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COVID-19 outcomes of venovenous extracorporeal membrane oxygenation for acute respiratory failure vs historical cohort of non-COVID-19 viral infections

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Abstract

Introduction: Veno-venous extracorporeal membrane oxygenation (VV ECMO) has become a support modality for patients with acute respiratory failure refractory to standard therapies. VV ECMO has been increasingly used during the current COVID-19 pandemic for patients with refractory respiratory failure. The object of this study was to evaluate the outcomes of VV ECMO in patients with COVID-19 compared to patients with non-COVID-19 viral infections.

Methods: We retrospectively reviewed all patients supported with VV ECMO between 8/2014 and 8/2020 whose etiology of illness was a viral pulmonary infection. The primary outcome of this study was to evaluate in-hospital mortality. The secondary outcomes included length of ECMO course, ventilator duration, hospital length of stay, incidence of adverse events through ECMO course.

Results: Eighty-nine patients were included (35 COVID-19 vs 54 non-COVID-19). Forty (74%) of the non-COVID-19 patients had influenza virus. Prior to cannulation, COVID-19 patients had longer ventilator duration (3 vs 1 day, $p = .003$), higher $PaCO_2$ (64 vs 53 mmHg, $p = .012$), and white blood cell count (14 vs 9 $\times 10^3/\mu L$, $p = .004$). Overall in-hospital mortality was 33.7% ($n = 30$). COVID-19 patients had a higher mortality (49% vs. 24%, $p = .017$) when compared to non-COVID-19 patients. COVID-19 survivors had longer median time on ECMO than non-COVID-19 survivors (24.4 vs 16.5 days $p = .03$) but had a similar hospital length of stay (HLOS) (41 vs 48 Extracorporeal Membrane Oxygenationdays $p = .33$).

Conclusion: COVID-19 patients supported with VV ECMO have a higher mortality than non-COVID-19 patients. While COVID-19 survivors had significantly longer VV ECMO runs than non-COVID-19 survivors, HLOS was similar. This data add to a growing body of literature supporting the use of ECMO for potentially reversible causes of respiratory failure.

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extracorporeal membrane oxygenation, COVID-19, acute respiratory failure, acute respiratory distress syndrome, critical care, influenza, viral

Introduction

The 1918 Spanish influenza pandemic, claimed over 50 million lives worldwide.[1] Over the next 90 years, the treatments and approach for viral respiratory pandemics have evolved.[1] In 2009, the publication of the CESAR trial marked a resurgence in the use of veno-venous extracorporeal membrane oxygenation (VV ECMO), a support modality historically used in the pediatric population, in adults with respiratory failure.[2] The improvement in technology and increase in refractory respiratory failure during the 2009 Influenza H1N1 outbreak quickly brought VV ECMO to the forefront. Reports from Italy, Australia, and New Zealand showed a trend towards increased survival with VV ECMO support in patient with H1N1.[3,4] In 2013, Avian influenza A (H7N9) carried a mortality greater than 60% and during this pandemic, centers in China showed VV ECMO to be a feasible and important supportive modality in refractory respiratory failure.[5] Furthermore, in 2015, Middle East respiratory syndrome-related coronavirus (MERS-CoV) carried a mortality rate 34.4% and the use of VV ECMO showed significantly lower mortality when compared to conventional therapy.[6,7]

One hundred years after the Spanish flu, the virus known as SARS-CoV-2 was discovered to cause coronavirus disease 2019 (COVID-19).[8] By March 2020, this global pandemic extended from Asia through Europe to North America leading to a dramatic loss of human life worldwide compared to previous viral respiratory pandemics.[9] VV ECMO has shown a promising role in the treatment plan for these patients and may play a pivotal role in this pandemic.[10,11] There are many differences between COVID-19 and other viral illnesses including pathophysiology, clinical presentation, and management challenges during resource strained settings. Current literature is mixed in comparison of COVID-19 and non-COVID-19 viral illness supported with VV ECMO in regards to survival, pre-cannulation factors, and hospital course.[12–14]

The purpose of this study was to evaluate outcomes in patients with COVID-19 and non-COVID-19 viral illness supported with VV ECMO at a tertiary care high volume ECMO center. We hypothesize that COVID-19 patients supported with VV ECMO will have a higher mortality than patients with non-COVID-19 viral illnesses requiring VV ECMO support.

Materials and methods

Patient selection

The institutional review board (IRB) at University of Maryland, Baltimore approved the study (HP-00093048), which waived the need for consent. All patients admitted to the Lung Rescue Unit (LRU), a dedicated intensive care unit for patients on VV ECMO, and the Biocontainment Unit (BCU), a dedicated intensive care unit for patients with COVID-19 on VV ECMO, were identified from August 2014 to August 2020 and were included in the study. The cohort of COVID-19 patients that required VV ECMO were a part of the initial surge of patients in our institution in a resource strained setting during the beginning of the COVID-19 pandemic. All patients included in this study were stratified by indications for cannulation of COVID-19 or other respiratory viral illness (non-COVID-19), then further stratified by non-survivors and survivors. Pre-ECMO and ECMO-related were collected for all patients. Sequential Organ Failure Assessment (SOFA) and Respiratory ECMO Survival Prediction (RESP) scores were calculated to assess overall organ dysfunction and pre-ECMO severity of acute respiratory distress syndrome (ARDS). The study's primary endpoint was in-hospital mortality.

Clinical outcomes

The primary outcomes of this study was to evaluate in-hospital mortality. The secondary outcomes included pre-ECMO variables, length of ECMO course, ventilator duration, hospital length of stay, incidence of adverse events through ECMO course including pneumothorax, blood stream infections and acute renal failure requiring renal replacement therapy, and discharge data.

VV ECMO management

The decision to cannulate a patient for VV ECMO is made in a multi-disciplinary fashion by a small cohort of experienced physicians based on our institutional

criteria.[15] The institutional preferred cannulation strategy is a peripheral, two site cannulation with a femoral vein cannula for drainage and a separate internal jugular vein cannula for return of blood. No dual lumen catheters were used during the study period. Once cannulated for VV ECMO, a lung-protective ventilator strategy is implemented. Utilizing pressure control ventilation, total pressure is set to 20 = cm H2O with a positive end-expiratory pressure of 10 cm H_2O and respiratory rate of 10 = breaths per minute. Inspiratory and expiratory times are set at a 1:1 ratio. FiO_2 on the ventilator is decreased as tolerated to 30% to maintain a peripheral capillary oxygen saturation (SpO_2) of ≥ 88%. Gas flows to the VV ECMO circuit were fixed at a FiO_2 of 100%, and the ECMO flow rates (liters per minute) were titrated to achieve a SpO_2 of ≥ 88%. Sweep gas flow rates (in liters per minute) were titrated to maintain a partial pressure of carbon dioxide ($PaCO_2$) of 35–45 mmHg based on patient's arterial blood gas analysis. For patients with impaired right ventricular function diagnosed on formal echocardiography a lower $PaCO_2$ goal (35–40 mm Hg) was utilized to minimize right ventricular afterload. Our institutional practice is to utilize low dose epinephrine for inotropic support and inhaled prostacyclin in cases of right ventricular dysfunction.[16] Patients were transfused with packed red blood cells to maintain a hemoglobin goal of ≥ 7 mg/dL. Platelets were transfused for a count ≤ 40,000/μL or active bleeding.

There were two units that cared for the patients supported with VV ECMO over this study period. The LRU was a 6 bed unit that existed before the COVID-19 pandemic and cared for all non-COVID-19 VV ECMO patients. The BCU was a 16 bed unit behind a single airlock that was created in response to the COVID-19 pandemic and admitted up to 32 patients during the initial 3 months of the pandemic with double-bunking to face a large surge of critically-ill patients. Both units were staffed by a small, dedicated group of intensive care physicians and advanced practice providers.

Analysis

A descriptive analysis stratified by etiology of illness that required VV ECMO cannulation was performed. Continuous variables were reported as the median and interquartile range (IQR) and categorical variables were reported as the number and percentage of patients. Descriptive statistics were generated using mean (with standard deviation) for parametric data, median (with interquartile range) for nonparametric data, and counts with proportions for categorical data. Data were compared using chi-square or t-test for categorical and continuous variables, respectively, with 2-sided p-values < 0.05 considered statistically significant.

Results

Eighty-nine patients with median age of 47 years [IQR 38, 54] were included in this cohort (Table 1). Sixty-three (70%) patients were male and median body mass index (BMI) was 33 kg/m2 [IQR 27.5, 37.9]. Overall mortality for the entire cohort was 33.7% (n = 30).

Thirty-five (39%) patients were cannulated due to COVID-19 and fifty-four (61%) patients were cannulated due to non-COVID-19 viral respiratory infections (Table 1). Non-COVID-19 infections included influenza A and B (combined 76%), adenovirus, and metapneumovirus. COVID-19 patients were younger, had a lower incidence of coronary artery disease, hypertension, and chronic obstructive airway disease (COPD)/asthma. Prior to cannulation, COVID-19 patients had more days on the ventilator, higher white blood cell counts, higher $PaCO_2$, a lower serum bicarbonate level, and a lower serum creatinine. Two (6%) COVID-19 patients and seven (13%) non-COVID-19 patients were on renal replacement therapy (RRT) prior to cannulation (p = .27). Eight (23%) COVID-19 patients and 24 (44%) non-COVID-19 patients went on RRT after initiation of ECMO support (p = .04).

Forty-two (47%) patients had bacteremia during their hospital stay (Table 2). COVID-19 patients had a higher incidence of bacteremia than non-COVID-19 patients [35 (71%) vs 14 (26%), p < .001). In addition, 4 (7%) non-COVID-19 patients had fungemia during their hospital stay. More COVID-19 patients had a pneumothorax than non-COVID-19 patients [21 (60%) vs 15 (28%), p = .002]. COVID-19 patients developed pneumothoraces at a higher incidence both before and after cannulation for VV ECMO than non-COVID-19 patients (Figure 1).

COVID-19 patients had a higher mortality (49% vs. 24%, p = .017) compared to non-COVID-19 patients (Table 1). Of the entire cohort, 69% (61/89) were decannulated from VV ECMO. Non-COVID-19 patients had a higher rate of decannulation from VV ECMO [78% (42/54) vs 51% (18/35)]. Only one patient in the cohort was decannulated from VV ECMO then proceeded to die before hospital discharge. 61% (33/54) of non-COVID-19 viral patients compared to 37% (13/35) of COVID patients were liberated from ventilator support prior to hospital discharge or transfer. When further stratified by survival, COVID-19 survivors had longer median time on ECMO than non-COVID-19 survivors (585 vs 395 h p = .03) but had a similar hospital length of stay (41 vs 48 days p = .33).

Table 1. All viral and comparison of non-COVID-19 and COVID-19 demographics, pre-extracorporeal membrane oxygenation (ECMO), ECMO variables, and outcomes.

Patient characteristic	Median [IQR] or n (%)			*p*-value
	All (*n* = 89)	Non-COVID-19 (*n* = 54)	COVID-19	
Age	47 [38, 54]	50 [41.25, 56]	43 [37, 50]	.03
Sex - M	63 (71%)	33 (61%)	30 (86%)	.13
BMI (kg/m^2)	33 [27.5, 37.9]	33.2 [28.0, 37.2]	32.4 [26.9, 39.2]	.59
Coronary artery disease	5 (5.6%)	5 (9.3%)	0 (0%)	.024
Diabetes mellitus	20 (22.5%)	9 (16.7%)	11 (31.4%)	.10
Liver disease	2 (2.2%)	2 (3.7%)	0 (0%)	.16
Congestive heart failure	3 (3.4%)	3 (5.6%)	0 (0%)	.083
COPD/Asthma	19 (21.3%)	17 (31.5%)	2 (5.7%)	.004
Substance abuse	9 (10%)	8 (14.8%)	1 (4.6%)	.68
Hypertension	43 (48.3%)	31 (57.4%)	12 (34.3%)	.03
Ventilation days before ECMO	2 [1, 4]	1 [0.25, 3]	3 [1.5, 4.5]	.003
Creatinine (mg/dl) before ECMO	1.25 [0.79, 2.95]	1.7 [1.1, 3.5]	0.85 [0.67, 1.5]	<.001
Lactate before ECMO	2.2 [1.5, 3.4]	2.1 [1.4, 4.2]	2.2 [1.9, 2.9]	.45
WBC before ECMO	11.8 [7, 17]	8.8 [4.6, 14.8]	14.1 [9.7, 20.5]	.004
Bicarb before ECMO	25 [20, 29]	22 [19, 26]	28 [14, 31]	<.001
pH	7.24 [7.16, 7.32]	7.23 [7.15, 7.32]	7.28 [7.19, 7.32]	.25
P/F ratio	69 [56, 84]	67 [56, 84]	73 [57, 79]	.70
PaCO2 (mmHg)	55 [45, 66]	53 [43, 63]	64 [51, 78]	.01
PIP (cm H2O)	37 [33, 41]	36 [33, 40]	37 [33, 41]	.52
PEEP (cm H2O)	16 [14, 18]	16 [14, 18]	16 [14, 18]	.94
RESP Score	3 [2, 5]	3 [2, 5]	3 [2, 5]	0.53
SOFA Score	11 [9, 13]	11 [9.5, 14]	10 [7, 12]	.02
ECMO duration (hours)	537 [343, 849]	394 [280, 713]	654 [514, 1092]	.002
Hospital LOS (days)	45 [24, 58]	41 [22, 57]	48 [30, 59]	.33
CRRT	41 (46.1%)	31 (57%)	10 (29%)	<.001
MARS	1 (1.1%)	1 (2%)	0 (0%)	.32
Prone positioning	67 (75.3%)	39 (72%)	28 (80%)	.41
Steroids	62 (69.7%)	33 (61%)	29 (83%)	.03
In-hospital mortality	30 (33.7%)	13 (24%)	17 (49%)	.02

ECMO: Extracorporeal Membrane Oxygenation; n; number; IQR: Interquartile Range; M: Male; BMI: Body Mass Index; Cr: Creatinine; WBC: white blood cell count; P/F: ratio of arterial oxygen partial pressure to fractional inspired oxygen; PCO_2: Partial Pressure of Carbon Dioxide; PIP: Peak Inspiratory Pressure; PEEP: Positive End Expiratory Pressure; RESP: Respiratory ECMO Survival Prediction; SOFA: Sequential Organ Failure Assessment; LOS: Length of Stay; CRRT: Continuous Renal Replacement Therapy; MARS: Molecular Adsorbent Recirculating System.

Table 2. Number of Patients with Adverse events through extracorporeal membrane oxygenation Course.

Adverse events	Median [IQR] or n (%)			*p* value
	All (*n* = 89)	Non-COVID-19 (n = 54)	COVID-19 (*n* = 35)	
Bacteremia	39 (44%)	25 (71%)	14 (26%)	**<0.001**
Fungiemia	4 (4%)	0 (0%)	4 (7%)	0.15
Pneumothorax	36 (40%)	15 (28%)	21 (60%)	**0.002**
Oxygenator changes	41 (46%)	20 (57%)	21 (39%)	0.09

n: number; IQR: Interquartile Range

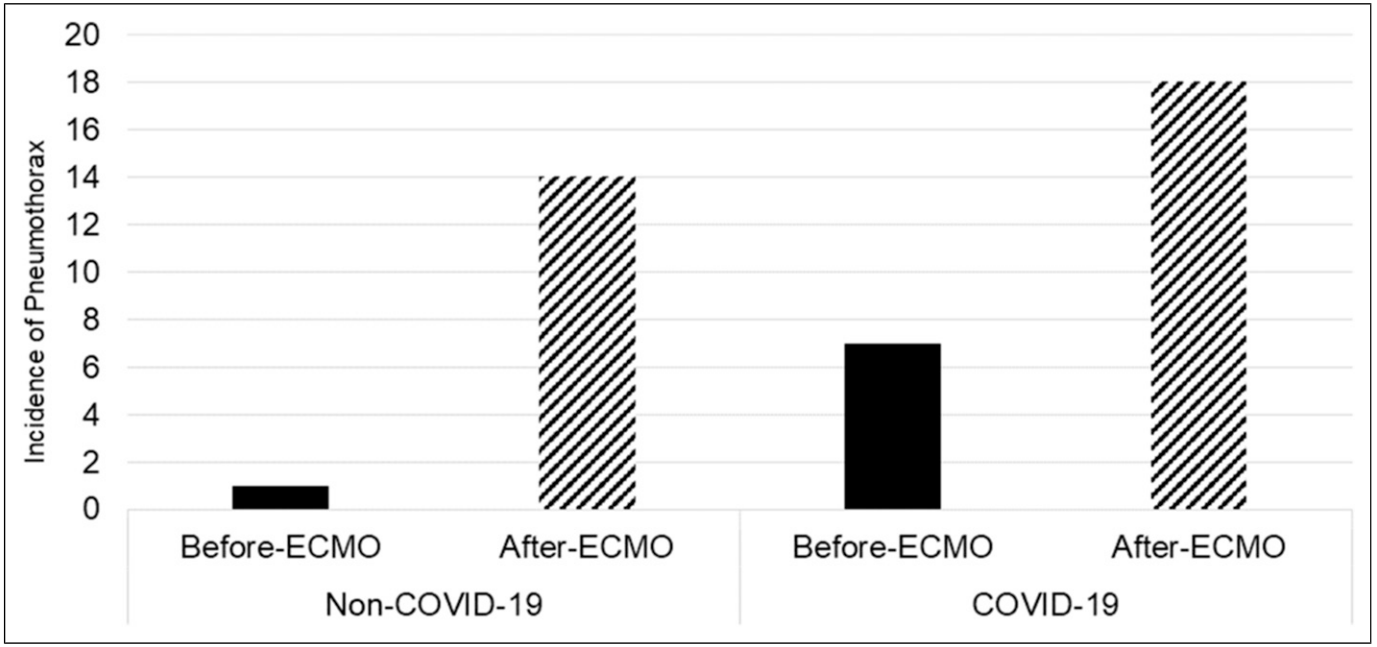

Figure 1. Incidence of pneumothorax. Legend: ECMO: Extracorporeal Membrane Oxygenation. Incidence of pneumothorax before ECMO: Non-COVID-19 (1) vs COVID-19 (7), $p = .003$. Incidence of pneumothorax after ECMO: Non-COVID-19 (14) vs COVID-19 (18), $p = .01$

Discussion

The use of VV ECMO in the adult population has increased since the publications of the CESAR trial and many reports of the role extracorporeal life support played during the 2009 H1N1 influenza pandemic.[2] Our institution has previously demonstrated a 15.4% mortality rate for patients supported with VV ECMO for severe influenza-related ARDS.[17] This is significantly lower when compared to those not supported with VV ECMO.[17] Despite success in previous respiratory pandemics, there is limited data comparing the role of VV ECMO in COVID-19 to other viral illnesses. In this study, we have demonstrated that COVID-19 patients supported with VV ECMO have a survival of 51%, which is comparable to the 49% survival reported in the Extracorporeal Life Support Organization registry.[18] We further explored the differences between COVID-19 and non-COVID-19 patients supported with VV ECMO. Our study showed that COVID-19 patients had a higher mortality than non-COVID-19 patients despite being younger, having a lower chronic disease burden and less organ failure at time of cannulation.

Survival for adult patients with severe respiratory failure secondary to viral pneumonia requiring ECMO is reported to be approximately 63%.[18] At our institution, a higher survival rate was observed for non-COVID-19 patients. Patient selection, regional disease patterns, selection criteria, and our dedicated unit to providing VV ECMO at a high volume center are all variables that may explain this lower mortality rate. However, our study also reported a lower survival rate in COVID-19 than non-COVID-19 viral illnesses, which is an inconsistent finding with current worldwide experience.[12,13]

Difference in mortality may be due to significantly longer time on the ventilator prior to VV ECMO cannulation in COVID-19. This is in contrast to other studies which showed longer time on the ventilator with COVID-19 patients with comparable survival to non-COVID-19 patients.[13] Time on the ventilator prior to cannulation has been shown to be inversely related to survival.[19] Our approach is in line with ELSO guidelines, which recommend greater than 7 days of ventilator time as a relative contraindication for cannulation for VV ECMO.[19–21] This inverse relationship between survival and ventilator time prior to cannulation has been attributed to ventilator induced lung injury (VILI) in traditional ARDS. With COVID-19, this may be more pronounced due to the proposed thromboinflammatory response in the pulmonary structures.[22] Our study data showed non-COVID-19 patients had less time on the ventilator prior to ECMO cannulation and had a higher survival rate. This suggests that less time on the ventilator prior to ECMO support may improve outcomes when comparing non-COVID-19 and COVID-19 patients. Future studies need a focused evaluation on the association with earlier cannulation and survival.

Pneumothorax has been an identified complication with mechanical ventilation and ARDS. It portends a poor prognosis and may have played a role in the difference in mortality between the two groups in our study.[23] COVID-19 patients may have a higher risk of pneumothorax due to inherent difference in disease process.[24] In our study, more COVID-19 patients had pneumothoraces than non-COVID-19 patients. Patients with COVID-19 also had increase rates of pneumothorax prior to cannulation as well as post-cannulation. Compared to previously reported experiences, our COVID-19 cohort had a higher rate of pneumothorax.[25–28] VILI and patient self-induced lung injury seen in COVID-19 patients due to extended time on the ventilator prior to cannulation may have led to this difference. This data further suggests reducing time on the ventilator prior to cannulation, as ECMO has been shown to decrease the rate of pneumothorax particular in high risk patients with ARDS.[29]

In our study, non-COVID-19 patients had a higher incidence of acute kidney injury and use of RRT both before and after cannulation for VV ECMO, which is similar to current literature.[12,14] As our institution limited VV ECMO support in COVID-19 patients with severe renal impairment or those already on renal replacement therapy, this may account for the difference in groups prior to cannulation. Limited literature on acute kidney injury and RRT for COVID-19 patients shows a trend towards poor outcomes.[30,31] Although there is a high rate of renal recovery for VV ECMO survivors, there is a well-established increase in mortality for VV ECMO patients who require simultaneous renal replacement.[32,33] Despite the high incidence of kidney injury and use of RRT in the non-COVID-19 population, mortality was still higher in the COVID-19 cohort.

Time on ECMO was longer for the COVID-19 group compared to the non-COVID-19 group, as well what is reported in other series of COVID-19 patients supported with VV ECMO.[34,35] One factor that may explain our longer ECMO times in COVID-19 survivors compared to non-COVID-19 survivors was the decision to extend no-sweep trials prior to decannulating COVID 19 patients. The non-COVID-19 patients had a 24 h no-sweep trial as a standard practice. However, COVID-19 patients had a 72 h no-sweep trial prior to decannulation due to concerns for emergent recannulation in an

airlock unit. As our approach was to decannulate prior to extubation, we had a shorter time on ECMO for COVID-19 compared to others that utilized a dual-lumen cannulation approach with an early extubation strategy.[36] The optimal strategy for early or delayed extubation or decannulation remains to be determined for patients with COVID-19 supported on VV ECMO.

The difference in mortality and patient demographics may have been due to the difference in the specific units and systematic criteria. The LRU had a small group of attending physicians and providers that specialized in the care of patients with VV ECMO. Each patient was in their own room with specific precautions and a dedicated nurse. The BCU was a single unit behind a single airlock that admitted up to 32 patients with double-bunking to face a large surge of critically-ill patients. Furthermore, due to resource allocation during the pandemic, providers, including physicians, advanced practitioners, nurses, respiratory therapists, ECMO specialists, were from varied backgrounds.

As an institution, VV ECMO selection criteria was stricter due to the reports of severity of ARDS associated with COVID-19.[9,37] In preparation for a surge of refractory respiratory failure with COVID-19 and suspected poor outcomes with traditional criteria, selection criteria was adjusted. Notable differences from previous non-COVID-19 VV ECMO criteria were age and BMI. Age has been previously noted to be an independent predictor of outcomes in VV ECMO.[38] The age cutoff was adjusted to 55 years due to the high mortality rate above this age group seen in other experiences with COVID-19.[39,40] Obesity itself has various reports on outcomes with patients supported on VV ECMO. Obesity has been cited as a risk factor for poor outcomes in critically ill patients and has raised technical concerns for vascular access from various institutions.[41,42] Yet Galvagno, et al., Kon, et al. and the PRESERVE study suggest that obesity itself should not routinely be considered a contraindication to VV ECMO support and may have a protective paradoxical improvement in outcomes.[43–45] However, the mortality associated with obesity in COVID-19 patients led us to use a BMI > 40 kg/m2 as a relative contraindication.[46,47] As a result of these changes in the institution's inclusion and exclusion criteria, there were differences between COVID-19 and non-COVID-19 patient's age, BMI, and comorbidities. Yet despite these differences, specifically in age which is universally accepted to be associated with outcomes, COVID-19 patients had higher rates of mortality. Though mortality for COVID-19 patients has improved over time, experience from post-pandemic influenza H1N1, shows populations are vulnerable and still at risk after the initial surge and ECMO implementation may continue to be needed in the future.[47]

Limitations

This study has several limitations. This was a single center study based on a retrospective chart review which may have missed key variables. Difference between the physical units, staffing models, and larger pool of providers working with COVID-19 patients may have been factors that were not individually analyzed. As different therapies emerge for COVID-19, it is possible that mortality may decrease, possibly approaching rates closer to those observed historically for severe viral pneumonias requiring VV ECMO. Furthermore, changes in patient selection criteria may have contributed to differences that were not examined.

Conclusion

In this single center study, COVID-19 patients supported with VV ECMO had a higher mortality when compared to patients with other viral illness. Although COVID-19 survivors had a significantly longer time on VV ECMO compared to non-COVID-19 survivors, both had similar HLOS. Future efforts to reduce mortality should focus on appropriate patient selection and optimization of care once on VV ECMO.

Declaration of conflicting interests

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