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Research Article

The Survival Benefits of Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO) in Severe COVID-19: A Single Center Retrospective Observational Analysis Of 10 Cases

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Abstract

Background: The precise role of veno-venous extracorporeal membrane oxygenation (VV-ECMO) in managing patients with COVID-19-induced acute respiratory distress syndrome (ARDS) remains uncertain. Therefore, we examined the clinical progression and survival outcomes of severe COVID-19 patients and to identify the factors linked to survivability.

Methods: A retrospective study was conducted at a single center on severe COVID-19 patients with ARDS who were on mechanical ventilator support and were treated with VV-ECMO. The study evaluated baseline characteristics, ventilatory and ECMO parameters, pre-ECMO laboratory parameters, and demographics. A close follow-up was conducted for the first three months following hospital discharge, followed by regular check-ups extending to two to three years.

Results: The mean duration of mechanical ventilation before ECMO and meantime under ECMO were 6.8 ± 10.9 days and 35.5 ± 30.6 days, respectively. The hospital length of stay was 101.1 ± 73.95 days. The survival rate for patients on ECMO was 60%, while 50% of the patients having survived to date. The duration of hospital stays, time on ECMO and mechanical ventilation, and age were not associated with the survivability outcome of the patients.

Conclusion: The success rate of VV-ECMO in this study may encourage the widespread use of ECMO in severe COVID-19 pneumonia besides refractory to conventional ventilator support and other therapies. No significant predictive factors for the duration of ECMO support were identified, the decision to discontinue therapy should not be based solely on the length of ECMO treatment.

Keywords: *Severe COVID-19; Hypoxia; VV-ECMO; ARDS; Mechanical Ventilator; COVID-19 Mortality*

Introduction

COVID-19 emerged as a pandemic in early 2020 with significant loss of life. While most infections with SARS-CoV-2 remain asymptomatic or mild [1], some patients develop severe clinical manifestations [2]. Severe COVID-19 in adults is defined as dyspnea, a respiratory rate of 30 or more breaths per minute, a blood oxygen saturation of 93% or less, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) of less than 300 mm Hg, or infiltrates in more than 50% of the lung field within 24 to 48 hours from the onset of symptoms. The mortality in critically severe COVID-19 cases is 49% [1], and the majority of these cases require prolonged mechanical ventilator support. Most severe cases start deteriorating after one week of the onset of symptoms, and rapid progression to respiratory failure and hypoxemia is a hallmark of keeping the threshold low for mechanical ventilator support. The severe COVID-19 cases generally follow the criteria for acute respiratory distress syndrome (ARDS), defined as the acute onset of bilateral infiltrates, severe hypoxemia, and bilateral pulmonary edema which is not fully explained by cardiac failure or fluid overload. ARDS in COVID-19 patients is associated with poor prognosis and higher mortality rates [3,4].

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is an invasive technique that oxygenates the blood and removes CO_2 while the failing lung is rested and is given time to recover. VV-ECMO has been widely used as a supportive therapy in severe COVID-19 patients on mechanical ventilation [5]. Other measures that can help improve oxygenation are prone ventilation and nitric oxide inhalation. The clinical trials revealed that prone ventilation for at least 16 hours a day improved oxygenation and reduced mortality in non-COVID-19 ARDS [6,7]. However, inhaled nitric oxide as a pulmonary vasodilator improved the oxygenation but no survival benefits in ARDS, which is not associated with COVID-19 [6].

The survival rate of COVID-19 patients with severe respiratory failure treated with VV-ECMO ranges around 60%, according to recent studies [8,9]. VV-ECMO was initiated in younger patients (i.e. < 71 years) and in those with rather short duration of mechanical ventilation (MV) prior to ECMO (i.e. < 7 or < 11 days, respectively) [10,11]. The role of ECMO therapy in this pandemic is still controversial, with some studies showing the beneficial effects of ECMO in critically ill patients with COVID-19 [10], while ECMO therapy has also been associated with poor outcomes and high mortality [12]. The ECMO to Rescue Lung Injury in Severe ARDS (EOLIA trial) is the largest randomized controlled trial of ECMO for ARDS, revealing 60-day mortality of 35% in the ECMO group versus 46% in the conventional management group (relative risk 0.76, 95% CI 0.55-1.04; p = 0.09) [11]. Some reports also indicate that individuals with ARDS caused by SARS-CoV-2 might need prolonged ECMO support with the associated requirement of ICU capacities [13]. Analyzing the success of VV-ECMO on the survival outcome of severe COVID-19 patients under different scenarios would guide in planning clinical guidelines and future healthcare policies as well as prepare patients for future challenges so that they receive the most effective and evidence-based care possible.

Although data from Western and Eastern countries on the survival benefits of VV-ECMO in severe COVID-19 patients are ample, data from Middle Eastern countries are very rare.

Purpose of the Study

The purpose of this study was to investigate the clinical course and survival outcome of patients supported with VV-ECMO for COVID-19-induced ARDS in a single center in Abu Dhabi. Furthermore, we aimed to identify characteristics associated with the survival of patients on VV-ECMO treatment.

Methods

This study was a single-center retrospective observational analysis. Data were collected from critically ill COVID-19 patients with VV-ECMO support for severe ARDS. Severe ARDS was defined according to Berlin's definition [5]. The diagnosis of COVID-19 was confirmed by real-time polymerase chain reaction (PCR) on nasopharyngeal swabs and lower respiratory tract aspirates. Patients received VV-ECMO

for refractory hypoxemia and/or hypercapnia that persisted despite ventilator optimization, in accordance with the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) criteria [11]. The patients were treated in the Burjeel Hospital, Abu Dhabi, between 11.04.2020 and 03.02.2022. The patient data were anonymized prior to analysis. The study was approved by the institute's ethics committee (BH/REC/035/22). The inclusion criteria of these patients were considered as per ELSO guidelines [5]. Patients who underwent veno-arterial ECMO (V-A ECMO) were excluded from the study.

Data collection

The patients were given a trial of maximum support of invasive mechanical ventilation before switching to the ECMO. All patients switched to VV-ECMO by venous access in the right heart and inferior vena cava through a triple-lumen catheter through the internal jugular vein. The pump speed was adjusted to maintain a blood-oxygen saturation of 100%. Cannula placement was guided by ultrasound, which was confirmed with a chest X-ray. Due to initial reports indicating a high incidence of thrombotic complications in COVID-19 patients on ECMO [12,14], systemic anticoagulation was maintained with heparin. Of the total, six patients were kept in a prone position during ECMO, but none of them received nitric oxide (NO) inhalation.

The primary endpoint of this study was survival following the safe discontinuation of ECMO support. The secondary endpoint was to describe the hospital mortality, duration of stay in the hospital, duration of ECMO, mechanical ventilation, rate of ECMO weaning, clinical parameters, respiratory support, and adverse events.

Statistical analysis

GraphPad Prism (version 6, San Diego, USA) was used for data analysis. Categorical data was presented as a percentage (%). Quantitative data were presented as mean ± standard deviation. A chi-square test, followed by Fischer's exact test, was performed to find the association of survival with different parameters. $p < 0.05$ was considered statistical significance.

Results

The VV-ECMO support was given to 10 patients between 27 to 64 years of age (mean age ± SD 46.8 ± 12.53 years). Of the 10 patients, 2 (20%) were female, 8 (80%) were male. Among them, 4 (40%) were Middle Eastern individuals, and 6 (60%) were Asian expatriates. The mean ± SD BMI was 32.23 ± 8.26 kg/m^2 (Range: 19.8 kg/m^2 - 45.7 kg/m^2). Pre-existing conditions before ECMO were present in 8 patients, type 2 diabetes and hypertension being the major ones. On admission, all patients displayed high levels of inflammation, as demonstrated by elevated CRP, ferritin, and neutrophil-to-lymphocyte ratio (NLR) (Table 1).

Characteristics	No. (%)
Age	
Mean (SD), y	46.80 (12.53)
Median (range), y	44 (27 - 64)
Male/Female	8/2 (80/20)
Nationality	
Indian	4 (40)
Sudanese	2 (20)
Bangladeshi	1 (10)
Filipino	1 (10)
Egyptian	1 (10)
UAE	1 (10)

BMI, mean (SD)	32.23 (8.26)
Medical History	
Type 2 diabetes	3 (30)
Hypertension	4 (40)
Hypothyroidism	1 (10)
Coronary artery disease	1 (10)
Hyperlipidemia	2 (20)
Anemia	1 (10)
Psoriasis	1 (10)
No comorbidity	2 (20)
Inflammatory markers	
C-reactive protein	160.3 (66.21)
Ferritin	456.2 (390.4)
Neutrophil to lymphocyte ratio	5.98 (1.6)
Pre-ECMO parameters	
Ventilator Settings	
FiO2, mean (SD)	100% (0)
PIP, mean (SD)	31.70 (11.19)
PEEP, mean (SD)	11.70 (3.26)
Arterial Blood Gas	
PaO_2	56.66 (5.21)
Post-ECMO complications	
Renal Failure	5 (50)
Septic shock	4 (40)
Encephalitis	2 (20)
Bleeding	2 (20)
Hemoptysis	1 (10)
Pneumothorax	2 (10)
Mediastinal and surgical emphysema	1 (10)

Table 1: *Patient demographics and clinical parameters.*

All patients were on invasive Pressure Control Ventilation (PCV) support before initiating ECMO support. The mean duration of PCV support before initiating ECMO was 6.8 days (range, 0-37 days), and six patients were placed in a prone position for ventilation. All patients were tracheostomized before the initiation of ECMO therapy to prevent surgical bleeding.

All patients were on 100% FiO_2 with a mean PIP (SD) of 31.70 (11.19) cm H_2O (range, 18.0-45.0 cm H_2O), mean PEEP (SD) was 11.70 (3.26) cm H_2O (range, 5.0-16.0 cm H_2O), and mean PaO_2 (SD) in blood gas analysis was 56.66 mm Hg (range, 49.9.0-66.0 mm Hg).

All patients were given systemic heparin (7.5 - 15 units/kg/hr infusion based on ACT (Activated Clotting Time)-Target ACT is 160 - 180 seconds) as an anticoagulant. For one patient, the membrane oxygenator had to be replaced due to multiple clot formation in the oxygenator. All patients were treated as per the guidelines for COVID-19 management issued by the Department of Health (DOH), Abu Dhabi. This included administration of HCQS (400 mg bid Loading on day 1 followed by maintenance of 200 mg bid for total 10 days), Lopinavir-Ritonavir (200/50 mg 2 tablets PO BID for 10 days) or Favipiravir (1600 mg PO BID for 2 doses then 600 mg PO BID for total 10 days), Remdesivir (200 mg intravenously for 1 day, followed by 100 mg IV for total 10 days), anticoagulant (Enoxaparin dose (Before ECMO support): when Crcl>30 - BMI < 40: 40 mg OD, BMI > 40: 40 mg BID, When Cr cl < 30 - BMI < 40: 20 mg OD, BMI > 40: 30 mg OD), broad-spectrum antibiotics (Meropenem 1 gm IV 8 hourly, Piperacillin+Tazobactam 4.5 gm IV 6 hourly, Linezolid 600 mg IV 12 hourly, Levofloxacin 750 mg IV 24 hourly), steroid (Dexamethasone 6 mg IV /PO daily for 7 - 10 days), Vitamin C (1 gm BID (Preferably IV) for 2 weeks), and Zinc (Zinc gluconate 10 mg BID Or Zinc acetate 50 mg OD-oral for 5 - 7 days). However, none were given convalescent plasma therapy or any other trial medication, including biologics.

The percentage of COVID-19 patients who survived ECMO was 60%. Higher survival was only observed in patients who had > 50 days of hospital stay ($p < 0.05$). Other factors, such as the number of days on ECMO, mechanical ventilation duration, age, and prone position, did not affect survival outcomes (Table 2). Only one patient (10%) died after discontinuing ECMO. Mortality was 50% in the present study. The major cause behind mortality was refractory severe septic shock. All patients developed sepsis and renal failure and required renal replacement therapy. Three patients (30%) had minor bleeding, and two patients (20%) had major bleeding complications. Two patients (20%) had COVID-19 encephalitis, two patients (20%) developed bilateral pneumothorax, and one patient (10%) had surgical emphysema.

Parameters	Survived n (%)	Expired n (%)	p-value
Age > 60 years	4 (40%)	3 (30%)	1.00
< 60 years	1 (10%)	2 (20%)	
Number of days on ECMO > 25 days	2 (20%)	1 (10%)	1.00
< 25 days	3 (30%)	4 (40%)	
Number of days in hospital > 50 days	5 (50%)	1 (10%)	<0.05
< 50 days	0 (0)	4 (40%)	

Table 2: *Factors affecting survival outcome in COVID-19 patients on VV-ECMO.*

Four patients were discharged from the hospital on room air oxygen saturations between 94% - 98%, while one patient was discharged on supplemental oxygen due to room air oxygen saturations of 70%. The survivors experienced critical illness polyneuropathy and myopathy. Over a follow-up period of 2-3 years, all of them have remained stable, without needing supplemental oxygen or antifibrotic medications, and have returned to work.

Discussion

Herein, we present a retrospective single-center study that analyzed the effect of VV-ECMO on the survival outcome of severe COVID-19 patients, both during the first 90-days and over a longer follow-up period, and investigated the various factors affecting recovery. The primary outcome of the study indicated 60% survival on VV-ECMO, although overall survivability is 50%. The survival outcome was

independent of the duration of ECMO, time on the mechanical ventilator, presence of pre-ECMO comorbidity, and age. There were indications that survival was directly associated with the duration of hospital stay, but it is not.

The critically ill patient requires ICU admission, and most of these patients have hypoxic respiratory failure, and mechanical ventilator support is essential for them. In some studies, invasive mechanical ventilation rates of 30% - 71% have been reported in these patients [15-17]. Patients who have a suboptimal response to the maximum support of invasive mechanical ventilation need alternative options to maintain oxygenation. The ECMO is a viable option for them, provided that expertise and equipment are available in the respective centers. As per the Extracorporeal Life Support Organization (ELSO) registry, so far, 17712 COVID-19 patients have been supported with an ECMO machine, and in 16307 patients, ECMO support was started at least 90 days prior, and in-hospital mortality reported in them is 48% [17,18]. In the early outbreak of COVID-19 in Wuhan City, six severe COVID-19 patients were supported with ECMO in Wuhan Jin Yin-tan Hospital between late December 2019 and January 26, 2020, showing a frightening mortality of 83% [19,20]. In our study, the mortality rate for ECMO was 40%, and overall, all-cause hospital mortality was 50% in these cases.

In our study, we preferred the early ECMO therapy if patients were not responding to the maximizing traditional therapies for ARDS, as mentioned in the literature [21]. In our study, one patient was switched to ECMO after 37 days of invasive ventilation due to the shortage of ECMO machines, and this patient survived and was subsequently discharged from the hospital after 161 days of total hospital stay. Nonetheless, the patient developed residual pulmonary fibrosis, probably due to the prolonged ventilation with high fraction inhalation of oxygen (FiO_2) as well as the disease itself.

The effect of the duration of ECMO on lung recovery and survival is enigmatic. While several studies have suggested that critically ill COVID-19 patients may need ECMO support for longer durations compared to ARDS patients [22-25]. A study by Falcoz., *et al*. found that COVID-19 patients need shorter ECMO treatment durations [22]. One study stated more than 2 weeks of ECMO negatively affected the recovery; on the other hand, another study reported favorable outcomes for ECMO durations between 34 and 39 days. The longest reported VV-ECMO duration in a COVID-19 patient with ARDS was 207 days before lung transplantation [23]. Extended ECMO support facilitated the recovery of the native lungs, eliminating the need for lung transplantation. This study compared survival outcomes in patients with median ECMO > 25 days and <25 days.

Our observation revealed that the high CRP, ferritin, and NLR are directly correlated with the severity of COVID-19 disease and are potential candidates for ECMO therapy. However, our observation did not predict the outcome of the ECMO, on the basis of specific demographic, clinical, and laboratory data. No correlation was observed between age, duration of ECMO therapy, or hospital stay. The youngest patient in this study could not survive. As learned from our previous experience of ECMO therapy in non-COVID-19 ARDS patients, we decided to do the early tracheostomy to avoid bleeding complications in the later stage of ECMO therapy.

Since COVID-19 disease is a hypercoagulable state [26], all of our patients received heparin infusion as an anticoagulant; dosage was based on the ACT score. Two patients had major bleeding events, but it did not alter their overall outcome at the time of bleeding.

We restricted the mobilization of all our patients while on ECMO due to the hemodynamic instability, risk of dislodgment of tubes, catheters, and lines, and the risk of COVID-19 transmission. Early mobilization while on invasive mechanical ventilation, or ECMO, fastens the recovery of neuromuscular function and minimizes the risk of myoneuropathy.

The major limitation of our study is the inclusion of very few patients. Moreover, this retrospective and monocentric study design could introduce potential confounding variables that might lead to analyses that lacked sufficient statistical power. Further, subgroup analysis should be performed to more clearly define the role of ECMO in severe COVID-19.

All our surviving cases are on regular follow-up after more than 2 years of weaning from the ECMO; none are on supplemental oxygen therapy.

Conclusion

VV-ECMO therapy is a potential rescue strategy in lung failure cases requiring invasive mechanical ventilator support, and the outcome depends on the experience of individual centers and available resources. We also observe that early initiation of ECMO in the lung failure secondary to severe COVID-19 pneumonia or ARDS translates into short course of ICU stay, less ventilator-associated complications, fewer chances of severe neuromuscular weakness, and lung fibrosis. Although no important predictive factors for survival outcomes were identified, deciding to discontinue ECMO should not be based on ECMO duration, as prolonged ECMO duration may lead to favorable outcomes.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval Statement

The study was approved by the institute's ethics committee (BH/REC/035/22).

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