The Use of Extracorporeal Membrane Oxygenation in COVID-19 Patients with Severe Cardiorespiratory Failure: The Influence of Obesity on Outcomes

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Abstract: Extracorporeal membrane oxygenation (ECMO) in the management of severely ill patients with COVID-19 has been reported in more than 5,827 cases worldwide according to the Extracorporeal Life Support Organization (ELSO). Several pre-existing conditions have been linked to an increase in COVID-19 mortality risk including obesity. The purpose of this research is to review the clinical experience from a cohort of 342 COVID-19 patients treated with ECMO in which 61.7% (211/342) are confirmed obese. Following institutional review board approval, we reviewed all 342 COVID-19 patients supported with ECMO between March 17, 2020 and March 18, 2021, at 40 American institutions from a multi-institutional database. Descriptive statistics comparing survivors to non-survivors were calculated using chi-square, Welch's ANOVA, and Kruskal-Wallis rank sum test as appropriate. Multivariable logistic regression was used to estimate the effect of body mass index (BMI) on the odds of survival while adjusting for age, gender, chronic renal failure, diabetes, asthma, hypertension, and pre-ECMO P/F ratio. Descriptive analysis showed that obese patients were more likely to be hypertensive (58.1% vs. 32%, $p < .001$), diabetic (42% vs. 30%, $p < .05$), and female (35% vs. 21%, $p < .05$), and had longer median days from intubation to cannulation (4.0 vs. 2.0, $p < .05$). Obese patients appeared to also have a slightly lower median age (47.9 vs. 50.5, $p = .07$), higher incidence of asthma (17.8% vs. 10.2%, $p = .09$), and a slightly lower pre-ECMO PaO_2/FiO_2 ratio (67.5 vs. 77.5, $p = .08$) though these differences were slightly less statistically reliable. Results from the logistic regression model suggest no statistically reliable association between BMI and odds of survival. Age had a moderately large and statistically reliable negative association with survival; the relative odds of survival for a 59-year-old patient were approximately half those of a 41-year-old patient (OR = .53, 95% CI: .36–.77, $p < .001$). Obesity does not seem to be a major risk factor for poor outcomes in COVID-19 patients supported with ECMO; however, age was moderately negatively associated with survival. The potential influence of other comorbidities on odds of survival among these patients warrant further investigation.
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The role of extracorporeal membrane oxygenation (ECMO) in the management of severely ill patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (COVID-19) continues to evolve (1). Several pre-existing conditions have been linked to an increase in COVID-19 mortality risk including obesity. The prevalence of obesity has been increasing among adults in the United States according to data from the National Health and Nutrition Examination Survey 2017–2018, which revealed that obesity occurs in 42.4% of Americans (2). Body mass index (BMI) is a measure of body fat based on height and weight that applies to adult men and women. BMI categories include underweight <18.5, normal weight = 18.5–24.9, overweight = 25–29.9, obesity >30, and severe obesity >40 kg/m^2. A BMI >40 kg/m^2 is also referred to as morbid obesity (3). Obesity is of particular importance because increased weight is also associated with the development of acute

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respiratory distress syndrome (ARDS), especially in patients with severe obesity (BMI $>40\,kg/m^2$) (4). Both obesity and ARDS appear to have alterations in inflammation, endothelial dysfunction, and oxidative stress, which increase the risk for respiratory failure (5). Obese patients are often also at risk for chronic hypoventilation, obstructive sleep apnea, pulmonary hypertension, and right ventricular dysfunction—all characteristics that predispose them to challenges with the management both acute and chronic respiratory illness (6). Obesity results in changes in respiratory anatomy and physiology; and when ARDS develops, obese patients have a wider sternum to vertebrae and a shorter apex to base lung area due to the greater mass of adipose tissue compressing the chest wall (7). This anatomy causes stiffening of the respiratory system resulting in pulmonary restriction. Respiratory compliance has been shown to decrease by more than two-thirds in obese compared to nonobese persons (7). The purpose of this research is to review whether obesity plays a significant role in outcomes in COVID-19 patients supported with ECMO.

METHODS

Following Institutional Review Board Approval,[1] a multi-institutional database was used to review all 342 patients with COVID-19 who were supported with ECMO at 40 institutions between March 17, 2020, and March 18, 2021. The database was extracted from the SpecialtyCare[2] Operative Procedural rEgistry (SCOPE™; https://specialtycareus.com/) (8). This manuscript describes the ECMO experience treating a subset of these patients with COVID-19. Data captured included patient characteristics, pre-COVID-19 risk factors and comorbidities, confirmation of COVID-19 diagnosis, features of ECMO support, specific medications used in an attempt to treat COVID-19, and short-term outcomes through hospital discharge.Survival was defined as being alive in the post-ECMO time period at last follow-up and up to discharge. Patients with BMI over 30 according to the patient medical records were coded as obese, and for 224 of 342 (65%) the BMI was recorded as well.

Statistical Analysis

Descriptive analysis was performed on the entire cohort of 342 patients according to obesity status (Table 1) and survival (Table 2), using chi square, Welch's ANOVA, and the Kruskal-Wallis rank sum test as appropriate. To assess the possible role of BMI in ECMO survival, we estimated a multivariable logistic regression model controlling for age, gender, chronic renal failure, diabetes, asthma, hypertension, and pre-ECMO PaO2/FiO2 (P/F) ratio. Additional covariates were available (as can be seen in Tables 1 and 2); however, we limited our model to a total of eight effects in accordance with current statistical guidelines to minimize the possibility of over-fitting, which can lead to biased model results. While every effort was made to collect complete data related to all pertinent aspects of health history, demographics, and treatment, some variables had missing data. The number of cases contributing complete data for each variable is given in Tables 1 and 2. To minimize bias and error associated with missing data, we used the multiple imputation strategy outlined by Harrell (9) to create 20 imputed data sets. Regression analysis was completed on all 20 imputed data sets and results pooled according to Rubin's rules (10). All statistical analysis was completed within the R statistical computing environment, together with the packages "compareGroups" and "rms" (11).

RESULTS

Descriptive analysis by obesity status (Table 1) showed that obese patients were more likely to be hypertensive (57.6% vs. 31.7%, $p < .001$), diabetic (42.3% vs. 29.9%, $p < .05$), and female (34.6% vs. 20.9%, $p < .05$), and had longer median days from intubation to cannulation (4.0 vs. 2.0, $p < .05$). Obese patients appeared to also have a slightly lower median age (48 vs. 51, $p = .07$), higher incidence of asthma (18% vs. 10%, $p = .09$), and a slightly lower pre-ECMO PaO_2/FiO_2 ratio (67.5 vs. 77.5, $p = .08$), though these differences were slightly less statistically reliable.

Descriptive analysis by survival (Table 2) showed that survivors had fewer median days between COVID diagnosis and the start of mechanical ventilation (5.0 vs. 10.0, $p < .001$), lower median age (47.0 vs. 54.0, $p < .001$), and a lower pre-ECMO P/F ratio (65.9 vs. 74.3, $p < .05$). Survivors also appeared to have fewer median days on EMCO (14.0 vs. 20.5, $p = .056$), and may have been less likely to have diabetes (31.6% vs. 41.6%, $p = .083$).

Results from our logistic regression model suggest no statistically reliable association between BMI and odds of survival. Age had a moderately large and statistically reliable negative association with survival; the relative odds of survival for a 59-year-old patient were approximately

[1]Protocol #012017, ADVARRA Center for IRB Intelligence, 6940 Columbia Gateway Drive, Suite 110, Columbia, Maryland, USA.

[2]SpecialtyCare is a United States provider of Allied Health services, and the SCOPE Registry contains data from over 1 million perfusion procedures in over 40 states at more than 300 hospitals. https://specialtycareus.com/.

Table 1. Descriptive statistics by obesity.

	ALL N = 340*	Non-Obese N = 129	Obese N = 211	p-value	N
Days from COVID diagnosis to intubation, mean (SD)	8.79 (7.13)	9.36 (6.48)	8.45 (7.49)	.373	193
Days from COVID diagnosis to intubation, median [25th; 75th]	9.00 [2.00; 13.0]	10.0 [3.75; 14.2]	7.00 [2.00; 13.0]	.135	193
Days from intubation to cannulation, mean (SD)	4.57 (4.42)	4.04 (4.73)	4.91 (4.20)	.189	199
Days from intubation to cannulation, median [25th; 75th]	4.00 [1.00; 7.00]	2.00 [1.00; 6.00]	4.00 [1.00; 7.00]	.038	199
Days from COVID diagnosis to cannulation, mean (SD)	4,607 (57,839)	12.3 (10.3)	7,391 (73,229)	.158	318
Days from COVID diagnosis to cannulation, median [25th; 75th]	12.0 [6.00; 17.0]	11.0 [6.00; 17.2]	12.0 [6.00; 17.0]	.847	318
Days on ECMO, mean (SD)	22.0 (17.9)	23.4 (18.7)	21.2 (17.4)	.267	339
Days on ECMO, median [25th; 75th]	18.0 [9.00; 29.0]	19.0 [9.75; 32.2]	17.0 [9.00; 28.0]	.288	339
Hours on ECMO, mean (SD)	517 (430)	552 (449)	496 (417)	.251	339
Hours on ECMO, median [25th; 75th]	409 [216; 678]	445 [220; 763]	397 [214; 651]	.275	339
Age, mean (SD)	48.9 (12.1)	50.5 (12.5)	47.9 (11.8)	.062	340
Age, median [25th; 75th]	50.0 [41.0; 59.0]	51.0 [43.0; 59.0]	48.0 [39.0; 57.0]	.065	340
Gender, N (%):				.01	340
Female	100 (29.4%)	27 (20.9%)	73 (34.6%)		
Male	240 (70.6%)	102 (79.1%)	138 (65.4%)		
Asthma, N (%):				.085	335
No	285 (85.1%)	114 (89.8%)	171 (82.2%)		
Yes	50 (14.9%)	13 (10.2%)	37 (17.8%)		
Cancer, N (%):				.307	336
No	327 (97.3%)	122 (96.1%)	205 (98.1%)		
Yes	9 (2.68%)	5 (3.94%)	4 (1.91%)		
Chronic Renal Failure, N (%):				1	331
No	303 (91.5%)	116 (91.3%)	187 (91.7%)		
Yes	28 (8.46%)	11 (8.66%)	17 (8.33%)		
Diabetes, N (%):				.031	335
No	209 (62.4%)	89 (70.1%)	120 (57.7%)		
Yes	126 (37.6%)	38 (29.9%)	88 (42.3%)		
Heart Disease, N (%):				.676	335
No	299 (89.3%)	115 (90.6%)	184 (88.5%)		
Yes	36 (10.7%)	12 (9.45%)	24 (11.5%)		
Hypertension, N (%):				<.001	336
No	175 (52.1%)	86 (68.3%)	89 (42.4%)		
Yes	161 (47.9%)	40 (31.7%)	121 (57.6%)		
One or more comorbid conditions (excl. obesity), mean (SD)	0.66 (0.48)	0.56 (0.50)	0.72 (0.45)	.006	330
Proned before ECMO, N (%):				1	334
No	109 (32.6%)	41 (32.3%)	68 (32.9%)		
Yes	225 (67.4%)	86 (67.7%)	139 (67.1%)		
P/F ratio pre-ECMO, mean (SD)	71.2 (33.6)	77.5 (46.6)	67.5 (22.4)	.08	210
ECMO type, N (%):				.49	328
VA	24 (7.32%)	11 (9.02%)	13 (6.31%)		
VV	304 (92.7%)	111 (91.0%)	193 (93.7%)		

VA, veno-arterial; VV, veno-venous.
*Two patients with missing data for BMI/Obesity are not included in this table.

half those of a 41-year-old patient (OR = .53, 95% CI: 0.36–0.77, $p < .001$) (Figure 1).

DISCUSSION

COVID-19, caused by SARS-CoV-2 virus, is characterized by pneumonia, lymphopenia, exhausted lymphocytes, and a cytokine storm. Both obesity and severe obesity are reported to be amongst the strongest risk factors for COVID-19 hospitalization and the need for mechanical ventilation (12). Obesity may affect the severity of COVID-19, with a direct correlation between increasing BMI and the proportion of patients with severe COVID-19. Associated comorbidities related to obesity are also correlated with increased COVID-19 mortality and morbidity, such as cardiovascular disease, hypertension, diabetes, respiratory disease, and cancers (13). Our observations showed in descriptive analysis by obesity status that obese patients were more likely to be hypertensive (57.6% vs. 31.7%, $p < .001$), diabetic (42.3% vs. 29.9%, $p < .05$), and female (34.6% vs. 20.9%, $p < .05$).

When ARDS is refractory to mechanical ventilation, the use of veno-venous ECMO is an option. However, for an obese patient with severe hypoxia, circuit flow indexed to either weight or body surface area can pose a significant challenge to obtaining sufficient indexed flow (14). In addition, given the access angle through a thick extremity, successful cannulation is technically

Table 2. Descriptive statistics by survival.

	ALL N = 342	Non-Survivors N = 209	Survivors N = 133	*p*-value	*N*
Days from COVID diagnosis to intubation, mean (SD)	8.81 (7.11)	10.3 (7.34)	6.68 (6.23)	<.001	194
Days from COVID diagnosis to intubation, median [25th; 75th]	9.00 [2.25; 13.0]	10.0 [4.00; 14.0]	5.00 [2.00; 10.0]	<.001	194
Days from intubation to cannulation, mean (SD)	4.57 (4.41)	4.86 (4.73)	4.15 (3.88)	.241	200
Days from intubation to cannulation, median [25th; 75th]	4.00 [1.00; 7.00]	4.00 [1.00; 7.00]	3.00 [1.00; 5.75]	.366	200
Days from COVID diagnosis to cannulation, mean (SD)	4,592 (57,749)	13.7 (9.72)	11,249 (90,253)	.158	319
Days from COVID diagnosis to cannulation, median [25th; 75th]	12.0 [6.00; 17.0]	13.0 [8.00; 19.0]	9.00 [5.00; 16.0]	.001	319
Days on ECMO, mean (SD)	22.0 (17.9)	23.4 (19.1)	19.8 (15.5)	.059	341
Days on ECMO, median [25th; 75th]	18.0 [9.00; 29.0]	20.5 [10.0; 29.0]	14.0 [9.00; 28.0]	.056	341
Hours on ECMO, mean (SD)	516 (429)	549 (460)	464 (372)	.063	341
Hours on ECMO, median [25th; 75th]	409 [216; 676]	477 [234; 680]	319 [204; 671]	.057	341
Age, mean (SD)	48.9 (12.1)	51.1 (11.7)	45.6 (12.0)	<.001	342
Age, median [25th; 75th]	50.0 [41.0; 59.0]	54.0 [44.0; 59.0]	47.0 [35.0; 55.0]	<.001	342
Gender, *N* (%):				.261	342
Female	100 (29.2%)	56 (26.8%)	44 (33.1%)		
Male	242 (70.8%)	153 (73.2%)	89 (66.9%)		
Asthma, N (%):				.672	335
No	285 (85.1%)	170 (84.2%)	115 (86.5%)		
Yes	50 (14.9%)	32 (15.8%)	18 (13.5%)		
Cancer, *N* (%):				1	336
No	327 (97.3%)	197 (97.0%)	130 (97.7%)		
Yes	9 (2.68%)	6 (2.96%)	3 (2.26%)		
Chronic Renal Failure, *N* (%):				1	331
No	303 (91.5%)	182 (91.5%)	121 (91.7%)		
Yes	28 (8.46%)	17 (8.54%)	11 (8.33%)		
Diabetes, *N* (%):				.083	335
No	209 (62.4%)	118 (58.4%)	91 (68.4%)		
Yes	126 (37.6%)	84 (41.6%)	42 (31.6%)		
Heart Disease, *N* (%):				.775	335
No	299 (89.3%)	179 (88.6%)	120 (90.2%)		
Yes	36 (10.7%)	23 (11.4%)	13 (9.77%)		
Hypertension, *N* (%):				.345	336
No	175 (52.1%)	101 (49.8%)	74 (55.6%)		
Yes	161 (47.9%)	102 (50.2%)	59 (44.4%)		
One or more comorbid conditions (excl. obesity), mean (SD)	.66 (.48)	.68 (.47)	.62 (.49)	.261	330
Proned before ECMO, *N* (%):				.77	335
No	109 (32.5%)	64 (31.7%)	45 (33.8%)		
Yes	226 (67.5%)	138 (68.3%)	88 (66.2%)		
P/F Ratio Pre-ECMO, Mean (SD)	71.2 (33.6)	74.3 (39.0)	65.9 (21.1)	.043	210
ECMO type, N (%):				.396	330
VA	24 (7.27%)	17 (8.50%)	7 (5.38%)		
VV	306 (92.7%)	183 (91.5%)	123 (94.6%)		

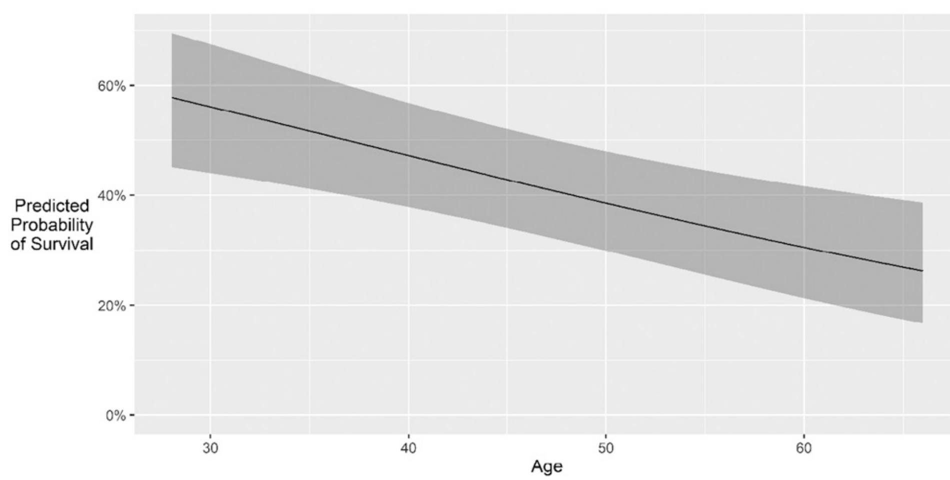

Figure 1. Predicted probability of survival by age.

difficult and kinking of the cannula is frequent (15). In 2009, as reported by Vaillant et al. obesity was not considered a risk factor in previous pandemics or seasonal influenza, but that there was an underlying disease in at least half of the fatal cases (16). During the novel influenza A (H1N1) virus pandemic, morbid obesity increased the hospitalization rate and was associated with higher rates of renal failure and altered inflammatory mediator profile (17). ECMO was studied in a propensity-matched analysis and overall survival did not differ between ECMO-treated patients and those managed conventionally (18).

Our descriptive analysis stratified by survival (Table 2) showed that survivors had fewer median days between COVID diagnosis and the start of mechanical ventilation (5.0 vs. 10.0, $p < .001$), lower median age (47.0 vs. 54.0, $p < .001$), and a lower pre-ECMO PaO_2/FiO_2 ratio (65.9 vs. 74.3, $p < .05$). Survivors also appeared to have fewer median days on ECMO (14.0 vs. 20.5, $p = .056$), and may have been less likely to have diabetes (32% vs. 42%, $p = .083$), though these differences were slightly less statistically reliable.

Visceral adiposity acts like an immune organ and causes low-grade chronic inflammation (19). When obesity is combined with hyper-inflammation (i.e., a "cytokine storm" phenomena as seen in COVID-19), increased morbidity may be unavoidable (20). In the recent "Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome" (EOLIA) study performed in patients with very severe ARDS, including obese patients (only patients with BMI $>45\,kg/m^2$ were excluded), 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy (21). However, 28% of the patients in the control group crossed over to ECMO for refractory hypoxemia. Based on these data, as well as data reported by others, ECMO support in patients with ARDS should not be withheld from the obese patient population (22). Our study included obese patients with BMI $>30\,kg/m^2$ and confirms these findings. Lee et al. in a small ($n = 60$) single-center trial reported that overweight status was associated with lower mortality in patients with acute myocardial infarction supported with ECMO. One theoretical explanation for these finding is that patients with high BMI have a greater metabolic reserve on which they can depend on in times of high metabolic demand such as illness (23). A consensus document from an international group of interdisciplinary ECMO providers released the ELSO COVID-19 interim guidelines suggesting that BMI >40 is a relative contraindication for ECMO (24). Results from our logistic regression model suggest no statistically reliable association between BMI and odds of survival; and therefore, our analysis supports offering ECMO to these challenging patients.

Others support the relative contraindication of advanced age and ECMO, which is more significant if frailty or other comorbidities are present (25). In our analysis, age had a moderately large and statistically reliable negative association with survival; the relative odds of survival for a 59-year-old patient were approximately half those of a 41-year-old patient (OR = .53, 95% CI: .36–.77, $p < .001$).

Limitations

The present study has limitations. This study was conducted using a national registry of data collected in a prospective, but nonrandomized manner. Registry data does not permit the investigation of certain factors that may be pertinent in determining effects not found with limited variable analysis. We created a subset database of COVID-19 patients who were supported with ECMO during the pandemic. Due to the heightened acuity of all health care workers during the time frame of the study, and increase work demands, it was not always possible to gain complete information on their treatment. The retrospective study design is subject to limitations of inherent selection bias, and the reported results are limited to describe observed associations between the implementation of the described protocol and the improved patient outcomes and do not demonstrate a direct cause-and-effect relationship. All results are limited to short-term outcomes until hospital discharge, and intermediate or long-term follow-up data were not available. And finally, there exists a potential for the miscoding of data, which despite steps for validation, must be considered in any secondary analysis of registry data.

CONCLUSIONS

Obesity does not seem to be a major risk factor for poor outcomes in the use of ECMO for patients with COVID-19; however, age was moderately negatively associated with survival. The potential influence of other comorbidities on odds of survival among patients with COVID-19 supported with ECMO warrant further investigation.

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