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Experiences with extracorporeal membrane oxygenation in severe COVID-19 infection: A single-center retrospective study

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ABSTRACT

Objectives: This study aimed to share our experiences using extracorporeal membrane oxygenation (ECMO) for severe coronavirus disease 2019 (COVID-19) to explain the mechanisms of disease and death related to COVID-19 and improve ECMO supportive treatment.

Patients and methods: This retrospective study was conducted with 26 COVID-19 patients (10 males, 16 females; mean age: 34.4±11.5 years; range, 12 to 59 years) who received ECMO support between January 1, 2021, and December 31, 2021. A multidisciplinary team closely followed patients with COVID-19 who required ECMO support. The data were carefully recorded, and their effects on ECMO follow-up and the results obtained were examined.

Results: Only 34.6% of the patients were able to come off ECMO support, and the mortality rate during ECMO support was 80.8%. However, the mortality rate for weaned patients decreased significantly over the last six months.

Conclusion: Overall, our findings suggest that ECMO intervention should be done early for better treatment outcomes, and mild sedation in ECMO follow-up for COVID-19 patients is linked to lower mortality rates.

Keywords: Conscious sedation, COVID-19, ECMO, respiratory distress syndromes.

Coronavirus disease 2019 (COVID-19) is a pandemic with a high mortality rate, particularly among patients who require mechanical ventilation. Much is still unknown about this virus, such as its natural history, long-term complications, virus persistence, or prognosis in different patient subgroups.[1] Extracorporeal membrane oxygenation (ECMO) may be appropriate for patients with severe heart and lung failure due to COVID-19, resistance to mechanical ventilation, and other optimal medical treatments.[2] The mortality rate is higher in patients on ECMO support due to the progression of COVID-19 to acute respiratory distress syndrome (ARDS).[3,4] Available data on using ECMO in these patients are limited, and earlier results are discouraging.[5]

In this study, we shared our experiences using ECMO for severe COVID-19 in a pandemic hospital. We believe that, with similar studies, the mechanisms of disease and death related to COVID-19 can be better understood, and ECMO-supportive treatment can be applied more healthily in patients.

PATIENTS AND METHODS

In this retrospective study, 26 patients (10 males, 16 females; mean age: 34.4±11.5 years; range, 12 to 59 years) hospitalized in the intensive care unit of the Sancaktepe Sehit Prof. Dr. İlhan Varank Education and Research Hospital due to COVID-19 infection between January 1, 2021, and December 31, 2021 were evaluated. Patients with COVID-19 who required ECMO support during

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the follow-up period were included in the study. Patient demographics, clinical information, and laboratory findings were obtained from the medical records.

Indications for ECMO for patients whose hypoxic respiratory failure persisted despite adequate ventilation therapy were determined following the Extracorporeal Life Support Organization (ELSO) Guidelines on ARDS as severe hypercapnia (pH <7.2 and $PaCO_2$ (partial pressure of carbon dioxide) >80 in 6 h), prolonged ventilation (>7 days), and refractory cardiogenic shock (determined as Murray score >3 or one organ failure in COVID-19 patients with or without comorbidity).

The patients were closely followed during ECMO support in the intensive care unit by a multidisciplinary team of cardiovascular surgeons, intensivists, and perfusion specialists. The ventilator values, time required for intensive care, need for mechanical ventilation afterward, and treatment protocols received during this process before ECMO support for ARDS were recorded. The treatments and doses administered to the patients with underlying diseases were evaluated during ECMO support. Data on ECMO-related complications and their etiologies were examined to evaluate complications associated with ECMO support.

During this process, different levels of sedation were applied to patients, and their alertness levels were recorded. A reanimation and anesthesiology specialist prepared the sedation protocol using ECMO support. The Richmond Agitation Sedation Scale (RASS) was used in the follow-up of patients to evaluate the level of sedation in detail and allow drug titration. We applied light (RASS +1/–1), moderate (RASS –2/–3), and deep (RASS –4/–5) sedation according to the RASS. It was evaluated whether the data obtained varied among the patients in whom ECMO support could be safely terminated.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to test the normality of the data distribution. Continuous variables were expressed as mean ± standard deviation (SD) and median (25^{th}-75^{th} percentiles), and categorical variables were expressed as frequency (percentage). Nonnormally distributed continuous variables were compared between the groups using the Mann-Whitney U test. Categorical variables were compared between the groups using Fisher exact chi-square test and Yates' chi-square test. Statistical significance was defined as a two-sided p-value <0.05.

RESULTS

The patients' mean body mass index was 27.38±2.71. All the patients had severe ARDS that

Table 1
Mean times and values in patient follow-up

	First 6 months			Last 6 months			
	Median	25^{th}-75^{th} percentile	Min-Max	Median	25^{th}-75^{th} percentile	Min-Max	*p*
Time from onset of symptoms to admission to intensive care unit (days)	6	3-8	1-14	9	6-10	2-20	0.830
Time from admission to intensive care unit to intubation (days)	1	0-1	0-3	1	0-5	0-37	0.778
Duration of mechanical ventilator support (days)	14	10-28	9-79	24	5-38	1-100	0.778
Time from intubation to ECMO support (days)	6	1-20	0-24	2	0-7	0-30	0.254
Duration of stay in the intensive care unit	16	11-48	9-66	24	8-38	2-100	0.778
Average values before ECMO support							
pO_2 (mmHg)	49.6	46.7-53.8	34-128	46.1	37.4-73.6	30.2-88.1	0.231
pCO_2 (mmHg)	49.6	46.7-53.8	34-128	42	35.2-61	23-116	0.461
FiO_2 (%)	100	100-100	100-100	1000	100-100	100-100	0.692

ECMO: Extracorporeal membrane oxygenation; pO_2: Partial pressure of oxygen; pCO_2: Partial pressure of carbon dioxide; FiO_2: Fractional inspired oxygen.

progressed rapidly during the follow-up period. All adult patients were healthy before the COVID-19 diagnosis. Known coronary artery disease and smoking rates were 3.8%. Two of the three patients in the pediatric age group had different syndromes, such as hemolytic uremic syndrome and Kawasaki syndrome.

The median time from the onset of all patients' symptoms to the time they needed intensive care was 8.62 days. Support with ECMO was required with a median of 4.27 days after intubation (Table 1). While venovenous ECMO support was performed in 76.9% of the patients, venoarterial ECMO (VA-ECMO) support was provided in 23.1% due to septic conditions. Femorojugular access was performed in 84.6% of the patients. Distal perfusion was achieved in all patients receiving VA-ECMO support. The median intubation duration was 17.5 days. Tracheostomy was required in 34.6% of the patients. Although ECMO support was initiated under sedation, almost 19.2% of the patients were awake during ECMO. The median length of stay of the patients in the intensive care unit was 22.50 days, and the hospitalization period was 35.27 days (Table 1).

All patients were administered appropriate antibiotics according to the recommendations of the Department of Infectious Diseases, and additional antiviral treatment was administered to 73.1%. Various complications developed due to the length of intensive care unit stay. The infection progressed to sepsis in 92.3% of the patients, and multiple organ failure developed in 26.9%. All the complications are presented in Table 2.

Table 2
Rates of ECMO supportive therapy

	n	%
Rates pertaining to the application		
Venovenous ECMO	20	76.9
Venoarteriel ECMO	6	23.1
Femoro-jugular access	22	84.6
Femoro-femoral access	4	15.4
Distal perfusion	6	100
Awake ECMO	5	19.2
Need for tracheostomy	9	34.6
Applied medical treatments:		
Antibiotic therapy	26	100
Antiviral therapy	19	73.1
Steroid therapy	24	92.3
Inotrope support	25	96.2
Vasopressor therapy	21	80.8
Renal replacement therapy	4	15.4
Plasmapheresis	7	26.9
Heparin (Anticoagulant therapy)	8	30.8
Bivalirudin (Anticoagulant therapy)	18	69.2
Antiplatelet therapy	3	11.5
Complications and outcome of ECMO support		
Sepsis	24	92.3
Multiple organ failure	7	26.9
Renal failure	3	11.5
Major bleeding	5	19.2
Ischemic CVD	1	3.8
Pneumothorax	9	34.6
Pulmonary hemorrhage and hemothorax	4	15.4
Weaning	9	34.6
Mortality	21	80.8

ECMO: Extracorporeal membrane oxygenation; CVD: Cerebrovascular disease.

It was observed that in the first six months after ECMO support treatment was started, weaning could be performed in three out of seven patients, but all of the patients died. Weaning was performed in six of the 19 patients over the next six months, and five survived. No statistically significant difference was observed between the mortality and weaning rates (p=0.342 and p=0.661, respectively). However, a statistically significant 83.3% of patients who underwent weaning in the last six months survived.

DISCUSSION

Coronavirus disease 2019 is a highly contagious disease that infects millions of people worldwide.[6] Symptoms in COVID-19 patients are variable and can progress from mild to severe symptoms that can result in ARDS, multiple organ failure, or death.[7] A practical and specific treatment for COVID-19 has yet to be proven. According to the World Health Organization, COVID-19 management mainly focuses on infection prevention, case detection and monitoring, and supportive care.

The World Health Organization and Centers for Disease Control and Prevention have published recommendations regarding ECMO support in patients with severe or critical respiratory failure and cardiac involvement who do not respond to conventional therapy.[8] Extracorporeal membrane oxygenation is a form of extracorporeal life support that temporarily compensates for deficient lungs or a failing heart by oxygenating the blood while minimizing iatrogenic ventilator-induced lung injury.[9]

Poor outcomes in patients undergoing ECMO during the COVID-19 pandemic include old age, low PaO_2 (arterial oxygen partial pressure)/FiO_2 (fractional inspired oxygen) ratio, immunocompromised status, comorbidities, and need for VA-ECMO.[9] Decisions on ECMO support should also consider these factors and the patient's condition.[10] In our study, only one patient had coronary artery disease. One patient had a history of smoking but no chronic obstructive pulmonary disease diagnosis. Our patients were mainly young, with a mean age of 34.4±11.5 years. No statistically significant correlation was found between the patient's age, other diseases, smoking history, prolonged intensive care follow-up, and the need for ECMO support.

ECMO therapy can be organized into two basic methods: venovenous ECMO and VA-ECMO. For ARDS, such as COVID-19, and its respiratory complications, the predominantly used ECMO mode is venovenous.[4,11] However, pulmonary complications, such as ARDS, and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection may also cause cardiovascular damage. In this case, VA-ECMO mode was used. The rate of cardiorespiratory combined ECMO support (VA or venoarteriovenous ECMO) among COVID-19 patients was <10%, and these patients were found to have poor prognosis.[12] In our study, only 11.53% of the patients required VA-ECMO, and 66.6% survived. Three of these patients were in the pediatric age group and received VA-ECMO support for multisystem inflammatory syndrome.

It is thought that there is a relationship between the early initiation of ECMO treatment and survival. It is not recommended after lung damage due to advanced mechanical ventilation support and after end-organ dysfunction has started.[13] However, in the first and last six months, no significant statistical difference existed between the start of the patient's symptoms and the timing of intensive care unit hospitalization, intubation, or the beginning of ECMO support and treatment (p=0.083, p=0.778, and p=0.254, respectively). In addition, there were no significant statistical differences in the first and last six months' levels of pO_2 (partial pressure of oxygen), pCO_2 (partial pressure of carbon dioxide), and FiO_2 values obtained before ECMO support. (p=0.231, p=0.461, and p=0.692, respectively).

Weaning could be performed in only 42.92% of the patients who were in the first six months of follow-up, but none survived among these patients. In the last six months of follow-up, weaning was performed in 31.6% of the patients; 83.3% of these patients achieved weaning, and the mortality rate was 16.6%. While there was no significant statistical difference between the mortality rates in the first and last six months, it was observed that mortality between weaning decreased, particularly in the previous six months (p=0.002).

Patients with COVID-19 may require more sedation than critically ill patients due to their younger age, higher respiratory pathologies, increased clearance from other drugs, and intense inflammatory responses.[14] Sedatives and neuromuscular blocking drugs eliminate asynchronies that occur with mechanical ventilation.[15] There are more detailed studies on the effects of sedative agents on oxygen

and energy consumption;[16] however, these studies are few and contradictory.[17,18] Murphy et al.[19] showed that critical respiratory events in the postanesthesia care unit are closely related to the high incidence of severe residual blockade. In this study, most patients were curarized (80.76%). Patients (19.23%) who did not experience tachypnea, deep hypercarbia, or hypoxia during the intensive care follow-up and whose hemodynamics were more stable than others were not curarized during their follow-up.

The sedation follow-up of the patients was performed using the RASS since it shows the sedation levels in detail and allows the titration to be made more easily in drug treatment.[20] Propofol, remifentanil, midazolam, remifentanil, and dexmedetomidine with or without remifentanil were alternately administered as sedation agents. Short-acting sedation agents were preferred and stopped once daily, and the state of consciousness was evaluated and monitored neurologically. The mean RASS of the patients who were followed up for the first six months was −4.6±0.467, and for the patients who were followed up in the last six months, it was −4.0±1.76. In the previous six months, the patients who underwent weaning from ECMO and survived were not curarized, and four of them were followed by RASS -1 and one with −3 (mean: −1.4±0.89). This difference was statistically significant ($p<0.001$).

The use of ECMO is associated with significant risks, such as bleeding, infection, need for frequent transfusions, stroke, and embolisms of small blood clots or air bubbles.[21] Major bleeding, pulmonary hemorrhage, and hemothorax were detected in 19.2% and 15.4% of the patients, respectively. Multiple organ failure, renal failure, ischemic cerebrovascular events, and pneumothorax were also observed. Sepsis was detected at a high rate (92.3%). This finding was interpreted to be primarily due to ARDS and pneumonia. Only one patient required circuit replacement due to issues with ECMO return.

The European chapter of the ELSO determined the in-hospital mortality rate to be 44% in the first 1,531 COVID-19 patients who received ECMO support.[22-23] However, this rate might be slightly higher than what is known since long-term survival information about patients is unavailable. Another study by Lebreton et al.[24] reported that 46% of the patients were alive 90 days after ECMO onset. The ELSO reported independent mortality factors, such as temporary circulatory support (VA-ECMO support), advanced age, low PaO_2/FiO_2 ratio, acute kidney injury, chronic respiratory failure, immunosuppressed conditions, and a history of cardiac arrest before ECMO.[12] In this study, cardiopulmonary failure was the leading cause of death (73.1%), followed by multiple organ failure (23.1%) and neurological pathologies (3.8%). Only 34.6% of patients were weaned off ECMO. The mortality rate during ECMO support was 80.8%. Of the patients, 42.9% were weaned in the first six months, and 31.6% were weaned in the next six months. In patients who were weaned in the first six months, mortality was 100%, while this rate remained at 16% in the last six months. The mortality ratio of weaning patients was statistically significant ($p<0.001$). Based on our team's increasing experience, we believe that mild sedation was applied to the departure of patients diagnosed with ARDS associated with COVID-19.

There are some limitations to this study. The limited number of patients and retrospective nature of the study make it impossible to evaluate other factors affecting the results and conduct further examinations. The results would be more meaningful if the study had progressed with more patients and instant observations.

In conclusion, venovenous ECMO support remains a salvage treatment for patients with COVID-19 who have refractory hypoxemia despite mechanical ventilation therapy. However, based on these criteria, early intervention is vital for a successful treatment. In light of this retrospective examination, mild sedation during ECMO follow-up in patients with COVID-19 is associated with more positive results. However, more data are needed to finalize this situation and to examine its causes.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences, Sancaktepe Şehit Prof. Dr. Ilhan Varank Training and Research Hospital Scientific research Ethics Comitee (date: 08.09.2021, no: 2021-188). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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