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Outcomes of extracorporeal membrane oxygenation (ECMO) in acute respiratory distress syndrome due to COVID-19: comparison of the first and the second wave

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Abstract

Introduction: For decades, extracorporeal membrane oxygenation (ECMO) has been used to support severe, refractory acute respiratory distress syndrome (ARDS). Across the world, there has been an increase in ECMO utilization due to Coronavirus disease 2019 (COVID-19). This study was conducted to explore outcomes of ECMO for ARDS due to COVID-19, focusing on the outcome differences between the first and second wave.

Methods: All adult patients treated with ECMO for ARDS due to COVID-19 at our institution between April 2020 and March 2021 were stratified as first wave patients (ECMO started on April 2020 – September 2020) or second wave patients (ECMO started on November 2020 – March 2021), as no ECMO was initiated during October 2020. Clinical characteristics and outcomes were compared.

Results: A total of 41 COVID-19 ECMO patients were identified, including 28 patients (mean age 53 years, male 68%) in the first wave and 13 patients (mean age 45 years, male 69%) in the second wave. All ECMO was performed with veno-venous ECMO for these patients. Pre-ECMO immunomodulators were more often utilized in the second wave than the first wave, such as steroids (54% in first wave vs. 100% in second wave, p=0.003) and remdesivir (39% vs. 85%, p=0.007). The second wave patients were also more often placed in prone position prior to ECMO initiation (11% vs. 85%, p<0.001). ECMO survival was significantly decreased in second wave patients compared to first wave patients (19/28, 68% in first wave vs. 4/13, 31% in second wave, p=0.026).

Conclusions: Despite more standardized pre-ECMO treatment, second wave COVID-19 patients experienced higher mortality on ECMO than first wave patients. More strict inclusion/exclusion criteria for ECMO and control of sepsis may be necessary to improve outcomes.

Introduction

The development of acute respiratory distress syndrome (ARDS) is a common and often significant complication of coronavirus disease 2019 (COVID-19).[1] Pulmonary injury due to ARDS has historically been an important concern in previous viral outbreaks such as influenza H_1N_1 and middle east respiratory syndrome (MERS),[2,3] and was associated with increased mortality in these outbreaks. Similarly, COVID-19 patients that develop ARDS have experienced increased mortality, and evidence suggests that ARDS due to COVID-19 is more severe than ARDS

due to other causes.[4,5] Also unique to COVID-19 ARDS is the mortality rates of otherwise healthy patients who die from ARDS-induced multi-organ failure.[6]

The high incidence of ARDS due to COVID-19 has necessitated the implementation of alternative support for patients who do not improve with standard medical treatment and ventilator management. Extracorporeal membrane oxygenation (ECMO) has thus been used in certain COVID-19 patients with refractory ARDS.[7–9] ECMO is a mechanical cardiopulmonary bypass support that is used to temporarily support patients that develop respiratory and/or cardiac shock. However, there remain bodies of literature that both support and refute the benefits of ECMO in patients with refractory ARDS.[10]

The COVID-19 pandemic was first identified in China in December 2019, before spreading around the world and to the United States in early 2020; the exact date of arrival to the United States remains unclear. In the first wave of COVID-19, knowledge on COVID-19-induced ARDS was limited; treatment recommendations evolved over time as the disease spread and more evidence was obtained. We previously published data on the outcomes of ECMO for patients in the first wave of COVID-19.[11,12] A resurgence or "second wave" of COVID-19 infections began around the autumn of 2020, potentially due to various factors including relaxation of the initial strict societal interventions to contain the spread and mutation of the virus leading to more infectious variants.[13] Differences have been noted between the first and second waves of the COVID-19 outbreak around the globe; however, respiratory failure remained a highly concerning complication of COVID-19 in the second wave in spite of improvements in treatment strategies for the disease.[14]

Although the number of studies on the use of ECMO in COVID-19 patients that develop ARDS is growing, evidence for its overall efficacy remains unclear.[7,15] Additionally, it remains to be seen how infections by future variant strains and the evolution of pharmacologic therapies may affect the clinical course of the disease and the utility of ECMO support. This paper will compare outcomes and efficacy of ECMO in treating first wave patients and second wave patients to further elucidate the value of ECMO for treating refractory ARDS due to COVID-19.

Methods

All adult patients who tested positive for COVID-19 and who underwent ECMO at our institution between April 1, 2020 and March 31, 2021 were identified from an IRB-approved ECMO database (IRB approval # 11D.185) and included in this study. The data from these patients was retrospectively analyzed and further details were extracted by reviewing medical records. Based on the timing of the ECMO initiation date, patients were stratified to the first wave (ECMO began between April 2020 and September 2020) or the second wave (ECMO began between November 2020 and March 2021), as no ECMO was initiated in the month of the October 2020. The specific strain of COVID-19 with which patients were infected was not studied, but infections by the B.1.617.2 (Delta) variant strain were not believed to be significant, as this strain became the dominant strain in the United States in late June 2021.[16] None of the patients received COVID-19 vaccination because of the lack of availability of the vaccine to the general public, based on the demographics and time frame of this study.

The indications for ECMO placement were the same as those listed in our previous papers.[17] All cannulations for COVID-19 ECMO were performed as VV-ECMO. The typical cannulation of VV-ECMO for COVID-19 was using the femoral and internal jugular veins. A small number of patients underwent VV-ECMO via single double-lumen cannula (Avalon© cannula, Getinge, Wayne, NJ) if there was an anatomical issue with the femoral vessels.

The general management of ECMO has been described in prior papers.[18,19] Briefly, after placement of ECMO, the ventilator was set to the ultra-lung protective strategy.[20] The typical setting for COVID-19 patients was pressure-controlled ventilation (rate 15 per minute, PEEP 15 cm H_2O, delta P 15 cm H_2O, and inspiratory time 1.5 seconds) depending on pre-ECMO ventilator setting and airway pressure until recovery of respiratory function. Paralytics were discontinued within 24 hours of ECMO initiation, unless ventilatory desynchrony resulted in hemodynamic instability. Sedatives were used to achieve a Richmond-Agitation-Sedation Scale of negative 1–2. Blood pressure was maintained at a mean arterial pressure of at least 60 mm Hg with vasopressors

and/or fluid as appropriate. Anticoagulation with heparin infusion was started if PTT fell below 60 seconds after cannulation and was 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.

Baseline characteristics and clinical outcomes were compared between the two groups, including ECMO mortality and incidence of other complications. ECMO death was defined as care withdrawal during ECMO. Cause of death was also defined for patients who died on ECMO. Sepsis was defined as a bacterial infection disseminated in the blood culture. Failure of lung recovery was determined by multidisciplinary discussion including critical care, pulmonary, and cardiothoracic surgery. Cerebral vascular accident was defined as either stroke or intracranial hemorrhage. Patients were followed at least 30 days after decannulation and defined as 30-day survival.

Data was expressed with number (percentage), mean ± standard deviation, or median (quantile) as appropriate. The two groups were compared using standard t-tests for continuous normally distributed variables, a two-proportion z-test for categorical variables, or a Mann-Whitney u-test for non-normally distributed data as appropriate, with significance accepted at a p-value < 0.05.

Results

41 patients with ARDS due to COVID-19 underwent ECMO placement. All ECMO was performed with veno-venous ECMO (VV-ECMO). No veno-arterial ECMO (VA-ECMO) was performed. Among these 41 patients, 28 patients (mean age 53.3 years, male 68%) were stratified to the first wave and 13 patients (mean age 44.7 years, male 69%) were stratified to the second wave. There were no significant differences between groups with regards to pre-ECMO vital signs and comorbidities (Table 1).

Patients received varying treatments prior to ECMO placement as the standard of care evolved over the course of the COVID-19 outbreak. Steroids were used in 15 patients (54%) in the first wave and 28 patients (100%) in the second wave (p=0.003). Remdesivir was used in 11 patients (39%) in the first wave and 11 patients (85%) in the second wave (p=0.07). Second wave patients were more often tried in the prone position prior to initiating ECMO (11% in the first wave vs. 85% in the second wave, p<0.001). An overview of treatments is given in Table 2.

The median length of ECMO support was 14 days in first wave patients compared to 20 days in second wave patients (p=0.728). ECMO survival was 68% (19/28) in the first wave, and 31% (4/13) in the second wave (p=0.026). Survival to 30 days after ECMO decannulation was 54% (15/28) in the first wave and 31% (4/13) in the second wave (p=0.173); no patient died within 24 hours of decannulation. There was no significant difference in the incidence of other complications except for cerebral vascular accident (i.e., stroke or intracranial hemorrhage), which was observed in 7% (2/28) of first wave patients and 31% (4/13) of second wave patients (p=0.046). Other notable complications observed during ECMO are summarized in Table 3.

In both groups, of the 18 who died on ECMO, sepsis (7/18, 39%) and failure of lung recovery (7/18, 39%) were the two leading causes of death. Pathogens detected in the blood of patients who expired due to sepsis included Pseudomonas (2/7, 29%), Enterococcus (2/7, 29%) and E. coli (2/7, 29%); one patient was coinfected with Enterococcus and E. coli. There was not significant difference in terms of cause of death between first wave and second wave patients. Causes of mortality are summarized in Table 4.

Discussion

The principal finding of this study relates to the ECMO mortality rate in patients with ARDS due to COVID-19. Second wave COVID-19 patients had significantly higher mortality on ECMO in comparison to first wave COVID-19 patients despite improvements in pre-ECMO immunomodulation therapy and other adjunctive therapies such as prone position prior to initiating ECMO. Incidence of other complications was not significantly different between groups, except that significantly more second wave patients experienced cerebral vascular accident than first wave patients.

The mortality rate of COVID-19 in the general population has appeared to decline in the second wave compared to the first wave around the world. In a study of 53 countries with the highest COVID-19 death tolls, Fan et al. found that 43 countries had lower case fatality rate estimates in the second wave compared to the first wave, though it should be noted that these results may be biased by increased testing capacity.[21] Another study conducted across 26 public health units in Ontario, Canada found that the pooled relative risk estimate of second wave case fatality was 0.24 compared to the first wave.[22]

Table 1: Demographics and baseline characteristics of studied patients. Data is expressed with number (percentage), median (1st quartile, 3rd quartile) or mean ± standard deviation, as appropriate.

Group	All patients	First wave	Second wave	
	n = 41	n = 28	n = 13	P-value
Characteristics				
Age (years)	51 ± 11	53 ± 10	45 ± 11	0.015
Male	28 (68%)	19 (68%)	9 (69%)	0.930
Body surface area (cm^2)	2.09 ± 0.25	2.04 ± 0.25	2.20 ± 0.22	0.047
Body mass index	34 ± 6.8	33 ± 6.6	36 ± 6.9	0.188
Underlying Conditions				
Pre-ECMO culture-positive sepsis	8 (20%)	7 (25%)	1 (8%)	0.193
Pre-ECMO hours on ventilator	77 ± 84	79 ± 88	74 ± 77	0.853
Smoking	5 (12%)	5 (18%)	0 (0%)	0.104
Coronary artery disease	1 (2%)	0	1 (8%)	0.137
Chronic lung disease	2 (5%)	2 (7%)	0 (0%)	0.323
Diabetes mellitus	12 (29%)	8 (29%)	4 (31%)	0.886
Liver failure	0	0	0	
Chronic immunosuppression	3 (7%)	3 (11%)	0	0.220
Pre-ECMO acute renal injury	9 (22%)	6 (21%)	3 (23%)	0.650
Cardiogenic shock	0	0	0	
Pre-ECMO vital signs and laboratory data				
Length of symptoms (days)	12 ± 6	11 ± 6	15 ± 6	0.060
Temperature (F)	100 ± 2	99 ± 2	100 ± 2	0.619
Pre-ECMO days in hospital	2.8 ± 4.3	2.1 ± 3.6	4.2 ± 5.4	0.158
Heart rate	100 ± 22	102 ± 24	97 ± 16	0.497
Respiratory rate	28 ± 5	28 ± 5	28 ± 5	0.957
Mean arterial pressure (mm Hg)	85 ± 14	85 ± 15	84 ± 13	0.917
FiO_2 (%)	95 ± 12	95 ± 12	95 ± 11	0.994
PEEP	15 ± 4.0	15 ± 4.6	16 ± 2.5	0.654
White blood cell count	15 ± 9	14 ± 11	17 ± 5	0.512
C-reactive protein	19 (8, 51)	19 (5, 102)	19 (14, 26)	0.772
Other				
Duration on ECMO (days)	16 (8, 30)	14 (8, 32)	20 (9, 28)	0.728
ECMO initiated outside hospital	18 (44%)	14 (50%)	4 (31%)	0.248

Table 2: Rates of pre-ECMO treatments for studied patients. Data is expressed with number (percentage).

Group	All patients	First wave	Second wave	
	n = 41	n = 28	n = 13	P-value
Pre-ECMO Treatment				
Steroids	28 (68%)	15 (54%)	13 (100%)	0.003
Interleukin inhibitor	18 (44%)	15 (54%)	3 (23%)	0.067
Remdesivir	22 (54%)	11 (39%)	11 (85%)	0.007
Plasma	10 (24%)	7 (25%)	3 (23%)	0.894
Naristonib	1 (2%)	0 (0%)	1 (8%)	0.137
Prone	14 (34%)	3 (11%)	11 (85%)	<0.001

Table 3: Rates of complications during ECMO in studied patients. Data is expressed with number (percentage).

Group	**All patients**	**First wave**	**Second wave**	
	n = 41	n = 28	n = 13	P-value
Survival				
Survival on ECMO	23 (56%)	19 (68%)	4 (31%)	0.026
Survival 30 days after decannulation	19 (46%)	15 (54%)	4 (31%)	0.173
Complications during ECMO				
Any Bleeding/hemorrhage	25 (61%)	17 (61%)	8 (62%)	0.959
Cannulation site bleeding	4 (10%)	4 (14%)	0 (0%)	0.151
Oral pharyngeal bleed	19 (46%)	15 (54%)	4 (31%)	0.173
Gastrointestinal bleed	8 (20%)	6 (21%)	2 (15%)	0.650
Any new infection	22 (54%)	14 (50%)	8 (62%)	0.491
Blood culture positive Sepsis	13 (32%)	9 (32%)	4 (31%)	0.930
Bacterial pneumonia	4 (10%)	3 (11%)	1 (8%)	0.762
Pneumothorax	11 (27%)	7 (25%)	4 (31%)	0.698
New acute kidney injury	11 (27%)	8 (29%)	3 (23%)	0.712
Liver failure	4 (10%)	2 (7%)	2 (15%)	0.408
Cerebral vascular accident	6 (15%)	2 (7%)	4 (31%)	0.046

Table 4: Cause of mortality in patients who died during ECMO. Data is expressed with number (percentage).

Group	All patients	First wave	Second wave	
	n = 18	n = 9	n = 9	P-value
Cause of death				
Failure of lung recovery	7 (39%)	4 (44%)	3 (33%)	0.629
Sepsis	7 (39%)	3 (33%)	4 (44%)	0.629
Multi-organ failure	2 (11%)	1 (11%)	1 (11%)	1.000
Cerebral vascular accident	2 (11%)	1 (11%)	1 (11%)	1.000

Despite this overall modifications of management there has been little to no change in outcomes for patients with COVID-19 that require intensive care. A comparison of the first and second waves of the COVID-19 pandemic in Germany revealed that although the proportion of patients requiring ICU admission (30% in the first wave to 14% in the second wave) and requiring mechanical ventilation in the ICU (64% to 54%) dropped, the number of patients requiring mechanical ventilation after being admitted to the ICU increased to almost double that of the first wave during the second wave (30–35% in the first wave, 60–70% in the second wave).[23] Another comparison conducted on patients admitted to ICUs in France between the first and second wave found no difference in ICU mortality (50% in the first wave, 52% in the second wave, p=0.96).[14] Based on these studies, it appears that patients who develop severe disease due to COVID-19, such as the patients included in our study, have not had an improvement in outcomes between the first and the second wave.

Specifically with respect to patients treated with ECMO, the mortality rate not only remained unchanged but increased from the first wave to the second according to our data and reports from across the country. This increase in ECMO mortality rate we observed between the first and second wave is comparable to the results reported by Broman et al., who surveyed ECMO outcomes for 1442 first wave patients and 1723 second wave patients across Europe and found that the percentage of patients who were successfully weaned off ECMO dropped from 58% in the first wave to 47% in the second wave, despite similar changes to pre-ECMO support protocols.[24] Broman et al. also reported a survival rate of 44% in second wave patients compared with a survival rate of 53% in first wave patients when including patients who died after successfully being weaned off ECMO.[24]

Despite the concerns of COVID-19 inducing a hypercoagulable state, there was no significant occurrence of thrombotic events in either first wave or second wave patients in our study. Incidence of thromboembolic adverse events has historically been a significant complication of ECMO, and has been reported both in prior studies on ECMO as well as in the treatment of COVID-19 patients with ECMO.[25,26] However, we did observe a significant increase in the proportion of patients that experienced cerebral vascular accident in the second wave compared to the first wave; additionally, more than half of the patients included in this study experienced some kind of bleeding or hemorrhagic event. Thus, patients placed on ECMO due to COVID-19 should continue to be closely monitored for vascular or hemorrhagic complications.

Incidence of bacterial infection was another common complication of ECMO in COVID-19 patients. Concomitant bacterial infection rate during ECMO was consistently high between first and second wave patients (50% and 62%, respectively) in our study. Additionally, sepsis was the most common cause of death in first wave patients (44%) and the second most common cause of death in second wave patients (33%) who died on ECMO. Since the majority of the patients received immunomodulation therapy as a part of the COVID-19 treatment, the control of the infection during ECMO may be the key to decrease the mortality rate of the ECMO for COVID-19. However, usage of

immunomodulation therapies in COVID-19 patients is controversial, and numerous metanalyses exploring the benefits of these therapies have been conducted.[27,28] Furthermore, previous papers have shown that prolonged administration of systemic steroids may impair wound healing, further complicating recovery for these patients.

Our study was primarily limited by sample size, with a total of 41 patients meeting the inclusion criteria and 13 patients undergoing ECMO cannulation during the second wave. Another limitation of our study was being based in only one hospital center. In spite of these limitations, this study draws an important comparison between first and second wave patients. Although there was not an improvement in mortality rate from the first wave to the second, ECMO still appears to be a useful supportive therapy for COVID-19-induced ARDS. Similar to the EOLIA trial, ECMO patients in this study often had few other options to provide oxygenation support.[29] Further research to revise inclusion and exclusion criteria, as well as continuing improvements with pre-ICU management, may be necessary.

Conclusion

Despite improvements in pre-ECMO treatment, second wave COVID-19 patients experienced a significantly higher ECMO mortality rate than first wave COVID-19 patients. There are many factors that affect ECMO outcomes. This study highlights one potential variable. The largest difference between first wave and second wave patients was the increased use of immunosuppression. Although immunosuppression could be associated with infection risk, the effects on overall healing needs to be considered as well. Control of infection is challenging for the patients with COVID-19 who are on immunomodulation therapy. More research to develop stricter inclusion/exclusion criteria and improve pre-ECMO management may be required to improve outcomes.

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