-Dimer [ng/mL]	592.5 (501.2-683.7)	574.7 (471-678.4)	694.5 (345.5-1043.5)	.36
Lymphocytes [$\times 10^3/\mu L$]	6.42 (5.33-7.52)	6.3 (4.5-7.6)	7.1 (4.4-9.8)	.96
Body temperature [°C]	37.2 (37.1-37.3)	37.2 (37.1-37.3)	37.2 (36.6-37.8)	.99
Diabetes mellitus [%]	53.8 (34.2-72.4)	52.4 (31.0-73.7)	60 (17.1-1.03)	.76
Hypertension [%]	61.5 (41.1-78.6)	52.4 (31.0-73.7)	100	.05
Hyperlipidemia [%]	11.5 (3.6-31.6)	14.3 (0-29.3)	0	.37
Chronic kidney disease [%]	15.4 (5-35.8)	14.3 (0-29.3)	20 (−15.1 to 55.1)	.75
Ischemic heart disease [%]	11.5 (3.6-31.6)	9.5 (−3-22.1)	20 (−15.1 to 55.1)	.51

Note: All values are given as mean (CI) or as median [IQR] respectively. *P* value corresponds to the comparison between survivors and non-survivors.

TABLE 2 Treatment and outcome variables

Variable	All ($N = 26$)	Survivors ($n = 21$)	Non-survivors ($n = 5$)	*P* value
Number of CytoSorb adsorbers used [n]	2 [1-3]	2 [1-3]	1 [1-1]	.97
Hemoperfusion mode only set-up [%]	26.9 (12.9-47.8)	28.6 (9.3-47.9)	20 (−15.1 to 55.1)	.70
Mechanical ventilation [%]	46.2 (27.6-65.8)	33.3 (13.2-53.5)	100	<.01
Days on MV				
Total	6 [5-11]	10.5 [5-11]	5 [5-6]	.10
Pre	2 [1-5]	4 [1-5]	2 [1-2]	.35
During	1.5 [1-2]	1 [1-2]	2 [1-2]	1.00
Post	3 [1-5]	4.5 [3-7]	1 [1-3]	.23
Time to CytoSorb therapy start [days]	10.2 (8.8-11.5)	9.4 (8-10.8)	13.2 (9.9-16.4)	.02
CytoSorb duration [h]	35 [18-48]	36 [24-48]	12 [12-18]	.32
CRRT duration [h]	27 [0-47]	36 [0-47]	18 [8-30]	1.00
ICU length of stay [days]	9 [6-12]	10 [7-12]	8 [3-11]	1.00

Note: All values are given as mean (CI) or as median [IQR] respectively.

2.3 | Rationale for CRRT start and CytoSorb application

Once the patient developed acute kidney injury (AKI) or met AKI criteria stage 2 and 3 and/or showed a hyperinflammatory picture with profound hemodynamic instability requiring increasing doses of vasopressors over the last 12-24 hours, CytoSorb therapy was initiated, either in combination with continuous renal replacement therapy (CRRT) or in standalone mode. The latter approach was used to either enable use of CytoSorb therapy prior to the need for renal replacement therapy, or due to non-availability of CRRT devices.

In the case of combined CRRT and CytoSorb treatment, CRRT (Diapact, B.Braun, Melsungen, Germany)

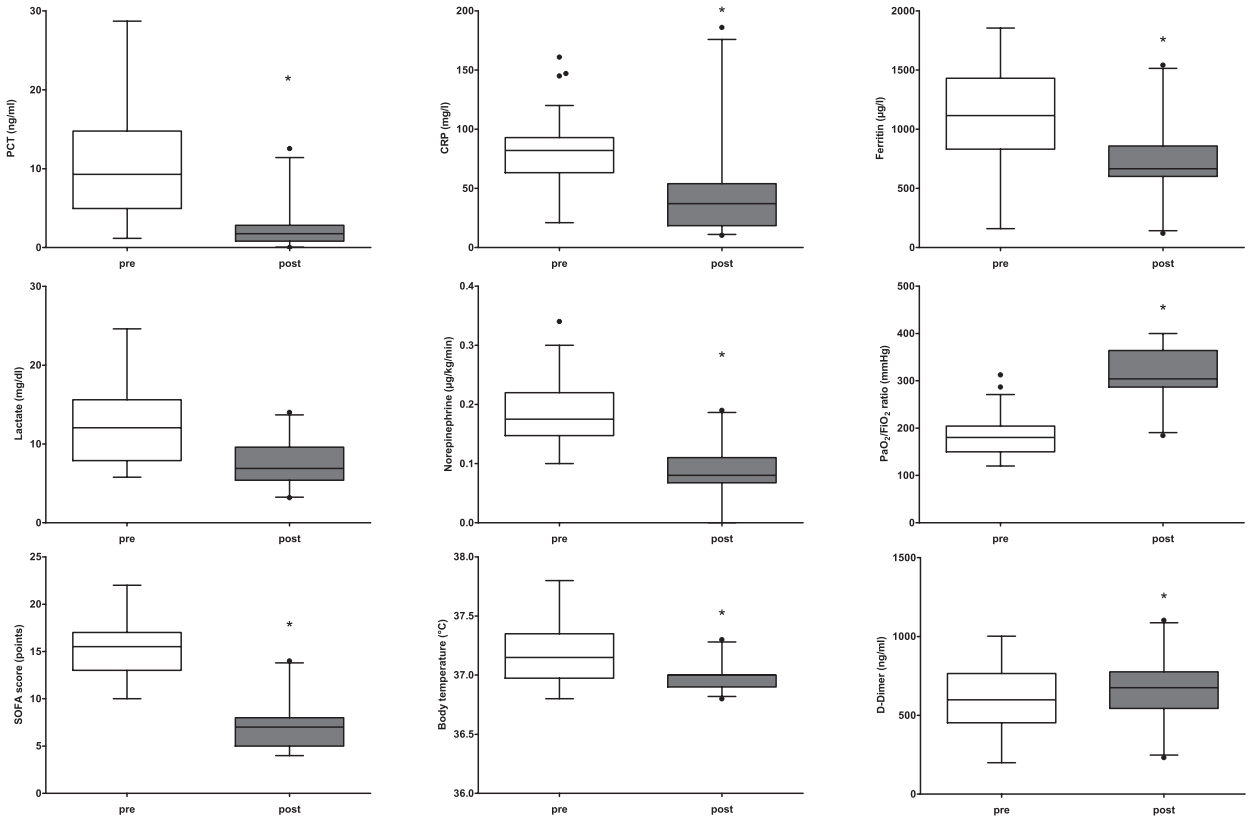

FIGURE 1 Pre- and post-treatment levels of relevant inflammatory, hemodynamic and organ function parameters. Depicted are boxplots with whiskers (5%-95% percentile). Dots represent outliers. Asterisks indicate statistical significance ($P < .05$) Please note that not all values were available for some patients. [Color figure can be viewed at wileyonlinelibrary.com]

was performed in continuous veno-venous hemodialysis/hemofiltration (CVVHD/CVVH) mode using a heparin-based anticoagulation protocol and supplemented by a CytoSorb adsorber that was installed in line in the CRRT circuit in a pre-dialyzer position. Blood flow rates were kept between 200 and 250 mL/min while dialysis doses ranged between 25 and 30 mL/kg per hour, according to routine procedure. In both scenarios (hemoperfusion mode only, combined CRRT and CytoSorb), the adsorber was changed after 12 hours for the first cartridge, and after 24 hours for the next therapy session with CytoSorb.

CytoSorb treatment was stopped when there were clear signs of improvement in oxygenation (increase in PaO_2/FiO_2 ratio above 250 mm Hg), and/or decreasing vasopressor requirements and/or decreased levels of inflammatory markers (serum ferritin). In one patient CytoSorb treatment was stopped after the second session, as severe thrombocytopenia (<20 000/µL) had developed.

We measured COVID-19 relevant laboratory biomarkers of inflammation (ie, procalcitonin—PCT, CRP, and ferritin) as well as hemodynamics (vasopressor requirements). Additionally, we evaluated changes in lung function (PaO_2/FiO_2 ratio) and Sequential Organ Failure Assessment (SOFA) score before and after CytoSorb treatment.

All sets of data were statistically analyzed and graphically presented using STATA 16 software. Data are displayed as mean (CI) or median [IQR] when appropriate.

3 | RESULTS

In total, 26 patients met the inclusion criteria and were therefore analyzed. Baseline characteristics are summarized in Table 1. Out of 26 patients, 5 died in the ICU (non-survivors), while 21 survived, giving an ICU mortality of 19.2%.

Overall, 46.2% of all patients received mechanical ventilation, but it has to be stated that according to the high workload and intermittent additional resource problems some patients could not receive mechanical ventilation when they would have done normally. On average 2 CytoSorb adsorbers were used per patient (Table 2). In most patients (73.1%), CytoSorb was used in a CRRT setup due to AKI, while in 26.9% of the patients, the adsorber was used in hemoperfusion mode only. In regard to anticoagulation, only heparin was used. The average bolus at therapy initiation was 5000 IE, while the average cumulative dose during treatment was also 5000 IE. Concerning the baseline characteristics, non-survivors had a significantly higher SOFA score and higher ferritin as well as

TABLE 3 List of concomitant medications per patient

Patient	Remdesivir	Favipiravir	Lopinavir/ Ritonavir	Interferon beta-1a	Hydroxychloroquine	Meropenem	Ceftriaxone	Vancomycin
1	×	×	×	×		×	×	×
2	×		×	×		×		×
3	×		×	×		×		
4	×		×	×		×		
5	×			×		×	×	
6	×		×	×	×	×	×	×
7	×		×	×			×	
8					×	×		×
9			×	×		×	×	
10			×		×	×	×	×
11	×	×	×	×	×	×		×
12	×	×	×	×		×	×	×
13	×	×	×	×		×	×	×
14			×	×		×	×	×
15	×	×	×			×		
16	×	×	×	×		×	×	
17	×	×	×	×		×	×	
18	×		×	×		×	×	
19	×	×	×	×		×	×	
20	×			×		×		×
21	×			×		×	×	
22	×		×	×		×		×
23		×	×	×		×		×
24	×		×	×		×		
25		×	×			×		
26	×		×	×			×	

lactate levels. There were no significant differences in treatment characteristics between survivors and non-survivors, apart from the fact that all non-survivors required mechanical ventilation, and that the time from onset of symptoms until start of CytoSorb treatment was significantly shorter in the survivor group (Table 2). A comparison between ventilated and non-ventilated patients showed an even lower median baseline PaO_2/FiO_2 ratio for the non-ventilated patients (Table 4). For the whole cohort, mechanical ventilation was provided for 3.1 days on average before treatment and patients required ventilation for a mean of 7 days, with no substantial differences between survivors and non-survivors. Mean ICU length of stay was 9 days. The administered medications including antivirals, corticosteroids and other supplementary therapies throughout the clinical course of individual patients are outlined in Table 3.

Comparing pre- and post-treatment levels (Figure 1) for the overall patient population, we found that inflammatory markers (ie, PCT, ferritin, and CRP) had decreased significantly throughout the therapy sessions. Moreover, we observed a stabilization in hemodynamics as demonstrated by a reduction in norepinephrine requirements during hemoadsorption therapy. All patients had a norepinephrine requirement >0.1 μg/kg/min before CytoSorb therapy was initiated. After treatment, 18 patients (69.2%) had a norepinephrine requirement <0.1 μg/kg/min. PaO_2/FiO_2 ratio and therefore lung function/oxygenation as well as SOFA score improved significantly. Twenty three patients (88.5%) had a P/F ratio <250 mm Hg prior to hemoadsorption from which 82.6% (19 patients) reached P/F ratio above 250 mm Hg post intervention. Comparisons of pre and post levels regarding relevant laboratory and clinical parameters are shown in Table 4 between ventilated and non-ventilated patients as well as in Table 5 between survivors and non-survivors. Of note, non-survivors basically improved to the same degree as survivors, except for their CRP levels.

Azithromycine	Levofloxacin	Prednisolone/ Methylprednisolone	Dexamethasone	Hydrocortisone	Hydroxyzine	Colchicine	Acetaminophen/ Paracetamol/ Naproxen	Bromhexine
×		×	×				×	
			×				×	
×		×	×			×	×	
×			×				×	×
×		×	×				×	×
×	×	×	×				×	×
×			×				×	
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Worth mentioning, death of non-surviving individuals could not be attributed to any specific treatment. Four of five patients died because of multiple organ failure and one patient died after developing cardiogenic shock.

Combined CRRT and hemoadsorption treatment appeared to be well-tolerated in almost all cases. Only in one patient did we observe the development of thrombocytopenia of unclear origin, which led to termination of CytoSorb hemoadsorption therapy. Otherwise we did not observe any device-related adverse events and there were no problems installing the adsorber into the CRRT circuit or when using it in hemoperfusion mode only.

4 | DISCUSSION

To the best of our knowledge, this is one of the largest case series to date reporting early experiences in extracorporeal hemoadsorption therapy in COVID-19 critically ill patients. Clinical and laboratory variables measured in this case series have shown that: (i) a clear reduction in inflammatory mediator plasma levels potentially consistent with a rebalancing of the hyperinflammatory response (ii) hemodynamic stabilization accompanied by a rapid decrease in vasopressor requirements and (iii) a significant improvement in lung function/oxygenation and overall organ functions (SOFA). COVID-19 has to be understood as a systemic disease and various additive treatment have so far been used and investigated, partly based on the rationale of the very early described severe cytokine-mediated hyperinflammation.[18]

Our results of using CytoSorb therapy in COVID-19 patients are consistent with other observations that describe stabilization in hemodynamics as one of the most immediate effects of CytoSorb therapy.[19,20] On the other hand, reports on the use of CytoSorb hemoadsorption therapy in cases of severe ARDS requiring ECMO support, as well as

TABLE 4 Comparison of pre and post treatment levels in non-ventilated and ventilated patients

	Non-ventilated ($n = 14$)			Ventilated ($n = 12$)		
	Pre	Post	*P* value	Pre	Post	*P* value
SOFA [points]	14.93 (13.52-16.33)	7.43 (5.56-9.29)	<.01	14.22 (12.60-15.84)	7.78 (5.72-9.84)	<.01
PCT [ng/mL]	11.99 [6.49-21.73]	2 [1.36-4.77]	<.01	7.87 [4.43-11.11]	1.03 [0.32-1.87]	<.01
Ferritin [µg/L]	939.76 (700.46-1179.1)	726 (511.95-941.98)	.02	1180.99 (881.36-1480.61)	764.7 (567.52-961.96)	<.01
Norepinephrine [µg/kg/min]	0.18 (0.15-0.21)	0.09 (0.07-0.12)	<.01	0.20 (0.15-0.24)	0.08 (0.05-0.11)	<.01
CRP [mg/L]	83.1 [67-95.5]	35.5 [18.3-41.1]	<.01	79.9 [61-90.4]	55.3 [44.1-78.5]	.50
PaO_2/FiO_2 ratio [mm Hg]	168.6 [150-202.7]	302 [286.67-364]	<.01	186.5 [145.1-245.5]	308 [289.29-328.57]	<.01
Lactate [mg/dl]	12.14 (9.85-14.44)	8.06 (6.51-9.60)	<.01	9.49 (7.17-11.80)	6.57 (4.14-8.99)	<.01
D-Dimer [ng/mL]	566.57 [434.40-698.75]	642.71 [512.42-773.00]	<.01	640.56 [488.20-792.91]	723.78 [559.67-887.88]	.04
Lymphocytes [$\times 10^3$/µL]	5.95 (4.30-7.61)	6.34 (4.38-8.29)	.26	7.14 (5.76-8.53)	7.58 (6.02-9.14)	.11
Body temperature [°C]	37.23 (37.09-37.37)	37.01 (36.94-37.09)	.02	37.13 (36.90-37.37)	36.98 (36.90-37.05)	.22

Note: All values are given as mean (CI) or as median [IQR] respectively.

in pneumogenic sepsis further support a potential benefit of CytoSorb therapy on the respiratory function[21,22] We hypothesize that CytoSorb treatment may potentially also have a positive effect on pulmonary integrity and therefore on lung function/oxygenation, which was a consistent clinical finding in our set of patients with ARDS. In this context, evidence from animal models of sepsis suggests that a phenomenon known as leukocyte trafficking can effectively restore chemokine gradients towards infected tissue and away from healthy organs, which might explain some of the beneficial effects of this treatment.[23] Besides these effects, its successful application in syndromes associated with an excessive release of inflammatory mediators such as in CAR-T cell associated cytokine release syndrome[24] or Hemophagocytic lymphohistiocytosis[25] underline the potential benefits of this adjuvant therapy option also in COVID-19 patients.

Interestingly, time from onset of symptoms until start of CytoSorb therapy was significantly shorter in the survivors. Obviously, COVID-19 has a rather long interval between onset of the first symptoms and development of a more critical clinical state and so admission to ICU. However, once progression to a more severe status has started, CytoSorb therapy is thought to be more effective if used very early which has also been the approach in various investigations on the use of the therapy in septic shock as well as COVID-19.[12,19,22,26]

Recent results on the early use of hemoadsorption in COVID-19 patients requiring ECMO therapy, however, pointed towards negative effects on outcome, so a better understanding of the ideal timing of hemoadsorption therapy in COVID-19 patients is still needed.[27]

Overall, patients received 2 treatments only on average in the early course of their ICU stay, and improvement in the investigated outcome parameters (before vs after CytoSorb therapy) was found in both survivors and non-survivors. Due to the observed improvement in both the clinical and laboratory parameters we decided to terminate cytokine removal. However, patients stayed on the ICU for a mean of 9 days with no major difference between survivors and non-survivors. These suggest that patients who died developed organ dysfunction and/or complications later on during the course of the disease that eventually led to fatal outcome, independent of the initial improvement during CytoSorb therapy. The phenomenon, that patients only needed a couple of treatments after which therapy was terminated, but patients stayed on the ICU several days longer, has also been reported in other studies.[12,26] A very recent retrospective, propensity score matched analysis on 84 patients with septic shock also reported very similar findings.[26] In this study, overall survival was significantly better in the CytoSorb treated patients compared to the matched controls. The authors also compared survivors to non-survivors in the CytoSorb group and found that the lactate levels and norepinephrine requirements rapidly improved after a mean of one treatment only, regardless

TABLE 5 Comparison of pre and post treatment levels in survivors and non-survivors

	Survivors ($n = 21$)			Non-survivors ($n = 5$)		
	Pre	**Post**	***P* value**	**Pre**	**Post**	***P* value**
SOFA [points]	14.7 (13.6-15.7)	7 (5-8)	<.01	18.4 (13.2-23.6)	11.5 [10-13]	1.00
PCT [ng/mL]	9.6 [6-12.9]	1.9 [1.1-3.5]	<.01	9 [3.6-13.3]	0.3 [0.2-0.9]	.06
Ferritin [µg/L]	943.4 (755.2-1131.6)	708.7 (553.5-864)	<.01	1465.3 (1140.8-1789.7)	898.6 (354.7-1442.6)	.03
Norepinephrine [µg/kg/min]	0.19 (0.16-21.5)	0.09 (0.07-0.11)	<.01	0.19 (0.11-0.27)	0.07 (0.02-0.12)	.02
CRP [mg/L]	85.2 [67-92]	36 [18.3-44.2]	<.01	67.4 [64-83]	65.3 [49.1-131.3]	.71
PaO_2/FiO_2 ratio [mm Hg]	180.6 [150-202.9]	304 [286.7-344]	<.01	180 [148.7-192.3]	347.7 [300-395.5]	.50
Lactate [mg/dL]	11.2 (3.9-9.4)	6.9 (5.4-8.5)	<.01	16.8 (6.4-8.8)	9.9 [5.8-14]	1.00
D-Dimer [ng/mL]	574.7 (471-678.4)	662 (559-765)	<.01	694.5 (345.5-1043.5)	733.5 (1043.5-1168.0)	.40
Lymphocytes [$\times 10^3/\mu L$]	6.3 (4.5-7.6)	6.6 (5.1-8.1)	.25	7.1 (4.4-9.8)	8 (5.5-10.4)	<.01
Body temperature [°C]	37.2 (37.1-37.3)	37.0 (37-37.1)	.20	37.2 (36.6-37.8)	37 (36.8-37.0)	.25

Note: All values are given as mean (CI) or as median [IQR] respectively.

of whether patients were survivors or non-survivors eventually. On the contrary, in another recent case series in 50 COVID-19 critically ill patients on renal replacement therapy treated with CytoSorb, the authors report a clear distinction between survivors and non-survivors.[12] While there was a significant improvement in every parameter in survivors, non-survivors in general also behaved as non-responders: showing no improvement or in fact deterioration of values before and after hemoadsorption. Therefore, the question of defining responders and finding the best indicators to choose which patients would benefit the most, remains open. All of these studies, including ours, share most of the limitations of small sample size, missing data, arbitrary indications for starting CytoSorb, retrospective design and the possibility of a positive publication bias. Our cases do represent clinical reality and real-world experiences in times of a pandemic with limited resources and high workload preventing, eg, the use of mechanical ventilation in every single patient in which it was being considered. Interestingly the outcome of the non-ventilated patients was better than those patients being ventilated, despite an even lower median baseline PaO_2/FiO_2 ratio in the non-ventilated patients' group. Importantly non-invasive ventilation approaches were not available for us, but still these findings inevitably lead to the question of when to start mechanical ventilation in COVID-19 patients, which seems to require further investigation.[28] Last but not least it remains also speculative to which extend CytoSorb contributed to patient recovery or whether this was also supported by concomitant medications such as corticoids and antivirals. Furthermore, as it has to be seen as a multimodal approach also from a technical perspective, an additive effect also of hemofiltration cannot be ruled out.[29]

Changes in core body temperature, which might be an issue particularly in hemoperfusion where the temperature effect of the dialysate or warmed substitution fluid is absent, could also have had an impact on cardiovascular stability[30] However, differences in body temperature when comparing pre- and post-treatment values were overall small and should therefore not have had a relevant impact on cardiovascular stability.

Nevertheless, our case series provides further data to understand the nature of critically ill COVID-19 patients, and the potential role of extracorporeal cytokine adsorption in this subgroup.

In summary, based on our observations in this case series we feel that CytoSorb therapy might potentially represent a promising and important adjuvant therapeutic option to help manage the serious complications caused by hyperinflammation in critically-ill COVID-19 patients.

5 | CONCLUSION

To the best of our knowledge, this is one of the largest case series to date reporting early experiences on extracorporeal hemoadsorption therapy in SARS-CoV-2 positive patients with hyperinflammation and ARDS. Treatment proved to be effective, technically feasible and well-tolerated.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHORS CONTRIBUTIONS

Dr Amir Ahmad Nassiri was mainly responsible for the concept/design, patient treatment, interpreting the data and for writing the manuscript. Dr Monir Sadat Hakemi contributed to the writing. Dr Tahereh Sabaghian and Dr Azadeh Ahmadi

Koomleh did the data collection and brought them into format including figures and tables. Dr Tahereh Sabaghian was responsible for statistical analysis. Dr Mir Mohammad Miri was responsible for treatment of the patients, data recording and revising the article. Dr Reza Shahrami did a critical revision and approval of the article.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board of the Ethical Committee of Imam Hossein Hospital (Shahid Beheshti University of Medical Sciences of Iran) [Reg # A1210023]. Written informed consent for publication was obtained from the patient or their legal representatives.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during this study is available from the corresponding author on reasonable request.

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