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Outcomes of extracorporeal membrane oxygenation in acute respiratory distress syndrome due to COVID-19: The lessons learned from the first wave of COVID-19

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Abstract

Introduction: Extracorporeal membrane oxygenation (ECMO) has been used as a refractory treatment for acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19), but there has been little evidence of its efficacy. We conducted this study to share our experience using ECMO as a bridge to recovery for ARDS due to COVID-19.

Methods: All adult patients who were placed on ECMO for ARDS due to COVID-19 between April 2020 and June 2020 (during the first wave of COVID-19) were identified. The clinical characteristics and outcomes of these patients were analyzed with a specific focus on the differences between patients who survived to hospital discharge and those who did not.

Results: In total, 20 COVID-19 patients were included in this study. All patients were placed on veno-veno ECMO. Comparing survivors and non-survivors, older age was found to be associated with hospital mortality ($p = .02$). The following complications were observed: renal failure requiring renal replacement therapy (35%, $n = 7$), bacteremia during ECMO (20%, $n = 4$), coinfection with bacterial pneumonia (15%, $n = 3$), cannula site bleeding (15%, $n = 3$), stroke (10%, $n = 2$), gastrointestinal bleeding (10%, $n = 2$), and liver failure (5%, $n = 1$). The complications associated with patient mortality were culture-positive septic shock ($p = .01$), culture-negative systemic inflammatory response syndrome ($p = .01$), and renal failure ($p = .01$). The causes of death were septic shock (44%, $n = 4$), culture-negative systemic inflammatory response syndrome (44%, $n = 4$), and stroke (11%, $n = 1$).

Conclusions: Based on our experience, ECMO can improve refractory ARDS due to COVID-19 in select patients. Proper control of bacterial infections during COVID-19 immunomodulation therapy may be critical to improving survival.

KEYWORDS
ARDS, COVID-19, ECMO

1 | INTRODUCTION

Since its outbreak in 2019, there have been over 50 million cases of coronavirus disease 2019 (COVID-19) and 1.25 million recorded deaths.[1] While most patients experience mild-to-moderate symptoms, COVID-19 can progress to acute respiratory distress syndrome (ARDS), a rapidly progressive inflammatory syndrome that impairs oxygen transport in the lungs.[2,3] The pulmonary injury in ARDS due to COVID-19 has been shown to resemble ARDS unrelated to COVID-19, and even with mechanical support, ARDS is associated with significant mortality among COVID-19 patients.[2,4,5]

The high mortality rate of ARDS due to COVID-19 increased the demand for other treatment options, and the use of extracorporeal membrane oxygenation (ECMO) was encouraged for select cases of refractory ARDS with severe hypoxemia.[5–8] ECMO is a temporary form of mechanical cardiopulmonary support for patients with severe cardiac and/or respiratory shock. First clinically used in 1972, ECMO's use has exponentially increased in the past two decades.[9–11] While its efficacy in lowering mortality rates is still debated, ECMO is now a common treatment for patients with refractory ARDS.[11–14]

Despite some recent publications,[15–17] there remains a lack of evidence documenting the overall efficacy of ECMO in treating ARDS due to COVID-19. The purpose of this study is to share our experience using ECMO as a bridge to recovery for patients with ARDS due to COVID-19 during the first wave of the COVID-19 pandemic in our area.

2 | METHODS

Adult patients positive for COVID-19 who underwent ECMO at our institution from April 1, 2020 to June 11, 2020 were included in this study. Patients were identified by an IRB-approved, prospectively maintained ECMO database (IRB approval: #11D.185). The data from these patients were retrospectively extracted and details were further studied by reviewing medical records. Inclusion criteria included a positive COVID-19 test and a diagnosis of ARDS. ECMO placement was determined by a multidisciplinary team that included a cardiac surgeon, a pulmonary critical care physician, and a cardiovascular intensivist.

The indications for ECMO placement were the same as our previous paper,[18] and contraindications for ECMO placement in treating COVID-19 patients are listed in Table 1. The exclusion criteria may be more restricted than in non-COVID-19 patients due to the limitations of resources during this pandemic.

The primary mode of ECMO in COVID-19 ARDS was veno-venous ECMO (VV-ECMO) using the femoral and internal jugular veins (Figure 1). All cannulation was performed in the intensive care unit without transport to either the operating room or catheterization lab unless an issue occurred during bedside cannulation. Since Avalon Dual Lumen ECMO Cannula placement always requires fluoroscopy and echocardiography, which requires additional personnel, including radiology technicians and an echocardiography technician, the utilization of the Avalon cannula was discouraged.[18] Veno-arterial ECMO (VA-ECMO) should be reserved for only those who had severe but reversible cardiac dysfunction, such as COVID-19-related myocarditis. ECMO-assisted cardiopulmonary resuscitation for patients with COVID-19 was discouraged due to its known poor outcomes.

Due to the COVID-19 pandemic, we no longer offer a mobile ECMO program outside of our institutional network due to the concern of exposure of required personnel, including the ECMO surgeon, perfusionist, and transfer nurses at the local site. Instead of activating mobile ECMO cannulation teams, we encouraged local cardiac surgeons to place ECMO at their institutions and then transport the patient to our facility.

The general management of ECMO has been described in one of our prior papers.[19] Briefly, after placement of ECMO, the ventilator was set to the ARDSnet protocol. The typical setting was pressure-controlled ventilation, rate 15 beats/min, PEEP 15 cm H_2O,

TABLE 1 Contraindications for ECMO in COVID-19

Standard contraindications
Age >70 years
Body mass index >45 with a high risk of vascular access
Mechanical ventilation >7 days
Multiorgan failure
End-stage liver disease
Irreversible neurological damage
Contraindications of anticoagulation
Cardiac arrest without ROSC
Relative contraindications
Age >65 years
Body mass index >35
Mechanical ventilation >5 days
Active bacterial bloodstream infection
Severe COPD
Cirrhosis
Chronic heart failure
Inability to access neuro status
High lactate related to low perfusion status
Limited activity at home
No family or appropriate power of attorney
Outside of the institutional network
Considering veno-arterial cannulation
Cardiac arrest with ROSC
Poor left or right ventricular function
Known pulmonary hypertension

Abbreviations: COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ROCS, return of spontaneous circulation.

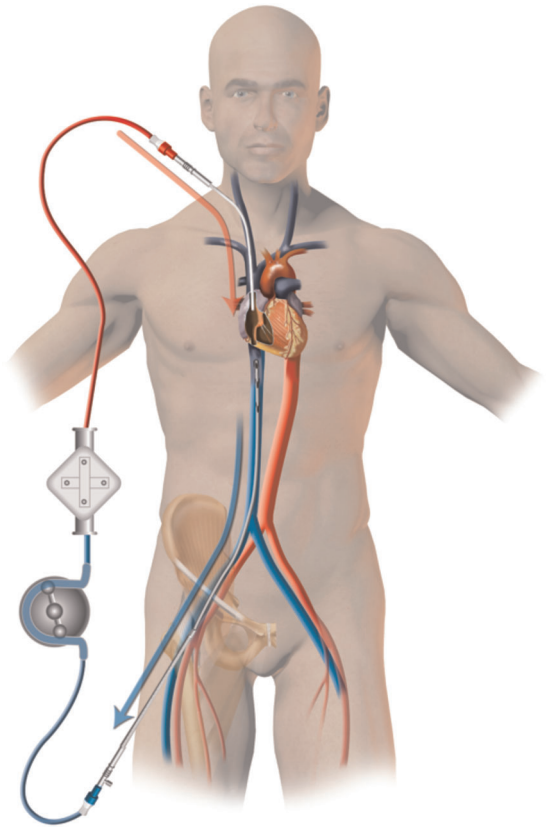

FIGURE 1 Typical veno-venous cannulation in COVID-19 case. Patients were primarily cannulated via the right internal jugular vein and right femoral vein due to anatomical preference

delta P 15 cm H_2O until recovery of the respiratory function. Paralytics were discontinued within 24 h of ECMO initiation, unless the respiratory function was deteriorated. Sedatives were adjusted based on Richmond agitation-sedation (RAS) scale negative 1-2. Blood pressure was maintained at least mean arterial pressure of 60 mmHg with vasopressors and/or fluid as appropriate. A heparin drip was started once partial thromboplastin time fell below 50 sec after cannulation and maintained at an anti-Xa level of 0.3–0.5 IU/ml. If bleeding complications were observed, the anticoagulation was held and then restarted at a lower anti-Xa goal of 0.1–0.3 IU/ml.

The timing of the decannulation was determined by chest X-ray findings and lung mechanics. Before decannulation, the sweep gas was discontinued for at least 24 h to ensure the lungs were able to exchange oxygen and carbon dioxide appropriately. For COVID-19 cases, we encourage bedside decannulation rather than transporting to the operating room to limit exposure to COVID-19.

The primary endpoints of this study were ECMO survival and hospital survival. ECMO survival was defined by the withdrawal of care or death within 24 h of decannulation. All patients who survived to hospital discharge were classified as "survivors" and all patients who did not survive to hospital discharge were classified as "non-survivors." The baseline characteristics, clinical characteristics, and outcomes were calculated and compared between the two groups.

Data were expressed as the number with percentage, mean ± standard deviation (*SD*), or median (quantile) as appropriate. Two groups were compared using χ^2 tests for categorical variables and standard *t* tests for continuous variables as appropriate. Significance was accepted at $p < .05$.

3 | RESULTS

During this study period, 20 patients with ARDS positive for COVID-19 underwent ECMO placement. All patients were placed on VV-ECMO. No patients underwent VA-ECMO or were converted to VA-ECMO after VV-ECMO placement. The mean length of ECMO placement was 14.0 days. The average length of symptoms before ECMO placement was 11.4 days, with the average patient spending 10.3 days in the hospital before ECMO placement. The average time spent on a ventilator before ECMO placement was 147 h. 75% of patients ($n = 15$) were transferred from another institution to our hospital, and 60% of patients ($n = 12$) had ECMO initiated at another institution before transfer. Pre-ECMO characteristics and patient demographics are displayed in Table 2. Patients were also treated with different therapies before starting ECMO placement. Therapy was administered in the form of steroids (65%, $n = 13$), interleukin-6 inhibitors (55%, $n = 11$), remdesivir (20%, $n = 4$), and plasma (15%, $n = 3$). None of the treatment therapies was associated with better or worse mortality rates. The types of treatment and their statistics are displayed in Table 3.

The ECMO survival rate was (15/20), and the survival rate to hospital discharge was 55% (11/20). In total, 11 patients were labeled as survivors and 9 as non-survivors based on their survival to hospital discharge. The only baseline characteristic that was statistically different between the two groups was age, as non-survivors were significantly older than survivors (58.4 vs. 49.6; $p = .02$).

The causes of death were septic shock (44%, $n = 4$), culture-negative systemic inflammatory response syndrome (SIRS) (44%, $n = 4$), and stroke (11%, $n = 1$). The most common complication observed was renal failure requiring renal replacement therapy (35%, $n = 7$). Complications that were associated with patient mortality between the two groups were blood culture-positive sepsis ($p = .01$), culture-negative SIRS ($p = .01$), cannula site bleeding ($p = .04$), and renal failure ($p = .01$). The complications are displayed in Table 4.

4 | DISCUSSION

The primary finding of this study is that among the 20 COVID-positive patients that we treated with ECMO, the survival rate to hospital discharge was 55%. Also, our results suggest that proper patient selection and control of bacterial infections before and/or during ECMO placement may be key to improving survival, as culture-positive septic shock and culture-negative SIRS were the main causes of death and were only observed in patients who failed to survive to hospital discharge.

TABLE 2 Demographics and baseline characteristics of studied patients

Category Number of patients	All patients *n* = 20	Survivors *n* = 11	Non-survivors *n* = 9	*p* value
Characteristics				
Age (years)	54 ± 8.7	50 ± 8.5	58 ± 6.4	.020
Male	12 (60%)	7 (64%)	5 (56%)	.713
Body surface area (cm^2)	2.1 ± 0.3	2.1 ± 0.3	2.0 ± 0.3	.259
Body mass index	35 ± 7	38 ± 7	32 ± 7	.057
Underlying conditions				
Pre-ECMO-positive blood culture	5 (25%)	3 (27%)	2 (22%)	.795
Pre-ECMO time on ventilator (h)	148 ± 255	206 ± 344	76 ± 68	.280
Smoking	4 (20%)	3 (27%)	1 (11%)	.369
Chronic lung disease	2 (10%)	0 (0%)	2 (22%)	.099
Diabetes	6 (30%)	2 (18%)	4 (44%)	.202
Liver failure	1 (5%)	0 (0%)	1 (11%)	.257
Chronic immunosuppression	1 (5%)	0 (0%)	1 (11%)	.257
Pre-ECMO acute renal injury	6 (30%)	2 (18%)	4 (44%)	.202
Pre-ECMO vital signs				
Length of symptoms (days)	11.4 ± 6.5	9.9 ± 4.6	13.5 ± 8.4	.237
Temperature (°F)	99.4 ± 1.4	99.7 ± 1.6	99.0 ± 1.1	.281
Heart rate	102 ± 24	111 ± 23	91 ± 21	.064
Respiratory rate	28 ± 5.3	27 ± 3.9	29 ± 6.7	.330
Mean arterial pressure (mmHg)	85 ± 17	87 ± 16	84 ± 20	.759
FiO_2 (%)	93 ± 14	90 ± 15	96 ± 13	.390
PEEP (cm H_2O)	16 ± 4.8	17 ± 5.6	15 ± 3.6	.345
Plateau pressure, 24 h post-ECMO placement (cmH_2O)[a]	24.7 ± 5.1	24.9 ± 6.8	24.6 ± 6.8	.933
Other				
Pre-ECMO days in the hospital (days)	10 ± 13	12 ± 16	8.8 ± 7.7	.654
Transfer from outside hospital	15 (75%)	8 (73%)	7 (78%)	.795
ECMO initiated outside hospital	12 (60%)	6 (55%)	6 (67%)	.582
Length on ECMO (days)	14 ± 9.6	11 ± 6.2	17 ± 12	.183
Plateau pressure, 24 h post-ECMO placement (cmH_2O)	24.7 ± 5.1	24.9 ± 6.8	24.6 ± 6.8	.933

Note: Data are expressed as number (percentage) or mean ± *SD*.

Abbreviations: ECMO, extracorporeal membrane oxygenation; PEEP, positive end-expiratory pressure.

[a]Pre-ECMO plateau pressure was not always available; thus plateau pressure 24 h after ECMO placement is listed.

The treatment of ARDS with ECMO remains disputed even though its use in treating ARDS has increased in the past decade.[11,12] While the exact mortality rate of treating ARDS with ECMO varies by research study, it is generally accepted to range between 34% and 39%.[11,13,14] Thus, it is generally recognized that ECMO should be primarily used for refractory cases of ARDS, in which a patient remains severely hypoxic despite aggressive treatment.[12]

Interestingly, our study and others on COVID-19 have found that the mortality rates of treating ARDS due to COVID-19 with ECMO are similar to the previously reported mortality rates of treating non-COVID

TABLE 3 Treatment modalities provided pre-ECMO placement

Category Number of patients	All patients *n* = 20	Survivors *n* = 11	Non-survivors *n* = 9	*p* values
Pre-ECMO treatment				
Steroids	8 (40%)	5 (45%)	3 (33%)	.582
Interleukin inhibitor	11 (55%)	7 (64%)	4 (44%)	.391
Remdesivir	4 (20%)	3 (27%)	1 (11%)	.369
Plasma	3 (15%)	2 (18%)	1 (11%)	.660

Note: Data are expressed as number (percentage).
Abbreviation: ECMO, extracorporeal membrane oxygenation.

ARDS. Recently, there have been a few articles published that specifically investigated the use of ECMO in treating ARDS due to COVID-19. The largest of these studies was conducted by Barbaro et al.,[15] who drew from an Extracorporeal Life Support Organization (ELSO) registry to analyze the outcomes of 1035 COVID-positive patients who were treated with ECMO. The researchers found that among these patients, the 90-day post-ECMO mortality rate was 37.4%. The study included data from 213 different hospitals and included patients treated from January 16th to May 1st of 2020. Another study that more closely resembles our own is from Schmidt et al.,[16] who documented the outcomes of 83 COVID-positive patients who were treated at their hospital. They discovered that the 60-day mortality of these patients was 31%. Compared with these studies, our patients had a slightly higher mortality rate of 45%; however, it should be noted that our sample size was significantly smaller than either of these two articles.

Based on this current research on the use of ECMO in ARDS due to COVID-19, the mortality rate appears to be anywhere between 31% and 45%. This mortality rate is similar to the 34%–39% mortality rate in treating non-COVID ARDS with ECMO in select patients. Therefore, it is possible that ECMO is just as effective at treating ARDS due to COVID-19 as it is at treating ARDS due to non-COVID-19 etiologies if an appropriate patient selection was applied. For example, none of the patients in our study had cardiac dysfunction. This is because our selection committee considered COVID-19 patients with cardiac dysfunction and ARDS to have a multiorgan failure, which was a contraindication for ECMO placement. While there needs to be far more research done on this topic to definitively state that ECMO is effective in treating COVID-19, it is possible that it is an effective treatment option for refractory cases of ARDS due to COVID-19.

Sepsis and SIRS were the causes of death in all but one patient in our study, suggesting that bacterial infections during ECMO placement may be a significant factor in mortality rates. While immunomodulation therapy has been shown to decrease the mortality rate of COVID-19,[20,21] it has also been associated with an increased infection rate. For example, one study demonstrated that 13% of patients treated with tocilizumab were diagnosed with new infections, compared with only 4% of patients treated solely with the standard of care.[21] There should be particular attention to preventing, monitoring for, and responding early to bacterial infections in COVID-19 patients placed on ECMO.

During the first wave of COVID-19 in Pennsylvania, the highest number of daily COVID-19 cases occurred on April 8th, with 2059 cases. By the end of our study period on June 11th, the daily number of cases fell to 680, which was one of the lowest numbers of daily cases in Pennsylvania since the beginning of the pandemic. Our study beings on April 1st and ends on June 11th, which fairly accurately represents the beginning and end of the first wave of COVID-19 in Pennsylvania. Beginning in late October, Pennsylvania entered a

TABLE 4 Rates of ECMO complications

Category Number of patients	All patients *n* = 20	Survivors *n* = 11	Non-survivors *n* = 9	*p* values
Complications				
Renal failure	7 (35%)	1 (9.1%)	6 (67%)	.007
Liver failure	1 (5%)	0 (0%)	1 (11%)	.257
Stroke	2 (10%)	0 (0%)	2 (22%)	.099
Intracranial bleed	1 (5%)	0 (0%)	1 (11%)	.257
Bacterial pneumonia	3 (15%)	2 (18%)	1 (11%)	.660
Cannula site bleed	3 (15%)	0 (0%)	3 (33%)	.037
Gastrointestinal bleed	2 (10%)	0 (0%)	2 (22%)	.099
New infection during ECMO	9 (45%)	3 (27%)	6 (67%)	.078
Culture-positive sepsis	5 (25%)	1 (9.1%)	4 (44%)	.069
Septic shock	4 (20%)	0 (0%)	4 (44%)	.013
Systemic inflammatory response	4 (20%)	0 (0%)	4 (44%)	.013

Note: Data are expressed as number (percentage).
Abbreviation: ECMO, extracorporeal membrane oxygenation.

second wave, with daily cases greatly exceeding those of the first wave. Future studies of the second wave of COVID-19 will differ from this study for multiple reasons, including changes in pre-ECMO immunomodulation treatment. During the second wave, interleukin inhibitors are no longer recommended and steroids are more widely used.

Our study is limited by its small sample size and being based in one hospital center. It is also possible that there was selection bias in this study, even though ECMO placement was determined by a multidisciplinary team of physicians.

Despite its limitations, this study provides extensive data on 20 patients with ARDS due to COVID-19 who were treated with ECMO. While we cannot extrapolate from a sample size of 20 patients, we hope our evidence can complement other studies and contribute to meaningful meta-analyses and statistical analyses. Cases of ARDS due to COVID-19 will continue in the coming months and years, and we hope that our analysis contributes to the growing research on how to treat this deadly disease.

5 | CONCLUSION

Based on our results, we conclude that ECMO placement can improve refractory cases of ARDS due to COVID-19. More research is needed to better understand the true efficacy of ECMO in treating COVID-19 and the mortality rate associated with it.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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