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The Efficacy of Continuous Renal Replacement Therapy and Hemoabsorption Treatments in COVID-19 Patients in the Intensive Care Unit: A Retrospective Evaluation

Yoğun Bakımda Yatan COVİD-19 Hastalarında Sürekli Renal Replasman Tedavisinin ve Hemoabsorbsiyon Tedavilerinin Etkinliğinin Retrospektif Değerlendirilmesi

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ABSTRACT *Objective:* The World Health Organisation has emphasized that as there is no specific anti-COVID-19 treatment, supportive care according to disease severity is important. Previous studies have shown that acute kidney injury (AKI) develops in 30% of severe COVID-19 patients followed up in intensive care units and most these require renal replacement therapy. This study aimed to evaluate the COVID-19 prognosis, renal function, and organ systems of adult, severe COVID-19 patients treated with continuous renal replacement therapy (CRRT) and the effects on secondary hemophagocytic lymphohistiocytosis with the additional application of absorption filters.
Materials and Methods: A retrospective examination was made of the data of COVID-19 patients who applied for CRRT between 11/3/20 and 15/06/2021. The demographic data of the patients were recorded together with the renal function test results before and after CRRT, and the biochemical parameters were included in the COVID-19 prognosis.
Results: Positive changes were determined in the kidney functions with CRRT applied to patients who developed AKI. No statistically significant difference was observed in the biochemical parameters included in the COVID-19 prognosis. In the 14 patients who applied with hemoabsorption, the need for short-term inotropic support was reduced. In our study, the mortality of the patients who were treated with CRRT was 95% (2 patients transferred to the ward), while the average intensive care unit stay was 18.2±11 days. While improvement was detected in renal function tests with CRRT applied to patients with AKI, no statistically significant difference was found in biochemical parameters in the prognosis of COVID-19. While mortality was 92.8% in 14 patients who underwent hemoabsorption, a short-term improvement was observed in the need for inotropes in these patients.
Conclusion: Although vaccinations are expected to definitively eliminate COVID-19, for critical COVID-19 patients for whom the treatment options are limited, it would seem rational to adopt immunomodulator strategies including extracorporeal blood purification and supportive treatment such as CRRT. The results of this study have shown that CRRT applied to severe COVID-19 patients who develop AKI is an effective treatment for kidney failure. However, the effect on the progression of COVID-19 could not be clearly shown.
Keywords: COVID-19, kidney failure, continuous renal replacement therapy, kidney functions, prognostic factors

ÖZ *Amaç:* COVID-19 enfeksiyonu için spesifik ANTI-COVID-19 tedavisinin olmadığı ve hastalığın şiddetine göre destekleyici bakımın önemli olduğu, Dünya Sağlık Örgütü tarafından vurgulanmıştır.
Çalışmalarda yoğun bakım ünitelerinde takip edilen, ciddi COVID-19 hastalarında %30 oranında akut böbrek hasarı (AKI) geliştiği ve çok büyük bir kısmında renal replasman tedavisi ihtiyacı olduğu görülmüştür
Çalışmamızda; yetişkin ağır COVID-19 hastalarında sürekli renal replasman tedavisi (SRRT) ile organ sistemleri, böbrek fonksiyonları, COVID-19 prognozu ve ek olarak uyguladığımız sitokin absorblama filtreleri ile sekonder hemofagositik lenfohistiyositoza etkilerini değerlendirmeyi amaçladık.
Gereç ve Yöntem: 11/03/2020-15/06/2021 tarihleri arasında SRRT uygulanmış olan COVID-19 hastalarının verileri retrospektif olarak incelendi. Hastaların demografik verileri, SRRT öncesi ve sonrası böbrek fonksiyon testleri ve COVID-19 prognozunda yer alan biyokimyasal parametreler kaydedildi.
Bulgular: Çalışmamızda SRRT tedavisi uygulanan hastaların mortalitesi %95 (2 hasta servise devir) olarak tespit edilirken ortalama yoğun bakım yatış süresi 18.2±11 gün olarak değerlendirildi. AKI oluşan hastalara uygulanan SRRT ile böbrek fonksiyon testlerinde düzelme tespit edilirken COVID-19 prognozunda yer alan biyokimyasal parametrelerde istatiksel olarak anlamlı fark bulunmadı. Hemoabsorbsiyon uygulanan 14 hastada mortalite %92.8 olarak tesbit edilirken bu hastaların inotrop ihtiyacında kısa süreli bir iyileşme olduğu tespit edildi.
Sonuç: Aşıların COVID-19'u kesin olarak ortadan kaldırmasını beklerken, sınırlı tedavi seçenekleri olan COVID-19'lu kritik hastalara, SRRT gibi destek tedavisi ve ekstrakorporal kan pürifikasyonunun dahil olduğu immünomodülatör stratejileri benimsemek mantıklı görünmektedir.
Çalışmamıza göre AKI gelişen ağır COVID-19 hastalarına uygulanan SRRT, böbrek yetmezliğinde etkin bir tedavidir. Ancak COVID-19 progresyonunda etkinliği net olarak ortaya konulamamıştır.
Anahtar Kelimeler: COVID-19, böbrek yetmezliği, sürekli renal replasman tedavisi, böbrek fonksiyonları, prognostik faktörler

Introduction

COVID-19 in adults and children is a disease with a broad clinical spectrum from asymptomatic or simple upper respiratory tract infection to severe respiratory or multiorgan failure with a need for intensive care. Previous studies have shown a significant association between multiorgan involvement and mortality (1). The clinical course in severe COVID-19 patients can be separated into three main phases; the early infection phase, the pulmonary phase, and the hyperinflammation phase. Phase 2 and phase 3 do not follow consecutively but overlap and this causes the development of multiorgan failure (2).

The first data coming from China at the beginning of the pandemic showed a relatively low incidence of acute kidney injury (AKI). It was reported to be seen at the rate of 0.5% in all cases and 2.9% of severe cases (3). In the subsequent period, this rate was seen to be as high as 28-37% in reports from the USA, and it was emphasized that the risk of AKI was even higher in hospitalised patients. In previous studies, the requirement for acute dialysis has been seen to vary between 20% and 50% in patients with COVID-19-related AKI (4).

The etiology of kidney damage associated with COVID-19 is multifactorial. These factors include hemodynamic instability, inflammation, cytokine expression, endothelial dysfunction, changes in the microcirculation, nephrotoxic exposure, and the effects of invasive mechanical ventilation (5).

In the Intensive Care Unit (ICU) follow up of severe COVID-19 patients who develop AKI, continuous renal replacement therapy (CRRT) is generally selected rather than intermittent hemodialysis methods as patients are hemodynamically unstable (4, 5). The advantage of CRRT methods is that in patients with septic shock, cytokine absorption systems can be integrated at the same time while applying this method, and the hyperininflammation phase of COVID-19 infection can also be treated at the same time (2).

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. Another way for immunomodulation is the abovementioned extracorporeal blood purification (6).

The aim of this study was to evaluate the effect of CRRT on COVID-19 prognosis, renal functions and organ systems of COVID-19 patients who developed AKI during intensive care follow up and the effects on secondary hemophagocytic lymphohistiocytosis (sHLH) with the additional application of absorption filters.

Materials and Methods

Approval for the study was granted by the Non-Interventional Clinical Research Ethics Committee of

Eskişehir Osmangazi University Medical Faculty (Decision No: 32, Dated: 06.04.2021). All procedures were in compliance with the principles of the Helsinki Declaration.

A retrospective evaluation was made of the data of severe COVID-19 patients applied with CRRT during follow up in the Anaesthesiology Intensive Care Unit of Eskişehir Osmangazi University Medical Faculty Hospital between 11/3/2020 and 15/06/2021.

Study Design

In the examination of the ICU patient records, it was seen that renal functions were evaluated according to the standard clinical guidelines criteria (Kidney Disease Improving Global Outcomes -KDIGO). According to these, patients with <0.3ml/kg/hr within 24 hours were accepted as oliguria or within 12 hours as anuric, evaluated as KDIGO Grade 3 and above as indication for CRRT, and the records of these patients were examined.

Accordingly, the indication for starting CRRT evaluated according to the KDIGO recommendations (7) was determined as prescribed when effluent flow rate was 25-30 ml/kg/hr (8), there was regional citrate anticoagulation of the anticoagulant selection and ionised calcium (iCa) after filtering for follow up was measured once in 6 hours. The application was performed in our centre with two devices for Continuous Veno-Venous Hemodiafiltration (CVVHDF). Multifiltrate (Fresenius, Bad Homburg vor der Höhe, Germany) and a 1.8 m^2 membrane (AV1000 set; Fresenius) and Prismaflex (Baxter Inc., Deerfield, IL, USA) and a 0.9 m^2 membrane (AN69 M100 and M150 filter set; Gambro) were used, and for hemoabsorption, CytoSorb (CytoSorbents Corporation, USA) and Oxirus (Baxter Inc., Deerfield, IL, USA).

Study Population

Patients were excluded from the study if they were aged <18 years, had a history of any renal disease, or did not have COVID-19 infection confirmed with a PCR test during follow up. After exclusion of these patients, there were 280 patients remaining in the relevant time period. Of these 280 patients, 123 developed AKI, of which 41 met the KDIGO Grade 3 criteria and were applied with CRRT. All other patients were excluded from the study and these 41 were included for analysis.

A retrospective record was made for each of these 41 patients applied with CRRT of demographic characteristics, comorbid diseases, medical treatments applied, the SOFA score (Sequential Organ Failure Assessment), inotrope requirements, daily urine follow-up, CRRT modalities applied and the settings, the duration and number of applications, hemoabsorption column if applied, length of stay in ICU, requirement for mechanical ventilation, and mortality status.

To evaluate the efficacy of the CRRT treatment, kidney functions (urea, creatinine, glomerular filtration rate (GFR), Na, K, Cl, Ca, phosphorus), acute phase reactants, LDH, ferritin, D-dimer, CRP, lymphocyte, procalcitonin, and lactate values were recorded pre and post-treatment.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS Statistics vn. 21.0 software (IBM Corpn. released 2012, SPSS Statistics for Windows, Armonk, NY, USA). Continuous data were stated as mean ± standard deviation values. In the comparisons of two groups of data with normal distribution, the Independent Samples t-test was used. For repeated measurements, two-way repeated measures ANOVA analysis (One Factor Repetition) was applied. A value of $p<0.05$ was accepted as statistically significant.

Results

Initial examination was made of the data of PCR (+) COVID-19 cases followed up in ICU between 11/03/2020 and 15/06/2021. Of 280 patients, 41 were applied with CRRT. The demographic data and laboratory parameters were recorded from the patient files. The patients comprised 51.21% males and 48.78% females with a mean age of 69.0±11.3 years. Comorbidities were determined as hypertension in 70.7% of the patients, diabetes mellitus in 48.8%, and malignancy in 21.9%. The demographic data are shown in Table 1.

When evaluated in terms of mortality, 95% (2 patients were transferred to the service, 39 patients died in the intensive care unit) mortality was detected in the patients we applied CRRT treatment. The time from symptom onset to the start of CRRT was determined as mean 12.1 days. The day of starting CRRT corresponded to phase 2 of the clinical stages of the disease. The access region selected for CRRT was determined to be the right jugular vein followed by the femoral vein. The severe COVID-19 patients with a need for CRRT were determined to have a high SOFA score (10.08±2.85). From the clinical observations of the patients who required CRRT, they were determined to be

hemodynamically unstable, required inotropic support, and were oliguric or anuric in follow up. The anticoagulants were determined to be mostly regional citrate. Ionised calcium (iCa) after filtration was monitored by measuring once in 6 hours. The kidney functions routinely tested before and after CRRT and the acute phase reactants evaluated in the disease prognosis are summarised in Table 2. Following treatment, a significant improvement was determined in the urea, creatinine, GFR, potassium, chlorine and phosphorus values of the kidney functions.

The patients were observed to have elevated inflammation markers. Pre-treatment values were measured as ferritin: 1569.25 (13-150 ng/ml), D-dimer: 12.47 (0-0.5 mg/lt), CRP: 171.64 (0-5 mg/lt), neutrophil-lymphocyte ratio (NLR): 30.36 (1-3), lactate: 3.21 (0.56-1.39 mmol/lt), and procalcitonin: 8.74 (0-0.046 ng/ml). Following CRRT, the mean values were determined to be ferritin:1243.07 (13-150 ng/ml), D-dimer: 7.72 (0-0.5 mg/lt), CRP: 147.32 (0-5 mg/lt), NLR: 26.0 (1-3), lactate: 3.00 (0.56-1.39 mmol/lt), and procalcitonin:7.56 (0-0.046ng/ml). The inflammation marker values were numerically better after CRRT, but the difference was not statistically significant. The values before and after CRRT of the biochemical parameters included in the disease prognosis are shown in Table 3.

Throughout the defined study period, CytoSorb (CytoSorbents Corporation, USA) or Oxirus (Baxter Inc., Deerfield, IL, USA) was used as cytokine filter in 14 patients in addition to CRRT. The inotrope requirement of the patients where cytokine filter was used in the clinical follow up was seen to be reduced in the short-term.

Table 1. Demographics of 41 patients with COVID-19 infection

Age	**69±11.3**		
Gender	Male	21	51.21%
	Female	20	48.78%
Concomitant diseases	Hypertension	29	70.7%
	Diabetes Mellitus	20	48.8%
	Malignancy	9	21.9%

Table 2. Laboratory data before and after the start of SRRT

	Number of patients	Pre-SRRT values	Post-SRRT values	p
Ferritin	22	1569.25 (104-7403)	1243.07 (153-3248)	0.300
D-dimer	26	12.47 (0.480-80.0)	7.72 (0.310-34.1)	0.095
CRP	31	171.64 (11.5-383)	147.32 (24.4-420)	0.157
NLR	41	30.36 (2.30-97.0)	26.01 (4.40-96.0)	0.076
Lymphocyte	38	1.06 (0.200-7.10)	1.15 (0.140-5.40)	0.472
Lymphocyte %	37	5.13 (0.100-28.0)	5.49 (0.700-16.2)	0.595
Urea	40	62.07 (20.9-138)	32.13 (10.1-72.0)	<.001
Kreatinin	40	2.80 (0.980-6.89)	1.59 (0.570-5.20)	<.001
GFR	40	27.90 (6.91-128)	51.63 (10.7-90.0)	<.001
Na	41	141.24 (126-149)	140.24 (128-149)	0.444
K	41	5.05 (3.11-7.04)	3.70 (2.44-5.16)	<.001
Cl	40	105.32 (91.6-120)	99.83 (92.8-106)	<.001
Ca	40	7.68 (6.16-9.50)	8.56 (2.87-11.1)	0.001
P	40	5.63 (1.40-10.5)	3.82 (1.60-10.2)	<.001
Lactate	41	3.21 (1.20-15.0)	3.00 (0.300-18.0)	0.570
Procalcitonin	31	8.74 (0.0200-68.0)	7.56 (0.270-58.0)	0.674
SOFA	41	10.80±2.848	10.83±3.016	0.931

Table 3. Biochemical parameters in the prognosis of COVID-19 before/after SRRT treatment				
	SRRT (Before treatment)	SRRT (After treatment)	P value	Normal values
Ferritin	1569.25 (104-7403)	1243.07 (153-3248)	0.300	13-150 ng/ml
D-dimer	12.47 (0.480-80.0)	7.72 (0.310-34.1)	0.095	0-0.5 mg/lt
CRP	171.64 (11.5-383)	147.32 (24.4-420)	0.157	0-5 mg/lt
NLR	30.36 (2.30-97.0)	26.01 (4.40-96.0)	0.076	1-3
Lactate	3.21 (1.20-15.0)	3.00 (0.300-18.0)	0.570	0.56-1.39 mmol/lt
Procalcitonin	8.74 (0.0200-68.0)	7.56 (0.270-58.0)	0.674	0-0.046ng/ml
"Two way reapeated mesasures ANOVA (One Factor Repetition)" test was used (p<0.05).				

Discussion

Several observational and retrospective studies have contributed to the understanding of the clinical status of COVID-19. However, in addition to providing supportive medical care, there continues to be uncertainty about the real efficacy of treatments which have been recommended by testing under dramatic clinical conditions (2).

Contradictions have emerged in therapeutic recommendations (antiviral drugs, steroids, anti-IL) and guidelines, and in the effects of rescue and supportive treatments applied to severe patients in emergency conditions. It must also be emphasized that guidelines and recommendations are being constantly developed as a result of new trials. The WHO has stressed the importance of supportive treatments according to the severity of the disease, as there is no evidence on which to recommend any specific anti-COVID-19 treatment for severe cases with confirmed disease (9).

Although the respiratory system is the main target of COVID-19, other organs in the body can be infected by the virus through the circulation system (10). In literature, it can be observed that kidney involvement is frequent and can vary from mild proteinuria to advanced acute kidney injury (11).

The pathophysiology of AKI can be associated with COVID-19-specific mechanisms (direct viral entry, disproportional RAS activation, proinflammatory cytokines increased by viral infection, and thrombotic status) and non-specific mechanisms (right heart failure, hypovolemia, nosocomial sepsis, nephrotoxic drugs, mechanical ventilation, and hemodynamic changes). There is no specific treatment for AKI due to COVID-19 (10).

Current literature shows the frequency of AKI in COVID-19 patients varying between 0.5% and 45% and it has been reported to indicate a poorer prognosis. The reasons for the variability in incidence have been stated to be that different definitions are used to classify AKI, different populations have been studied, different criteria have been accepted and different countries have different resources (12)

In a study of 192 patients, Gameiro et al. reported that AKI developed in 55.2%, of which 12.5% were determined to meet the KDIGO Grade III criteria (12). Of the 280 COVID-19 patients in ICU screened in the current study, AKI was determined to have developed in 123 (43.9%). Of this patient group, 14% met the KDIGO Grade III criteria, which was consistent with the literature.

The time to starting CRRT was mean 12.5 days in a study by Lowe et al. (13) and Ronco et el. reported the start of CRRT on the 15th day after disease onset (11). From an examination of the records of the AKI patients in the current study, the time of starting CRRT was determined to be mean 12.5 days, consistent with the literature. It was also seen that the day on which CRRT was started corresponded to Phase 2 of the clinical stages of the disease.

In a study by Sabaghian et al., the mean age of AKI patients was reported to be older (72±15 years) ($p<0.001$) and there was male gender predominance (69%) ($p<0.05$) (14). A large-scale meta-analysis which included 21.060 COVID-19 patients, showed that in 39 of 41 studies there was a higher probability of severe disease in males than in females (15). In the current study, the mean age of the patients was 69.0±11.3 years, and unlike other studies, the numbers of male (51.21%) and female (48.78%) patients were close to each other.

There has been reported to be a significantly high frequency of hypertension and cardiovascular disease accompanying AKI (14). In a study by Gameiro et al., comorbidities in AKI patients were determined to be significantly high as hypertension (78.3%vs. 56.5%, $p=0.001$), chronic renal failure (28.3% vs. 9.4%, $p=0.001$), and

COPD (19.8% vs. 7.1%, p=0.012) (11). In the current study patients, comorbidities were determined as hypertension in 70%, diabetes mellitus in 48.8, and malignancy in 21.9%.

Paek et al. reported in-hospital mortality at the rate of 90% in AKI patients (16). Likewise in the current study, the frequency of mortality was 90%. In a study by Zarebska-Michaluk et al., the mean time to mortality was determined as 8 days in 82 patients classified as kidney function GFR <30 ml/L/min (17). From the records of the current study patients, the time to mortality was mean 18 days. Although the mortality rate of the AKI Grade III patients in the current study was high, with the rehabilitation including CRRT in ICU, the time to mortality was longer than reported in previous studies.

If organ dysfunction is to be measured objectively, the SOFA score can be used. Although this score was developed as a measure of the severity of organ dysfunction, it has prognostic value and has been used for that purpose in many studies (18). In a multicentre cohort study by Zhou et al., a high SOFA score (7, 15) in 191 patients was determined to be a potential risk factor for mortality (18). The severe COVID-19 patients who required CRRT in the current study were determined to have a high SOFA score (10.08±2.85).

There are various aims of extracorporeal blood purification for severe COVID-19 and AKI patients (2). These include the removal of solid loads such as creatinine and urea, convection of inflammatory mediators, cleaning wth absorption or therapeutic plasma exchange, reshaping immune homeostasis (20), correcting the body fluid compartment and decreasing excessive fluid burden (21), correcting the electrolyte and acid-base balance, and physically decreasing hyperthermia (21). In the patients examined in the current study, although the diuretic need arose associated with positive fluid balance, due to hemodynamic instability and the need for vasopressor asssociated wth endothelial damage, fluid loss to the third space, and renal hypoperfusion, there was progression to Grade III AKI, and therefore CRRT was started. All the AKI patients who required CRRT were hemodynamically unstable and receiving inotropic support. Before CRRT, the urea (62.07) creatinine (2.80), potassium (5.05), phosphorus (5.63) and chlorine (105.32) values were determined to be high. Following CRRT, a significant improvement was determined in these kidney function values of urea (32.13) creatinine (1.59), GFR (51.63), potassium (3.70), phosphorus (3.82), and chlorine (99.83). Rhabdomyolysis, metabolic acidosis, and hyperkalemia can develop in COVID-19 patients and are almost always associated with hemodynamic instability (21). Urine analyses of AKI and biomarkers are usually abnormal in COVID-19 patients and can be used to characterise AKI in these patients (22). In the current study, the effects were evaluated of CRRT and hemoabsorption treatments applied to severe COVID-19 patients who developed AKI. In the light of these data, it can be considered that further prospective studies related to severe COVID-19 treatment and organ failure that may subsequently develop will reduce the uncertainty of treatment processes in the ongoing pandemic.

It has been reported that systemic inflammation markers, primarily ferritin, CRP, procalcitonin, and LDH, are higher in patients who develop AKI after COVID-19 infection compared to COVID-19 patients with normal kidney functions (22).

In a meta-analysis by Zarebska-Michaluk et al., CRP was determined as 107 mg/l, procalcitonin as 2.83 ng/ml, and D-dimer as 5.113 mg/lt in patients with eGFR <30 mL/min/1.73m^2, and CRP as 65.5 mg/l, procalcitonin as 0.28 ng/ml, and D-dimer as 1.638 mg/lt in patients with eGFR >60 mL/min/1.73m^2. The inflammatory parameters were determined to be high in the eGFR <30 mL/min/1.73m^2 patient group (17). Gameiro et al. compared the NLR in patients with and without AKI, and determined higher values in the patient group with AKI (7.8±6.5 vs. 4.9±4.0). In addition, the ferritin value of 7600ng/ml and lactate value of 0.89 mmol/lt were determined to be higher in the AKI group, but not at a significant level (12).

The inflammation markers of the patients in the current study were determined to be higher than data in literature. Pre-treatment values were measured as ferritin: 1569.25 (13-150 ng/ml), D-dimer: 12.47 (0-0.5 mg/lt), CRP: 171.64 (0-5 mg/lt), neutrophil-lymphocyte ratio (NLR): 30.36 (1-3), lactate: 3.21 (0.56-1.39 mmol/lt), and procalcitonin: 8.74 (0-0.046 ng/ml). Following CRRT, the mean values were determined to be ferritin:1243.07 (13-150 ng/ml), D-dimer: 7.72 (0-0.5 mg/lt), CRP: 147.32 (0-5 mg/lt), NLR: 26.0 (1-3), lactate: 3.00 (0.56-1.39 mmol/lt), and procalcitonin:7.56 (0-0.046ng/ml). Although the inflammation marker values included in the COVID-19 prognosis were numerically better after CRRT, the difference was not statistically significant.

In a study in which Chen et al evaluated inflammatory markers separately, COVID-19 patients with AKI were found to have higher serum CRP levels than the patients without AKI. CRP is a marker for renal replacement therapy and for mechanical ventilation required by COVID-19 patients.

Therefore, a high CRP value is associated with a poor clinical prognosis in COVID-19 patients. However, the role of CRP and the mechanisms in which it is included in AKI associated with COVID-19 are not fully known (23). When literature is examined, it can be seen that there may be a relationship between lymphopenia and the severity of infection. In a cohort of 450 COVID-19-positive patients, Qin et al. analyzed the markers related to immune response irregularity, and reported that severe cases tended to have a lower lymphocyte count, higher leukocyte count, and a higher NLR than mild cases (24, 25). The hematological (lymphocyte count, leukocyte count, NLR), inflammatory (CRP, sedimentation, Il-6), and especially biochemical (D-dimer, troponins, CK) parameters were found to be associated with a severe prognosis or mortality in COVID-19 patients, and therefore, it can be concluded that these can be used as estimation-based biomarkers (25). A laboratory score including hematological, inflammatory, biochemical, and immunological parameters would be useful in differentiating risk categories in the treatment methods and clinical follow-up of COVID-19 patients (25). The potential risk factors in the current study patients were determined to be high before starting CRRT. These risk factors explain the poor prognosis and high mortality of these patients. On the basis of these findings, laboratory scoring would be useful for clinicians to identify patients with a poor prognosis at the early stage and to organise treatments.

Since the reporting of the first cases, cytokine storm has been observed in the clinical course of severe COVID-19 patients (1,26). Similar to sepsis and septic shock, the nature of cytokine storm in COVID-19 patients has been observed to be organ dysfunction, increased vascular permeability, hypovolemia, hypoperfusion, hypotension, cardiomyopathy, tissue oedema, pleural effusion, increased intra-abdominal pressure and cross-reactions of organs with each other (18). Despite the initial low number of clinical studies therapeutic approaches have entered clinical practice to reduce severe acute pulmonary damage and multiorgan failure associated with COVID-19 (27). Of the treatments directed at suppressing the increased cytokine response with anti-inflammatory treatments, promising results have been obtained from reducing IL-6 (eg., tocilizumab, sarulimab, siltuximab), IL-1 receptor antagonist (eg., anakınra. canakinumab, rilonacept), and even TNF-αinhibitors (eg., adalimumab). The theoretical basis of only cytokine inhibition has been expanded with the hypothesis that potential benefits could be obtained from other immunomodulators which could be effective by targetting different cytokine types (26).

Consistent with findings in literature, it was seen in the current study that by using CRRT and cytokine absorption columns, both renal replacement and supportive treatment for sHLH developing in the course of the disease could be given. In a prospective, observational study, Villa et al. determined a significant decrease in IL-6 concentrations, and a decrease in the SOFA score associated with an improvement in organ functions in patients treated with cytokine absorption (Oxiris membrane;Baxter, IL, USA) (27).

The mean day of starting CRRT in the current study was the 12th day when hyperinflammation started. For the 14 patients where cytokine filter was used in addition to CRRT, CytoSorb (CytoSorbents Corporation, USA) or Oxirus (Baxter Inc., Deerfield, IL, USA) was used. From the daily monitoring records of the patients, there was determined to be a reduced need for short-term inotropes in patients applied with cytokine filtration.

Another point which is usually found in discussions related to treatment of sepsis-like syndromes is the timing and monitoring of treatment. Clinical conditions such as rhabdomyolysis (28), multiorgan failure related to thrombocytopenia (29), multiple myeloma (29), and acute rejection after organ transplantation (29) benefit from extracorporeal blood purification. The decision to start treatment is made when a series of mediators reach a peak (29). Together with the onset of symptoms, it is possible to determine biomarkers of the disease (eg., myoglobin, von Willebrand factor and ADAMTS-13, donor-specific antibodies). The same biomarkers can be examined repeatedly and the treatment efficacy is followed up objectively. Extracorporeal blood purification is directed at the target and the timing of starting and finishing the treatment is evident and clear (29). However, in the timing of extracorporeal blood purification treatment for COVID-19 cases, there are no specific biomarkers for starting and finishing the treatment.

Although vaccinations create immunity and are expected to definitively eliminate disease, for critical COVID-19 patients for whom the treatment options are limited, it would seem to be rational to adopt immunomodulator strategies including extracorporeal blood purification and supportive treatment such as CRRT. The results of this study have shown that CRRT applied to severe COVID-19 patients who develop AKI is an effective treatment for kidney failure. However, the

effect on the progression of COVID-19 could not be clearly shown.

Limitations of this study could be said to be the relatively limited number of patients, the variability in antibiotic levels because of CRRT, and that there was no information about whether or noot there was secondary infection in patients with a high SOFA score. There remains a need for further prospective studies on this subject.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Non-Interventional Clinical Research Ethics Committee of Eskişehir Osmangazi University Medical Faculty (Decision No: 32, Dated: 06.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.P.Ş., O.Ö.A., B.Y., Design: E.P.Ş., O.Ö.A., B.Y., Data Collection and Process: E.P.Ş., Z.G., B.Y., Analysis or Interpretation: E.P.Ş., E.K., Z.G., B.Y., Literature Search: E.P.Ş., E.K., O.Ö.A., B.Y., Writing: E.P.Ş., E.K., Z.G., B.Y.

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