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Cytokine Adsorption in Critically Ill COVID-19 Patients, a Case-Control Study

Ruslan Abdullayev, MD[1], Fethi Gul, MD[1], Beliz Bilgili, MD[1], Seda Seven, MD[2], and Ismail Cinel, MD, PhD[1]

Abstract

Aim: New coronavirus disease (COVID-19) has become an international emergency. As many of the intensive care unit (ICU) patients with the disease also present multiple organ failure, blood purification techniques might be a good choice in their treatment. In this study we aimed to investigate the role of cytokine removal in COVID-19 patients managed in ICUs. **Methods:** For this case-control study we have investigated the role of the cytokine removal by means of two resin membranes (HA330 and Mediasorb) in COVID-19 patients managed in ICUs. Particularly, we investigated the overtime variation in clinical severity scores, laboratory variables, and effects on hospital and ICU stay and mortality. **Results:** Seventy-two patients have been evaluated, of which half constituted Cytokine Filtration (CF) Group, and other half the Case-Control (CC) Group. Mortality was 55.6% and 50% in CF and CC groups, respectively. In the CF Group, there was decrease in C-reactive protein (CRP) and fibrinogen levels measured at the end of cytokine adsorption; lymphocyte count and ratio were increased, whereas neutrophile ratio was decreased. There were no differences between the groups regarding other laboratory variables, SOFA scores and vasopressor uses. **Conclusions:** We have demonstrated decrease in CRP, fibrinogen and increase in lymphocyte count in the patients having cytokine adsorption, but there was no clinical reflection of these benefits, and no decrease in mortality as well. Even though there is physio-pathologic rationale to use cytokine adsorption techniques for immunomodulation in critically ill COVID-19 patients, it is early to make strong suggestions about their benefits.

Keywords

adsorption, blood purification, COVID-19, cytokine filtration, intensive care unit

Introduction

World Health Organization (WHO) identified the new coronavirus disease (COVID-19) that is caused by SARS-CoV-2 as an international public health emergency in March 2020.[1] Mild infection manifests itself as myalgia, fatigue, fever, cough, dyspnea, diarrhea, dehydration. Severe infection can present with acute respiratory distress syndrome (ARDS) or multi-organ failure.[2]

As there is still no definitive antiviral treatment for the disease, the treatment mainly consists of oxygen administration, thromboprophylaxis, and organ system supports. These supports of the organ systems include vasoactive medications for cardiovascular, mechanical ventilation for respiratory, and hemodialysis/hemofiltration for renal support. Although the majority of the patients can be treated at home, or on hospital wards, those requiring organ support systems are usually managed in the intensive care units (ICU).

About 20–40% of COVID-19 patients admitted to ICU develop acute kidney injury (AKI), and this is thought to be a marker of severity with the negative impact on survival.[3] Thus, renal replacement therapy (RRT) in ICUs is higher compared with the general ICU population. Early reports have documented RRT need for COVID-19 patients in ICU to be about 23–36%.[3] As many of these patients also present multiple organ failure, sequential extracorporeal blood purification (EBP) techniques in combination with RRT might be a good choice in the treatment. The rationale in this is that hyper-inflammatory state and excess cytokine activation is responsible for multiple organ failures in the disease, and EBP is one of the options to ameliorate this hyper-inflammation. Even though their efficacy is still not well established, and their mechanism of action is still under research, many authors suggest their application to attenuate systemic inflammation in COVID-19.

Blood purification therapies can particularly be beneficial in cytokine storm syndrome (CSS). This syndrome is the result of overproduction of inflammatory mediators and biochemical consequences, like vascular injuries, increased vascular

[1]Department of Anesthesiology and Reanimation, Marmara University School of Medicine, Istanbul, Turkey
[2]Department of Anesthesiology and Reanimation, Marmara University Training and Research Hospital, Istanbul, Turkey

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Corresponding Author:
Prof. Dr. Ismail Cinel, Marmara University School of Medicine, Department of Anesthesiology and Reanimation, Istanbul, Turkey.
Email: cinelismail@yahoo.com

permeability, edema, necrosis, cell death, etc. Clinical presentations of these reactions include high fever, blood clot formation on micro-vessels, hypotension, increased oxygen demand, acidosis, pulmonary edema. Common clinical sequels of CSS are ARDS and multiple organ dysfunction syndrome (MODS).[4] Elevated levels of blood inflammatory mediators are predictive of the fatal outcome in COVID-19 patients. For this reason, immunomodulation therapies are considered as a part of standard practice in the management of severely ill COVID-19 patients. One way to make immunomodulation is specific or non-specific antagonism of the parts of the immune system. Examples for specific blockade are anakinra, tocilizumab, and baricitinib for IL-1, IL-6, and Janus kinase (JAK) inhibition, respectively. Examples for non-specific immune system modulators are glucocorticoids, colchicine, mesenchymal stem cells, convalescent plasma.[5] Another way for immunomodulation is the abovementioned extracorporeal blood purification.

The HA330 membrane (Jafron, Zhuhai, China) is a highly biocompatible membrane cartridge that is used for removing specific solutes in extracorporeal blood purification therapies. It contains resin adsorbing beads made of styrene-divinylbenzene copolymer. The resin pore size ranges from 500 Da to 60 kDa, and it has characteristics of specific recognition and adsorption capacity to different molecular weight molecules in this range. As blood passes through the absorbent bed, molecules less than 60 kDa enter the device pores and attach onto the surface of the polymer. By means of adsorption the membrane is able to thoroughly remove endogenous and exogenous materials such as middle uremic toxins, protein-bound uremic toxins, hydrophobic or protein-bound exogenous substances, cytokines (eg, IL-1, IL-6, IL-8, TNFα, IFNɣ), complements (eg, C3a, C5a), free hemoglobin, and residual drugs. The device can be applied in hemoperfusion modality or in series with hemodialysis-based treatments.[6] Many studies have demonstrated beneficial results of the application of HA330 membrane in sepsis, septic shock, acute lung injury in terms of patients' hemodynamics, reduced ICU length of stay, and mortality.[7–9]

Mediasorb cartridge (Medtronic, Minneapolis, USA) is composed of an adsorbent resin with microporous structure. It can be added to coupled plasma filtration adsorption (CPFA) therapy. The resin adsorbs inflammatory mediators. This cartridge can be used in clinical conditions, like sepsis and multiple organ failure.[10]

In this study we have investigated the role of cytokine removal by the means of two resin membranes (HA330 and Mediasorb) in COVID-19 patients managed in ICUs. Particularly, we investigated the overtime variation in clinical severity scores, laboratory variables, and effects on ICU stay and mortality.

Methods

This study considered data of the patients with the diagnosis of COVID-19 admitted to the ICU of a University Hospital between March and December 2020, who received treatment with cytokine adsorption membrane for immunomodulation. The study was designed as case-control, and data of the same number of the patients with similar clinical and laboratory characteristics were also collected to be compared with the study group. Investigational Review Board approval was obtained for the study (Marmara University School of Medicine Investigational Review Board, 09.2021.603). The study was observational in design and did not involve any pharmacological or behavioral interventions other than the standard practices regardless of the study. The study was carried out in the agreement with the principles laid out in the Declaration of Helsinki.

Diagnosis of SARS-Cov-2 infection was made by either real-time reverse transcriptase polymerase chain reaction (PCR) at nasal/oral swab, or clinical evaluation supported by thorax computerized tomography. Cytokine adsorption was planned according to our national guidelines published and updated by the Ministry of Health. It was applied to the patients admitted to ICU with the diagnosis of COVID-19 who had cytokine storm. The diagnosis of cytokine storm was made based on clinical and laboratory findings like fever, leukocytosis, lymphopenia, thrombocytopenia, hypofibrinogenemia, elevated ferritin, CRP and D-dimer levels.

Objectives of the study were to compare overtime variation of laboratory, multiorgan dysfunction scores of the patients in cytokine adsorption and control groups; their ICU and hospital length of stays; and mortality rates as well. Data considered for the study included demographic, clinical and biochemical parameters (including inflammatory markers) of the patients; comorbidities; organ dysfunction scores (Acute Physiology and Chronic Health Evaluation II [APACHE II], Sequential Organ Failure Assessment [SOFA]); vasopressor use; use of tocilizumab; and mechanical ventilation. Clinical and laboratory evaluation was performed in the morning of the cytokine adsorption and the following morning of the last dose of cytokine adsorption application.

All the patients in this study received treatment drugs (antimicrobials, anti-thrombotic agents, immunomodulators, etc), mechanical ventilation, organ support treatments (vasopressors, renal replacement therapy, etc) in accordance with the clinical judgement of the hospital. We have standardized protocols for the treatment of the COVID-19 patients in ICU. Our treatment consists of favipiravir (2×1600 mg on first day, then 2×600 mg for 4 days PO), vitamin B complex (B1 200 mg/day, B2 16 mg/day, B3 400 mg/day, B5 68.8 mg/day, B6 40 mg/day IV), vitamin C (6 g/day IV), vitamin D (50.000 U/week PO), corticosteroid (dexamethasone 6 mg/day IV or methylprednisolone 1-2 mg/kg/day IV), enoxaparin ($2 \times$ 60 mg SC). Stress peptic ulcer prophylaxis, enteral/parenteral nutrition, physical therapy is also applied. All the patients routinely receive oxygen. As a standard, oxygen treatment with reservoir oxygen mask is started for all patients. De-escalation to nasal cannula or face mask is made with clinical improvement and decreased oxygen demand; whereas escalation is made to high-flow nasal cannula or noninvasive mechanical ventilation in case of clinical deterioration and increased oxygen demand. In case of resistant hypoxemia, patients are intubated, and mechanical ventilation support is provided. Other organ systems are also supported in accordance

with our ICU protocols (eg, inotropic support for heart failure, fluid and vasopressors for shock, renal replacement therapies for kidney failure, etc). Tocilizumab 400–800 mg IV or high dose corticosteroid therapy (methylprednisolone 250 mg IV per day, for 3 days) is applied in the clinical and laboratory suspicion of cytokine storm syndrome.

Cytokine adsorption was carried out by HA330 membrane (Jafron, Zhuhai, China), or Mediasorb cartridge (Medtronic, Minneapolis, USA) in accordance with our local ICU protocol. Patients with the diagnosis of AKI had CRRT based on the institutional protocols. Cytokine adsorption was carried out for 4 hours at each time, and the duration was determined by the senior physician. Pre-filtration clinical and laboratory evaluation of the patient was done in the morning of the first cytokine filtration, whereas post-filtration evaluation was done the next morning of the last adsorption treatment.

Statistical analysis was performed by Statistical Package for the Social Sciences (SPSS 22.0, IBM, NY, USA). Shapiro-Wilk test were used to test normal distribution of numerical data. Categorical variables were expressed as frequency and percent. Numerical variables were expressed as mean ± standard deviation (SD) if they were normally distributed, and median ± interquartile range (IQR) if not. Independent sample t-test was used in the analysis of numerical variables, and Mann-Whitney U test, if the assumptions of the test were not provided. Paired sample t-test was used in the analysis of paired numerical data, and Wilcoxon test, if the assumptions of the test were not provided. Chi-square test was used in the comparison of categorical variables, and Fisher's exact test, if the assumptions of the test were not provided. $P < 0.05$ was assumed as significant.

Results

A total of 72 patients have been evaluated, of which half constituted the cytokine filtration group (Group CF), and other half the case-control group (Group CC). Demographics and clinical characteristics of the patients are presented in Table 1. About half of the patients had AKI, and more than 80% of the patients required mechanical ventilation in both the groups. There were no significant differences between the groups, except for the Gr(+) bacterial infection rates, which was significantly higher in the Group CF ($P = 0.014$). Tocilizumab was used in approximately 64% and 47% of the patients in the CF and CC groups, respectively, but the difference was not statistically significant ($P = 0.155$). Mortalities were 55.6% and 50% in the groups CF and CC, respectively ($P = 0.637$).

Laboratory variables of the patients consisting of acute phase reactants and inflammatory cells are presented in Table 2. The two study groups were comparable in the means of laboratory variables except D-dimer levels and neutrophile ratio, which were significantly higher in Group CF compared with Group CC ($P = 0.03$ for D-dimer and $P < 0.001$ for neutrophile ratio).

Clinical and laboratory variables of the patients measured at pre-filtration and post-filtration are presented in Table 3. There was a significant decrease in CRP and fibrinogen levels at post-filtration ($P = 0.012$ and 0.016, respectively). Lymphocyte count and ratio were significantly increased at post-filtration ($P = 0.001$ and 0.013 for lymphocyte count and ratio, respectively). Neutrophile ratio was significantly decreased at post-filtration ($P = 0.046$). There were no significant changes regarding other laboratory variables, SOFA scores and vasopressor uses at post-filtration.

Cytokine filter application start times from the COVID-19 diagnosis and duration of the adsorption in the Group CF, as well as the membrane types used are presented in Table 4. When we compare survivors and non-survivors, there was no significant difference in diagnosis-cytokine adsorption start times between the patients. The EBP start times were 10.7 and 12 days for survivors and non-survivors, respectively.

Table 1. Patient Demographics and Clinical Characteristics.

	Group CF (n = 36)	Group CC (n = 36)	*P*
Age (years)	56.69 ± 11.58	56.89 ± 16.74	0.954
Sex Male	27 (75.0)	20 (55.6)	0.083
Female	9 (25.0)	16 (44.4)	
APACHE II	15 (11-19)	16 (10-19)	0.937
SOFA	9 (3-11)	7 (5-9)	0.328
P/F ratio	104 (70-134)	108 (80-195)	0.219
Comorbidity	24 (66.7)	25 (69.4)	0.800
DM	14 (38.9)	13 (36.1)	0.808
HT	12 (33.3)	14 (38.9)	0.624
CVD	9 (25.0)	8 (22.2)	0.781
COPD	4 (11.1)	2 (5.6)	0.337
CKD	1 (2.8)	4 (11.1)	0.179
CeVD	2 (5.6)	3 (8.3)	0.500
Other	2 (5.6)	6 (16.7)	0.130
Secondary infection	27 (75.0)	21 (58.3)	0.134
Gr(+) bacterial	18 (50.0)	8 (22.2)	0.014*
Gr(-) bacterial	16 (44.4)	15 (41.7)	0.812
Fungal	8 (22.2)	9 (25.0)	0.781
AKI	19 (52.8)	17 (47.2)	0.637
Vasopressor use	23 (63.9)	28 (77.8)	0.195
Mechanical ventilation	31 (86.1)	29 (80.6)	0.527
Tocilizumab use	23 (63.9)	17 (47.2)	0.155
Mortality	20 (55.6)	18 (50)	0.637
ICU length of stay (days)	18 (10-30)	17 (10-20)	0.443
Hospital length of stay (days)	24 (17-38)	24 (19-36)	0.937

Note. Data is expressed as number of the patients (percent of total) for categorical; and mean (SD), mean (minimum-maximum) or median (IQR) for numerical variables. APACHE II, Acute Physiology and Chronic Health Evaluation II score; SOFA, Sequential Organ Failure Assessment Score; P/F ratio, PaO_2/FiO_2 ratio; DM, diabetes mellitus; HT, hypertension; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CeVD, cerebrovascular disease; Gr, gram; AKI, acute kidney injury; ICU, intensive care unit. *$P < 0.05$.

Discussion

This study aimed to investigate the clinical and laboratory data of critically ill COVID-19 patients in ICUs, undergoing EBP by membranes with cytokine adsorptive capacities. The major

Table 2. Laboratory Variables of the Patients.

	Group CF (n = 36)	Group CC (n = 36)	*P*
Procalcitonin (μg/L)	0.65 (0.20-1.70)	0.32 (0.18-1.48)	0.569
CRP (mg/L)	89 (38-163)	118 (97-178)	0.145
Ferritin (μg/L)	966 (476-1643)	663 (375-1262)	0.230
Fibrinogen (mg/dL)	525 ± 211	614 ± 178	0.061
D-dimer (mg/L)	3.39 (1.87-10.82)	1.96 (1.03-3.29)	0.030*
Lymphocyte count (x10^3/μL)	0.6 (0.4-0,9)	0.6 (0.4-1.1)	0.580
Lymphocyte ratio (%)	4.4 (3.3-8.8)	6.1 (3.2-12.1)	0.327
Neutrophile ratio (%)	89 (85-92)	57 (48-72)	<0.001*
N/L ratio	20.7 (9.7-27.7)	15.0 (7.5-27.8)	0.265
Platelet count (x10^3/μL)	248.8 ± 99.8	241.5 ± 119.6	0.781

Note. Data is expressed as mean (SD), mean (minimum-maximum) or median (IQR). CRP, C-reactive protein; N/L ratio, neutrophile/lymphocyte ratio. *$P < 0.05$.

Table 3. Pre- and Post-Filter Clinical and Laboratory Variables of the Patients in the Group CF.

	Pre-filter	Post-filter	*P*
SOFA	9 (3-11)	9 (3-11)	0.868
Procalcitonin (μg/L)	0.63 (0.20-1.73)	0.32 (0.13-2.29)	0.093
CRP (mg/L)	90 (36-163)	38 (12-105)	0.012*
Ferritin (μg/L)	960 (471-1450)	1060 (374-1368)	0.422
Fibrinogen (mg/dL)	526 ± 213	438 ± 234	0.016*
D-dimer (mg/L)	3.42 (1.89-10.24)	4.99 (1.97-10.44)	0.891
Lymphocyte count (x10^3/μL)	0.6 (0.4-0.8)	1 (0.5-1.4)	0.001*
Lymphocyte ratio (%)	4.4 (3.3-8.8)	6.4 (2.8-10.5)	0.013*
Neutrophile ratio (%)	90.1 (85.0-92.9)	87.6 (81.8-92.9)	0.046*
N/L ratio	20.7 (9.6-28.0)	13.8 (7.6-31.3)	0.095
Platelet count (x10^3/μL)	249 ± 101	217 ± 106	0.064
Vasopressor use	23 (63.9)	23 (63.9)	1.0

Note. Data is expressed as number of the patients (percent of total) for categorical; and mean (SD), mean (minimum-maximum) or median (IQR) for numerical variables. CRP, C-reactive protein; N/L ratio, neutrophile/lymphocyte ratio. *$P < 0.05$.

Table 4. Cytokine Filter Characteristics of the Patients in the Group CF.

	Survivors (n = 16)	Non-survivors (n = 20)	*P*
Diagnosis-CF time (days)	10.7 ± 3.8	12 ± 5.9	0.432
Membrane			
HA330	11 (52.4)	10 (47.6)	0.257
Mediasorb	5 (33.3)	10 (66.7)	
CF duration (days)			
1	1 (14.3)	6 (85.7)	
2	4 (57.1)	3 (42.9)	
3	7 (58.3)	5 (41.7)	
≥4	4 (40.0)	6 (60.0)	

Note. Data is expressed as number of the patients (percent of total) for categorical; and mean (SD) for numerical variables. CF, cytokine filter.

finding of the study was that acute phase reactants, including CRP and fibrinogen decreased; and lymphocyte count was increased in the patients having cytokine filtration. A significant decrease in CRP and fibrinogen levels measured at the end of EBP were observed (P = 0.012 and 0.016, respectively). Lymphocyte count and ratio at the end of EBP were significantly increased (P = 0.001 and 0.013 for lymphocyte count and ratio, respectively). But there was no clinical reflection of these improved laboratory variables on the patients. Vasopressor use and SOFA scores of the patients measured at the end of EBP were not changed. Mortality was found to be 55.6% and 50% in the cytokine filtration and control groups, respectively.

EBP is proposed as promising adjunctive treatment modality in hyperinflammatory states. Its action is based on the principle of removing inflammatory mediators, including cytokines, complement and coagulation system components. The mechanism relies on the removal of solutes, substances and fluid from the blood through diffusion, convection and adsorption. The mechanism of hemoperfusion relies on the elimination of endotoxins and inflammatory mediators passing blood through an adsorbent membrane. The beneficial effects of EBP in the treatment of dysregulated inflammatory conditions have been reported.[11] Villa *et al.* have investigated oXiris membrane in the treatment of COVID-19 patients, and found improved SOFA scores, particularly for hemodynamic and pulmonary parameters. This result was together with decreased IL-6 levels.[3] Turani *et al.* have demonstrated similar results in their study on septic patients with decreased cytokine and endotoxin levels, as well as improved

SOFA scores, respiratory parameters, noradrenalin dosage. We have not observed changes in neither SOFA scores, nor in vasopressor needs before and after EBP application in our study. Although, there were some changes in acute phase reactants (notably CRP and fibrinogen) and cell counts (lymphocytes), there were no clinical reflection of these changes on the patients.

Villa *et al.* have demonstrated 56% mortality in their study with cytokine adsorption on COVID-19 patients. They have found that early intervention time for cytokine adsorption (time from symptom onset to EBP initiation) were correlated with better survival.[3] The time for initiation of EBP from the start of the symptoms is 14–15 days in the literature.[3,12,13] This time in our study was 10.7 and 12 days for survivors and non-survivors, respectively. Symptom-cytokine adsorption times in our study can be considered slightly shorter compared with the literature. The mortality rates in our study were 55.6% and 50% in the CF and control groups, respectively.

Blood purification has been proposed for the treatment of COVID-19 patients with a high inflammatory response, and this has been included in some national guidelines for the treatment of the disease.[14] Some studies recommend early intervention with CRRT and immunoadsorption after clinical and/or laboratory detection of hyperinflammatory state.[15] Although CRRT may improve prognosis in critically ill patients, there are conflicting data about the timing and dosage of CRRT in the literature, and the details are beyond the scope of this paper.[16,17] Yet it is early to make strong evidence-based suggestions for COVID-19 patients.

Indeed, many national guidelines for COVID-19 treatment have recommended the use of cytokine adsorption in the treatment of the disease. The formal recommendation was made by the Italy Brescia Renal COVID Task Force to use CytoSorb membrane (CytoSorbents, NJ, USA) in severe COVID-19 patients with renal failure.[18] United States Food and Drug Administration (FDA) has given Emergency Use Authorization (EUA) for CytoSorb in ICU patients with respiratory failure.[19,20] Handbook of COVID-19 Prevention and Treatment from Zhejiang University School of Medicine is also recommending blood purification to treat cytokine storm in COVID-19 patients.[21]

Nevertheless, extracorporeal therapies are not without risks. They have innate complications that arise from central venous cannulation procedure, like hematomas at insertion sites, pneumothorax, infections. Indeed, higher prevalence of Gr(+) infections observed in CF group in our study can be linked to central line insertion and its infectious complication. But retrospective nature of the study, and lack of data from the patient records does not allow us to make strong conclusions about this. We do not have clear protocols on the central line insertion for COVID-19 patients, and it is at the discretion of the primary physician. But we generally use femoral vein for cannulation, even at the expense of contamination and increased bacterial infections. Furthermore, this approach obviates possible pneumothorax associated with internal jugular or subclavian cannulation, and keeps the physician away from the patient's airway, the major cite of contamination. Another complication of extracorporeal therapy is unselective loss of substances; like electrolytes, nutrients, and drugs.[22] These all must be considered and treated, particularly paying attention to the antibiotic dose adjustments in these patients.

Our study had some limitations, the first being retrospective in nature. This hindered creation of homogeneous groups regarding indications and timing of cytokine adsorption. Another limitation was the fact that we have used two different membranes for adsorption. Taking into consideration their characteristics and their possible beneficial roles in COVID-19, homogeneous groups should be created to properly demonstrate their effects. Prospective studies with homogeneous groups in this regard could be performed. In addition, clinical and laboratory data were collected from the standard patient records, particularly obtained in the morning of the day as a part of routine clinical and laboratory evaluation. Investigation made just before and after the absorption would yield more precise data. Finally, we were unable to measure the cytokine levels, as there were technical deficiencies in our institution at the time of the patient treatments. It would have been more precise to demonstrate the decline in acute phase reactants together with interleukin levels.

In conclusion, critically ill COVID-19 patients often present with systemic inflammation and organ dysfunction. Even though there is physiopathologic rationale to use cytokine adsorption techniques for immunomodulation in these patients, it is early to make strong suggestions about their benefits. We have demonstrated decrease in acute phase reactants (CRP, fibrinogen) and increase in lymphocyte count in our patients having cytokine adsorption, but there was no clinical reflection of these benefits. There was no decrease in mortality as well. Future randomized trials with homogenous groups are required in this context.

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

ORCID iD

Ruslan Abdullayev https://orcid.org/0000-0002-1025-4026

References

1. Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to: clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46(5):846-848.

2. AL Shareef K, Bakouri M. Cytokine blood filtration responses in COVID-19. *Blood Purif*. 2021;50(2):141-149.
3. Villa G, Romagnoli S, De Rosa S, et al. Blood purification therapy with a hemodiafilter featuring enhanced adsorptive properties for cytokine removal in patients presenting COVID-19: a pilot study. *Crit Care*. 2020;24(1):605.
4. Safari S, Salimi A, Zali A, et al. Extracorporeal hemoperfusion as a potential therapeutic option for severe COVID-19 patients; a narrative review. *Archives of Academic Emergency Medicine*. 2020;8(1):e67.
5. Kim JS, Lee JY, Yang JW, et al. Immunopathogenesis and treatment of cytokine storm in COVID-19. *Theranostics*. 2021;11(1):316329.
6. Montin DP, Ankawi G, Lorenzin A, Neri M, Caprara C, Ronco C. Biocompatibility and cytotoxic evaluation of New sorbent cartridges for blood hemoperfusion. *Blood Purif*. 2018;46(3):187-195.
7. Ankawi G, Fan W, Pomare Montin D, et al. A New series of sorbent devices for multiple clinical purposes: current evidence and future directions. *Blood Purif*. 2019;47(1-3):94-100.
8. Huang Z, Wang SR, Su W, Liu JY. Removal of humoral mediators and the effect on the survival of septic patients by hemoperfusion with neutral microporous resin column. *Therapeutic apheresis and dialysis : official peerreviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy*. 2010;14(6):596-602.
9. Huang Z, Wang SR, Yang ZL, Liu JY. Effect on extrapulmonary sepsis-induced acute lung injury by hemoperfusion with neutral microporous resin column. *Therapeutic apheresis and dialysis* 2013;17(4):454-461.
10. Hazzard I, Jones S, Quinn T. Coupled plasma haemofiltration filtration in severe sepsis: systematic review and meta-analysis. *J R Army Med Corps*. 2015;161(Suppl 1):i17-i22.
11. Bonavia A, Groff A, Karamchandani K, Singbartl K. Clinical utility of extracorporeal cytokine hemoadsorption therapy: a literature review. *Blood Purif*. 2018;46(4):337-349.
12. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513.
13. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in wuhan, China. *Lancet*. 2020;395(10223):497-506.
14. National Health Commission of the People's Republic of China: Guidelines for novel coronavirus infection prevention and treatment (Trial 7th edition). Available from: https://wwwchinalaw translatecom/en/coronavirus-treatment-plan-7/.
15. Chen G, Zhou Y, Ma J, Xia P, Qin Y, Li X. Is there a role for blood purification therapies targeting cytokine storm syndrome in critically severe COVID-19 patients? *Ren Fail*. 2020;42(1): 483-488.
16. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA*. 2016;315(20):2190-2199.
17. Joannes-Boyau O, Honore PM, Perez P, Bagshaw SM, Grand H, Canivet JL. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. *Intensive Care Med*. 2013;39(9):1535-1546.
18. Nephrology ISo. Brescia Renal Covid Task Force: Alberici F, Del Barba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Gaggia P, Movilli E, Bove S, Malberti F, Farina M, Bracchi M, Costantino EM, Bossini N, Gaggiotti M, Scolari F. GESTIONE DEL PAZIENTE IN DIALISI E CON TRAPIANTO DI RENE IN CORSO DI INFEZIONE DA CORONAVIRUS COVID-19 2020. www.era-edta.org/en/wpcontent/uploads/2020/03/COVID_guidelines_finale_engGB.pdf.
19. FDA has authorized the emergency use of CytoSorb 300 mL device: CytoSorb 300mL device is manufactured under and ISO 13485 and CE Mark approved 2020. https://www.fda.gov/media/136866/download.
20. Friesecke S, Trager K, Schittek GA, et al. International registry on the use of the CytoSorb(R) adsorber in ICU patients : study protocol and preliminary results. *Med Klin Intensivmed Notfmed*. 2019;114(8):699-707.
21. Commission CNH. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th Edition) 2020. http://kjfy.meetingchina.org/msite/news/show/cn/3337.html.
22. Ronco C, Bagshaw SM, Bellomo R, et al. Extracorporeal blood purification and organ support in the critically Ill patient during COVID-19 pandemic: expert review and recommendation. *Blood Purif*. 2021;50(1):17-27.