ORIGINAL ARTICLE

Extracorporeal Membrane Oxygenation for Severe COVID-19 in Indian Scenario: A Single Center Retrospective Study

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Abstract

Background: Initial reports from Wuhan (China) suggested poor outcomes for severe COVID-19 patients treated with Extracorporeal Membrane Oxygenation (ECMO). Extracorporeal Life Support Organization (ELSO) interim 2019 guidelines also recommended using ECMO only when all conventional therapies are exhausted. However, later studies showed that delayed ECMO initiation may lead to longer ECMO runs, offsetting any benefit from resource conservation by delaying the initiation. Hence, this study was intended to analyze the sociodemographic characteristics, type of ECMO, and complications of its outcome in the Indian scenario.

Materials and methods: Demographic and patient clinical outcome data of all the patients of severe ARDS due to COVID-19 being treated with ECMO from 1st June 2020 to 31st May 2021 at Medica Super-specialty Hospital (Kolkata, India), were retrospectively compiled and analyzed.

Results: Total number of patients treated was 79 with 10% female representation. The mean age was 43 ± 3.2 years and the mean body mass index 37 ± 4.3. Fifty percent of the patient survived. The mean duration of the ECMO run was 17 ± 5.2 days. Sepsis (65%) was the commonest complication observed followed by acute kidney injury (39%).

Conclusion: This study provides significant insight into the outcomes of patients of COVID-19 treated by ECMO in the Indian scenario. Mortality rates of COVID-19 patients on ECMO were comparable to the non-COVID-19 patients, although the ECMO run time was relatively longer. Our study concluded that ECMO should be considered as a treatment option in appropriate COVID-19 cases. However, if the capacity diminishes in a pandemic situation, ECMO consideration should be based on more stringent criteria.

Keywords: Acute respiratory distress syndrome, COVID-19, Extracorporeal membrane oxygenation.

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Highlight

Extracorporeal membrane oxygenation has a definite role in appropriate cases of severe COVID-19. It should be considered when conventional therapies fail. Whenever indicated, ECMO should be initiated timely as undue delay may lead to a longer ECMO run, offsetting any benefit from resource conservation by delaying the initiation.

Introduction

COVID-19 has emerged as a global threat to humanity with widespread implications. It involves multiple organs with major affection to the respiratory system. About 20% of the infected population requires hospitalization, out of which around 26% require intensive care unit (ICU) admission.[1,2] About 30–88% of patients afflicted with COVID-19 have been shown to require invasive mechanical ventilation in various settings due to the development of severe acute respiratory distress syndrome (ARDS).[3–5] Despite, the best supportive care with lung protective ventilation, pulmonary vasodilators, neuromuscular blockade, and prone ventilation, the mortality is still very high.[6] One limitations of any new emerging disease is the lack of predictive knowledge. As the disease evolves, measures to combat the disease are learned in a better way with growing evidence, experiences, and researches. Extracorporeal membrane oxygenation is an established component of the organ support algorithm in case of severe ARDS Initial data from China showed a very high mortality of 83% among the COVID-19 patients treated on ECMO.[7–9] Moreover, the provision of ECMO could be challenging due to ethical concerns as well as resource limitations.[10] But, those were small studies and earlier experiences of ECMO with swine flu, MERS kept the healthcare professionals exercise the feasibility of ECMO in cases of severe ARDS.[11,12] Keeping this in view Extracorporeal Life Support Organization (ELSO) interim guidelines were formulated in 2019. The indications of ECMO initiation were not different from the usual existing guidelines, however, it was emphasized that it should not be initiated prior to exercising maximal conventional therapies especially prone positioning.[6] The evolution of the pandemic went through the emergence of several variants like delta, omicron having different morbidity and mortality. Besides the variant-specific impact on the case fatality, the effect of the acute surge in a number of cases put a strain to healthcare resources. Shortage of resources also

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has a definite contribution on overall mortality from the disease. Mortality rates varied significantly over the multiple waves of the pandemic, ranging between 11 and 16.7% during the first wave to around more than 60% during the second wave.[13] The first wave of the pandemic witnessed a strict lockdown, exposing the relatively healthier population to the risk. While in the subsequent waves, the sicker patients with various co-morbidities were exposed with a possible contribution to greater mortality.

As the disease progressed, ELSO came up with updated 2021 guidelines on the use of ECMO in COVID-19. While there was no difference in guidelines regarding indications for ECMO initiation, it was emphasized that delayed ECMO initiation may lead to longer ECMO runs, offsetting any benefit from resource conservation by delaying the initiation. Also, appropriate patients should be referred early for ECMO consideration from non-ECMO centers in view of safer transport and allowing time to organize mobile ECMO rescue.[14] Increased use of ECMO had varied outcomes in different setups and countries owing to various factors. Published data on ECMO in COVID-19 from different countries have shown different results. So, this study was intended to analyze the sociodemographic characteristics, type of ECMO, duration and complications while on ECMO, and ultimately the outcome in the Indian scenario. This article/thesis also looks into the possible factors which could have contributed to the difference in our data from other centers' data.

Materials and Methods

It was a single-centre retrospective observational cohort study done at Medica Super-specialty Hospital, Kolkata, India. The study population consisted of all patients admitted or transferred to our Tertiary-care Center with laboratory-confirmed COVID-19 pneumonia who received ECMO between June 1, 2020, and May 31, 2021. Data collection included the demographic details, duration of mechanical ventilation pre-ECMO, ECMO specific data like ECMO configuration, ECMO run time, complications, and outcome (survival to ECMO weaning and home discharge). Indications and contraindications for ECMO initiation were as per ELSO guidelines.[6]

> ($PaO_2/FiO_2 < 100$, with $FiO_2 > 90\%$ and/or Murray score 3–4 for more than 6 hours
> Or, $PaO_2/FiO_2 < 80$, with $FiO_2 > 80\%$ for more than 3 hours Or, pH ≤ 7.20 with RR of 35 rpm, tidal volume of 4–6 mL/kg of predicted weight and DP ≤ 15 cmH_2O

All patients meeting the criteria for ECMO initiation were offered therapy. Those who were able to bear the expenses were finally put on ECMO. ARDS was defined as per Berlin's criteria.[15] Septic shock was defined as per international guidelines for the management of septic shock: 2018 update.[16] Anticoagulation was maintained through heparin infusion with target-activated partial thromboplastin time (aPTT) of 60–90 sec. The decision to wean from ECMO was on the clinical judgement of the ECMO team depending on improvement in gaseous exchanges, hemodynamic parameters, and vital signs. Being a retrospective study, the need for informed consent was waived off by the institutional ethical committee as per institutional protocol, and anonymity was ensured while collecting the data from electronic records. The authors declare that there was no conflict of interest. Data of patients treated with ECMO for COVID-19 ARDS were compiled from the hospital medical records. Descriptive statistics were used to analyze clinical and sociodemographic profiles. Categorical variables were reported as percentages or frequencies and analyzed using the Chi-square or Fisher exact test, as appropriate. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile ranges (IQR) and compared across groups using the student unpaired *t*-test or the equivalent non-parametric test if applicable. Statistical analyses were performed using Microsoft Excel 2010 (Microsoft Corp., Redmond, USA) and IBM SPSS Statistics software, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

A number of cases of COVID-19 treated with ECMO was 79 and of these 50% (37 patients) survived while 5 cases were still on ECMO on the last date of data collection (Fig. 1). Out of those 5 cases, three survived and two expired while on ECMO. The study population was predominantly male (M:F 71:8). Mean age of male patients was 45 ± 2.5 years while females was 41 ± 3.8 years. Out of this, 38% patients (30 cases) were retrieved from another institution for ECMO support. Two cases were retrieved through air-ambulance and the rest were ground retrieval. The mean duration from hospital admission to intubation was 5.1 ± 3.8 days (49 cases). The mean duration of intubation to ECMO initiation was 54 ± 36 hours. About 15% of cases were having morbid obesity. ECMO cannulation was venovenous in 87% (69 cases), veno-arterial in 9% (7 cases), and veno-arterial venous in 4% (3 cases). Awake ECMO was done in two cases. Pruning before ECMO initiation was tried in 65% of cases. Proning was tried in 25% of cases while on ECMO. Cytokine removal was tried in 20% of total cases, out of which 25% four patients survived. Prolonged ECMO (more than 14 days) was observed in 60% of cases. The mean duration of the patient on ECMO was 17 ± 5.2 days. A Sudden oxygenator clot was observed in two cases and both of them died. Sepsis (65%) was the commonest complication observed followed by acute kidney injury (39%) requiring continuous renal replacement therapy. Intracerebral bleed was observed in one case. Tracheostomy was performed in about 70% (56) of patients. Mean duration from intubation to tracheostomy 28.2 ± 12.2 days. Repeat ECMO was tried in 5 cases, out of which none survived. No patient on venoarterial venous ECMO survived. The survivor mean duration from intubation to extubation was 20.6 ± 8.9 days and the survivor mean duration from intubation to tracheostomy decannulation was 38.4 ± 20.9 days. The mean duration from hospital admission to discharge in survivors was 48.2 ± 30.2 days (Table 1).

Discussion

COVID-19 is being a highly contagious disease, putting the available healthcare resources under constant strain in the pandemic situation. Also, the initial reports from Wuhan (China) reported a very high mortality rate of 83% of COVID-19 patients being treated on ECMO. But, that was a very small case series of 6 cases only.[8] Hence, with the prior experiences of ECMO in MERS or swine flu, the 2019 ELSO interim guidelines recommended to use of ECMO in cases where all the conventional measures have been exhausted, especially prone positioning. However, the indications or contra-indications for ECMO initiation remained the same as in any severe ARDS case.[1] Later studies from the United Kingdom published in November 2020, presented data from 18 cases having a favorable outcome of only 22% mortality.[17] Various other studies also suggested better outcomes than the initial Wuhan experience.[18,19]

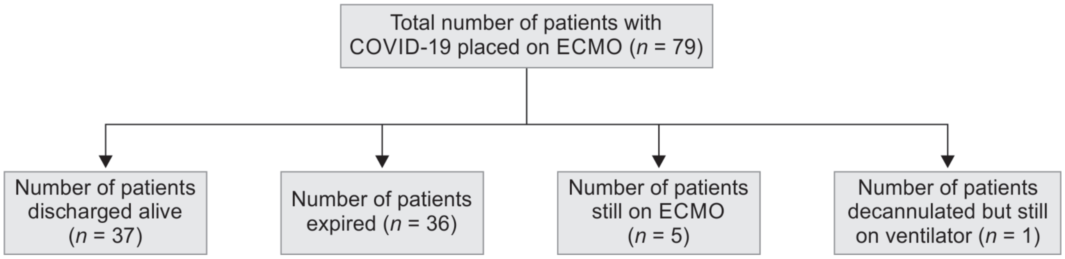

Fig. 1: CONSORT diagram depicting study population and clinical outcome

Table 1: Patient characteristics in ECMO COVID-19 positive cohort (1st June 2020 to 31st May 2021)

Characteristic	*Value*
Age (M;F)	45 ± 2.5 years; 41 ± 3.8 years
Female sex	10%
Body mass index	37 ± 4.3
Morbid obesity (BMI >40)	15%
Hospital admission to intubation (applicable to 49 cases out of 79)	5.1 ± 3.8 days
Proning pre-ECMO	65%
Intubation to ECMO initiation	54 ± 36 hours
Proning on ECMO	25%
Awake ECMO	2.5%
Prolonged ECMO (>14 days)	60%
Tracheostomy	70%
Sepsis	65%
Renal replacement therapy	39%
Bleeding complication	1.25%
Sudden oxygenator clot	2.5%
Cytokine removal	20% (80% survived)
Mean length of ECMO run	17 ± 5.2 days
Highest duration of COVID ECMO (non-survivor)	66 days
Highest duration of COVID ECMO (survivor)	48 days
Lowest duration of COVID ECMO (survivor)	9 days
Initial venovenous ECMO	87%
Initial venoarterial ECMO	13% (3 cases converted to veno-arterial venous)
Repeat ECMO	6.33% (none survived)
Ongoing ECMO	5%
Decannulated but on ventilator	1.25%
Mean duration from intubation to extubation	20.6 ± 8.9 days
Mean duration from intubation to tracheostomy	28.2 ± 12.2 days
Mean duration from intubation to tracheostomy decannulation	38.4 ± 20.9 days
Mean duration from hospital admission to discharge in survivors	48.2 ± 30.2 days
Referred cases (air;ground retrieval)	30 cases (2;28)

A retrospective multicenter study from the United States showed that survivors were offered ECMO sooner after admission than non-survivors.[20] Hence, the 2021 ELSO guidelines clearly recommended not delaying ECMO therapy whenever indicated.[1] Representation of the male gender was disproportionately high in our study also as shown in other studies.[21] This gender disparity might be due to immunological female-biased protection or due to more prevalence of comorbidities among males as proposed by other studies. Also, the role of socioeconomic factors cannot be denied. ECMO being a very costly therapy, it is possible that families opined for this final resort only when the life of the breadwinner of the family was endangered.

Patients having severe ARDS requiring ECMO support were on the heavier side in terms of body mass index, reiterating obesity as a risk factor for severe COVID-19, as suggested by other studies as well.[22,23] Sixty-five percent of patients were prone prior to ECMO initiation. This looks contrary to the ELSO guidelines, where ECMO should be considered only when conventional therapies fail. However, as 38% of patients were referred cases and reliable data regarding ventilation therapy pre-ECMO initiation was not available, the possibility of bias cannot be denied. The majority patients who were retrieved from other centers were cannulated and then shifted to our center. Hence, those patients were prone post ECMO initiation, if required. The decision for ECMO initiation from referring centers was as per ELSO guidelines with close communication between the treating physician, ECMO physician at our institution, and family. The Tracheostomy rate was higher in our study (70%) as compared to the 51% reported in other study.[24] Prolonged ECMO run might be a contributory factor for that. Mortality rates reported in the literature are quite varying (22%–83%) depending on the study design and sample size. However, the mortality rate of our study (50%) was comparable to the result of pooled analysis (48.8%) or multicenter study (42%).[20,25] ECMO configuration was almost similar to those reported elsewhere with veno-venous being the predominant type followed by veno-arterial and veno-arterial venous respectively.[20] Secondary infections (defined as positive culture) were the major complication (65%) associated with ECMO in our study which is higher than reported in another study (55%).[20] Despite the pandemic situation, a 1:1 nurse-patient ratio was maintained for ECMO patients. A higher rate of secondary infections might be due to longer ECMO runs, use of steroids, or immunedysregulation due to COVID-19 itself. Cytosorb was used in 16 cases where only 25% of patients survived which is in quite a contrast to another study where all patients survived in the Cytosorb group.[26] Cytosorb hemadsorption was offered to those patients who met both the criteria of Cytoscore (dynamic scoring system) >6 after 6 hours of starting the therapy and interleukin-6 level was >1000 pg/mL.[27,28] Unlike other studies reporting thromboembolic phenomenon and heparin-induced thrombocytopenia in COVID-19 cases, we didn't observe any such incidence.[29] Two cases of sudden oxygenator clot was observed and one incidence of intracranial hemorrhage was reported.

The major limitation of the study was its retrospective and observational nature. Hence, patient selection criteria for ECMO were not stringent. Also, about 38% of patients were retrieved from different peripheral centers for ECMO. Hence, the duration of intubation to ECMO support initiation could not be protocolized. It was a single-centre study with a functional ECMO unit of eight year of experience. Hence, the results cannot be projected to the pan-India scenario where many centers initiated ECMO during COVID-19 pandemic due to increased demand with lesser experienced ECMO teams. Organ failure assessment score or illness severity score could not be applied to analyze the results due to missing data. RESP, SAVE, and Frailty scores were not calculated. This study didn't study ventilation strategy pre- or post-ECMO initiation despite several studies suggesting its definite role in patient outcome.

Conclusion

This study, though limited by the single center experience and retrospective design, provides significant insight into the outcomes of patients of COVID-19 treated by ECMO in the Indian scenario. Retrospective studies have several biases and limitations owing to study design as criteria for ECMO and supportive therapies could not be standardized and outcomes will vary depending on the timing of support, center expertise, and ECMO delivery models. Our study showed that the mortality rates of COVID-19 patients on ECMO were comparable to the non-COVID-19 patients as reported in literature elsewhere. ECMO run time was longer in COVID-19 ARDS than for non COVID-19 indications similar to those reported in other studies as well. More reliable data on mortality can be estimated with randomized controlled trials which are however difficult in a pandemic situation.

Clinical Significance

ECMO should be considered as a treatment option in COVID-19 cases as per current recommendations of ELSO guidelines. Whenever indicated, it should not be delayed. Otherwise, it may lead to longer ECMO run and poorer outcome However, if the capacity diminishes, the ECMO consideration should be based on more stringent criteria.

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