RESEARCH ARTICLE

Outcomes of Prolonged Extracorporeal Membrane Oxygenation (>30 days) in COVID-19 Patients on Conservative Management

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Abstract

Introduction: The onset of COVID-19 pandemic overwhelmed hospital resources with a high admission rate to critical care units. In patients experiencing progressive respiratory failure despite conventional therapies such as mechanical ventilation and prone positioning, venovenous extracorporeal membrane oxygenation (VV-ECMO) offered the only hope for survival. The VV-ECMO duration for COVID-19 is often described as longer than other respiratory illnesses. The outcome of these cases varies from country to country. As the literature available on the outcome of prolonged ECMO in an Indian setting is sparse, we planned to study the same.

Methods: This retrospective study included all adult patients who had undergone VV-ECMO of more than 30 days for COVID-19 illness at Medica Medica Superspecialty Hospital, Kolkata, West Bengal, India between 1 April 2020 and 31 March 2022. Patients who were still in the hospital at the end of the study period were excluded from the study. Data on total ECMO days, in-hospital mortality, age, sex, BMI, symptom onset to ECMO duration, intubation to ECMO duration, mechanical complications such as oxygenator failure or pump failure, patient complications such as major hemorrhage, ischemic stroke, liver/renal dysfunction, thrombocytopenia, culture-proven infection and use of prone position ventilation were collected from an electronic database. Patients who were discharged from the hospital were followed up at 6 months. The data were analyzed using the statistical package for the social sciences (SPSS) software, version 26 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and evaluated using Student's *t*-test. Categorical data were expressed as frequency (in %) and evaluated using the Chi-square test or Fischer's exact *t*-test as applicable.

Observation: Twenty patients who had prolonged ECMO (>30 days) were found eligible for the study. The average ECMO days and in-hospital mortality were 54.75 ± 33.14 and 60%, respectively. An early decision to ECMO after symptom onset and prone positioning during ECMO were factors associated with a favorable outcome. The requirement of renal replacement therapy (RRT) for renal failure was a poor prognostic factor.

Conclusion: Prolonged ECMO for COVID-19 poses many challenges in terms of thrombotic and bleeding complications, major organ dysfunction, and high mortality. However, this remains the only survival hope for sick COVID-19 acute respiratory distress syndrome (ARDS) patients.

Keywords: COVID-19, Extracorporeal membrane oxygenation, Venovenous extracorporeal membrane oxygenation.

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has led to a pandemic associated with a high critical care unit admission rate (14.2%).[1] Many of the admitted patients required mechanical ventilation (12%).[1] Hypoxia in COVID-19 patients has been found to be refractory to conventional mechanical ventilation as well as lung protective strategies, prone positioning, and pulmonary vasodilators. In an article by Macedo et al., mortality in hospitalized patients varied from 11.5% in general hospital patients to 40.5% in the critical care unit during the first wave of COVID-19.[2] For patients who experience progressive respiratory failure despite these conventional therapies, VV-ECMO may be considered to support gas exchange. The overall outcome of an ECMO center may vary from place to place and heavily depends on the previous experience and expertise of the center, the severity of COVID-19 respiratory illness, patient ethnicity, genetic constitution, and preoperative comorbidities. Thus, mortality data in the literature on ECMO in COVID-19 patients varies from country to country. Further, the literature on the outcome of ECMO in the Indian population is scarce. Thus, we planned to study the outcomes of COVID-19 patients requiring long-term ECMO in Indian patients.

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Methods

The data were collected retrospectively from the ECMO unit of Medica Superspecialty Hospital, Kolkata, West Bengal, India as a part of the ECMO fellowship program thesis. All patients who

Table 1: Comparison between the two groups

Variable	*Discharged patients (8)*	*Death (12)*	*p-value*
Age (in years)	42.38 ± 8.4	46.75 ± 13.17	0.418
Sex (M:F)	4:4	9:3	0.35
BMI	22.91 ± 3.64	25.06 ± 5.01	0.268
Onset of symptom to initiation of ECMO (in days)	5 ± 2.67	10.9 ± 4.35	0.003
Intubation to ECMO (in days)	2.13 ± 2.03	4.5 ± 3.3	0.09
Total ECMO (in days)	46.75 ± 21.66	60.08 ± 39	0.39
Use of prone position ventilation	7/8	4/12	0.025
Oxygenator failure in number of patients (nil/once/twice)	6/1/1	8/3/1	0.77
Renal failure requiring RRT	0/8	5/12	0.042
Liver dysfunction	0/8	2/12	0.40
Thrombocytopenia <50,000/mm^3	2/8	3/12	0.24
Infection episodes (culture proven) (Bacteraemia/ECMO cannula site/CVC/UTI/VAP)	17 (2.12 per patient)	29 (2.41 per patient)	0.63

Continuous variables expressed as mean ± SD; Categorical variable expressed as frequency and percentage. BMI, body mass index; CVC, central venous catheter; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy; UTI, urinary tract infection, VAP, ventilator associated pneumonia

had a VV-ECMO run of more than 30 days due to COVID-19-related severe respiratory illness [severe ARDS; PaO_2:FiO_2 (P:F) ratio <100 as per Berlin criteria] between 1 April 2020 to 31 March 2022 were included in the study. Patients who were sent for lung transplants while on ECMO were excluded from the study. The electronically saved data were accessed with due permission from the appropriate authorities and information on the following variables [age, sex, body mass index (BMI), date of onset of symptom, date of intubation, date of initiation of ECMO, total number of ECMO days, mechanical complications like oxygenator failure or pump failure, patient complications such as major intracerebral bleed, liver/renal dysfunction, coagulation abnormality, thrombocytopenia, severe sepsis, and use of prone position ventilation] were obtained. The primary outcome studied was hospital discharge. Based on the hospital discharge the patients were divided into two groups (Survivor patients who were discharged from the hospital and non-survivor patients who died during their hospital stay). The Statistical analysis was done using SPSS, version 26 (IBM, Armonk, NY, USA). The continuous data were expressed as mean and SD. The categorical data were presented as frequency and percentage. A $p < 0.05$ was considered significant. The continuous data and categorical data between the two groups were compared using the Student's *t*-test and Chi-square test/Fischer's exact *t*-test, respectively. The significant variables in the univariate analysis were noted. Patients who were discharged from the hospital were followed up at 6 months to check their quality of life and physical activity.

Observation

Data on above mentioned variables were collected for all patients who had an ECMO run of above 30 days for COVID-19-related severe respiratory illness between 1 April 2020 and 31 March 2022.

The average age of patients in the study cohort was 45 years. There were more male patients as compared to female patients. The mean duration of ECMO was 54.75 days. Although 10 patients were weaned from ECMO, only 8 patients could be discharged from the hospital (2 patients had a failure of ventilator weaning). Prone position ventilation was attempted in 55% of patients while on ECMO. Oxygenator failure was the most encountered mechanical complication. Thrombocytopenia and renal failure were the leading patient-related complications. At least one episode of sepsis was seen in all patients on ECMO. A total of 46 culture-proven sepsis episodes were seen in this study. A total of 8 patients were discharged from the hospital and 6 patients had already been assessed at 6 months follow-up before the time of data collection. Five out of 6 patients had normal physical endurance and maintained a normal social life. All of them had joined back work. However, one of them still needed assistance with the day-to-day work.

Based on the hospital discharge the patients were divided into the following two groups:

- Group I: Patients who were discharged from the hospital.
- Group II: Patients who died during hospital stay.

The comparison of patient variables in both groups is tabulated in Table 1.

The average age of the patients was higher in patients who died although it was not statistically different from the patients who were discharged. The time from symptom onset to ECMO initiation was significantly longer in patients who died. The use of prone position ventilation seemed to have led to a favorable outcome. Renal dysfunction requiring RRT was implicated in a poor outcome.

Discussion

This retrospective study was conducted to assess the outcomes of severe COVID-19 patients requiring long-term ECMO (>30 days). The primary aim of the study was to record mortality and the secondary aim was to assess variables contributing to mortality.

In the pre-COVID-19 era, the average duration of VV-ECMO for severe respiratory illness was typically around 2 weeks. However, during the recent COVID-19 pandemic, it was realized that long ECMO runs invariably averaging more than 2 weeks was the norm rather than the exception. Also, COVID-19 ARDS often required an extended period of lung rest thus necessitating long periods

of ECMO. Prolonged ECMO runs are likely to lead to multiple complications like bleeding and other coagulation issues, infections, and oxygenator and pump failure. The literature pertaining to outcomes in long-term ECMO (>30 days) from Indian authors is sparse. Thus, we designed this study.

Our study cohort included 20 patients who had an ECMO run of above 30 days. Overall mortality in this study was high (60%). Although 10 (50%) patients were weaned from ECMO, two of them could not be weaned from a ventilator and succumbed. In the literature, mortality in severe COVID-19 ARDS patients requiring ECMO ranged 3.7–75.6%.[1,3] The mortality of the COVID-19 patients on ECMO also depended on the time of pandemic that the patients were affected (early or late).[3] Two meta-analyses conducted in the year 2021 and 2022, respectively, concluded that prolonged ECMO duration was associated with improved survival contradicting the popular belief.[4,5]

Most patients in this study were middle-aged groups and age was not found to be a factor contributing to mortality. Although there was wide variability in the patient age groups across studies, many studies reported the average age of the patient to be in the fourth decade of life like those in our study.[6–8]

However, few studies observed that the patients were nearly a decade older than those in our study.[9–11] The literature on the effect of a higher age on mortality is inconclusive. Most studies could not elicit an association between age and mortality which is like our result.[1,6,12] However, few authors found age as a significant contributor to mortality.[3,9,11]

Male gender constituted 65% of the total study population at our study center. Various other studies on ECMO in COVID-19 patients also reported a higher proportion of males in their cohort.[1,3,6,13] Interestingly, Kurihara et al. observed that non-COVID-19 ECMO cohorts had a lesser proportion of males as compared to COVID-19 patients.[6] Most of the earlier studies could not establish an association between gender and mortality in COVID-19 patients undergoing VV ECMO.[1,3,11,13] Higher weight and BMI is often considered poor risk factor for adverse outcomes. Although the mean BMI of non-survivors was slightly higher than survivors in this study, it did not reach statistical significance. Moreover, it was interesting to note that the study cohort had a normal average BMI (24.33) with the mean BMI of the non-survivor group (25.06) slightly drifting towards the overweight range. Many of the authors reported a high BMI (>30) in their study group.[8,9,11,13]

All these studies came from the Western world which is nutritionally better than Indian subcontinent. This explains why BMI was higher in the cited studies as compared to our study population. In contrast to the result of the aforementioned studies, Daviet et al. reported obesity as an independent factor associated with improved survival in VOVID-19 patient undergoing ECMO.[14]

This study suggests that early decision on initiation of ECMO after diagnosis of COVID-19 was useful in improving outcomes. The average time from onset of symptoms to ECMO initiation was 8.5 days in this study which was longer than the time period described by Biancari et al. (5.5 days).[1] However, Dreier et al. and Shaefi et al. reported a longer time interval of 18 days and 13 days, respectively.[12,13] The survivors in this study had a significantly shorter time to ECMO initiation as compared to non-survivors which is in agreement with the study by Shaefi et al. [13] Although the intubation to ECMO initiation interval was longer in non-survivors as compared to survivors, it did not reach statistical significance in this study cohort. This finding is similar to that reported by a few other authors.[3,9,13]

Kurihara et al. reported mortality of 100% in patients who required mechanical ventilation more than 1 week prior to the institution of ECMO and those with less than 1week of ventilation had 63.5% mortality.[6] In a study by Barbaro et al., the mean duration of intubation before the institution of ECMO was 4 days and 3 days in centers that adopted ECMO care early in the pandemic (A1) and late in the pandemic (A2), respectively.[3] Outcome at A1 centers was more favorable than that at A2 centers. It may be because the early adoption centers had better prior experience in ECMO and thus had a better outcome. A meta-analysis conducted recently also could not find an association between intubation to ECMO initiation interval and mortality.[5]

The prone position is often used in patients with severe ARDS to improve hypoxia. Some centers practice prone positioning even while the patient is on ECMO support. Eleven patients (55%) patients received prone positioning during ECMO in our study. The incidence of prone positioning ranges 15.2–81%.[7,10,13] This study found that prone positioning was associated with improved outcomes and agrees with a study by Barbaro et al.[3] However, other authors could not elicit any effect of prone positioning on mortality.[9,11,13]

Mechanical complications on ECMO are a nightmare for the ECMO physician. Due to the prothrombotic tendency observed in many sick COVID-19 patients, clots in membrane oxygenators, circuits, pump heads were described by many authors.[3,6,7]

Hemolysis, pulmonary embolism, deep vein thrombosis ischemic stroke were also frequently reported.[1,3,6,7,13] Oxygenator change was required in 6 (30%) of our ECMO patients and 2 patients needed oxygenator replacement twice during their intensive care unit (ICU) stay. The incidence of oxygenator failure in COVID-19 VV-ECMO ranges 5.8–42.3%.[3,6,9,15]

Ischemic stroke has also been reported as a complication of the prothrombotic milieu. Ischemic stroke incidence described in the literature varies in the range 1–14.4%. Major hemorrhage was a common complication during COVID-19 ECMO. Incidence as high as 45% has been reported.[15] The most common sites of bleeding reported in the literature are the cannula site, oronasal, gastrointestinal tract, intracranial and retroperitoneal bleed outs, urinary tract (Hematuria), lungs, and pleura (hemothorax).[3,7,9,13,15]

Renal decompensation requiring RRT was also a frequent complication reported by many authors and the incidence in our study (25%) falls within the range reported in the literature (5–37.9%).[1,6,7,9,13,15]

The rate of infection was remarkably high in our study. A possible explanation could be the inclusion of only long-term ECMO patients in our study. This obviously meant more hospital stays and more susceptibility to nosocomial infections.

Long-term recovery after hospital discharge in patients who had severe COVID-19 illness is not straightforward. A constellation of symptoms popularly known as "post-COVID-19 syndrome" continues to affect the quality of daily living in these patients.[16,17] The symptoms may range from simple fatigue, headache, and insomnia to more complicated chest pain, dyspnea, and palpitations. Although five patients in our cohort were leading a normal social life post-discharge and joined back work, they all were experiencing some form of mild post-COVID-19 syndrome symptoms. The commonest symptom presented were fatigue, joint pain, paroxysmal palpitations, and insomnia. One patient continued to require help with daily living due to significant

dyspnea. The computed tomography (CT) scan of this patient at 6 months follow-up showed significant lung fibrosis.

Limitation

This is a single-center retrospective study and has a small sample size. Thus, it is likely to have a biased outcome. Many patients included in the study, received treatment at other hospitals during the earlier part of their illness. They were either cannulated at the primary hospital by the ECMO mobile team or were cannulated immediately upon arrival at the study center. Thus, we could not collect data on many preoperative variables such as the use of sedation or neuromuscular blockers during ventilation. The details on renal function test, liver function test, and sequential organ failure assessment (SOFA) score at the time of ECMO cannulation was also missing from many case files. Thus, these variables could not be included in the study. Further multicentric studies with a higher number of patients are required to validate the results of this study.

Conclusion

An ECMO run offers the only hope for survival in desperately ill COVID patients. ECMO runs for these patients are often longer than conventionally described ECMO for another viral disease. Mortality in Long term COVID-19 ECMO is high. An early decision to ECMO after symptom onset and prone positioning were factors significantly affecting favorable outcomes and the requirement of RRT was associated with poor outcomes.

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