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RESEARCH ARTICLE

Early versus Late Application of Hemoadsorption in Critically Ill COVID-19 Patients with Cytokine Release Syndrome

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ABSTRACT

Objectives: Cytokine release triggered by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) depends on a dysregulated immune response and is associated with high mortality. Extracorporeal cytokine hemoadsorption (HA) can be considered a possible adjuvant therapy. This study aimed to review the outcomes of critically ill patients with COVID-19 treated with HA and analyze possible factors associated with mortality.

Methods: Data of patients who received HA for at least one cycle from April 17, 2020, to January 31, 2021, were collected. Clinical and laboratory features were recorded, and mortality was evaluated based on the extracorporeal treatment application time and intensive care units (ICU) admission.

Results: Data from 177 patients among 4733 ICU patients were analyzed. Their mean age was 60.9±10.9, and 40 (22.6%) of them were females. About 83% of them were mechanically ventilated, and the overall mortality was 76%. In univariate analysis, the mean age, median acute physiology and chronic health evaluation (APACHE)-II score, respiratory support rate, and duration between ICU admission and first cytokine filter were lower in the survivor group than in the non-survivor group. In binary logistic regression analysis, higher APACHE-II with an odds ratio of 1.06 (95% confidence interval [CI]: 1.005–1.128, p=0.033), invasive mechanical ventilation with an odds ratio of 138.4 (95%CI: 24.2–791.8, p<0.001), and later application of HA with an odds ratio of 1.190 (95%CI: 1.009–1.404, p=0.039) were independently associated with in-hospital mortality.

Conclusion: Cytokine HA was applied to a large number of patients at our center. Although this was conducted in a severe population with high mortality, besides invasive mechanical ventilation, late application of the cytokine filter was found as one of the factors independently associated with higher mortality.

Keywords: Extracorporeal purification, hemoadsorption, intensive care, SARS-CoV-2

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory disease (SARS-CoV-2) can present with heterogeneous clinical characteristics ranging from mild flu-like syndrome to life-threatening pneumonia with acute hypoxemic respiratory failure.[1] The cytokine release syndrome triggered by the virus in patients with severe COVID-19 is due to a dysregulated immune response and is associated with high mortality.[2] As elevated cytokines and immune markers were considered potential treatment targets, corticosteroids and some anti-interleukin therapies have been used in patients with severe hypoxemia.[3,4] Although the underlying mechanism is not yet fully understood and definite treatment has not yet been established, beneficial effects of immunosuppressant agents have been recorded in particular patients with hypoxemia.[5]

Extracorporeal hemadsorption (HA) techniques for adsorbing pro- and anti-inflammatory cytokines are increasingly used in several clinical conditions such as sepsis and other hyperinflammatory syndromes in intensive care units (ICU).[6,7] However, no specific recommendation has been established regarding hemoadsorption therapies in the survival sepsis guideline, due to the lack of consistent evidence.[8] Hyperinflammation has a significant role in the pathophysiology of multiple organ failure in critically

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ill patients; therefore, as an alternative therapeutic regimen, cytokine HA techniques have been tried in critically ill patients with COVID-19.[9] Different outcomes have been observed due to varied hemoadsorption methods, application times, and patient characteristics, and clear characteristics of the clinical effects have not been elucidated yet.

As a referral hospital for COVID-19 in our region, we could collect data on a large COVID-19 critically ill population treated with HA. Based on the scope of this study, the outcomes of these patients were retrospectively reviewed analyzing possible factors associated with differences in survival.

Methods

This retrospective study was conducted in tertiary ICUs of our hospital, including patients with severe COVID-19 infection. Adult patients with confirmed molecular diagnosis of SARS-CoV-2 infection who were admitted to the ICU due to acute respiratory failure and treated with HA were included in this study.

We collected the data of patients treated with at least one cycle of HA in our hospital during the first and second waves of the COVID-19 pandemic, from April 17, 2020, to January 31, 2021. During this period, ICU admission and treatment were planned based on the Ministry of Health guidelines of the Republic of Türkiye. HA was used as an add-on therapy to the standard regimen consisting of corticosteroids, anticoagulants, favipiravir, and supportive therapies. The national guideline indicated that some patients were treated with anti-interleukin drugs depending on the presence of some clinical findings such as refractory fever, increasing CRP levels despite appropriate therapy, elevated d-dimer, lymphopenia, thrombocytopenia and neutrophilia, and deteriorated liver function tests. HA was administered to some patients who clinically deteriorated and had increased oxygen demand even after receiving the standard regimen. Demographic data (age and sex); comorbidities (diabetes, hypertension, heart failure, asthma, chronic obstructive lung disease, chronic renal disease, and malignancy); acute physiology and chronic health evaluation (APACHE-II) score at the ICU admission; length of ICU stay; respiratory support (noninvasive and invasive mechanical ventilation); drugs used to treat COVID-19 (favipiravir, corticosteroids, and anti-interleukin [IL-6 and IL-1 antagonists]; CRP, ferritin, and procalcitonin levels and lymphocyte count at the first day of cytokine filtration; IL-6 levels at the ICU admission, first day of HA, and after HA administration; number of HA cycles; duration between ICU admission and the first application of HA; and in-hospital mortality data were recorded. HA was performed using a standard extracorporeal circuit with an HA-330 cartridge (Jafron, Zhuhai, China). Priming and delivery of therapy were performed according to the manufacturer's instructions for use. Each session lasted 4 h/day, and the treatment was prescribed for three consecutive days.

The statistical analysis was performed using the statistical software package SPSS 23.0.0.2. Medians (interquartile ranges [IQR]) for non-normally distributed data and percentages for categorical variables were used. Mann–Whitney U-test was used to compare continuous variables, and Fisher's exact test and chi-squared test were used for categorical variables. ROC analysis was used to detect a cut-off for the duration between ICU admission and the first HA application. The clinical and laboratory characteristics of the two groups were compared based on mortality. Inflammatory markers detected in different periods were compared using the Kruskal–Wallis test. Binary logistic regression analysis was used to determine independent variables for mortality after performing the Hosmer–Lemeshow goodness-of-fit test. Clinical and statistically significant variables in univariate analysis were included in the model. Statistical significance was set at two-sided ($p<0.05$) for all of the above analyses.

All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of our hospital (number: E2-22-2388, date: 07/09/2022). Due to the retrospective study design, no informed consent was obtained.

Results

We collected the data of 177 patients from 4733, who were treated with cytokine filtration from April 17, 2020, to January 31, 2021, in our tertiary ICU clinics. Their mean age was 60.9±10.9, and 40 (22.6%) of them were female. Demographic and clinical features are presented in Table 1. Hypertension, diabetes, and coronary artery disease were the most common comorbidities. A significant percentage of patients (83%) were intubated. Corticosteroid was prescribed to all study patients, while 38.4% was treated with anti-interleukin agents. All patients received at least one cycle, and 72.9% received three cycles of cytokine blood filtration using HA330. Median IL-6 levels at the ICU admission, on the first day of cytokine filtration, and after the last filtration were 66.5 pg/ml (25.2–134), 65 pg/ml (24.1–180.5), and 44.5 pg/ml (17–168.5), respectively, reflecting no statistically significant difference between the medians (p=0.62).

Table 2 compares the clinical features of the survivor and non-survivor groups. In univariate analysis, the mean age,

Table 1. Demographic and clinical features of patients

	n=177	
	n	%
Age, (years) (mean±SD)	60.9±10.9	
Sex		
Female	40	22.6
Comorbidities		
Hypertension	74	41.8
Diabetes mellitus	40	22.6
Coronary artery disease	37	20.9
Chronic obstructive pulmonary disease	12	6.8
Solid organ malignancy	9	5.1
Chronic renal disease	8	4.5
Cerebrovascular event	5	2.8
APACHE-II at 24 h of ICU admission, median (IQR)	19 (14–29)	
Laboratory parameters at ICU admission, median (IQR)		
Lymphocyte count (µl)	525 (340–760)	
CRP (mg/dl)	150 (112–210)	
Procalsitonin (ng/ml)	0.19 (0.09–0.71)	
D-dimer (ng/ml)	1.44 (0.78–3.50)	
Ferritin (mg/L)	997 (453–1543)	
IL-6 (pg/ml)	66.5 (45.2–134.0)	
Respiratory support		
High-flow nasal cannula	52	29.4
Noninvasive ventilation	18	10.2
Invasive mechanical ventilation	148	83.6
COVID-19 specific therapies		
Corticosteroid	177	100
Anti-IL-1	52	29.3
Anti-IL-6	16	9
Cytokine filtration		
1 cycle	27	15.2
2 cycles	21	11.9
3 cycles	129	72.9
Time period between ICU admission and first day of cytokine filtration (days), median (IQR)	4 (2–7)	
Length of ICU stay (days), median (IQR)	15 (10–24.5)	

n: Number; SD: Standard deviation; APACHE: Acute physiology and chronic health evaluation; ICU: Intensive care unit; IQR: Interquartile range; CRP: C-reactive protein IL: Interleukin.

median APACHE score, respiratory support rate (high-flow nasal cannula, and invasive mechanical ventilation), and duration from the ICU admission to the first cytokine filter was lower in the survivor group. Inflammatory mediator levels of the survivor and non-survivor groups in the ICU admission and pre- and post-filtration periods are presented in Table 3. In ROC analysis, the area under the curve for the time period from the ICU admission to the first application of the cytokine filter was 0.65 (95% CI: 0.56–0.74; p=0.004), with 7 days cut-off having a sensitivity of 35.3% and specificity of 90.2% (Fig. 1).

Age, APACHE-II score, use of high-flow nasal cannula and invasive mechanical ventilation, and the number of days between the ICU admission and first cytokine filtration were put in a binary logistic regression model (Table 4). The p-value for the Hosmer–Lemeshow test was 0.81. Binary logistic regression analysis showed that a higher APACHE-II score with an odds ratio of 1.06 (95% CI: 1.005–1.128, p=0.033), invasive mechanical ventilation with an odds ratio of 138.4 (95% CI: 24.2–791.8, p<0.001), and later application of cytokine removal with an odds ratio of 1.190 (95% CI: 1.009–1.404, p=0.039) were variables independently associated with mortality.

Table 2. Comparison of demographic and clinical features according to mortality data

	Survivors (n=41, 23.2%)		Non-survivors (n=136, 76.8%)		p
	n	%	n	%	
Age (years) (mean±SD)	55.9±10.8		62.1±10.6		**<0.001**
Sex					
Female	9	22.0	31	22.8	>0.99
Comorbidities					
Hypertension	14	34.1	60	44.1	0.34
Diabetes mellitus	7	17.1	33	24.3	0.45
Coronary artery disease	5	12.2	32	23.5	0.18
Chronic obstructive pulmonary disease	4	9.8	8	5.9	0.48
Solid organ malignancy	1	2.4	8	5.9	0.69
Chronic renal disease	3	7.3	5	3.7	0.39
Cerebrovascular event	1	2.4	4	2.9	>0.99
APACHE-II at 24 h of ICU admission, median (IQR)	15.0 (8.5–29.0)		20.0 (14.0–30.7)		**0.02**
Laboratory parameters at ICU admission, median (IQR)					
Lymphocyte count (µl)	580 (340–820)		515 (330–760)		0.58
C-reactive protein (mg/dl)	160 (98–196)		151 (114–210)		0.57
Procalsitonin (ng/ml)	0.15 (0.10–0.51)		0.26 (0.08–0.75)		0.44
D-dimer (ng/ml)	1.35 (0.79–3.3)		1.49 (0.78–3.54)		0.94
Ferritin (mg/L)	879 (450–1617)		1056 (453–1530)		0.75
IL-6 (pg/ml)	64 (21–103)		68 (26–137)		0.40
Respiratory support					
High-flow nasal cannula	19	46.3	33	24.3	**0.01**
Noninvasive ventilation	5	12.2	13	9.6	0.57
Invasive mechanical ventilation	15	36.6	133	97.8	**<0.001**
COVID-19 specific therapies					
Pulse steroid	41	100	136	100	>0.99
Anti-IL-1	10	24.4	42	30.9	0.55
Anti-IL-6	4	9.8	12	8.8	0.76
Cytokine filtration					0.11
1 cycle	4	9.8	23	16.9	0.26
2 cycles	2	4.9	19	14.0	0.11
3 cycles	35	85.3	94	69.1	**0.04**
Time period between ICU admission and first day of cytokine filtration (days), median (IQR)	3.0 (1.5–5.0)		5.0 (3.0–8.0)		**0.004**
Length of ICU stay (days), median (IQR)	17.0 (11.5–27.5)		15.0 (9.0–24.0)		0.29

Discussion

In this study, we evaluated the mortality outcome of critically ill patients with COVID-19 who were administered at least one cycle of cytokine filters as an add-on therapy to the standard regimen. In univariate analysis, the mean age, median APACHE score, respiratory support (high-flow nasal cannula and invasive mechanical ventilation) rate, and duration between the ICU admission and first cytokine filter were found to be lower in the survivor group. Logistic regression analysis showed that higher APACHE-II score with an odds ratio of 1.06 (95% CI: 1.005–1.128, p=0.033), invasive mechanical ventilation with an odds ratio of 138.4 (95% CI: 24.2–791.8, p<0.001) and later application of cytokine removal with an odds ratio of 1.190 (95% CI: 1.009–1.404, p=0.039) were variables independently associated with mortality.

As a referral hospital for COVID-19 since the beginning of the pandemic, more than 20,000 patients were followed up in our ICU clinics. Many patients with severe respiratory failure were admitted, and to our knowledge, this study is one of the largest population studies conducted in Türkiye on the use of cytokine filtration to manage COVID-19. Mortality did not reflect the general ICU mortality data as only patients treated with cytokine filters were included in the scope of the

Table 3. Inflammatory markers at different periods

	At ICU admission	Pre-filter	Post-filter
Procalcitonin (ng/ml)			
Survivor group	0.15 (0.10–0.51) (n=39)	0.16 (0.06–0.54) (n=41)	0.16 (0.08–0.59) (n=41)
Non-survivor group	0.24 (0.08–0.82) (n=131)	0.56 (0.15–2.52) (n=136)	0.77 (0.22–3.81) (n=134)
p	0.43	<0.001	<0.001
C-reactive protein (mg/dl)			
Survivor group	0.16 (0.09–0.19) (n=39)	0.10 (0.03–0.16) (n=41)	0.47 (0.02–0.15) n=41
Non-survivor group	0.15 (0.11–0.21) (n=132)	0.14 (0.07–0.21) (n=136)	0.11 (0.05–0.17) (n=134)
p	0.57	0.002	0.03
Interleukin-6 (pg/ml)			
Survivor group	64 (21.3–103) (n=39)	31 (14.2–102) (n=41)	22.8 (9.6–53.5) (n=41)
Non-survivor group	67.8 (26–137) (n=127)	68.8 (25.1–196) (n=132)	54.7 (20.8–237) (n=128)
p	0.40	0.004	<0.001

All values are presented as medians (interquartile ranges). P-value is used to compare the survivor and non-survivor groups.

Table 4. Risk factors for mortality

Variables	OR	95% CI	p
Age	1.022	0.973–1.074	0.381
APACHE-II score	1.065	1.005–1.128	**0.033**
High-flow nasal cannula	1.661	0.473–5.837	0.429
Invasive mechanical ventilation	138.489	24.221–791.835	**<0.001**
Days between ICU admission and the first use of the cytokine filter	1.19	1.009–1.404	**0.039**

OR: Odds ratio; CI: Confidence interval.

study. Invasive mechanical ventilation was applied in 83% of them. A study representing the first wave of the pandemic and aiming to assess the effect of early invasive mechanical ventilation on mortality showed that 60-day mortality was 20.8% higher in the invasive ventilation group.[10]

Several studies on sepsis and COVID-19 reported that proinflammatory cytokines were related to endothelial damage, pro-coagulation, multiple organ failure, and increased mortality.[11,12] However, increased inflammatory cytokine levels in severe COVID-19 were lower than those in acute respiratory distress syndrome and sepsis. Individual responses are heterogeneous, and the importance of biomarker levels is still uncertain. In our study, the inflammatory mediator levels were higher in the non-survivor group before and after the cytokine filter, but we do not have enough data to attribute higher mortality to just higher biomarker levels.

HA330 is a synthetic resin hemofilter that adsorbs proinflammatory cytokines such as TNF-alpha, IL-1, and IL-6, and its cytokine removal effect has been considered to be beneficial for the hyperinflammatory state of COVID-19.[13,14] In a study conducted in patients with severe COVID-19, decreased SOFA score, improved chest X-ray, and decreased mortality were recorded in patients who received at least three hemoperfusion sessions.[15] The control group of the concerned study consisted of patients with <3 sessions and the median time for the first filtration was 24 h in the hemoperfusion group. In another study by Esmaeili Vardanjani et al.,[16] early use of hemoperfusion in a patient with COVID-19 prevented the progression of acute respiratory distress syndrome and intubation.[16] The concerned study hypothesized that removing inflammatory mediators might contribute to preventing multiple organ failure, such as acute kidney injury, liver failure, and septic shock in severe patients. The therapeutic benefit of cytokine elimination was considered likely depending on timing. In the present study, however, the median time for starting the first session was shorter (3 vs.

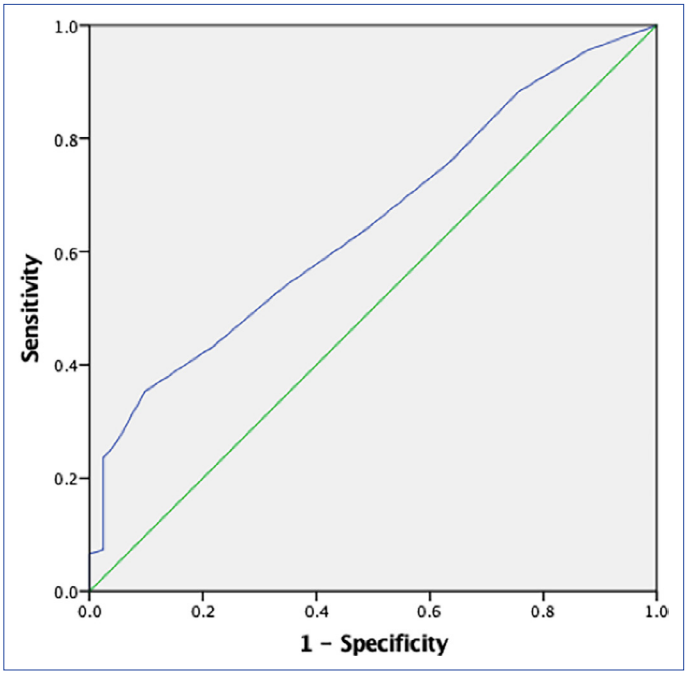

Figure 1. The area under the curve for the duration from ICU admission to the first application of a cytokine filter was 0.65 (95% CI: 0.56–0.74; p=0.004), with 7 days cut-off having a sensitivity of 35.3% and specificity of 90.2%.
ICU: Intensive care unit; CI: Confidence interval.

5 days) in the survivor group, and early application benefits persisted after regression analysis.

This study has some limitations. No specific protocol has been established for cytokine filter indications and application processes due to the retrospective design of the study. It was applied based on the clinician's decision. Since the cytokine removal was dependent on the clinician's decision and the data were collected retrospectively, information about why <3 cycles were performed in six patients who survived and could not be obtained. However, our treatment protocols in ICUs were compatible with the COVID-19 guidelines published by the Ministry of Health of the Republic of Türkiye. Second, this study has no control group without cytokine removal since the primary aim of the study was to investigate the effects of timing in subjects undergoing cytokine filtration. Therefore, we considered it appropriate to include in the study the patients who underwent cytokine filtration at different times.

In conclusion, in a severe population with high mortality, late application of the cytokine filter, besides invasive mechanical ventilation, was found among the risk factors independently associated with mortality. The fact that the treatment was applied in a group with a high mortality rate that did not respond to standard treatment may have affected the results. Different results can be obtained by studying appropriate phenotypes that may benefit from this treatment.

Disclosures

Ethics Committee Approval: The study was approved by The Ankara Bilkent City Hospital No 2 Clinical Research Ethics Committee (Date: 07/09/2022, No: E2-22-2388).

Informed Consent: Due to the retrospective study design, no informed consent was obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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