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Extracorporeal membrane oxygenation experiences during COVID-19 pandemic, third wave with younger patients: A retrospective observational study

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Abstract:

OBJECTIVES: In this article, the results of severe coronavirus disease 2019 (COVID-19) cases followed with extracorporeal membrane oxygenation (ECMO) support in a 3-month period in the third wave when there were an increased number of cases of young patients in our intensive care unit (ICU) were presented.

METHODS: The study was carried out with all COVID-19 patients who were given ECMO support in our tertiary referral hospital ICU after obtaining the consent of the Ministry of Health Scientific Research Platform and after the approval of the local ethics committee. Patient data were obtained retrospectively from intensive care bedside follow-up charts and computer records. The demographic and clinical characteristics of the patients were presented in average, median, and percentages. The data of the patients were evaluated and compared with the current literature.

RESULTS: ECMO treatment was applied in seven patients who were followed up with severe COVID-19 pneumonia in the last 3 months. Venovenous extracorporeal membrane oxygenation (VV-ECMO) was applied to all patients. Five (71.5%) of seven patients were weaned from ECMO. Four (57.2%) of seven patients were discharged from the ICU and hospital in good health. While two of the patients had a cesarean section (C/S) before ECMO, one patient underwent C/S under ECMO. All three newborns were delivered via C/S and all were premature (C/S dates were 35 weeks, 32 weeks, and 27 weeks), and all were discharged from the hospital in good health.

CONCLUSION: Our experience shows that ECMO in COVID-19 patients is a lifesaving treatment option that can be successfully applied in severe acute respiratory distress syndrome cases who do not respond to conventional treatments.

Keywords:

Coronavirus disease 2019, extracorporeal membrane oxygenation, mortality, pregnancy, SARS-CoV-2

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Introduction

Coronavirus disease 2019 (COVID-19)-associated acute respiratory distress syndrome (ARDS) has a high mortality rate and can be seen not only in the elderly and those with chronic diseases but also in young and healthy patients. Venovenous extracorporeal membrane

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Box-ED Section

What is already known on the study topic?

- Extracorporeal membrane oxygenation (ECMO) is a lifesaving treatment method for collapsed lung in coronavirus disease 2019 (COVID-19) patients
- Performing ECMO treatment is not easy and unfortunately has high mortality.

What is the conflict on the issue? Has it importance for readers?

- Mortality rates are higher in Turkey than European Union countries, besides the mortality rates are higher in COVID-19 patients than other critical ill patients under ECMO treatment
- The main question is: How can we increase our survive rates?

How is this study structured?

- This was a single-center, retrospective observational study.

What does this study tell us?

- Contrary to routine recommendation, early weaning from mechanical ventilation (weaning than ECMO) and letting the patients breath can be beneficial in COVID-19 patients.

oxygenation (VV-ECMO) for the clinical management of severe respiratory failure has been used effectively during the 2009 influenza A (H1N1) pandemic.[1,2] ECMO is an invasive support strategy for cardiac, respiratory, or combined cardiorespiratory failure when conventional treatment options have failed. Considering the limited healthcare resources, the use of VV-ECMO as a therapeutic intervention in selected COVID-19 cases who resistant to standard medical and mechanical ventilation strategies is recommended by The Extracorporeal Life Support Organization (ELSO).[3] In this study, we present our results on severe COVID-19 patients who received ECMO support in a tertiary referral hospital intensive care unit (ICU).

Methods

The study includes all COVID-19 patients who were given ECMO support in our ICU during the third wave; last 3 months (March–May 2021) when the disease was most prevalent among young people in our country. In addition to informed consent of the patients, the study was approved by the Ministry of Health Scientific research platform with registration number of 2021-05-14-T20_34_19 regarding COVID-19–related studies and by the local ethics committee (Karadeniz Technical University, School of Medicine, No: 2021/368 dated November 15, 2021). The diagnosis of SARS-CoV-2 pneumonia was based on radiological and microbiological (upper respiratory tract SARS-CoV-2 PCR) samples. All data pertinent to the patients were obtained retrospectively from intensive care bedside follow-up charts and computer records.

The clinical characteristics, demographic data, comorbidities, first admission laboratory data, intensive care patient severity scores, mechanical ventilation and ECMO settings, medical treatments for COVID-19, ECMO-related complications, and patient outcomes were recorded. In all patients who underwent ECMO, the lung protective ventilation strategy recommended by the ELSO COVID-19 guideline was followed. This strategy includes achieving a targeting plateau pressure (PPLAT) $\leq$25 cmH_2O, respiratory rate 4–10, breath per minute, positive end-expiratory pressure (PEEP) 10–15 cmH_2O, driving pressure <15 cmH_2O, and FiO_2 50% to maintain saturation $\geq$85%. Again, ECMO decisions were made based on the indications of the same guideline for ECMO. These indications included (1) partial pressure of arterial oxygen (PaO_2) over a FiO_2 ratio of less than 50 mmHg for more than 3 h; (2) PaO_2/FiO_2 less than 60 mmHg for more than 6 h; or (3) arterial blood pH less than 7.25 with a partial pressure of arterial carbon dioxide of 80 mmHg or more for 6 h or more and the absence of absolute contraindications for ECMO.[3]

VV-ECMO was applied to all patients. Deciding whether to start and leave ECMO in our intensive care clinic is made by the intensive care and cardiovascular surgery team. Cannulation procedure is performed with ultrasonography as recommended and adequate position of the cannulas was verified by ultrasonography and chest X-ray.[3] VV-ECMO was percutaneously and ultrasonographically inserted with a 23–29-Fr drainage cannula and an 18–23-Fr return cannula by two intensive care physicians. A 24-h cardiovascular surgery and perfusionist team is available for possible complications and support. All our patients were anticoagulated with unfractionated (UF) heparin and the partial thromboplastin time (PTT) target was as 40–55 s as in the EOLIA study.[4] In general, recommendation for hemoglobin is >7–8 mg/dl (in the case of resistant hypoxemia, it can be increased up to 10 mg/dl), for platelets >50,000 10^9/l. Although targets are recommended, low platelet counts and fibrinogen values are tolerated unless a bleeding problem occurs.[3,5] When ECMO was adjusted, cardiac output (CO) was measured by bedside echocardiography, and the target flow adjustment was set to be at least 80% of CO. Flows were maintained greater than 3 l/min to minimize risk of spontaneous clot formation. EOS ECMO®-Hollow Fiber Oxygenator (LivaNova) and SCP + SCPC® The Centrifugal Pump System (SORIN) were used in ECMO treatments.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or as median (interquartile range [IQR]) according to the distributions examined by the Kolmogorov–Smirnov test. Categorical variables are presented as numbers (proportions). Data were analyzed with SPSS V23, IBM, Chicago, USA.

Results

ECMO treatment was applied to seven patients who were followed up with severe COVID-19 pneumonia in the last 3 months. Four of the patients were men and three were women, and the median age was 40 years. Five (71.4%) of seven patients were weaned from ECMO. Four (57.2%) of seven patients were discharged from the ICU and the hospital in good health. All patients were discharged to the ward and then to their homes with a Glasgow coma scale of 15 and reduced oxygen demand. None of the discharged patients died in the 90-day follow-up. All of them continue their lives with their normal physical performances. The clinical features, ECMO and mechanical ventilation-related parameters, and outcome information of the patients are detailed in Table 1. VV-ECMO cannulation was performed in all patients in the femoral-internal jugular configuration. Before the ECMO, the median P/F ratio of the patients was 65 (61–78). While the median driving pressure value before ECMO was 20 (16–23) mmHg, the median driving pressure value under ECMO was 9 (8–11) mmHg. The median FiO_2 support at initial ECMO settings was 90% (90–90), the median blood flow was 3.7 l/min (3.5–4), and the median sweep gas flow was 5 l/min (5–6). Prone position was applied in 6 of 7 patients. While two of the patients had a cesarean section (C/S) before ECMO, one patient underwent C/S under ECMO. All three newborns were delivered via C/S and all were premature (C/S dates were 35 weeks, 32 weeks, and 27 weeks), and all were discharged from the hospital in good health. Tube thoracostomy was performed after pneumothorax in two patients, while pneumothorax was bilateral in these two patients. During the follow-up period, ventilator-associated pneumonia (VAP) developed in four patients, and catheter-related bloodstream infection developed in three patients. While all patients were anticoagulated with UF heparin, no thrombotic events occurred in the membrane oxygenator during ECMO support.

The median day from diagnosis of COVID to mechanical ventilation in patients was 13 (IQR: 9–17), and the median day from mechanical ventilator to ECMO was 1 (IQR: 1–4). The median duration of mechanical ventilator, median ECMO treatment time, and median intensive care hospital stay were, respectively, 22 (IQR: 8–35) days, 16 (IQR: 8–18) days, 35 (IQR: 17–36) days. The timeline chart of the patients after the diagnosis of COVID-19 is shown in Figure 1.

Discussion

Severe ARDS associated with COVID-19 can rapidly cause profound hypoxemia and death. Although the efficacy of ECMO is unclear in this selected patient group where mechanical ventilation is not sufficient, many of major health organizations recommend the use of ECMO support as a rescue therapy for acute hypoxemic respiratory failure associated with COVID-19.[3,6-9] However, due to the limited capacity and constrained resources during the pandemic for hospitalization of patients, the consensus among clinicians is to admit young patients with single organ failure and previously healthy patients who are likely to see maximum benefit.[10,11] In parallel with these predilections, the average age of our patients was also younger because of the second wave. As the median age was 40, the successful wean rate from ECMO was 71.4%, and the survival rate in the ICU was 57.2%. None of the patients had serious comorbidities, and all of them were taken to ECMO in the early period of mechanical ventilation (day 6 at the latest). Contrary to this result in our small group of the study, initial data on the use of ECMO in COVID-19 patients at the beginning of the pandemic resulted in high mortality.[12] For these critically ill patients, it is recommended that ECMO is better to be implemented in centers with enough number of specialist and also to organize mobile ECMO teams for expedited patient transfer.

Lebreton *et al*. have published a report on the ECMO results of critically ill patients with COVID-19 from 17 ICUs, covering the Paris region of France with a population of approximately 12 million. The survival rate of 90 days after ECMO was 46% of 302 adult patients who did not have serious comorbidities but requiring ECMO.[13] These results contradict the findings from the 2018 EOLIA study, which reported a 60-day survival of 65% in the ECMO group, suggesting that lung failure due to SARS-CoV-2 has a worse prognosis compared to acute respiratory distress from other causes.[4] On the other hand, in an international registry study, ELSO reported an estimated 90-day survival rate of 62% in 1035 patients treated with ECMO for refractory lung failure associated with COVID-19.[8] In our study, while two patients to whom VV-ECMO applied were in the early postpartum period, while one patient gave birth with C/S under ECMO and two of three survived. All female patients were unvaccinated patients who were admitted to ICU and connected to ECMO in the postpartum/pregnancy period completely by chance. Within the patient profile we accepted in the third wave, there were approximately 37 pregnant/postpartum patients that we followed in the

Table 1: Characteristics of the extracorporeal membrane oxygenation patients due to coronavirus disease 2019*

Characteristic	Patients							Median (25th-75th percentiles)
	1	2	3	4	5	6	7	
Age (years)	46	22	32	40	45	26	63	40 (26-46)
Gender	Male	Female	Female	Male	Male	Female	Male	
BMI<30	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Smoking	Yes	No	No	Yes	No	No	No	
Score points								
SOFA score	8	8	10	15	2	5	5	8 (5-10)
APACHE II score	16	20	17	14	12	20	18	17 (14-20)
Comorbidity	Hypertension	None	None	Diabetes mellitus	Hypertension Diabetes mellitus	None	Hypertension CAD	
Laboratory values on admission								
C-reactive protein (mg/L)	206	103	14.3	9.1	42.9	77.4	324	77.4 (14.3-206)
White blood cell (10^3 cells/mm^3)	7.95	23.5	10.29	13.6	7.9	11.1	22	10.1 (7.9-22)
Platelet (10^3 cells/mm^3)	134	405	211	142	225	328	302	225 (142-328)
Hematocrit (%)	44.8	24.8	31	41.5	36.2	26.7	38.1	36.2 (26.7-41.5)
Hemoglobin (g/dl)	15.5	8.4	9.7	13.3	10.8	8.8	12.8	10.8 (8.8-13.3)
Creatinine (mg/dl)	1.11	0.22	0.62	0.37	1.29	0.24	0.97	0.62 (0.24-1.11)
Lactate dehydrogenase (U/l)	987	574	594	586	733	551	515	586 (551-733)
D-dimer (mg/l)	0.96	6.22	5.89	0.63	1.46	2.28	2.04	2.05 (0.96-5.89)
Lactate (mg/dl)	20	9	11	10	30	17	18	17 (10-20)
Ferritin (µg/l)	2116	62	40	279	78	1812	98.1	98.1 (62.3-1812)
Median arterial blood gas values before ECMO								
pH	7.43	7.46	7.46	7.26	7.36	7.41	7.07	7.41 (7.26-7.46)
FiO_2 (%)	100	100	75	100	100	100	100	100 (100-100)
P/F	63	61	80	65	53	78	78	65 (61-78)
PO_2 (mmHg)	83	61	58.9	65	53.2	78	78	63 (58-78)
pCO_2 (mmHg)	43	27	48.8	114	65.3	44.1	103	48.8 (43-103)
HCO_3 (mmol/L)	28	21	32.5	41.2	33	27.5	21.7	28 (21.7-33)
sO_2 (%)	85	83	86	84	84	87	87	85 (84-87)
Mechanical ventilation parameters before ECMO								
FiO_2 (%)	100	100	75	100	100	100	100	100 (93.75-100)
PEEP (mmHg)	11	10	13	7	12	10	9	10 (9-12)
Tidal volume (ml)	550	310	560	326	530	350	350	350 (326-550)
Respiratory rate (breath/min)	20	20	18	24	20	20	22	20 (20-22)
Plato pressure (mmHg	31	32	29	32	28	30	32	31 (29-32)
Driving pressure (mmHg)	20	22	16	25	16	20	23	20 (16-23)
ECHO evaluation before ECMO†								
EF (%)	55	50	50	60	60	55	55	55 (50-60)
Valve insufficiency	None	1º	1º	None	None	None	1º	

Contd...

Table 1: Contd...

Characteristic	Patients							Median (25th-75th percentiles)
	1	2	3	4	5	6	7	
CO (l/min)	4.9	5.8	5.5	5	5.2	6.2	6.8	5.5 (5-6.2)
ECMO initial settings								
Blood flow (l/min)	4	3.2	3.6	3.7	3.5	3.83	4.1	3.7 (3.5-4)
Sweep gas flow (l/min)	6	4	5	6	5	5	6	5 (5-6)
FiO_2 support (%)	100	90	90	80	90	90	90	90 (90-90)
Mechanical ventilation parameters after ECMO								
FiO_2 support (%)	100	50	40	45	85	60	40	50 (40-85)
PEEP (mmHg)	8	11	14	12	10	11	9	11 (9-12)
Tidal volume (ml)	320	240	350	200	350	240	200	240 (200-350)
Respiratory rate (breath/min)	15	10	14	11	10	11	10	11 (10-14)
Plato pressure (mmHg)	18	20	22	18	18	22	20	20 (18-22)
Driving pressure (mmHg)	10	9	8	6	8	11	11	9 (8-11)
Treatments								
Medical‡	Pulse steroid Tocilizumab NM blocker	Tocilizumab NM blocker	Pulse steroid Tocilizumab NM blocker	Pulse steroid Tocilizumab NM blocker	Pulse steroid Tocilizumab NM blocker	Pulse steroid NM blocker	Pulse steroid NM blocker	
Prone position	Yes	Yes	Yes	Yes	Yes	No	Yes	
Surgical	None	Tube thoracostomy Thoracotomy Cesarean section	Cesarean section			Tube thoracostomy Thoracotomy Cesarean section	None	
Complications	None	Hemothorax Pneumothorax Thrombocytopenia VAP CRBSI	Thrombocytopenia	Thrombocytopenia VAP Septic shock	Cardiac arrhythmia VAP CRBSI Septic shock	Hemothorax Pneumothorax Thrombocytopenia VAP CRBSI	None	
Outcomes								
Wean from ECMO	Yes	Yes	Yes	No	Yes	No	Yes	
Mortality	Survived	Survived	Survived	Nonsurvived	Nonsurvived	Nonsurvived	Survived	

*BMI denotes body mass index, †Cardiac output was estimated with the Doppler velocity time integral method and ejection fraction with the Simpson method, ‡Pulse steroid means 250 mg metilprednisolone/day. The P/F ratio equals the arterial pO_2 divided by the FiO_2. CAD=Coronary artery disease, FiO_2=Fraction of inspired oxygen, PO_2=Partial pressure of oxygen, pCO_2=Partial pressure of carbon dioxide, SO_2=Arterial oxygen saturation, SOFA=Sequential organ failure assessment, APACHE II=Acute physiology and chronic health evaluation II, PEEP=Positive end expiratory pressure, ECMO=Extracorporeal membrane oxygenation, ECHO=Echocardiography, EF=Ejection fraction, CO=Cardiac output, NM blocker=Neuromuscular blocker, VAP=Ventilator-associated pneumonia, CRBSI=Catheter-related bloodstream infection, BMI=Body mass index

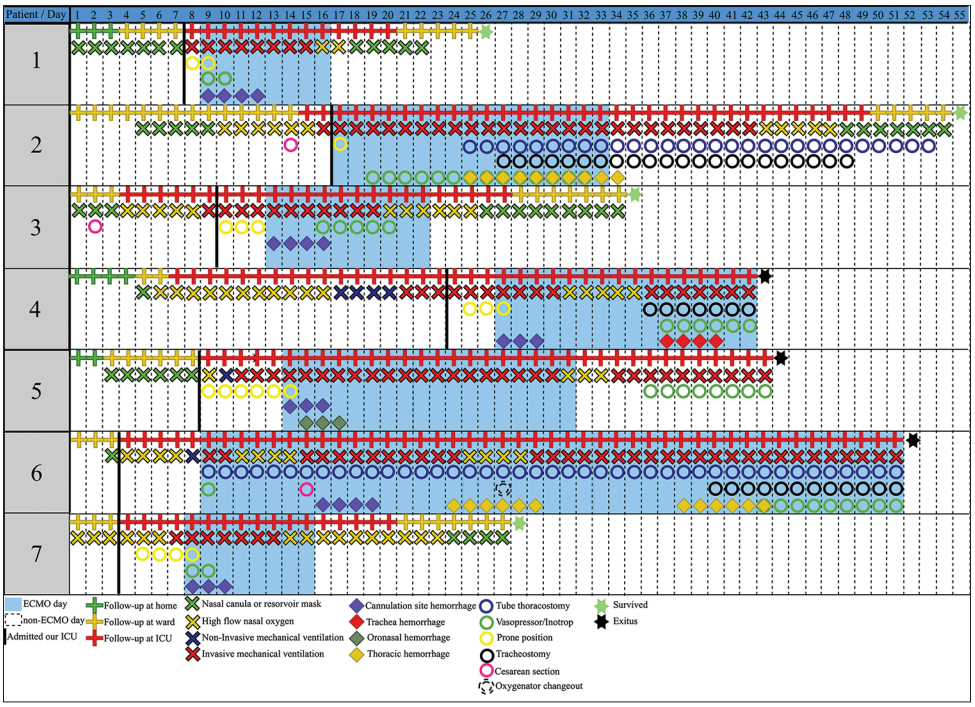

Figure 1: Extracorporeal membrane oxygenation timeline of coronavirus disease 2019 patients

ICU, and these three patients were among those patients who needed ECMO. Pregnant women are younger, are healthier than the general population, and thus have probably higher survival than patients undergoing ECMO for other indications.[14-16] Case reports on the application of ECMO in COVID-19 ARDS in pregnant women are scarce. Barbaro *et al*. reported on the successful use of ECMO in COVID-19 in an international cohort study (22 patients out of 1035 were pregnant).[8]

Currently, there is no known effective treatment for SARS-CoV-2. All treatments approaches including ECMO are supportive and aim saving time for the body's immune response to be activated. Appropriate patient selection for ECMO is extremely important, especially in times of inadequacy of equipment. Before choosing the right patient for ECMO, different mechanical ventilation modes that the patient can adapt to should be tried, and clinicians should be encouraged to follow up in the prone position using neuromuscular blocking agents before ECMO. First of all, to provide protection from ventilator-induced lung injury, ultra-protective lung ventilation should be applied to minimize tidal volume (VT), respiratory rate (RR), and airway and driving pressure. Thus, patients who have not been exposed to mechanical ventilation and its harmful mechanical effects for a long time and who have not developed organ failure and are in the early period of intubation after acute progression can be selected. The median duration of mechanical ventilation in our patients was 1 (IQR: 1–4) days before ECMO. It is thought that the most important point in our dropout rates from successful ECMO is the right patient selection.

We decided to VV-ECMO after trying new mechanical ventilation modes, including Airway pressure release ventilation (APRV), Adaptive support ventilation (ASV), and other traditional modes in our patients in the prone position. As VV-ECMO provides a "window period" in which damaged lungs can rest and heal, it is the primary ECMO mode used in patients with ARDS. In our ICU, the decision to start and wean ECMO is made by two of our well-experienced intensive care specialists who also performed cannulation. Since three ECMO devices are available for 24 h a day in our 16-bed unit, ECMO can be started immediately as soon as the decision was made.

Although ECMO treatment is considered as lifesaving in selected patients, the number of serious complications is quite high, especially as a result of the pathophysiological effects of COVID-19–related disease in the vascular bed. In contrast to the previous EOLIA study, high number of serious complications such as intracranial hemorrhage, VAP, and pulmonary embolism were reported with ECMO in COVID-19 patients.[13,17] Furthermore, as opposed to the previous reports, pump failure, oxygenator dysfunction, and circuit embolism, among other mechanical complications reported in COVID-19 patients were not seen in our patients.[8] In one of our patients, the cannula in the right femoral vein was switched to the left femoral vein in the following days since the target oxygenation could not be achieved because of insufficiency in the drainage cannula. An increase in the frequency of secondary hospital-acquired infections was observed due to some reasons such as high-dose steroid administration and infusion catheter

requirements due to multiple medications. On the other hand, erythrocyte replacement was required due to leaks from the tracheotomy area, especially in our patients who were heparinized and tracheotomized. In our patients, thrombocytopenia was generally observed in the 2nd week of ECMO follow-up (in 4 of our patients (57.2%), but interruption of heparinization for a short time due to of massive chest tube bleeding was needed in two of our patients (Patient No.: 2 and 6).

Considering that the resources for ECMO may be limited, the ELSO recommends weaning COVID-19 patients from ECMO as early as possible before mechanical ventilation. Desired targets for obtained to facilitate weaning from ECMO are; sweep gas remaining at 0 l/min, increasing of ventilatory support as needed until the VT ≤6–8 ml/kg, PPLAT ≤30 cmH2O, PEEP ≤16 cmH2O, FiO2 ≤0.5, pH >7.3 and arterial oxygen saturation >88%. It has been suggested that the patient can be decannulated if gas exchange is adequate for a period of 2–4 h.[3] Most of our patients were extubated in 9.5 (IQR: 7.25–22.25) days and weaned from ECMO in 10 (IQR: 8–17.5) days. The reason for this approach is the variability of COVID-19–related radiological involvement between days, the re-progression phase following rapid regression, the increase in oxygen consumption, and the need in cases such as sepsis/septic shock due to frequent secondary infections. In these cases, it would be rational to benefit from ECMO support against the possibility of reintubation in the early period.

Another important issue in the follow-up of the ECMO patient is the effective provision of anticoagulation. All our patients were anticoagulated with UF heparin with the recommendations of the guideline.[4] Although there were higher PTT target recommendations, PTT values were close to the lower limit (PTT 45–55 s) in our patients due to mucosal leaks and bleeding from the tracheostomy areas, in general, but no thrombotic complications were encountered. Tranexamic acid 10–20 mg/kg and fibrinogen 1–2 g/day were additionally used in a patient with heavy bleeding but closely monitored for the circuit and the oxygenator thrombosis. Heparinization was interrupted for a maximum of 24–48 h in our patients who had active bleeding and were planned for invasive intervention. In our patients, platelet transfusions were not used except in the case of severe thrombocytopenia (<50 × 10^3/mm^3 cell) or bleeding.

Limitations

We are aware of that our data and interpretations are limited by the small sample size. However, as management strategies and treatments are constantly evolving during the pandemic, we felt that it was important to share our data to assist clinicians at the bedside.

Conclusion

Our experience shows that ECMO in COVID-19 patients is a lifesaving treatment option that can be successfully applied in severe ARDS cases who do not respond to conventional treatments. To have faster access to the equipment, fast and accurate communication between the referring team, cardiovascular surgery department, and intensive care teams is crucial when a transfer to a reference site for ECMO is made, since there are no dedicated ECMO teams in our country. With the experience of intensive care specialists and intensive care teams, and 24-h uninterrupted follow-up, less complications and satisfactory results can be obtained.

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Author contributions

AOK: Conceptualization (equal), Formal analysis (lead), Writing – original draft (equal), Methodology (equal). MPK: Conceptualization (equal), Writing – original draft (equal), Methodology (equal). OA: Writing – review and editing (support), Supervision (support), Methodology (equal). GA: Writing – review and editing (support), Supervision (support), Methodology (equal). ACÖ: Writing – review and editing (support), Supervision (lead), Methodology (equal)

Conflicts of interest

None Declared.

Consent to participate and Ethics committee approval

The STROBE guideline was used as a guide for this manuscript. The study was prepared in accordance with the rules of the Helsinki Declaration. Our study was planned as a retrospective examination of the patient records of the Faculty of Medicine, Pulmonary Medicine Clinic, ICU. In addition to the informed consent of the patients, the study was approved by the Ministry of Health Scientific research platform with registration number of 2021-05-14-T20_34_19 regarding COVID-19 related studies and by the local ethics committee (Karadeniz Technical University, School of Medicine, No: 2021/368 dated November 15, 2021).

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