



Continuous renal replacement therapy with the addition of CytoSorb cartridge in critically ill patients with COVID-19 plus acute kidney injury: A case-series

Abdulrahman Alharthy¹ | Fahad Faqihi¹ | Ziad A. Memish² | Abdullah Balhamar¹ |
Nasir Nasim¹ | Ahmad Shahzad¹ | Hani Tamim³ | Saleh A. Alqahtani⁴ |
Peter G. Brindley⁵ | Dimitrios Karakitsos^{1,6} 

¹Critical Care Department, King Saud Medical City, Riyadh, Saudi Arabia

²Research and Innovation Center, King Saud Medical City, Riyadh, Saudi Arabia

³Biostatistics Unit, Clinical Research Institute, American University of Beirut Medical Center, Beirut, Lebanon

⁴Department of Medicine, The Johns Hopkins University Hospital, Baltimore, MD, USA

⁵Department of Critical Care, Faculty of Medicine and Dentistry, The University of Alberta, Alberta, Canada

⁶Critical Care Department, Keck School of Medicine, USC, Los Angeles, CA, USA

Correspondence

Dimitrios Karakitsos, Critical Care Department, King Saud Medical City, PO Box 331905, Shemaisi 11373, Riyadh, Saudi Arabia.

Email: karakitsosdimitrios@gmail.com

Abstract

Our aim was to investigate continuous renal replacement therapy (CRRT) with CytoSorb cartridge for patients with life-threatening COVID-19 plus acute kidney injury (AKI), sepsis, acute respiratory distress syndrome (ARDS), and cytokine release syndrome (CRS). Of 492 COVID-19 patients admitted to our intensive care unit (ICU), 50 had AKI necessitating CRRT (10.16%) and were enrolled in the study. Upon ICU admission, all had AKI, ARDS, septic shock, and CRS. In addition to CRRT with CytoSorb, all received ARDS-net ventilation, prone positioning, plus empiric ribavirin, interferon beta-1b, antibiotics, hydrocortisone, and prophylactic anticoagulation. We retrospectively analyzed inflammatory biomarkers, oxygenation, organ function, duration of mechanical ventilation, ICU length-of-stay, and mortality on day-28 post-ICU admission. Patients were 49.64 ± 8.90 years old (78% male) with body mass index of 26.70 ± 2.76 kg/m². On ICU admission, mean Acute Physiology and Chronic Health Evaluation (APACHE) II was 22.52 ± 1.1 . Sequential Organ Function Assessment (SOFA) score was 9.36 ± 2.068 and the ratio of partial arterial pressure of oxygen to fractional inspired concentration of oxygen (PaO₂/FiO₂) was 117.46 ± 36.92 . Duration of mechanical ventilation was 17.38 ± 7.39 days, ICU length-of-stay was 20.70 ± 8.83 days, and mortality 28 days post-ICU admission was 30%. Nonsurvivors had higher levels of inflammatory biomarkers, and more unresolved shock, ARDS, AKI, and pulmonary emboli (8% vs. 4%, $P < .05$) compared to survivors. After 2 ± 1 CRRT sessions with CytoSorb, survivors had decreased SOFA scores, lactate dehydrogenase, ferritin, D-dimers, C-reactive protein, and interleukin-6; and increased PaO₂/FiO₂ ratios, and lymphocyte counts (all $P < .05$). Receiver-operator-curve analysis showed that posttherapy values of interleukin-6 (cutoff point >620 pg/mL) predicted in-hospital mortality for critically ill COVID-19 patients (area-under-the-curve: 0.87, 95% CI: 0.81-0.93; $P = .001$). No side effects of therapy were recorded. In this retrospective case-series, CRRT with the CytoSorb cartridge provided a safe rescue therapy in life-threatening COVID-19 with associated AKI, ARDS, sepsis, and hyperinflammation.



KEYWORDS

acute kidney injury, acute respiratory distress syndrome, continuous renal replacement therapy with cytosorb, COVID-19, hyperinflammation, thromboembolism

1 | INTRODUCTION

The novel coronavirus SARS-CoV-2 disease (COVID-19) has caused worldwide upheaval, and spurred unprecedented research.¹ While most patients remain asymptomatic, a portion develop critical illness, characterized by acute respiratory distress syndrome (ARDS), sepsis, multi-system organ failure (MSOF), thromboembolic disease, and associated cytokine release syndrome (CRS).²⁻⁵ Acute kidney injury (AKI) occurs in 2% to 25% of severe COVID-19 cases, and is associated with worse prognosis.²⁻⁸ Care for patients with sepsis, ARDS, AKI, and COVID-19 is largely supportive and can include continuous renal replacement therapy (CRRT). Provocatively, CRRT may also remove deleterious cytokines, such as tumor necrosis factor (TNF) α and interleukin (IL) 1 β and might, therefore, ameliorate the underlying biochemical disorder.⁹⁻¹³

A single-use filter, CytoSorb, was developed to be used in addition to CRRT for patients with increased cytokines and endotoxins.¹⁴⁻²³ Experimental studies and small clinical series showed that hemadsorption with CytoSorb can remove up to 90% of circulating endotoxins and cytokines; however, clinical outcomes in ARDS patients are inconclusive.²⁴ The filter is compatible with routine extracorporeal techniques such as CRRT, hemoperfusion, hemodialysis, and extracorporeal membrane oxygenation (ECMO). To our knowledge, scarce data exist regarding the use of CytoSorb filters in critically ill COVID-19 patients.

The enormous medical, economic, and societal impact of COVID-19 means that myriad therapies are being pursued, including antivirals, vaccination, and convalescent plasma transfusion.²⁵⁻²⁷ To date, none but steroids have been shown to have a clear benefit.²⁸ In a previous report, we showed that therapeutic plasma exchange might be a rescue therapy for life-threatening COVID-19 with associated CRS.²⁹ We build upon that experience in this retrospective case-series by examining CytoSorb in conjunction to CRRT for patients with severe COVID-19 and AKI.

2 | PATIENTS AND METHODS

2.1 | Patients and study design

In this retrospective case-series, we analyzed patients with life-threatening COVID-19 and associated AKI admitted to our intensive care unit (ICU) between June 1 and July 30,

2020. Outcomes were: 28-day mortality post-ICU admission, changes in Sequential Organ Function Assessment (SOFA) score,³⁰ changes in inflammation biomarkers, days of mechanical ventilation, and ICU length of stay. Inclusion criteria were: (a) age ≥ 18 years old; (b) intubation and ICU admission; (c) AKI necessitating CRRT according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria³¹ and (d) life-threatening COVID-19 which was defined in turn as: (i) ARDS (according to the Berlin criteria); (ii) Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥ 20 upon ICU admission; (iii) severe sepsis/septic shock; (iv) and one or more criteria for defining cytokine release syndrome (CRS).^{29,32-36} The criteria for CRS are outlined in Table 1.^{3,5,6,29,37,38} Another study prerequisite was that CRRT with CytoSorb was initiated within 24 hours of developing life-threatening COVID-19 (as defined above).

The diagnosis of SARS-CoV-2 was made by real-time polymerase chain reaction (RT-PCR) nasopharyngeal swab assay using QuantiNova Probe RT-PCR kit (Qiagen) in a Light-Cycler 480 real-time PCR system (Roche, Basel, Switzerland).^{39,40} Exclusion criteria were: (a) terminally ill patients receiving palliative care; (b) patients with AKI that did not require CRRT; and (c) two consecutive negative RT-PCR nasopharyngeal swabs for SARS-CoV-2 taken at least 48 hours apart. The study was conducted according to the principles of the Declaration of Helsinki⁴¹ and approved by our Institutional Review Board. Permission for patient data collection via the Electronic Medical Record (EMR) was granted by the IRB, and written informed consent was obtained from eligible patients or their legal representatives.

TABLE 1 Criteria for defining CRS

One or more of the following criteria should be present^a

C-reactive protein >100 or >50 mg/L but doubled in the past 48 h

Lymphocyte count $<0.6 \times 10^9/L$

Serum interleukin-6 (IL-6) $\geq 3x$ upper normal limit

Ferritin >300 ug/L (or surrogate) with doubling within 24 hours

Ferritin >600 ug/L at presentation and LDH >250 U/L

Elevated D-dimer (>1 mcg/mL)

Abbreviations: CRS, cytokine release syndrome, LDH, lactate dehydrogenase.
^aWe defined as low risk for developing CRS the presence of one criterion, moderate risk the presence of two to three criteria, and high risk the presence of more than three criteria.



2.2 | Study procedure

2.2.1 | Continuous renal replacement therapy with the CytoSorb cartridge

COVID-19 patients with AKI, where AKI was defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria, underwent CRRT.^{31,42} Specifically, the KDIGO criteria had to be met despite patients being admitted to ICU and receiving adequate fluid resuscitation (as per the KDIGO guidelines), and intravenous norepinephrine to a mean arterial pressure >60 mm Hg. Patients also had to receive antibiotics within 2 hours of septic shock detection, hydrocortisone, and ARDS-net mechanical ventilation.³⁰⁻³⁶ If the patient met the AKI stage II criteria (defined as serum creatinine 2.0-2.9 times baseline, urine output <0.5 mL/kg/h for 12 h), then, we initiated CRRT in conjunction with the CytoSorb cartridge. The CytoSorb filter (CytoSorbents Europe GmbH, Berlin, Germany) was connected post-hemofilter via a close loop circuit to the CRRT pump (Prismaflex, Baxter Deutschland, Unterschleißheim, Germany). CRRT was performed in continuous hemodialysis mode (CVVHD) at a blood flow rate of 100-250 mL/min, and with citrate anticoagulant (again, as per KDIGO 2019 recommendations).⁴² CytoSorb was used according to the manufacturer guidelines, and the filter was changed every 24 hours.²⁰⁻²⁴ CVVHD with CytoSorb was discontinued if all of the following occurred: (a) oxygenation normalized [ie, a partial arterial pressure of oxygen to fractional inspired concentration of oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio >300]; (b) blood pressure normalized (defined as mean arterial pressure >65 mm Hg, with vasopressors discontinued and diuresis possible); (c) septic shock subsided (defined as a lactate level \leq 2mmol/L), and (d) homeostasis achieved (ie, the absence of electrolyte abnormalities or metabolic acidosis).

Specialized ICU staff performed the CRRT associated procedures (ie, placement of a temporary double-lumen catheter using ultrasound, and management of the CRRT machine and solutions). We insisted upon full COVID-19 personal protective equipment, and infection control measures for respiratory, droplet, and contact isolation.^{43,44} CRRT effluent was treated as biohazardous during its disposal.⁴⁵ All procedures were performed in negative-pressure isolation rooms in our COVID-19 designated ICU.

2.2.2 | Evaluation of CytoSorb therapy and data acquisition

We measured the association between the use of CytoSorb and levels of inflammatory biomarkers commonly reported in COVID-19 patients: C-reactive protein (CRP), D-dimer,

lactate dehydrogenase (LDH), ferritin, and interleukin-6 (IL-6).^{2-5,25-29} CRP was defined as elevated if >5.0 mg/L and IL-6 if >7.0 pg/mL.⁴⁶ We measured these biochemical parameters before and after the completion of therapy. We also measured the changes in $\text{PaO}_2/\text{FiO}_2$ ratio, and SOFA score before and after CytoSorb. The EMRs of those COVID-19 patients who met the study's inclusion criteria were retrospectively analyzed. The available epidemiologic, clinical, and paraclinical data of the enrolled cases were stored in an electronic data bank. We analyzed days on mechanical ventilation (MV), ICU length-of-stay, and 28-day mortality post-ICU admission.

2.3 | Statistical analysis

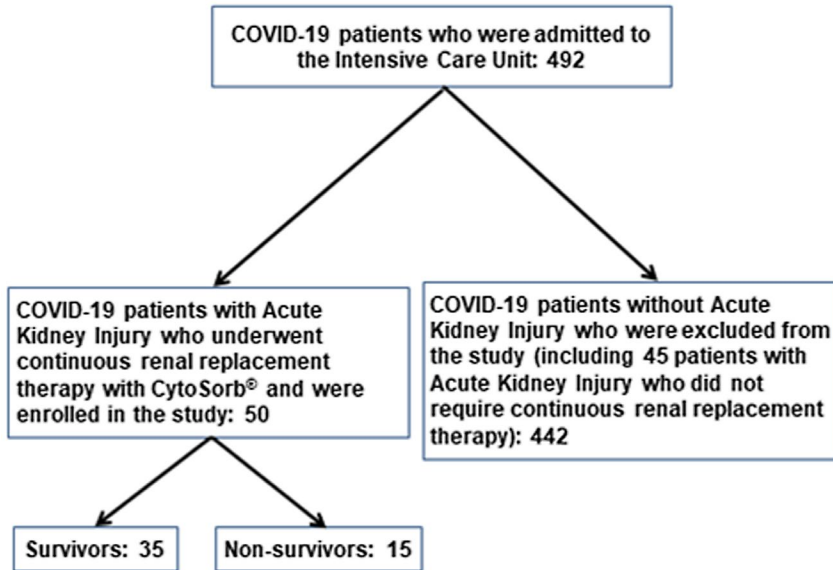
Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables were expressed as absolute numbers and/or percentages. We utilized the Wilcoxon signed rank sum test for nonparametric data to compare clinical and biochemical parameters before and after CRRT, and the Fisher's exact test to compare percentages. Also, we drew Tukey boxplots, with equal whisker lengths of 1.5 interquartile ranges for both whiskers, for parameters of interest such as lymphocytes, IL-6, $\text{PaO}_2/\text{FiO}_2$ ratio, and SOFA score, before and after therapy, in survivors and in nonsurvivors. Also, Receiver Operator curve (ROC) analysis of posttherapy values of IL-6 and SOFA score for predicting in-hospital mortality was performed. All tests were 2-tailed and considered statistically significant when the *P* value was <.05. Statistical analysis was performed using SPSS, version 23.0.

3 | RESULTS

Of 472 COVID-19 patients admitted to the ICU during the study period, 95 patients had AKI (19.3%). Forty-five patients of these AKI patients did not require CRRT and were, therefore, excluded. Fifty COVID-19 patients with AKI (10.16%) met inclusion criteria and were included in the final analysis (Figure 1). SARS-CoV-2 infection was confirmed by RT-PCR performed on nasopharyngeal swabs in all cases. The main characteristics and outcome measures of the 50 COVID-19 patients with AKI are outlined in Table 2, and the studied biochemical parameters are presented in Table 3. The most common symptoms of patients prior to hospital admission were cough (90%), fever (84%), and dyspnea (70%). Less common symptoms were sputum production (44%), vomiting/nausea (18%), diarrhea (14%), altered level of consciousness (8%), and anosmia (6%). Eleven of 50 patients (22%) acquired SARS-CoV-2 infection in areas where several other cases were simultaneously discovered (ie, residential area or shopping mall) and were, therefore, deemed a



FIGURE 1 Study flowchart



cluster infection. The most common comorbidities were arterial hypertension (50%), diabetes mellitus (28%), and cardiovascular disease (8%). Patients were aged 49.64 ± 8.90 years old, with a body mass index of 26.70 ± 2.76 kg/m², and 78% were male. Mean time from symptom onset to ICU admission was 6.34 ± 1.86 days. Admission APACHE II score, SOFA scores, and PaO₂/FiO₂ ratios were: 22.52 ± 1.11 , 9.36 ± 2.068 , and 117.46 ± 36.92 , respectively (Table 2).

COVID-19 patients who had refractory hypoxemia (PaO₂/FiO₂ ratio <80) for over 24 hours, plus increased suspicion for thromboembolic disease (Padua prediction score >4 and/or increased level of D-dimer) underwent chest computed tomography (CT) angiography to rule out pulmonary embolism (PE). Twelve of 50 COVID-19 patients were diagnosed with PE (24%). Four out of these twelve patients survived, whereas eight out of twelve did not. Ten of the twelve PE patients had subsegmental PEs, and two had segmental PEs by chest CT angiography. Eight of twelve PE patients also had deep vein thrombosis, confirmed by lower limb sonography. On ICU admission, echocardiography did not reveal any significant cardiac dysfunction in the 50 patients with AKI; however, high-sensitivity troponins were elevated. Upon ICU admission, all patients had leukocytosis with lymphocytopenia, and increased levels of lactate, creatinine, CRP, LDH, ferritin, D-dimers, and interleukin-6 (Table 3). Duration of MV was 17.38 ± 7.39 days, ICU length of stay was 20.70 ± 8.83 days, and mortality on day-28 post-ICU admission was 30% (Table 2).

3.1 | Therapeutic interventions

Upon ICU admission, all COVID-19 patients with AKI had anuria and metabolic derangement (ie, metabolic acidosis and electrolyte abnormalities), ARDS, septic shock, and CRS

(Table 3). All received ARDS-net/prone positioning ventilation, and empiric treatment with ribavirin, interferon beta-1b, antibiotics, hydrocortisone (200 mg daily), and ICU supportive care.^{29,47} All patients received low-molecular-weight heparin thromboprophylaxis adjusted to baseline weight and renal function, unless contraindicated. This worked out to enoxaparin 20 mg once daily if <50 kg; enoxaparin 40 mg once daily if 50-100 kg; 40 mg twice daily if 101-150 kg; 60 mg twice daily if >150 kg. Therapeutic anticoagulation was administered to all patients with confirmed PE (24%). Upon ICU admission, all patients had increased norepinephrine requirements (0.93 ± 0.19 mcg/kg/min); however, after the administration of vasopressin (infusion rate: 0.05 ± 0.02 units/min) the norepinephrine dose was universally reduced (0.39 ± 0.2 mcg/kg/min). CVVHD in conjunction with CytoSorb was administered in all cases (mean ultrafiltration rate: 180 ± 20 mL/min; daily time duration: 24 hours).

The 35 survivors (aka “responders”), received 2 ± 1 CRRT sessions. The 15 nonsurvivors (aka “non-responders”) received 6 ± 2 CRRT sessions. ECMO was used in four cases (one survived, three died). Table 4 illustrates the main studied parameters before and after CRRT completion. The 15 nonsurvivors had refractory ARDS, unresolved septic shock with increased norepinephrine requirements, and coagulopathy; characterized by increased international normalization ratio but relatively preserved platelet counts (Table 4).²⁻⁶ Platelet counts were reduced post-CRRT but no clinical significance was observed. Nonsurvivors had persistently abnormal renal function and lymphocytopenia, plus increased CRP, LDH, ferritin, and especially high levels of IL-6, posttherapy (Table 4, Figure 2). All nonsurvivors expired approximately within 2 weeks post-ICU admission (10 ± 4 days), (Figure 3).

For the 35 survivors, and after 2 ± 1 sessions of CVVHD with CytoSorb, diuresis could be initiated, vasopressors were weaned off, and renal function gradually improved. Survivors



TABLE 2 Summary of baseline characteristics and outcome measures of critically ill COVID-19 patients with acute kidney injury ($n = 50$)

Characteristic	Patients ($n = 50$)
Age (years)	49.64 ± 8.90
Sex (male; n, %)	39 (78%)
Body mass index (kg/m ²)	26.70 ± 2.76
APACHE II score upon ICU admission	22.52 ± 1.11
SOFA score upon ICU admission	9.36 ± 2.068
PaO ₂ /FiO ₂ ratio upon ICU admission	117.46 ± 36.92
Symptoms onset to ICU admission (days)	6.34 ± 1.86
Cluster infection (n, %)	11 (22%)
Pulmonary embolism (n, %)	12 (24%)
Veno-venous ECMO (n, %)	4 (8%)
<i>Symptoms prior to hospital admission</i>	
Cough (n, %)	45 (90%)
Fever (n, %)	42 (84%)
Dyspnea (n, %)	35 (70%)
Sputum production (n, %)	22 (44%)
Nausea/Vomiting (n, %)	9 (18%)
Diarrhea (n, %)	7 (14%)
Altered level of consciousness (n, %)	4 (8%)
Anosmia (n, %)	3 (6%)
<i>Comorbidities</i>	
Diabetes mellitus	14 (28%)
Hypertension	25 (50%)
Cardiovascular disease	4 (8%)
<i>Outcome measures</i>	
Duration of mechanical ventilation (days)	17.38 ± 7.39
ICU length of stay (days)	20.70 ± 8.83
Patients discharged from the hospital (n, %)	35 (70%)
Mortality day-28 (n, %)	15 (30%)

Note: Values are medians with interquartile ranges.

Abbreviations: APACHE II score, Acute Physiology and Chronic Health Evaluation II score; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PaO₂/FiO₂, partial arterial pressure of oxygen to fractional inspired concentration of oxygen; SOFA score, Sequential Organ Function Assessment score.

also had significantly increased PaO₂/FiO₂ ratio. Survivors had decreases in SOFA score, lactate dehydrogenase, ferritin, D-dimers, C-reactive protein, lactate, and interleukin-6. Survivors also had persistent increases in lymphocyte counts post-CRRT plus CytoSorb (Table 4, Figure 3). While detailed analysis of all potential cofounders affecting survival could not be performed due to the small sample size, PE prevalence was significantly lower in survivors versus nonsurvivors (4% vs. 8%, $P < .05$). Also, ROC analysis revealed that posttherapy values of IL-6, using a cutoff point >620 pg/mL,

TABLE 3 Summary of baseline parameters in the 50 COVID-19 patients with acute kidney injury

Parameters	Baseline patients ($n = 50$)
Urine output (mL/d)	112.98 ± 67.66
Noradrenalin infusion rate (µg/kg/min)	0.93 ± 0.19
White blood cells (cells/mm ³ , normal: 4-10)	13.16 ± 3.17
Lymphocyte count (10 ⁹ /normal: 1.1-3.2)	0.71 ± 0.26
Platelets (cells/mm ³ , normal: 150-450)	140.20 ± 35.62
International normalized ratio (normal: 0.8-1.2)	1.21 ± 0.32
Total bilirubin (µmol/L, normal: 0-26)	33.28 ± 6.67
Alanine aminotransferase (u/L, normal: 9-50)	87.46 ± 53.25
Aspartate aminotransferase (u/L, normal: 15-40)	107.48 ± 93.40
Serum creatinine (mg/dL, normal: 0.6-1.2)	2.13 ± 0.36
Hs-troponin I (ng/mL, normal: 0-0.04)	0.19 ± 0.138
Serum lactate (mmol/L, normal: 1-2.5)	6.88 ± 2.87
C-reactive protein (mg/L, normal:0-5)	140.3 ± 90.2
Lactate dehydrogenase (u/L, normal:100-190)	547.2 ± 149.64
Ferritin (ng/mL, normal: 23-336)	529.14 ± 112.40
D-dimers (µg/mL, normal: <1)	3.18 ± 2.16
Interleukin-6 (pg/mL, normal: 1-7)	645.56 ± 189.50

predicted in-hospital mortality of COVID-19 patients with a sensitivity of 0.79 [95% confidence intervals (CI): 0.74-0.88] and a specificity of 0.84 (95% CI: 0.79-0.89) [Area-under-the-curve (AUC): 0.87, 95% CI: 0.81-0.93; $P = .001$], (Figure 4). The same analysis showed that posttherapy values of SOFA score, using a cutoff point >10, had a sensitivity of 0.74 (95% CI: 0.71-0.82) and a specificity of 0.78 (95% CI: 0.73-0.85) (AUC: 0.80, 95% CI: 0.73-0.85; $P = .01$) for predicting in-hospital mortality of COVID-19 patients (Figure 5).

Survivors were successfully liberated from the mechanical ventilation, and discharged from the hospital to home isolation 32 ± 12 days post-ICU admission. SARS-CoV-2 RNA, assayed by RT-PCR and microbiology were negative in survivors after 22 ± 4 days post-ICU admission.

4 | DISCUSSION

In this retrospective case-series, we showed that CRRT in conjunction with CytoSorb was associated with reduced inflammatory biomarkers, improved oxygenation and better renal function in a subset of patients with life-threatening COVID-19. Approximately 70% responded favorably and survived. In contrast, nonresponders (30%) continued on a fulminant clinical course, characterized by high inflammatory biomarkers, lymphocytopenia, refractory ARDS,



TABLE 4 Comparison of parameters before and after the completion of continuous renal replacement therapy with CytoSorb in COVID-19 patients with acute kidney injury who survived ($n = 35$), and did not survive ($n = 15$)

Parameters	COVID-19 patients with AKI ($n = 50$)			
	Survivors ($n = 35$)		Nonsurvivors ($n = 15$)	
	Before therapy	After therapy	Before therapy	After therapy
Urine output (mL/d)	119.17 ± 73.43	997.6 ± 273.34*	98.53 ± 51.07	103.6 ± 40.89
Sequential organ function assessment score	9.86 ± 1.94	2.23 ± 1.03*	9.20 ± 1.93	10.8 ± 1.82*
PaO ₂ /FiO ₂ ratio	113 ± 34.68	303.43 ± 37.41*	127.87 ± 41.03	83.33 ± 21.27*
Noradrenalin infusion rate (µg/kg/min)	0.97 ± 0.16	0*	0.85 ± 0.23	1.467 ± 0.167
White blood cells (cells/mm ³ , normal: 4-10)	13.48 ± 3.245	10.11 ± 1.65*	12.40 ± 2.95	13.6 ± 3.24*
Lymphocyte count (10 ⁹ /L, normal: 1.1-3.2)	0.73 ± 0.23	0.92 ± 0.21*	0.67 ± 0.33	0.67 ± 0.47
Platelets (cells/mm ³ , normal: 150-450)	133.97 ± 31.80	115.94 ± 26.64*	154.73 ± 40.76	130.2 ± 42.08*
International normalized ratio (normal: 0.8-1.2)	1.12 ± 0.21	1.12 ± 0.19	1.21 ± 0.43	1.42 ± 0.51*
Total bilirubin (µmol/L, normal: 0-26)	32.63 ± 7.142	24.34 ± 3.92*	34.80 ± 5.33	37.33 ± 7.04*
Alanine aminotransferase (u/L, normal: 9-50)	69.51 ± 37.20	60.66 ± 32.38*	129.33 ± 62.30	340.6 ± 56.17*
Aspartate aminotransferase (u/L, normal: 15-40)	76.51 ± 61.73	40.28 ± 18.158*	179.73 ± 55.26	352.53 ± 51.63*
Serum creatinine (mg/dL, normal: 0.6-1.2)	2.11 ± 0.28	1.25 ± 0.18*	2.12 ± 0.38	1.88 ± 0.35
Hs-troponin I (ng/mL, normal: 0-0.04)	0.20 ± 0.15	0.04 ± 0.04*	0.18 ± 0.11	0.17 ± 0.14
C-reactive protein (mg/L, normal: 0-5)	145.4 ± 98.3	43.6 ± 26.2*	128.4 ± 69.3	144.3 ± 97.8*
Serum lactate (mmol/L, normal: 1-2.5)	6.77 ± 2.56	2.17 ± 0.79*	7.15 ± 3.59	8.48 ± 6.01*
Lactate dehydrogenase (u/L, normal: 100-190)	619.69 ± 181.39	333.14 ± 53.84*	378.07 ± 75.52	646.27 ± 116.48*
Ferritin (ng/mL, normal: 23-336)	602.34 ± 142.18	296.46 ± 62.93*	358.33 ± 175.24	729 ± 163.43*
D-dimers (µg/mL, normal: <1)	2.86 ± 0.78	1.15 ± 0.9*	3.94 ± 1.78	3.83 ± 1.41
Interleukin-6 (pg/mL, normal: 1-7)	612.85 ± 185.63	170.11 ± 77.78*	721.87 ± 506.93	1252.6 ± 859.19*

Abbreviations: AKI: acute kidney injury, PaO₂/FiO₂ = partial arterial pressure of oxygen to fractional inspired concentration of oxygen.

*Comparisons before and after the completion of therapy in survivors and in nonsurvivors; $P < .05$.

recalcitrant shock, and progressed towards MSOF and death.¹⁻⁵ Our preintervention incidence of AKI was 19.1%, while 10.16% of our critically ill COVID-19 met criteria for CRRT.^{1-8,48,49} The mortality rate in patients with life-threatening COVID-19 and AKI (30%) was comparable, or lower, than previous studies, which reported mortality rates up to 52%.^{1-8,48-50}

Our work also supplements the nascent evidence base supporting CRRT plus CytoSorb in COVID-19 patients with AKI. Previous studies suggested a putative benefit in patients with septic shock but failed to show any significant mortality effect.^{24,51} Notably, our 50 patients had life-threatening disease, as highlighted by multiple poor prognosticators: AKI, ARDS, and hyperinflammation^{1-8,29-36} This made it comparatively easy to justify this putative rescue therapy. Our work also bolsters the presumed link between continued biochemical derangement and COVID-19 death. Our nonsurvivors not only had persistent elevation in inflammatory biomarkers, but they also had lymphocytopenia, unresolved septic shock, refractory ARDS, and higher PE prevalence compared to survivors/responders. Our pilot work is encouraging, but larger

prospective studies are needed before claiming this therapy is clinically warranted, given that our feasibility study was underpowered and retrospective (see additional limitations below). Regardless, it does help build the case for that future work.

The RECOVERY trial showed that early suppression of inflammation using low-dose dexamethasone was beneficial in COVID-19.²⁸ CytoSorb therapy could also mitigate hyperinflammation in life-threatening COVID-19. In future work, we intend to further explore this by comparing CRRT as a stand-alone therapy versus CRRT with CytoSorb. The gradual resolution of renal function in our patients also supports, though does not confirm, the possibility that acute tubular necrosis is part of COVID-19 associated renal dysfunction.⁴⁸⁻⁵² Other possibilities include hemodynamic instability, prerenal injury, and even glomerulopathy and glomerulonephritis.^{1-8,49-56}

Future research could also focus on patients who did not respond to therapy. In addition to increased IL-6, our work suggests that this may be linked to increased PE prevalence. The current results support that COVID-19 is associated

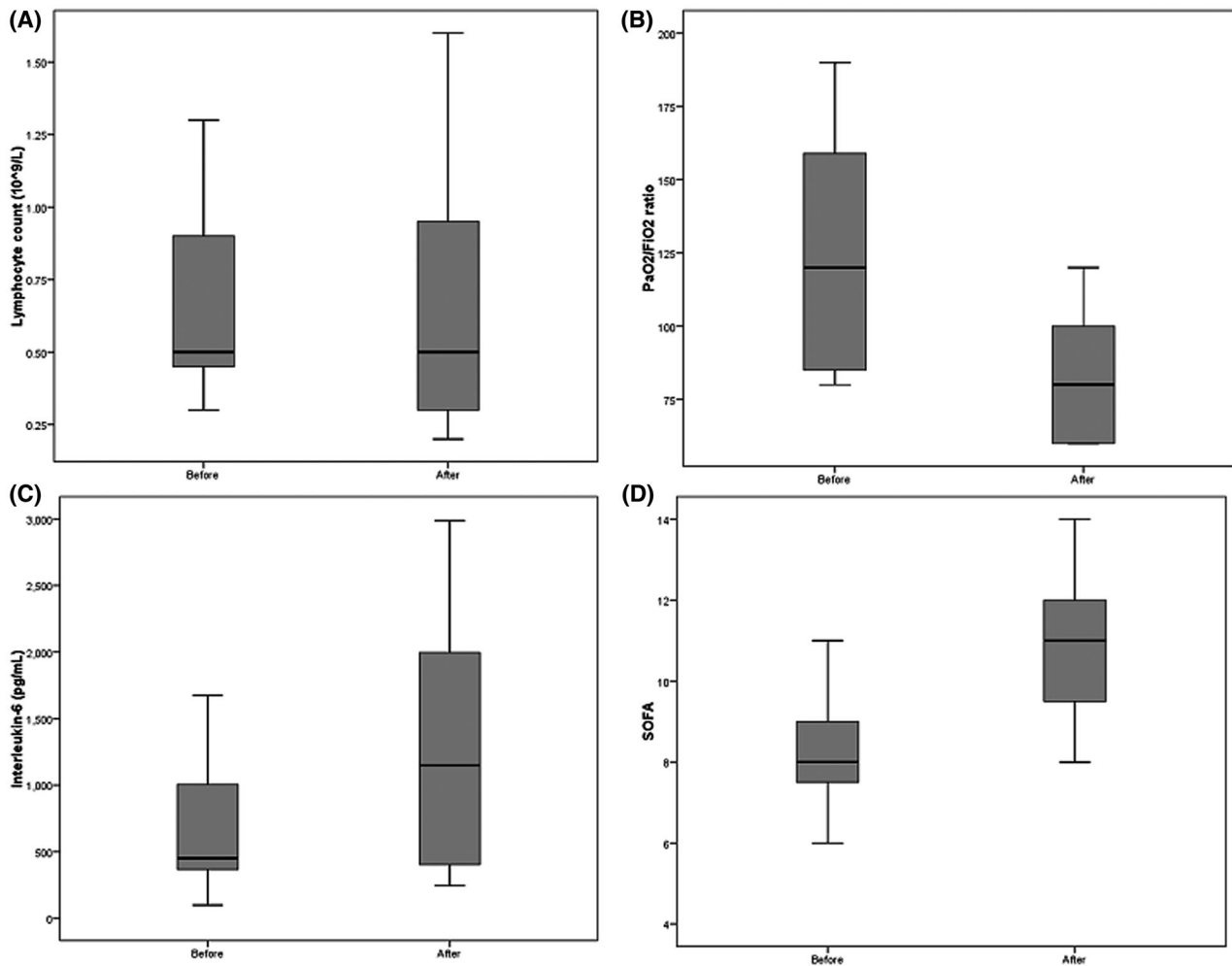


FIGURE 2 Tukey boxplots with equal whisker lengths of 1.5 interquartile ranges for both whiskers in the fifteen COVID-19 non-survivors depicting no changes in lymphocyte counts (A; $P = .89$), and reduced partial arterial pressure of oxygen to fractional inspired concentration of oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio (B), as well as increased interleukin-6 levels (C), and Sequential Organ Function Assessment (SOFA) score (D) (all $P = .0001$), post-continuous renal replacement therapy with CytoSorb

with an increased incidence of thromboembolic disease and that this portends a bad prognosis.⁵⁷⁻⁶⁰ In future work, we intend to measure levels of ADAMTS 13 activity, a marker of thromboinflammation, and a prognosticator in MSOF.⁶⁰⁻⁶² After all, extracorporeal blood purification therapy may ultimately be insufficient to rapidly counteract severe thromboinflammation during its late stages.

This case-series has limitations, which reduce its generalizability. In addition to its retrospective nature, there is always the possibility that our patients might have improved without our intervention, or because of the other empiric treatments. In other words, a detailed subgroup analysis was not possible due to the small sample size. Previously, it was suggested that continuous hemoadsorption with CytoSorb can remove circulating antibiotics.⁶³ Also, scarce data exist regarding the effect of extracorporeal blood purification therapies on the levels of antiviral agents. Regrettably, we did not have the capability to measure antibiotics/antivirals levels, additional cytokines or procalcitonin levels. A pilot study showed

positive effects on lactate and procalcitonin levels following CytoSorb therapy.⁶⁴ We confirmed the positive effect on lactate levels but not on procalcitonin.

Our patients had increased levels of IL-6, which appear to be central to the development of CRS.^{29,64-67} but we did not have access to tocilizumab (recombinant, humanized monoclonal antibody against both soluble and membrane bound IL-6 receptors) or plasma exchange or other immunomodulatory therapies. We did, however, find that nonsurvivors had a dramatic increase of inflammatory biomarkers, especially IL-6.⁶⁵⁻⁶⁸ Also, ROC analysis showed that posttherapy values of IL-6, using a cutoff point >620 pg/mL, predicted in-hospital mortality of critically ill COVID-19 patients (AUC: 0.87, 95% CI: 0.81-0.93; $P = .001$), which duplicates a recently published study.⁶⁹ However, IL-6 signaling is mediated by a distinctive IL-6 receptor system, which may also play a physiologic role in immune-inflammatory disorders.^{70,71} Two possible eradication routes of IL-6 from serum exist: receptor-mediated clearance and degradation of IL-6 protein.

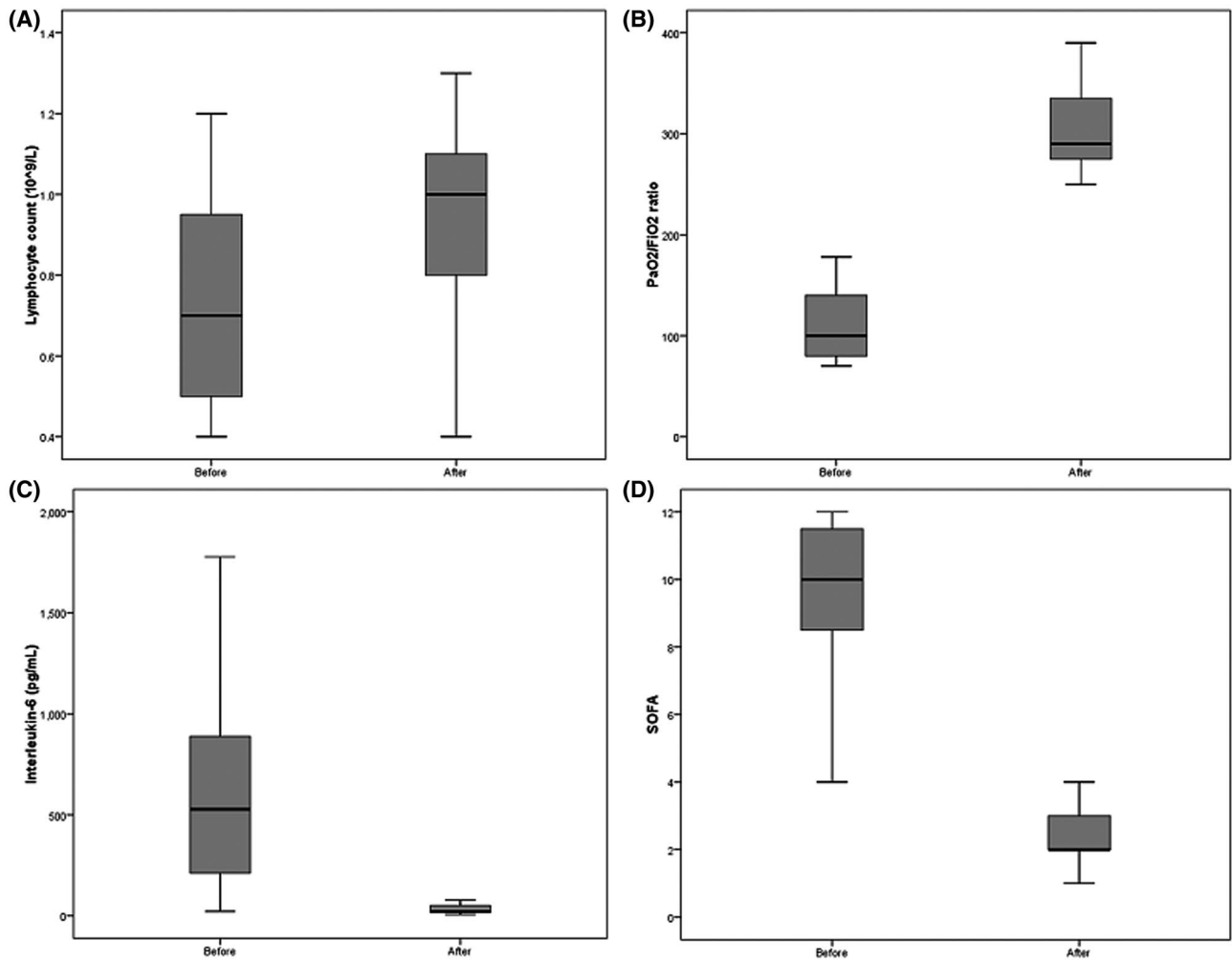


FIGURE 3 Tukey boxplots with equal whisker lengths of 1.5 interquartile ranges for both whiskers in the thirty five COVID-19 survivors depicting increased lymphocyte counts (A), and partial arterial pressure of oxygen to fractional inspired concentration of oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio (B), as well as reduced interleukin-6 levels (C), and Sequential Organ Function Assessment (SOFA) score (D) (all $P = .0001$), post-continuous renal replacement therapy with CytoSorb

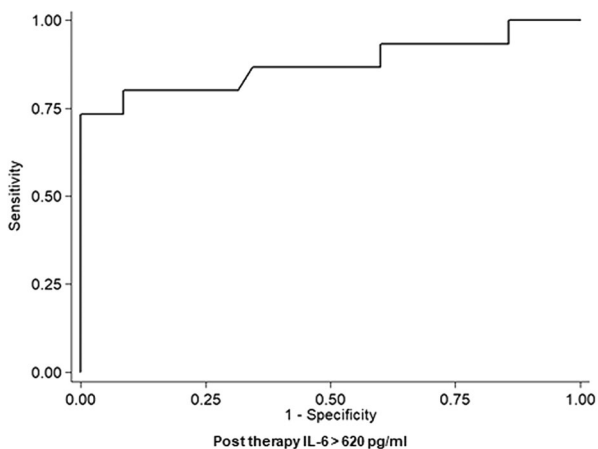


FIGURE 4 Receiver operator curve analysis of post therapy interleukin-6 values (IL-6), using a cutoff point >620 pg/mL, in predicting mortality for COVID-19 patients (area-under-the-curve: 0.87, 95% CI: 0.81-0.93; $P = .001$)

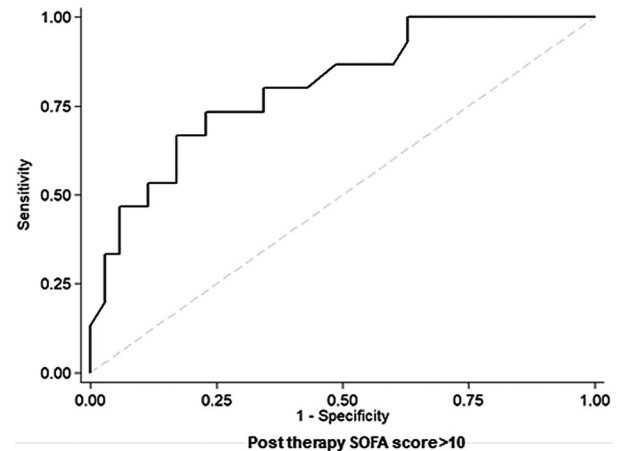


FIGURE 5 Receiver operator curve analysis of post therapy Sequential Organ Assessment Function (SOFA) score values, using a cutoff point >10 , in predicting mortality for COVID-19 patients (area-under-the-curve: 0.81, 95% confidence-intervals: 0.73-0.86; $P = .01$)



It was reported that serum levels IL-6 reflected true disease activity, after the administration of tocilizumab, in patients with rheumatoid arthritis.⁷² In our study, whether the applied extracorporeal blood purification therapy could remove soluble IL-6 receptors is uncertain as we did not measure their levels. However, we speculate that reduction of free serum IL-6 levels during CytoSorb treatment may indicate remission of the COVID-19 associated CRS, which remains to be confirmed by future studies.

Our patients received 200 mg of hydrocortisone (40 mg prednisone equivalent); hence, steroids might have affected the immune response or viral clearance. The natural course of SARS-CoV-2's viremia is still obscure, especially as reinfections, and persistently positive RT-PCR results have been reported.⁷³⁻⁷⁵ Hence, the correlation of viral RNA reduction and hemoabsorption, is a fertile area for future study, along with elucidating the optimal extracorporeal blood purification regime in COVID-19 associated sepsis and hyperinflammation.⁷⁶⁻⁸⁰

Despite limitations, this study suggests that CRRT with CytoSorb can mitigate the hyperinflammation of life-threatening COVID-19 with associated sepsis and AKI.^{28,29,73-81} Moreover, it appears to be safe and feasible. Although the CytoSorb cartridge was initially manufactured to remove cytokines, it has also shown the ability to remove pathogen-associated molecular pattern molecules (ie, bacterial exotoxins), and damage associated molecular pattern molecules.⁸¹⁻⁸⁴ In brief, as we continue the multi-pronged worldwide search for COVID-19 therapies, we should not rule out the combination of CRRT and hemoabsorption cartridges in life-threatening COVID-19 cases with AKI. Conceivably, the addition of hemoabsorption to CRRT or ECMO may expand their potential application in critically ill COVID-19 patients.

5 | CONCLUSION

In this retrospective case-series, we showed that the combination of CRRT and CytoSorb is a safe potential rescue therapy in critically ill COVID-19 patients with AKI, ARDS, septic shock, and hyperinflammation. The majority of critically ill COVID-19 patients who underwent CRRT with CytoSorb survived (70%); while nonresponders/non-survivors (30%) had increased prevalence of PE and progressed to MSOF. Future larger prospective studies are required to confirm or refute these encouraging, albeit initial, findings.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript and agree with its submission to the journal.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board of King Saud Medical City, Riyadh, Kingdom of Saudi Arabia [H-01-R-053, IORG0010374#, serial number: H1RI-22-20-03]. Written informed consent was obtained by all eligible patients or their legal representatives.

ORCID

Dimitrios Karakitsos  <https://orcid.org/0000-0003-3370-7099>

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