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| RESEARCH ARTICLE

Determining Extracorporeal Membrane Oxygenation Outcomes in Obese Patients with ARDS

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| ABSTRACT

Extracorporeal membrane oxygenation (ECMO) is crucial for managing acute respiratory distress syndrome (ARDS) refractory to conventional therapy, but its impact on obese ARDS patients remains inadequately understood due to relative contraindications per the Extracorporeal Life Support Organization (ELSO) guidelines. This study aimed to analyze the association between obesity and ECMO outcomes in ARDS patients. Using five years of National Inpatient Sample data (2016–2020), we identified ARDS patients through ICD-10 codes, classifying those with a BMI > 30 as obese. Univariate and multivariate analyses were performed to assess mortality, rates of left ventricular assist devices, and tracheostomy differences between obese and non-obese patients, with secondary outcomes examining the impact of obesity on length of stay (LOS) and total hospitalization charges (TOTCHG). Among 3,219 ARDS patients requiring ECMO, 8.2% were obese. While initial univariate analysis showed a non-significant 43% lower mortality odd in obese patients, adjusting for confounders revealed a statistically significant 46% lower odd of mortality compared to non-obese patients (adjusted odds ratio 0.54, 95% confidence interval 0.3-0.94, p 0.032). LOS and TOTCHG did not significantly differ between the two groups, nor did the rates of LVAD or tracheostomy. These findings suggest that obesity may confer a survival advantage in ARDS patients undergoing ECMO, potentially due to factors such as nutritional reserves and the obesity paradox observed in critical illnesses. Therefore, BMI alone should not preclude obese patients from ECMO treatment, emphasizing the need for further research to inform clinical decision-making in this population.

| KEYWORDS

Obesity; Extracorporeal Membrane Oxygenation; Acute Respiratory Distress Syndrome; Obesity Paradox.

| ARTICLE INFORMATION

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1. Introduction

Obesity, a global health pandemic, is linked to numerous chronic health conditions and has been associated with increased mortality and morbidity. According to the Centers for Disease Control and Prevention, obesity is defined as a body mass index (BMI) of 30.0 or above (May et al., 2013). It is associated with diseases such as hypertension, coronary artery disease, cerebrovascular disease, osteoarthritis, obstructive sleep apnea, and diabetes, among others (Abdelaal et al., 2017). Obesity significantly impacts cardiopulmonary physiology, leading to reductions in total lung capacity (TLC), functional residual capacity (FRC), and vital capacity (VC) due to increased abdominal pressure from obesity. Atelectasis is also seen, which contributes to compromised gas exchange and diminished lung compliance (Hibbert et al., 2012).

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With the numerous complications associated with obesity, one might anticipate that obese patients could suffer from severe complications and exhibit increased mortality. However, on the contrary, a phenomenon termed 'the obesity paradox', as evidenced by studies, explains that such patients demonstrate decreased mortality rates in specific scenarios (Habbu et al., 2006). This obesity paradox has been observed in various conditions like heart failure, acute respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, end-stage renal disease, and AIDS, among others (Horwich et al., 2007).

While the influence of obesity on the development of pneumonia remains unclear, there might be changes in the inflammatory response to pneumonia with ARDS in obese patients (Lazzeri et al., 2016). Recently, ECMO has been widely utilized in patients with severe ARDS who are unresponsive to mechanical ventilation or have failed conventional therapy (Fern et al., 2013). In severe ARDS, Extracorporeal Life Support (ECLS) sustains the exchange of oxygen and carbon dioxide, facilitating an optimal environment for restoring pulmonary function. In the past, obesity was recognized as an important risk factor for initiating ECMO, as per the ELSO guidelines (Hemmila et al., 2004). This was attributed to distinct challenges such as the presence of multiple comorbidities, difficulties in diagnosis and monitoring, and unique anatomical and physiological differences seen in obese patients. However, current literature suggests a correlation between obesity and improved outcomes in patients with a high BMI in contrast to those classified as underweight (Lazzeri et al., 2016; Tonna et al., 2021). The study aims to explore the plausible correlation between obesity and outcomes such as mortality rates, length of hospital stays, and total hospitalization charges in patients requiring ECMO for ARDS.

2. Literature Review:

Numerous theories have been put forward regarding the reluctance of providers and institutions to initiate ECMO support for obese patients. The challenges of initial cannulation in obese patients, supposedly limited by body habitus due to difficulty in identifying surface landmarks, have been extensively debated. However, studies have refuted these claims, finding no significant difference in outcomes, even among morbidly obese patients. It has been found that patient outcomes are more dependent on receiving appropriate support than being solely determined by anatomy (Keyser et al., 2018). Providers may hesitate to initiate ECMO in obese patients due to the presence of multiple comorbidities, such as heart disease, diabetes mellitus, and hyperlipidemia, which could potentially affect positive outcomes (Fruh et al., 2018). Obesity also results in impaired immunity, further aggravating inflammatory processes. Altered respiratory mechanics in obese patients, such as decreased compliance, ventilation-perfusion mismatch, and atelectasis, affect the ECMO's ability to provide adequate oxygenation and CO_2 removal. This can lead to hypoxemia and inadequate organ support (Spinelli et al., 2021).

Despite theories suggesting that obesity may be associated with poor prognostic outcomes in ARDS patients and is considered a relative contraindication for ECMO, evidence indicates otherwise (Reid et al., 2023). The inverse relationship between obesity and mortality could be explained by various mechanisms. One possible rationale for this paradox is that obese patients have overall lower cumulative drug dosing secondary to weight-based treatment and potential selection bias, leading to selection bias and improved outcomes. Also, a high BMI may help mitigate complications during the highly catabolic state experienced by critically ill patients and might offer survival advantages by providing adequate nutritional reserves in the form of adipose tissue (Oliveros et al., 2008). Additionally, sarcopenia has been proposed as a prognostic indicator for unfavorable outcomes in the nonobese patient population (Kizilarslanoglu et al., 2016). Another possible explanation involves the hormone Leptin, which acts as an anti-obesity factor and is elevated in obese patients, possibly due to resistance. Leptin is believed to play a crucial role in contributing to the adaptive response to critical illnesses such as sepsis or ARDS (Bornstein et al., 1998). Some animal studies have demonstrated that obesity appears to mitigate lipopolysaccharide (LPS)-induced lung injury and neutrophil chemotaxis despite an initially normal pulmonary cytokine response and elevated circulating neutrophil levels [Kordonowy et al.]. Additionally, it has been found that higher concentrations of total cholesterol may be beneficial in these patients, possibly due to the ability of lipoproteins to bind lipopolysaccharide, thus preventing its harmful effects (Rauchhaus et al., 2000). Obese patients undergoing ECMO may present with less severe lung parenchymal disease due to their restrictive pathophysiology secondary to abdominal compression and underlying atelectasis. (Ladosky et al., 2001; Peetermans et al., 2022).

3. Methodology

Our study utilized a retrospective cohort design to analyze the outcomes of adults hospitalized for ARDS in the United States from 2016 to 2020. We utilized data from the Nationwide Inpatient Sample (NIS) database, the largest publicly available database under the Healthcare Cost Utilization Project (HCUP). It represents 20% of random stratified inpatient hospitalizations and covers over 98% of the US population and around 1,000 hospitals during the same period. A discharge weight is employed for each discharge to estimate the overall inpatient hospitalizations. Hence, the ARDS patients requiring ECMO in this study are largely the estimate of total national inpatient patients in the United States meeting this criterion. NIS uses deidentified hospitalization details, demographics, and clinical data, including primary and secondary diagnoses. The NIS from 2016–2020 used in this study utilizes the International Classification of Diseases, 10th Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS).

Adult patients discharged with a diagnosis of ARDS and use of ECMO during the hospitalization were identified using ICD-10 CM/Procedure codes. These patients were subsequently divided into categories depending on whether they were diagnosed with obesity as a secondary diagnosis. Exclusion criteria comprised patients below 18 years of age or with elective admissions. A sub-group analysis was performed on morbidly obese patients (body mass index $\geq$40). Patient characteristics and comorbidities were recorded for all groups.

The primary outcome was to assess mortality rates and rates of LVAD (Left Ventricular Assist Device) placement or tracheostomy among nonobese, obese, and morbidly obese patients. Secondary outcomes, including length of stay and hospital charges, were evaluated to gauge healthcare utilization costs in the three groups. Statistical analyses were conducted using Stata® Version 18.0 BE software, with weighted samples employed for national estimates. The patient's comorbidities were obtained using Elixhauser's Co-Morbidity Index. Univariate analysis was used to assess potential confounders, and multivariate logistic and regression analysis was used to adjust for potential confounders. Alpha risk was set at 5%, and a p-value of 0.05 was considered statistically significant in multivariate analysis. The association between non-obese and obese subgroups was assessed using the Chi-squared test. The NIS database ensures patient anonymity by excluding patient identifiers since 2012, including state-level and hospital identifiers, in compliance with HIPAA regulations. Consequently, studies based on NIS data do not require approval from the institutional review board.

4. Results

The study comprised 3,219 weighted hospitalizations for ARDS patients necessitating ECMO, with 91.77% being non-obese and 8.22% obese. Among obese patients, 41.51% were classified as morbidly obese (BMI >40). Obese patients had a slightly higher mean age of 48.47 years compared to non-obese patients at 46.68 years. Females accounted for 41.5% of obese patients and 36.3% of non-obese patients. Caucasians (62% vs. 47.91%) and African Americans (24% vs. 19.31%) were more prevalent among obese individuals, while Hispanics (12% vs. 21.31%) and Pacific Islanders (2% vs. 3.46%) were more common in the non-obese group. Additionally, the non-obese group included some Native Americans (2.19%) and other races (5.8%), which were absent in the obese group. Obesity was associated with a higher incidence of Type 2 diabetes mellitus, essential hypertension, end-stage renal disease, chronic kidney disease, and atrial fibrillation. Regionally, the Northeast (9.43% vs. 17.6%) and West (9.43% vs. 17.77%) had fewer obese patients compared to non-obese, while the Midwest had a higher proportion of obese individuals than non-obese (37.74% vs. 22.34%). Comprehensive baseline characteristics are outlined in Table 1.

Table 1: Baseline characteristics of all the patients with ARDS who required ECMO support.

	Obese	Morbid Obesity	Non-Obese
Total			
Female	41.5%	50%	36.3%
Age (in years)	48.47	49.7	46.68
Race			
Caucasians	62%	70%	47.91%
African Americans	24%	30%	19.31%
Hispanics	12%	0	21.31%
Pacific Islanders	2%	0	3.46%
Native Americans	0%	0	2.19%
Others	0%	0	5.8%
Elixhauser's Co-Morbidity Index			
ECI = 1	0%	0	5.35%

ECI = 2	5.7%	9.09%	6.22%
ECI > or = 3	94.3%	90.91%	88.43%
Income quartile (median household income of the patient's ZIP Code)			
1-47,999$	32.08%	45.45%	33.45%
48,000-60,999$	28.3%	27.27%	23.28%
61,000-81,999$	30.19%	22.73%	25.17%
82,000$	9.43%	4.55%	18.1%
Insurance			
Medicare	8%	10%	14.9%
Medicaid	22%	20%	25.67%
Private insurance	62%	60%	54.04%
Self-pay	8%	10%	5.39%
Region			
Northeast	9.43%	0%	17.6%
Midwest	37.74%	36.26%	22.34%
South	43.4%	63.64%	42.3%
West	9.43%	0%	17.77%
Hospital Bedsize			
Small	3.77%	4.55%	4.06%
Medium	13.21%	18.18%	11.34%
Large	83.02%	77.27%	84.6%
Hospital Location			
Rural	0	0%	1.52%
Urban	100%	100%	98.48%
Teaching Hospital			
Yes	94.34%	100%	93.06%
No	5.66%	0%	6.94%
Type 2 Diabetes mellitus	3.77%	4.55%	1.35%

Essential Hypertension	18.87%	4.6%	7.78%
End stage renal disease	3.77%	9.09%	1.02%
Chronic Kidney Diease	3.77%	9.09%	2.37%
Atrial fibrillation	13.21%	13.64%	6.2%

Among all admitted patients, a total of 1,354 deaths occurred. The mortality rate was 30% among obese patients, 36.36% among morbidly obese patients, and 43.14% among non-obese patients. Initially, the odds ratio for obese patients with ARDS requiring ECMO was not statistically significant (OR 0.56, p 0.063, 95% CI 0.31–1.03). Nevertheless, after adjusting for demographics and co-morbidities, the adjusted odds of mortality for obese patients with ARDS and requiring ECMO were 46% lower than for patients without obesity (aOR 0.54, 95% CI 0.3-0.94, p 0.032). (Table 2) There was no significant difference in mortality between patients with morbid obesity and non-obese patients (aOR 0.77, 95% CI 0.35–1.7, p-value 0.52). Additionally, there were no statistically significant differences in the rates of tracheostomy and LVAD placement among non-obese, obese, and morbidly obese patients. (Tables 2 and 3).

Table 2. Primary outcome in obese patients

	Nonobese patients	Obese patients	Odds Ratio	Adjusted Odds Ratio	95% CI	p-value
Mortality rate	43.14%	30%	0.56	0.54	0.3-0.94	0.03
Tracheostomy	18.44%	20%	1.15	0.85	0.4-1.79	0.67
LVAD	3.04%	1.8%	0.61	0.18	0.005- 5.74	0.332

Table 3. Primary outcome in morbidly obese patients

	Nonobese	Morbidly obese	Odds Ratio	Adjusted Odds Ratio	95% CI	p-value
Mortality rate	43.14%	36.36%	0.78	0.77	0.35-1.7	0.52
Tracheostomy	18.44%	27.27%	1.67	1.35	0.51-3.53	0.53
LVAD	3.04%	0	-	-		-

The mean duration of hospitalization for non-obese, obese, and morbidly obese patients was 30.82, 32.03, and 37.13 days, respectively. However, multivariate regression analysis showed no significant disparity in the length of stay among the three groups. Likewise, the median total hospitalization charges for non-obese, obese, and morbidly obese patients were $982,458.5, $1,026,129, and $1,262,046, respectively. No statistically significant difference was observed in the total hospitalization charges among the three groups of patients. (Tables 4 and 5)

Table 4. Secondary outcomes in obese patients

	Nonobese	Obese	Coefficient	Adjusted Coefficient	95% CI	p-value
Avg LOS (in days)	30.82	32.03	1.21	-2.44	-8.13- 3.24	0.39
Total Hospital Charges	$982458.5	$1026129	$43670.94	$ -88709.16	$ -364020.8 - 186602.5	0.52

Table 5. Secondary outcomes in morbidly obese patients

	Nonobese	Morbid obesity	Odds Ratio	Adjusted Coefficient	95% CI	p-value
Avg LOS (in days)	30.82	37.13	6.43	2.47	-7.88- 12.84	0.63
Total Hospital Charges	$982458.5	$1262046	$285907.2	$185091.9	$ -344341.7 714525	0.69

Age and white race were identified as significant factors influencing mortality in ARDS-obese and morbidly obese patients requiring ECMO. Each year, an increase in age was associated with a 3.6% increase in adjusted odds of mortality (aOR 1.03%, 95% CI 1.02-1.05, p 0.000) for both obese and morbidly obese individuals. Additionally, obese and morbidly obese Caucasian patients exhibited 33.72% and 33.94% lower adjusted odds of mortality compared to patients of other races (aOR 0.67, 95% CI 0.46-0.98, p 0.04; aOR 0.66, 95% CI 0.45-0.95, p 0.03, respectively).

5. Discussion

Our study analyzed 3219 individual hospitalizations for ARDS patients necessitating ECMO, shedding light on the impact of obesity on patient outcomes. Among these, 8.22% were classified as obese, with 41.51% of these being morbidly obese (BMI $\geq$40). The mean age of obese patients was slightly higher compared to nonobese patients, and there was a slightly higher proportion of females in the obese group. Interestingly, Caucasians and African Americans were more prevalent among obese patients, whereas Hispanics and Pacific Islanders were more common in the nonobese group. Notably, the mortality rate among obese patients with ARDS requiring ECMO was lower compared to nonobese patients after adjusting for demographics and comorbidities.

Additionally, no significant differences were observed in the rates of tracheostomy or LVAD placement among nonobese, obese, and morbidly obese patients, indicating similar management strategies across these groups. This finding challenges the notion that obesity is a relative contraindication for ECMO in ARDS patients. Furthermore, while obese and morbidly obese patients had longer average lengths of stay and higher median total hospitalization charges compared to nonobese patients, these differences were not statistically significant on multivariate regression analysis. Factors affecting mortality in obese and morbidly obese ARDS patients requiring ECMO included age and race, with Caucasians exhibiting lower adjusted odds of mortality compared to other racial groups.

However, it's important to acknowledge the limitations of our study. Firstly, we rely on ICD-10 coding to classify obesity, which may introduce inaccuracies and lead to underreporting of obesity. Additionally, defining obesity based solely on BMI, following CDC guidelines, fails to capture nuances such as fat percentage or distribution. This omission hampers our understanding of patients' fat distribution and fitness-related lean mass index, which may have more significant implications than central obesity. Furthermore, although we have adjusted for potential confounding comorbidities, obese patients in the real world have multiple comorbidities influencing their outcomes. Considering these limitations, it's essential to approach the interpretation of the protective effect of obesity in critical care with caution. Higher BMI should not be automatically construed as indicative of advantageous fat accumulation, as individuals with concentrated abdominal or visceral fat are at a heightened risk of developing various health issues, including metabolic syndrome, diabetes, inflammation, or cardiovascular diseases, unlike those with subcutaneous adipose tissue (Galesanu et al., 2014). Before considering all patients with increased BMI requiring ECMO support in hopes of improving survival rates, it's imperative to gain a clearer understanding of which bodily compartment contributes to the observed positive correlation between higher BMI and enhanced survival (Després et al., 2006).

6. Conclusion

In summary, the primary objective of this study is to identify any potential differences in mortality on initiating ECMO in obese patients when compared to non-obese patients. The results show that obese patients have lower odds of mortality when adjusted for other factors. Therefore, the findings of this study challenge the conventional belief that obesity is associated with poor prognostic outcomes in ARDS patients requiring ECMO. Instead, it suggests that obesity may confer a survival advantage in this population. Hence, obesity itself should not be an independent variable for ECMO contraindication. The study's limitations are noteworthy, including potential inaccuracies from ICD-10 coding for obesity and BMI's narrow focus on fat distribution. Understanding patients' diverse health factors is essential, as real-world obesity often involves multiple comorbidities affecting outcomes. Caution is warranted in interpreting obesity's protective effect in critical care, as higher BMI doesn't universally indicate beneficial fat accumulation. Therefore, before assuming ECMO support improves survival based on BMI, it's crucial to discern which

bodily compartments contribute to this correlation. However, further research is warranted to elucidate the underlying mechanisms and optimize patient management strategies in the context of using ECMO in obese individuals.

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Ethical Approval: Since this study was done from publicly available de-identified data, as per the Healthcare Utilization Project (HCUP), it is exempt from institutional board review (IRB) approval. Also, it is a retrospective observational study, so there is no need to obtain ethical committee approval.
Informed Consent: The study uses only available data that is de-identified and is publicly available; hence, informed consent is waived.
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