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Extra corporeal membrane oxygenation therapy in acute respiratory distress syndrome due to Coronavirus-2019 (COVID-19): a retrospective study

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ABSTRACT

Aims: Extra corporeal membrane oxygenation (ECMO) has been used as a supportive treatment in ARDS due to COVID-19. Although different results have been reported in the literature regarding its efficacy, ECMO is recommended as a salvage therapy for severe forms of the disease after standard therapy fails. In our study,we aimed to evaluate the survival outcomes of patients supported with ECMO for COVID-19.

Methods: Our study was conducted by scanning the data of consecutive adult patients hospitalized in our intensive care unit due to COVID-19. The ECMO process was planned according to the Extracorporeal Life Support Organization (ELSO) and Berlin criteria.

Results: 51 patients hospitalized for acute respiratory failure due to COVID-19 were taken to ECMO. Demographic data of patients; 39 (76.5%) men and 12 (23.5%) women. 46 (90.2%) of the patients died. The mean intubation time before ECMO is 3.9 days, and the mean time for non-invasive mechanical ventilation is 5.8 days. The mean PaO_2 value before ECMO was79.09 mmHg, the mean PCO_2 value was 63.62 mmHg and the mean PaO_2/FiO_2 ratio was 82.80.

Conclusion: The use of ECMO by considering prognostic factors and guidelines is seen as factors that increase the chance of success.Despite the fact that the patients were admitted to ECMO in accordance with the guidelines in our study, the high mortality rate suggests that there is a need for investigation of other supportive treatments and studies to reduce ECMO complications.

Keywords: COVID-19, extracorporeal membrane oxygenations, respiratory distress syndrome, mortality, prognosis

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory distress syndrome has resulted in high economic costs for healthcare systems worldwide and placed a substantial burden on healthcare staff. During this pandemic, where mortality has been high globally, face masks, isolation, hand hygiene, and vaccines have been used as protective measures. As treatments, drugs, such as interleukin-1 antagonists, interleukin-6 antagonists, and remdesivir, have been tried. However, these drugs have not proved efficacious in COVID-19 patients with severe hypoxemia, where extracorporeal membrane oxygenation (ECMO) has been necessary as supportive therapy. The purpose of ECMO is to eliminate hypoxemia and to maintain tissue perfusion while allowing the patient to recover. Although different results have been reported in the literature regarding the efficacy of ECMO, it is recommended as a rescue treatment for severe forms of COVID-19 disease after standard treatment fails.[1] Early administration is recommended, especially in young patients before multiple organ dysfunction syndrome or severe ventilator-related lung injury occurs.[2,3] According to a report by the Extracorporeal Life Support Organization (ELSO) in 2018, the survival rate of patients receiving respiratory support provided by ECMO was 58.7-73.2%, whereas that of patients on circulatory support was 42.7-52.6%.[4] Despite continuous developments in technology, the incidence of ECMO-related complications and mortality remains high.[5] ECMO is a high-cost, extremely complex type of life support system, which is available only in specialized and experienced centers trained in its use. Thus, the use of ECMO is limited, which has led to insufficient studies and experience.[6]

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Our primary outcome is to evaluate the success of using ECMO by considering prognostic factors and guidelines in this patient group with high mortality and cost, and the secondary outcome is to evaluate the survival results of ECMO supported COVID-19 patients, and to share our clinical experiences and data.

METHODS

The study was carried out with the permission of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 06.01.2022, Decision No: 07). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In the present study, data were collected from the hospital records of consecutive adult patients hospitalized due to COVID-19 between 01.01.2021 and 01.11.2021 in the General Intensive Care Unit (ICU) of İstanbul Medipol University Faculty of Medicine Hospital.

All patients had SARS-CoV-2 infection, as documented by nasopharyngeal swabs or lower respiratory tract aspiration and real-time polymerase chain reaction (PCR) results (LightCycler 96; Roche). Demographic data of the patients, hemodynamic parameters, blood gas and laboratory values, drugs administered, ventilator and ECMO parameters, and complications during ECMO were evaluated. The relationship of these parameters with mortality and survival was calculated. Patients with severe liver disease, hypoxic encephalopathy, patients with vascular disease, metastatic cancer patients, patients with immune deficiency and patients over the age of 70 were not taken to ECMO.

All the patients, except those with comorbidities, were placed in the prone position prior to ECMO. Neuromuscular blocking agents were administered to patients without contrindications before ECMO. ECMO cannulation was performed by a team of anesthesiologists, cardiovascular surgeons, perfusionists, and intensive care specialists under ultrasound guidance and chest X-ray control. ECMO follow-up was undertaken by the intensive care team. Femoral vein cannulation was performed using a 23-27 Fr internal jugular cannula and a 17-21 Fr cannula.

In cases of acute respiratory distress syndrome (ARDS), the ELSO recommends initiating veno-venous (VV)-ECMO prior to conventional therapies. 4 In our study, despite ventilator optimization in ARDS cases, VV-ECMO was planned for patients with the following clinical conditions:

1. PaO_2/FiO_2<150 mmHg
2. Any of the following: i) PaO_2/FiO_2<60 mmHg for>6 hours, ii) PaO_2/FiO_2<50 mmHg for>3 hours, or iii) pH<7.20 and $PaCO_2$>80 mmHg for>6 hours
3. ECMO if no contraindications or $PaO_2/FiO_2 \geq 150$ mmHg; pH <7.20, with $PaCO_2$>80 mmHg for>6 hours; or no contraindications for ECMO

The activated clotting time was used for monitoring VV-ECMO anticoagulation with unfractionated heparin, with a target time of 150-250 seconds. The hemoglobin threshold was determined as 7-8 g/dl for red cell transfusions and (< 50 thousand/ml) for platelet transfusions.

For data analysis, SPSS 16.0 was used. <0.05 p value was conserved as statistically significant.

RESULTS

In total, 51 patients hospitalized in our ICU with acute respiratory failure due to COVID-19 received ECMO. In terms of demographic data, there were 39 (76.5%) males and 12 (23.5%) females (Table 1). Only 3 (5.9%) of our patients had received the COVID-19 vaccine (Sinovac vaccine was available in all three patients). Before ECMO, 40 (78.4%) patients were placed in the prone position, and 27 (52.9%) patients received a neuromuscular blocker. There were 28 (54.9%) patients with comorbidities and 3 (5.9%) pregnant patients. All our patients received VV-ECMO. ECMO support was terminated in 46 (90.2%) patients due to death. Of the surviving patients, 4 (7.8%) were discharged home, and one died in the hospital, with the death unrelated to COVID-19.

Table 1. Variables

	n= 51 (%)
Age (years)	51 (27-77)
Gender (male)	39 (76.5)
BMI (kg/m^2)	30 (23-42)
Comorbidities	
Obesity	2 (3.9)
Diabetes mellitus	6 (11.7)
Hypertension	9 (17.6)
Asthma	3 (5.8)
Coronary artery disease	4 (7.8)
Postpartum	3 (5.8)
PCR Positive	48 (94.1)
Vaccinated patients	3 (5.8)

Values are expressed as mean (interquartile range) or number (%)

Steroids (hydrocortisone, dexamethasone, or methylprednisolone) were administered to all patients before and during ECMO. Twenty-six (51%) patients

were taking vasopressors before ECMO. Before or during ECMO, drugs, including colchicine (n=32, 62.7%), remdesevir (n=3, 5.9%), IVIG (intravenous immunoglobulin) (n=2, 3.9%), an IL-6 antagonist (n=28, 54.9%), or an IL-1 antagonist (n=6, 11.8%), were administered. Patients also received immune plasma therapy (n=3, 5.9%), a sepsis filter (n=19, 37.3%), or continuous VV-hemodiafiltration (CVV-HDF) (n=32, 62.7%) (Table 2).

Table 2. Additional medications and supportive treatments

Additional medications and supportive treatments	Patients (N)	Percentage (%)
Steroid	51	100
Remdesevir	3	5,9
Colchisine	32	62,7
IVIG	2	3,9
IL-6 antagonist	28	54,9
IL-1 antagonist	6	11,8
Sepsis filter	19	37,3
CVV-HDF	32	62,7
Immune plasma	3	5,9

IVIG (intravenous immunoglobulin), IL-6 ((interleukin-6), IL-1 (interleukin-1), (continuous veno-venous hemodiafiltration), CVV-HDF (continuous veno-venous hemodiafiltration)

Bacterial growth occurred in blood (n=25, 49%) and endotracheal aspiration (n=35, 68.6%) cultures. Methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* and methicillin-sensitive *S. aureus* (MSSA) and *Stenotrophomonas maltophilia* constituted the majority of bacteria in both cultures. Complications (bleeding, thrombosis, thrombocytopenia, pneumothorax, and circulatory disorders) occurred in 35 (68.6%) of the ECMO patients. Only 7 (13.7%) patients did not receive blood or blood product replacement. In 19 (37.3%) patients with thrombocytopenia or other blood disorders, acetyl salicylic acid, dipyridamole, or clopidogrel was used rather than heparin.

Before ECMO, the average number of orotracheal intubation days and noninvasive mechanical ventilation days was 3.90 and 5.80, respectively. The average number of days on ECMO support was 12.73. The average number of ECMO devices sets used was 1.45. Table 3 shows the average driving pressure, PaO_2, PCO_2, and P/F ratio values prior to ECMO. Although these values were marginally improved on the first, third, and seventh days of ECMO, parameters for removal of ECMO support were reached in only five of the 51 patients. Compared to pre-ECMO levels, only IL-6 (1015-131) and ferritin (1212-709) levels were significantly decreased in patients who could be weaned. There was no change in D-dimer, lymphocyte, thrombocyte, and hemoglobin levels between pre- versus post ECMO levels.

Table 3. Pre ECMO data

	n= 51
Pre ECMO days	12 (2-42)
Intubation time	3.9 (1-16)
NIMV time	6.08 (1-20)
Blood gas	
pH	7.27 (6.80-7.50)
$PaCO_2$ (mmHg)	63.62 (37-113)
PaO_2/FIO_2	82 (49-131)
Ventilation parameters	
Respiratory rate (/min)	34 (18-40)
Tidal volüme (ml/kg)	350 (200-580)
PEEP (cmH_2O)	14 (10-18)
FIO_2 (%)	96 (60-100)
PIP (cmH_2O)	16 (10-32)
Neuromuscular blocker	27 (52.9)
Prone position	40 (78.4)
APACHE II	20 (9-32)
Driving pressure (cmH_2O)	20,66 (12-42)

Values are expressed as mean (interquartile range) or number (%), NIMV: non-invasive mechanical ventilation time

When we examined the data on the survivors, these patients had received only standard steroid therapy (i.e., no other drugs or procedures). One patient was given remdesevir and an IL-6 antagonist, and one patient was treated with a sepsis filter and CVV-HDF due to ETA and *S. maltophilia* growth in blood culture. Another patient was treated with an IL-6 antagonist, sepsis filter and CVV-HDF due to the growth of *S. maltophilia* and MSSA in blood culture. One patient was given remdesevir and an IL-6 antagonist.

The most common complications were bleeding (from drain sites), thrombocytopenia, thrombosis, and circulatory disorders. Pneumothorax was observed in only one patient (Table 4). The mean APACHE II score of the patients was 20.49.

Table 4. Clinical results

	n= 51
Decannulation (n)	5 (9.8)
Discharge from ICU (n)	5 (9.8)
Discharge from hospital (n)	4 (7.8)
ECMO time (days) median, IQR [Q1-Q3]	8 [5-18]
Complications	35 (68,6)
Blood products transfusion	44 (86.2)
Pneumothorax	1 (1.9)
Thrombosis	12 (23.5)
Positive blood cultures	25 (49)
Positive tracheal cultures	35 (68.6)

Datas were expressed as median IQR [Q1-Q3] or mean±SD

DISCUSSION

In our study, although the mean driving pressure, PaO_2, PCO_2, and P/F ratio values before ECMO improved marginally on the first, third, and seventh days of ECMO, the parameters for removal of ECMO support were achieved in only five of 51 patients. Compared with pre-ECMO levels, only IL-6 (1015-131) and ferritin (1212-709) levels were significantly reduced in weaning patients. There was no change in D-dimer, lymphocyte, platelet and hemoglobin levels between pre- and post-ECMO values.

During the COVID-19 pandemic, hospitals, especially ICUs, had to cope with a heavy patient load. Standard patient admission procedures were either not implemented or delayed. In our study, the Berlin criteria were used in the diagnosis and treatment of ARDS, and the criteria of the ELSO were used in in deciding whether to initiate ECMO. All of the 51 patients, the majority of whom were diagnosed with severe ARDS (mean P/F: 82.80), received ECMO. The P/F ratio in our study was higher than that reported in studies by Barbaro et al.[7] (P/F ratio: 72), Combes et al.[8] (P/F ratio: 51), and Schmidt et al.[9] (P/F ratio: 60). In our study, 78.4% of the patients were placed in the prone position before ECMO. In the study by Schmidt et al.[10] 94% of patients were placed in the prone position prior to ECMO,[8] whereas 56% and 26% of patients were placed in the prone position in the EOLIA study. As it has been see in literature, there is significant differences among studies in relation to the placement of the patient in the prone position before ECMO.

In our study, neuromuscular blockers were used in 52.9 % of patients before ECMO. The recruitment maneuver was applied in these patients. During ECMO, 56.8% of patients were placed in a prone position. In the study by Barbaro et al.[7] mortality 90 days after the start of ECMO was 37.4%. In the study of Combes et al.[8] 60-day mortality was 35% in the ECMO group and 46% in a conventional treatment group. In our study, mortality rate was 90.2%. The mean duration of invasive and noninvasive mechanical ventilation in our study was 3.8 and 5.8 days, respectively. We attribute the higher mortality rate in our study as compared with that in the literature to the late transition to ECMO, despite more prone positioning and a higher P/F ratio compared to that in the other studies. Henry et al.[11] stated that initiation of ECMO 10 days after invasive ventilator use in patients with COVID-19 reduced the probability of successful treatment. They also recommended close monitoring of IL-6 and lymphocyte levels. Previous studies reported a significant difference in lymphocyte counts and IL-6 concentrations of COVID-19 survivors and nonsurvivors.[12,13] Similarly, in our laboratory follow-ups, we observed a significant decrease in post-ECMO IL-6 and ferritin levels compared to pre-ECMO levels. However there was no difference between D-dimer, lymphocyte, thrombocyte, and hemoglobin levels pre- and post-ECMO. In our study, the mean driving pressure value before ECMO was 20.66 cmH_2O, and the mean value on the first day was 16.98 cmH_2O. Similar driving pressures (20±7 vs. 14±4 cm H_2O) were observed by Schmidt et al.[10]

In a previous study, Jacobs et al.[14] presented findings on 32 consecutive COVID-19 patients admitted to nine different hospitals who received ECMO for 24 days. In their study, 17 patients were still receiving ECMO at the time of writing, 10 died before or shortly after decannulation, five were successfully extubated after ECMO, and one of these five patients was discharged. The mortality rates in their study were similar to those in our study based on the literature, mortality rates were high in the early pandemic period and in centers where ECMO experience was insufficient.

Other than the timing of ECMO and associated treatment options, we think that the location of the cannula and the characteristics of the catheter are important factors affecting mortality. Among COVID-19 patients who receive ECMO, there is a strong positive correlation between mortality and high cytokine levels, the most important being IL-6.[15] Ruan et al.[16] noted that IL-6 concentrations differed significantly between COVID-19 survivors and nonsurvivors. Mehta et al.[17] found up to 1.7 times higher IL-6 levels in nonsurvivors as compared to those of survivors. In our study, IL-6 and ferritin levels of the survivors were lower than the baseline values, and a sepsis filter was applied to two of these patients. In addition, the surviving patients were given antibody treatments, such as IL-1 or IL-6 antagonists, remdesevir, and antivirals. In the European Union, an extracorporeal cytokine adsorbent approved to reduce toxic levels of cytokines can be used with ECMO to treat the cytokine storm associated with COVID-19 pneumonia. Additional research is needed on each of these treatment options.

In a meta-analysis by Tran et al.[18] which aimed to determine the relationship between pre-ECMO prognostic factors and mortality risk, patient-related factors, such as advanced age and male gender, were among the factors associated with increased mortality, with medium or high precision. Other factors, such as chronic lung disease, longer symptom duration, and longer duration of invasive mechanical ventilation, in addition to precannulation factors, such as higher arterial CO_2 partial pressure, higher driving pressure, and less ECMO experience, were also noted. In the study of Uysal et al.[19] it was stated that the mortality rate in COVID-19 patients with chronic renal failure hospitalized in intensive care is high, and as the severity of the disease increases, the rate of patients being connected to mechanical ventilation

and death increases.In our study, prognostic factors for high mortality included comorbidities, male gender, long symptom duration, and mechanical ventilation duration.

Study Limitations

One limitation was that this was a retrospective study. Another limitation was the lack of a randomized controlled study, making it impossible to draw definitive conclusions.

CONCLUSION

Treatment of ARDS associated with COVID-19 requires a multidisciplinary approach. In this patient group with high mortality and cost, the use of ECMO by considering prognostic factors and guidelines is seen as factors that increase the chance of success. The patients in our study were treated with ECMO in accordance with established guidelines. However, given the high mortality recorded in the present study, we believe that studies on the effectiveness of additional supportive treatments that can reduce ECMO-related complications are needed. As mortality in patients with ARDS due to COVID-19 is higher than that in patients with ARDS unrelated to COVID-19, potential risk factors for mortality other than ARDS need to be reviewed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 06.01.2022, Decision No: 07).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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