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Article

Outcomes of Obese Coronavirus 2019 Patients Treated with Extra Corporeal Membrane Oxygenation

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Abstract

Background: Veno-venous (VV) extracorporeal membrane oxygenation (ECMO) is used as salvage therapy in severe cases of acute respiratory distress syndrome (ARDS) caused by the coronavirus disease 2019 (COVID-19). Obesity has been linked to worse disease severity and poor outcomes in COVID-19, but there is also a hypothesized obesity survival paradox whereby obese patients fare better in severe illness than their non-obese complement. The effect of obesity on ECMO outcomes in patients with COVID-19 is not well understood. **Methods**: We performed a retrospective analysis of all patients admitted to our institution who underwent VV ECMO cannulation for COVID-19 in the span of one year. These were separated by body mass index (BMI) with a cutoff of 35 kg/m^2 (signifying class 2 obesity or higher) and compared with each other as well as a comparator group of patients with BMI >35 kg/m^2 who underwent VV ECMO cannulation for any cause between 2016 and 1 March 2021. Disease severity was categorized using established scoring systems including Apache-II, Charleson-Dayeo, and Murray. Primary endpoints were 30 day mortality, survival to decannulation, and survival to discharge. **Results**: The study groups were similar in all respects with the exception of BMI. Illness severity, as classified by Charleson-Dayeo, Apache II, and Murray scores not significantly different between groups. The primary outcomes (30-day mortality, survival to decannulation, and survival to discharge) were not significantly different between groups. There was a trend toward more delayed initiation of ECMO therapy in the obese group that was not statistically significant. There was also a trend toward shorter duration of ECMO therapy that did not reach the threshold for statistical significance. **Conclusions**: There was no significant difference in outcomes between obese and non-obese patients undergoing VV ECMO for COVID-19. Trends toward shorter duration of ECMO and shorter intensive care unit (ICU) and hospital length of stay could represent the "obesity survival paradox" that has been described. Given similar outcomes, obesity should not be a contraindication to ECMO therapy for COVID-19.

Keywords

COVID-19; coronavirus; extracorporeal membrane oxygenation; ECMO; obesit

Introduction

Extra corporeal membrane oxygenation (ECMO) is an effective supportive therapy for patients with acute respiratory distress syndrome (ARDS) that fail to improve with conventional management namely lung protective ventilation, sedation, paralysis, aggressive diuresis and proning. As ECMO is a labor intensive, expensive, and limited resource, triaging of patients based on comorbidities may be necessary. Our experiences placing COVID patients with a wide array of body mass indexes (BMIs) on ECMO lead us to examine the role of obesity (BMI >35) in outcomes of ECMO therapy. The patients that we serve are generally more obese than the average American population [1]. Our hypothesis was that obese patients undergoing VV ECMO therapy for COVID-19 would have similar outcomes as non-obese patients receiving VV ECMO therapy for COVID-19.

Even before the COVID-19 pandemic, researchers were interested in the best therapy for patients suffering from severe cases of ARDS. The conventional ventilatory support *vs*. extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) trial demonstrated ECMO to be an effective treatment for patients with ARDS [2]. The ECMO to Rescue Lung Injury in Severe ARDS trial (EOLIA) trial identified no significantly lower mortality rate in patients who underwent ECMO for ARDS than for patients who underwent conventional lung protective

ventilation with ECMO therapy as backup [3]. Since CESAR, various analyses including a post-hoc analysis of EOLIA data have suggested significant benefit to VV ECMO therapy [3]. Although early data demonstrated poor outcomes in COVID-19 infected patients, the clinical community used ECMO in COVID-19 for severe ARDS in the absence of other effective interventions. Since then multiple studies have shown improved survival and reduced mortality rate in this patient population [4,5]. Barbaro *et al*. [6] used data from the Extracorporeal Life Support Organization registry to describe the outcome for 1035 patients who received ECMO support for COVID-19 infection and describe a 90 day mortality rate of 37.4%, a rate similar to the 35% identified in the EOLIA trial. Similarly, Ramanathan *et al*. [7] performed a systematic review and meta-analysis of twenty two observational studies and reported a mortality rate of 37.1% for ECMO patients. Most of the current research suggests that VV ECMO is an accepted tool in management of COVID-19 patients with ARDS.

Early data noted that obese patients were at increased risk of both contracting the virus and experiencing poor outcomes. An early study, months after the virus was first described, reported that obese patients had a 3.4 fold increased risk in contracting a severe case of COVID (determined by presence of tachypnea, hypoxia, blood gas abnormalities, or respiratory or other organ failure) [8]. Conversely, research has indicated that there may be an obesity survival paradox associated with ECMO therapy in ARDS related to causes other than COVID-19 [1]. Multiple studies examining obesity related ECMO mortality in other conditions demonstrated no BMI associated differences [9–12]. Our project aimed to investigate that impact of obesity on outcomes in patients undergoing VV ECMO therapy for COVID-19. To our knowledge, it is the first study to compare obese and non-obese COVID-19 patients as well as obese patients on VV ECMO therapy for another cause to compare their outcomes.

Materials and Methods

Patient Population

This is a retrospective cohort study of all patients admitted to the University of Iowa Hospitals and Clinics who underwent cannulation for VV ECMO secondary to COVID-19 between 1 March 2020 and 1 March 2021 as well as patients with BMI >35 who underwent VV ECMO cannulation secondary to any cause between 1 January 2016 and 1 March 2021. 30 patients met the criteria for inclusion. COVID-19 was diagnosed by nasopharyngeal swab polymerase chain reaction assay. Data regarding patient demographics and hospital courses were collected from medical record review. Patients were divided into two groups based on BMI at the time of admission to the hospital. A BMI cutoff of 35 kg/m^2 was used to separate the two groups.

Inclusion criteria were any patients who underwent VV ECMO cannulation for COVID-19 between 1 March 2020 and 1 March 2021. Any patients with BMI >35 who underwent VV ECMO cannulation between 1 January 2016 and 1 March 2021 were also included. Patients who underwent venoarterial (VA) ECMO cannulation or at any time had an arterial limb of their ECMO circuit were excluded from the study. Patients who arrived at the author institution already on ECMO support were excluded from the study.

Patients were identified from an institutional registry of patients who were cannulated for ECMO. Patient information was obtained from chart review utilizing nursing flowsheets, daily progress notes, discharge summaries, and logged clinical data. These data included cannulation site, height, weight, length of stay data, *etc*. Complications were noted from daily notes, discharge summaries and follow up clinic appointments. Patients were not lost to follow up as survival to discharge was the longest follow up period measured.

Patient Management

Patients on ECMO were managed consistent with the management described by Kon *et al*. [13]. Patients were maintained on volume control settings on the ventilator with peak inspiratory pressures (PIP) of less than 35–40 mmHg, positive end expiratory pressures (PEEP) of 10–14 mmHg, respiratory rate of 16 breaths/min or less, and fraction of inspired oxygen (FIO_2) of 0.40 or less. These settings were maintained even in the face of ongoing hypoxia, which was tolerated if there was no evidence of end organ injury. The ECMO circuit flow was titrated to oxygenation needs but did not excess certain thresholds of revolutions per minute to reduce risk of hemolysis. For cases where persistent hypoxia was unable to be corrected by circuit flow, red blood cell transfusion thresholds were modified to achieve adequate tissue perfusion. Conversely, flow was maintained at 3 liters per minute or above to reduce risk of oxygenator thrombus formation. Oxygenator FiO_2 was maintained at 1.0 for the entirety of ECMO support. Partial pressure of CO_2 ($PaCO_2$) management was controlled by varying the sweep gas flow rate in the ECMO circuit with a goal $PaCO_2$ of less than 45 mmHg, and mechanical ventilation was not altered. When the sweep gas flow rate was less than 0.5 liters per minut, the gas flow was disconnected for two hours and a repeat arterial blood gas was obtained. If $PaCO_2$ remained less than 45 mmHg with a PaO_2/FiO_2 (P/F) ratio exceeding 200 on two sequential clamp trials greater than 24 hours apart, were considered appropriate for ECMO decannulation. This was performed at bedside in all cases.

Table 1. Patient Demographics. *significant against reference group: Obese with COVID ($p < 0.05$).

Variable	Non-Obese with COVID	*p*-value (relative to reference group)	Obese with COVID (reference group)	Obese without COVID	*p*-value (relative to reference group)
Total (N = 30)	N = 9		N = 8	N = 13	
Age (years)	42.3 ± 11.9	0.18	50.3 ± 9.4	46.5 ± 14.2	0.54
Gender (male)	5	0.20	2	5	0.53
Cannulation					
Femoral-femoral	4		5	0	
Femoral-RIJ	0		1	0	
Avalon (RIJ dual lumen)	3		2	13	
Fem-Fem converted to Avalon	2		0	0	
Height (cm)	171.0 ± 12.3	0.29	165.4 ± 6.1	169.9 ± 10.9	0.33
Weight (kg)	87.8 ± 19.2	<0.01	130.0 ± 27.9	138.8 ± 34.5	0.57
BMI (kg/m^2)	29.7 ± 3.1	<0.01	47.9 ± 9.6	48.7 ± 6.0	0.83
BMI range	24.0–32.2		37.3–64.0	35.2–96.3	
BSA	2.04 ± 0.27	0.04	2.35 ± 0.27	2.53 ± 0.29	0.19
Concurrent pneumonia	9 (100%)		8 (100%)	8 (62%)	
Race					
White	5	0.60	6	10	0.93
African American	3		1	2	
Hispanic	1		1	1	
Preexisting comorbidities					
CAD	0		3	4	
COPD	0		1	3	
Other lung disease	1		4	4	
DMII	2		3	2	
On dialysis preoperatively	0		0	0	
Creatinine (mg/dL)	0.99 ± 0.52	0.27	1.50 ± 1.10	1.46 ± 0.81	0.93
Apache II Score	23.1 ± 5.2	0.26	27.0 ± 7.5	26.1 ± 8.6	0.83
Charleson-Dayeo Score	0.55 ± 0.83	0.32	1.25 ± 1.27	2.08 ± 2.02	0.27
*Mechanical ventilation (days)	0.89 ± 1.52	<0.01	4.13 ± 2.57	2.46 ± 18.8	0.36
Murray Score	3.60 ± 0.34	0.13	3.90 ± 0.09	3.67 ± 0.23	0.06
**RESP Score	4.00 ± 1.90	0.66	3.50 ± 2.40	2.46 ± 3.37	0.48

BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DMII, type 2 diabetes mellitus; RIJ, right internal jugular vein. *Days of mechanical ventilation prior to initiation of ECMO. ECMO-Extracorporeal membranous oxygenation. **RESP, Respiratory ECMO Survival Prediction.

Table 2. Outcomes.

Variable	Non-Obese with COVID	*p*-value (relative to reference group)	Obese with COVID (reference group)	Obese without COVID	*p*-value (relative to reference group)
Total (N = 30)	N = 9		N = 8	N = 13	
ICU LOS (days)	29.5 ± 25.4	0.49	22.1 ± 11.8	20.5 ± 15.2	0.81
Hospital LOS (days)	42.4 ± 29.6	0.16	24.5 ± 13.6	26.8 ± 23.6	0.81
Duration ECMO (days)	17.9 ± 10.6	0.49	14.25 ± 10.6	12.6 ± 11.1	0.74
Major Bleeding	3		3	4	0.39
Major Thrombosis	1		1	1	
Hospital or 30 day mortality	3	0.49	4	4	0.89
Tracheostomy	5	0.81	4	6	0.86
Palliative Decannulation	3		3	2	
Survival to Decannulation	8	0.93	7	11	0.85
Survival to Discharge*	6	0.49	4	9	0.38

ICU, intensive care unit; LOS, length of stay; ECMO, extracorporeal membranous oxygenation. *One patient was discharged on VV Ecmo and transported to another facility for lung transplant.

Statistical Analysis

Primary outcomes were selected as 30 day mortality (including in hospital mortality), survival to decannulation and survival to discharge. Secondary outcomes included duration of support and complications (major bleeding or thrombosis and need for tracheostomy). Statistical significance was determined using group "Obese with COVID" as reference. For continuous data such as BMI, a two tailed *t*-test was performed assuming equal variance between groups. Significance was measured at significance level $p < 0.05$. For discrete data such as survival, a chi-squared test for categorical data was performed. Significance was measured at significance level $p < 0.05$.

This retrospective review was approved by the Iniversity of Iowa IRB 202201535.

Results

Patient demographics are compared in Table 1 between the three study groups: Obese with COVID as the reference group, non-obese with COVID and Obese without COVID. The obese with COVID group was used as reference group to which both other groups were compared. In terms of gender, age, height, the groups are similar. The non obese group was substantially lower in BMI than either of the other two groups. No significant difference existed in terms of comorbidities although a non statistically significant trend toward lower coronary artery disease and lower creatinine in the non-obese group. In terms of overall severity of disease as measured by Apache II or Charleson-Dayeo score, all groups were similar. Acute respiratory characteristics as determined by Murray score (consolidation on chest xray (CXR), PaO_2/FiO_2 ratio, positive end expiratory pressure (PEEP), and pulmonary compliance) are not different between groups. APACHE II, Charleson-Dayeo, and Murray scores were calculated using MDCalc, an online calculator. However, initiation of ECMO was more rapid in the non-obese group.

Primary outcomes were statistically similar across groups. As shown in Table 2, there were no significant differences between groups with respect to mortality or survival to decannulation/discharge. There were also no statistically significant differences in the secondary outcomes. There was a trend toward shortened hospital and intensive care unit (ICU) length of stay in the obese cohort that did not reach the level of statistical significance.

Discussion

We reviewed our experience in ECMO patients with both COVID and BMI >35 kg/m^2. We have a greater than average rate of obesity in our state. Overall, other than BMI, the COVID groups were similar: however, we were trending toward slower initiation of ECMO in the obese group. Although we do not have a definitive explanation for delay in initiation in ECMO, we have noted greater technical difficulties in proning obese patients which may delay initiation. Conversely, duration of ECMO support, as well as hospital and ICU length of stay (LOS) trended towards being shorter in both the obese groups relative to the non-obese group. As for the shorter duration of support, previous research has suggested that there may be an obesity survival paradox associated with ECMO therapy in ARDS [9,10]. Despite previous recommendations that morbid obesity be considered a relative contraindication to ECMO therapy, recent studies have indicated that there are no statistically significant differences in a variety of outcome markers between obese and non-obese patients [9,11,12,14]. The results of this study similarly suggest that there were no statistically significant differences between study groups.

Since emerging on the world stage in December 2019, the coronavirus disease 2019 (COVID-19) spread quickly, being declared a pandemic by the World Health Organization (WHO) in March of 2020. By August 2021, the WHO confirmed about 200 million cases and 4.25 million deaths of COVID-19 worldwide. Patients suffering from severe cases of COVID-19 exhibited ARDS that required intensive respiratory support. Similarly, obesity is a rapidly increasing in prevalence in the world. In select countries, the prevalence may be greater than 60% [15].

Overall, the interaction between obesity and COVID is complex but generally the data suggests worse outcome in obese patients infected with COVID. Pooled data from 35 studies showed a 48% increase to mortality in obese COVID-19 patients as compared to non-obese patients [15]. Du *et al*. [16] performed a meta-analysis and found that patients with a BMI $\geq$30 had a 2.35 fold increased risk for critical COVID-19 infection and a 2.68 fold increased risk for COVID-19 mortality. They describe a linear relationship between BMI and outcomes reporting a mortality risk increase of 6% for every 1 kg/m^2 of BMI over 30 kg/m^2 [16]. M. Nassar's [17] systematic review of COVID-19 also reported increased risk of contracting the virus and increased risk of mortality in obese patients. In total, the weight of the evidence suggests that patients with obesity are at increased risk of contracting COVID-19 as well as developing a severe case leading to hospitalization, ICU admission, or even death. An early finding, that COVID-19 utilizes the angiotensin converting enzyme II (ACE2) receptor as a cellular entry point, provided a possible explanation as adipose tissue has a higher rate of ACE2 receptor expression than even lung tissue [18]. Therefore, adipose tissue in overweight and obese patients may provide an entry point or reservoir for the virus [19,20]. Additional factors may include the chronic inflammatory state of obesity and the suppression of innate immunity as well as the effects of obesity on respiratory mechanics [20].

The prevalence of overweight or obese people in many countries around the world is now greater than 60% [15]. Despite the increased risk associated with COVID-19 and obesity previously discussed, research has indicated that there may be an obesity survival paradox associated with ECMO therapy in ARDS related to causes other than COVID-19 [1]. Multiple studies examining obesity related ECMO mortality in other conditions demonstrated no BMI associated differences [9–12]. Conversely, Kon *et al*. [9] even found that the cohort of super obese (BMI >50 kg/m^2) patients in their study had a 100% survival rate. Similarly, Galvagno *et al*. [11] found that survival rates were highest among their cohort of patients with class III obesity (BMI $\geq$40 kg/m^2). A recent meta-analysis concluded that obesity is not a contraindication to ECMO and not associated with survival differences in patients with ARDS from other causes [14].

Despite the fact that obesity is associated with an increased risk for several diseases including cardiovascular disease and type II diabetes mellitus, a phenomenon has been hypothesized whereby obese patients have a survival advantage over a non-obese cohort with the same disease such as pneumonia. Nie *et al*. [21] examined this phenomenon in obese patients with pneumonia and found that, although they were at higher risk for developing pneumonia, there was a suggested protective effect inobese patients. Multiple other studies have reported similar trends: that obesity appears to be protective of mortality in ARDS despite the fact that it is often a risk factor for developing ARDS [22,23]. Schetz *et al*. [24] found that obesity is associated with morbidity from ARDS, however, it was still associated with lower mortality rates.

Unfortunately, Covid has had a significant epidemic effect in the United States with over million deaths [25]. Obesity is also described afflicting 31.9% of Americans and is a risk factor for pulmonary disease so it is not surprising it is a risk factor for COVID infection [1].

In summary, the primary outcomes are similar between all groups. We included both obese and non-obese COVID-19 patients as well as obese COVID-19 patients to compare groups with one change in variable in order to determine if COVID-19 or obesity significantly impacted outcomes in our recent ECMO experience. To that end, no survival differences exist within our study. However, the ICU and hospital LOS tended to be shorter in the obese groups irrespective of why they needed ECMO therapy. Given that this is a retrospective review of our recent ECMO experiences only limited conclusions can be drawn from our data set. Similarly, the population size (N = 30) also allows only limited conclusions to be drawn. Due to the small sample size it was not feasible to further stratify patients by BMI to evaluate any dose-dependent effect of BMI on outcomes.

Conclusions

ECMO may be a useful treatment modality in obese patients with COVID and may have outcomes similar to non-obese patients. Therefore, obesity should not be a contraindication to using this therapy.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available as they were generated manually from the electronic medical record but are available from the corresponding author on reasonable request.

Author Contributions

KPW contributed to the design and drafting of this work as well as the interpretation of data. MHH contributed to the drafting of this work as well as interpretation of data. LA revised critically for important intellectual content and contributed to drafting of this work. CAR revised critically for important intellectual content and contributed to drafting of this work. MK analyzed the data. ALP, MAB, ASN and AKS contributed in collecting data and revising critically. AKS contributed to the design and drafting of the work as well as the interpretation of data and revised critically. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This was a retrospective review approved by the University of Iowa Instituitional Review Board: IRB 202201535. Patients did not need to sign the consent form.

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Conflict of Interest

The authors declare no conflict of interest.

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