original article

Sex-based outcomes of obesity in critically ill patients: a retrospective cohort study

Mohammed Alqahtani,[a] Farhan Alenezi,[a] Musharaf Sadat,[a] Hani Tamim,[b,c] Felwa Bin Humaid,[d] Nahla Awadh Albaalharith,[e] Yaseen Arabi[a]

From the [a]Department of Intensive Care Medicine, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [b]Department of Clinical Research Institute, American University of Beirut, Beirut, Lebanon; [c]College of Medicine, AlFaisal University, Riyadh, Saudi Arabia; [d]Intensive Care Unit, King Abdulaziz Medical City, King Abdullah International Medical Research Center, RIyadh, Saudi Arabia; [e]Nursing Services/Clinical Trial Unit, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Correspondence: Dr. Yaseen Arabi · Department of Intensive Care Medicine, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, PO Box 22490, Riyadh 11426, Saudi Arabia · yaseenarabi@yahoo.com · ORCID: https://orcid.org/0000-0001-5735-6241

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BACKGROUND: Obesity is increasingly prevalent among critically ill patients, generally more common among females than males. Whether the patient's sex influences the outcome in these patients is unclear.

OBJECTIVE: Evaluate the outcomes of critically ill-patients with obesity admitted to the intensive care unit (ICU).

DESIGN: A retrospective cohort study

SETTING: ICU of King Abdulaziz Medical City, Riyadh, Saudi Arabia

PATIENTS AND METHODS: All obese patients aged more than 18 years admitted to ICU between 2002 to 2017 were included.

MAIN OUTCOME MEASURES: The primary outcome was hospital mortality. Secondary outcomes included ICU mortality, ICU and hospital lengths of stay, mechanical ventilation duration, renal replacement therapy, vasopressor use, and tracheostomy. A multivariable analysis was conducted to evaluate the association of sex differences with hospital mortality.

SAMPLE SIZE: 7277 patients

RESULTS: Of the included patients with obesity, 3965 were females, and 3312 were males. The females were older, more likely to be admitted for medical reasons and less likely for trauma than males. The crude hospital mortality rate was significantly higher in females than males (1056 [26.7%] vs. 744 [22.5%], $P<.0001$). Multivariable analysis demonstrated no association between sex and hospital mortality (OR: 1.05, 95% CI: 0.94, 1.19, $P=.52$). However, age (OR: 1.04; 95% CI: 1.01-1.02; $P<.0001$), chronic liver disease (OR: 5.04; 95% CI: 4.19-6.06; $P<.0001$), and chronic renal disease (OR: 2.19; 95% CI: 1.86-2.57; $P<.0001$) were found to be associated with higher mortality while admission due to trauma showed lower mortality (OR: 0.69; 95% CI: 0.53-0.90; $P=.007$).

CONCLUSION: Obese females admitted to ICU have a higher hospital crude mortality rate than obese males. This difference does not appear to be related to sex, but rather to older age, higher comorbid conditions, and more frequent admissions related to non-trauma reasons among females.

LIMITATIONS: A single-center retrospective study

CONFLICT OF INTEREST: None.

The prevalence of obesity, in males and females, has been reported to be around 18-20% among patients who are admitted to the Intensive Care Unit (ICU).[1] Studies have shown that mortality rates vary between males and females depending on underlying comorbid conditions, with some demonstrating higher mortality in females who were admitted to the ICU.[2] It has been observed that obesity is associated with more favorable outcomes among critically ill patients, a phenomenon that has been called the "obesity paradox".[3,4] However, some studies showed that this paradox may not be observed similarly in both sexes in specific cohorts, particularly those with cardiac diseases. For example, studies have shown that greater body mass index (BMI) was associated with low mortality in males but not in females admitted with heart failure and cardiogenic shock.[5-7] However, this protective effect of obesity was not observed in severely obese patients.[8] In another large cohort study, higher mortality from cardiovascular causes were observed in severely obese men while higher mortality due to other causes were seen in severely obese females.[4] Obesity in critically ill patients may pose a significant challenge during critical illness.[9] However, whether sexual dimorphism exists in the association between obesity and mortality in ICU-admitted patients remains unclear. Therefore, in this study, we aim to evaluate the association of sex on the mortality and other outcomes of obese patients admitted to the ICU.

PATIENTS AND METHODS

This study is a retrospective cohort study of obese patients admitted to the ICU of King Abdulaziz Medical City, a large tertiary hospital located in Riyadh, Saudi Arabia. During the study period, the ICU had a capacity of more than 112 beds admitting all medical, surgical, and trauma patients. The hospital is accredited by the Joint Commission International (JCI). The ICU has a database for all admitted patients, with data collected by a full-time coordinator. The Institutional Review Board of the Ministry of National Guard Health Affairs, Riyadh - Saudi Arabia, has approved the study, referencing IRBC/1755/21.

Patients

We included all obese patients aged more than 18 years who were admitted to the ICU between 2002 and 2017. Obesity was defined as body mass index (BMI) >30 kg/m^2 based on World Health Organization (WHO) classification.[8] We excluded patients below the age of 18 years, those admitted with burns, and those declared brain dead on admission. For patients with multiple ICU admissions in the same hospitalization, only the first admission was included.

Data collection

The data were extracted from the ICU database. This included: age, admission diagnosis category, the APACHE II score (Acute Physiology And Chronic Health Evaluation II),[10] history of diabetes and chronic comorbidities, baseline Glasgow Coma Scale, mechanical ventilation requirement in the first 24 hours of admission, the ratio of partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2), requirement for vasopressors, admission lactic acid, creatinine, bilirubin, and International Normalized Ratio (INR) levels.

Outcomes

The primary outcome was hospital mortality. Secondary outcomes included ICU mortality, ICU length of stay, hospital length of stay, mechanical ventilation need and duration, tracheostomy insertion, code status, and whether renal replacement therapy was needed.

Statistical analysis

Data were analyzed using the Statistical Analysis System (SAS) (version 9.0; SAS Institute, CARY, NC, USA). Continuous variables were presented as median and interquartile ranges (IQR). Categorical variables were presented as frequencies and percentages. Subjects were categorized into two groups: obese males and obese females. Baseline variables and outcomes were compared between the two groups. Categorical variables were compared using the chi-square test and continuous variables using the Student *t* test. *P* values less than .05 were considered significant. A multivariate logistic regression analysis was performed to determine the predictors of mortality among critically ill obese females and males, adjusted for the following covariates based on univariate analysis as well as their clinical significance: age, admission due to trauma, chronic respiratory, chronic renal, chronic liver, or chronic cardiac diseases as well as immunocompromised status and diabetes. We also assessed the association between the obesity subgroups and hospital mortality (WHO classification-obesity class 1: BMI=30-35 kg/m^2 (reference), obesity class 2: BMI=35-40 kg/m^2, and and obesity class 3 (severe): BMI >40 kg/m^2).Lastly, we performed a subgroup analysis to assess the effect of specific subgroups on the association between sex difference and hospital mortality. These subgroups included: age using a cutoff of 45 years and admission periods of 2002-2005, 2006-2009, 2010-2013 and 2014-2017.

RESULTS

Baseline characteristics

Over the 16-year study period, there were 7277 critically ill obese patients (3312 males and 3965 females) who met the study eligibility criteria. Baseline characteristics are shown in **Table 1**. The median age was 62 years (Q1, Q3: 46, 73), with females being significantly older than males (median 65 [Q1, Q3: 52, 74], compared to 58 [39, 72], *P*<.0001). The median BMI for the whole cohort was 34.8 (32.0, 39.4), and was significantly higher in females than males (35.7 [32.5, 40.5] vs 33.8 [31.5, 42.9], *P*<.0001). Females were more likely to have higher prevalence of chronic comorbidities than males including diabetes (54.10% compared to 40.3%, *P*<.0001), chronic liver disease (8.2% vs 7.0%, *P*=.04), chronic respiratory disease (24.2% vs 13.1%, *P*<.0001), chronic renal diseases (13.0% vs 8.6%, *P*<.0001) and cardiovascular diseases (26.4% vs 22.3%, *P*<.0001).

Regarding the reasons for admission diagnosis, females were more likely to be admitted than males due to respiratory disease (27.1% vs 18.1%, *P*<.0001) and cardiovascular disease (41% vs 32.1%, *P*<.0001). However, females were less likely admitted than males due to neurological diseases (7.8% vs 10.7%, *P*<.0001) and trauma (2.7% vs 17.7%, *P*<.0001).

The median APACHE II score was similar between groups (21 [interquartile range, Q1, Q3: 16,27] and 20 [14, 26] *P*=.51). The median bilirubin level (13 [Q1, Q3: 8, 27] and 15 [Q1, Q3: 9, 30], *P*=.13) and the median PaO_2/FiO_2 level (210 [Q1, Q3: 138, 303] and 209 [Q1, Q3: 136, 300], *P*=.22) were also similar in both sexes, respectively. However, the median GCS was significantly higher in females than males (15 [Q1, Q3: 10, 15] vs 14 [Q1, Q3: 8, 15], *P*<.0001), and vasopressors were used more frequently in males than females (1324 [39.10%] vs 1549 [36.8%], *P*=.006).

Outcomes

Primary and secondary outcomes are shown in **Table 2**. Among the included patients, the crude hospital mortality rate was 24.8% (n=1800), with females more likely to die than males (26.7% vs 22.5%, *P*<.0001). Similarly, the crude overall ICU mortality rate was 15.5% (n=1114) and was also significantly higher in females than males (16.3% vs 14.1%, *P*=.008, respectively). At the hospital level, the overall median hospital length of stay was 22 days (Q1, Q3: 11, 48), with males staying significantly longer than females (23 days [Q1, Q3: 11, 50] vs 21 days [Q1, Q3: 11, 45], *P*=.05). The overall median ICU length of stay was 3.7 days with no difference between both groups (3.5 days [Q1, Q3: 1.2, 9.4] and 4.0 days [Q1, Q3: 1.3, 10.9], *P*=.37).

Females were more likely to require renal replacement therapy than males (20% vs 16.9%, *P*=.0005). However, males were more likely to require mechanical ventilatory support than females (59.8% vs 51.1%, *P*<.0001) with a median duration of mechanical ventilation use also being significantly higher in males than females (2 days [Q1, Q3: 0, 8] vs 1 day [Q1, Q3: 0, 6], *P*=.02). Lastly, males were more likely to be tracheostomized than females (10.6% vs 8.1%, *P*=.0002).

Multivariate analysis

There was no association between sex and hospital mortality in critically ill patients with obesity (OR: 1.05; 95% CI: 0.94-1.19; *P*=.39). There was also no association between obesity subgroups and hospital mortality. However, age (for each one-year increase OR: 1.02; 95% CI: 1.01-1.02; *P*<.0001), chronic liver disease (OR: 5.04; 95% CI: 4.19-6.07; *P*<.0001), and chronic renal disease (OR: 2.16; 95% CI: 1.83-2.53; *P*<.0001) were found to be associated with higher hospital mortality while admission due to trauma showed lower hospital mortality (OR: 0.69; 95% CI: 0.53-0.90; *P*=.006). In addition, there was no significant association between sex and hospital mortality using specific subgroups (age with a cutoff of 45 years and admission periods of 2002-2005, 2006-2009, 2010-2013 and 2014-2017) (**Table 3, Figure 1**).

DISCUSSION

Our study showed that critically ill females with obesity had significantly higher hospital crude mortality rate than their male counterparts. However, this was explained by differences in age, admission category, and co-morbid conditions. Evidence regarding the association of sex and outcome of ICU patients is inconsistent. For example, Modra et al found that females had a better crude survival rate than males. However, females in that study were younger and have a lesser severity of illness. After analysis was adjusted for APACHE III, hospital hours before ICU admission, and admission diagnosis, the survival rate was similar between females and males.[11] This is in line with our study, which showed that sex was not associated with higher mortality in obese females vs. obese males after adjustment for age, chronic medical diseases, and trauma. On the other hand, Romo et al studied the effect of sex on ICU mortality in medical and surgical ICUs at Erasme University Hospital in Brussels, Belgium. They found that being female is

Table 1. Comparison baseline characteristics of obese patients admitted to the Intensive care unit among males and females.

Variable	All N=7277	Male N=3312	Female N=3965	*P* value
Demographics				
Age (yrs), median (Q1, Q3)	62 (46, 73)	58 (39, 72)	65 (52, 74)	<.0001
BMI (kg/m^2, median (Q1, Q3)	34.8 (32.0, 39.4)	33.8 (31.5, 42.9)	35.7 (32.5, 40.5)	<.0001
BMI 30-<35, n (%)	3716 (51.1)	1952 (59.8)	1734 (43.7)	
BMI 35-<40, n (%)	1877 (25.8)	775 (23.4)	1102 (27.8)	<.0001
BMI ≥40, n (%)	1684 (23.1)	555 (1.8)	1129 (28.5)	
Admission diagnosis category, n (%)				
Respiratory	1669 (22.10)	597 (18.1)	1072 (27.1)	
Cardiovascular	2687 (36.10)	1063 (32.1)	1624 (41.0)	
Neurologic	661 (9.1)	353 (10.7)	308 (7.8)	<.0001
Other medical illness	337 (4.6)	152 (4.6)	185 (4.7)	
Non-operative trauma	531 (7.3)	456 (13.8)	75 (1.9)	
Post-operative	1383 (19.0)	687 (20.8)	696 (17.6)	
Trauma, n (%)	695 (9.6)	587 (17.7)	108 (2.7)	<.0001
Diabetes, n (%)	3514 (48.3)	1335 (40.3)	2179 (54.10)	<.0001
Chronic comorbidities, n (%)				
Chronic liver disease	556 (7.7)	230 (7.0)	326 (8.2)	.04
Chronic respiratory disease	1388 (19.1)	431 (13.1)	957 (24.2)	<.0001
Chronic renal disease	797 (11.0)	284 (8.6)	513 (13.0)	<.0001
Chronic cardiac disease	1782 (24.5)	740 (22.3)	1042 (26.3)	.0001
Immunocompromised disease	591 (8.1)	239 (7.2)	352 (8.9)	.01
Physiological Parameters				
Mechanical ventilation, n (%)	4007 (55.1)	1982 (59.8)	2025 (51.1)	<.0001
Vasopressor use, n (%)	2783 (38.2)	1324 (39.10)	1459 (36.8)	.006
APACHE II, median (Q1, Q3)	21 (15, 27)	20 (14, 26)	21 (16, 27)	.51
PaO_2/Fio_2 ratio, median (Q1, Q3)	209 (137, 300)	209 (136, 300)	210 (138, 303)	.22
GCS, median (Q1, Q3)	14 (9, 15)	14 (8, 15)	15 (10, 15)	<.0001
Laboratory parameters, median (Q1, Q3)				
Bilirubin (mmol/L)	14 (8, 29)	15 (9, 30)	13 (8, 27)	.13
Creatinine (µmol/L)	102 (66, 200)	103 (71, 201)	101 (62, 200)	.002
Lactic Acid (mg/dl)	1.9 (1.2, 3.5)	2 (1.2, 3.4)	1.9 (1.2, 3.5)	.01
INR	1.20 (1.07, 1.50)	1.20 (1.09, 1.42)	1.20 (1.05, 1.60)	<.0001

BMI: Body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II; PaO_2/FiO_2 ratio: the ratio of the partial pressure of oxygen to the fraction of inspired oxygen; GCS: Glasgow coma score; INR: International normalized ratio; Q1: first quartile, Q3: third quartile. Significant at $P<.05$. For all percentages, the denominator is the total number of subjects in the group.

Table 2. Outcomes of obese patients admitted to the ICU in males and females.

Variables	All N=7277	Male N=3312	Female N=3965	*P* value
Hospital mortality,[a] n (%)	1800/7268 (24.8)	744/3310 (22.5)	1056/3958 (26.7)	<.0001
ICU mortality, n (%)	1114 (15.3)	466 (14.1)	648 (16.3)	.008
ICU LOS, median (Q1, Q3)	3.7 (1.2, 10.0)	4.0 (1.3, 10.9)	3.5 (1.2,9.4)	.37
Hospital LOS, median (Q1, Q3)	22 (11, 48)	23 (11, 50)	21 (11, 45)	.05
Mechanical ventilation duration, median (Q1, Q3)	1 (0, 7)	2 (0, 8)	1 (0, 6)	.02
Code status, n (%)	822 (11.3)	334 (10.1)	488 (12.3)	.03
Tracheostomy, n (%)	674 (9.3)	352 (10.6)	322 (8.1)	.0002
Renal replacement therapy, n (%)	1352 (18.6)	558 (16.9)	794 (20.0)	.0005

ICU: Intensive care unit; Q1: first quartile, Q3: third quartile. For all percentages, the denominator is the total number of subjects in the group. LOS: Length of stay. *P* value significant at <.05. [a]Hospital mortality is not available for 9 patients.

Table 3. Predictors of hospital mortality among obese males and females admitted to the ICU.

Variables	OR	95% CI	*P* value
Sex (female vs male)	1.05	0.94, 1.19	.39
Age (for every 1-year increase)	1.02	1.01, 1.02	<.0001
≤45 years	0.80	0.59, 1.10	.16
>45 years	1.11	0.97, 1.26	.13
BMI 35-<40 versus 30-<35	0.89	0.77, 1.02	.10
BMI ≥40 versus 30-<35	0.94	0.81, 1.09	.41
Trauma	0.69	0.53, 0.90	.006
Chronic liver disease	5.04	4.19, 6.07	<.0001
Chronic cardiac disease	1.24	1.09, 1.41	.0018
Chronic renal disease	2.16	1.83, 2.53	<.0001
Chronic immunocompromised	2.49	2.07, 3.00	<.0001
Diabetes mellitus	1.05	0.92, 1.18	.49

OR: Odds ratio; CI: Confidence interval. Variables included age, sex, BMI, trauma, chronic respiratory, chronic renal, chronic liver disease; chronic cardiac, chronic Immunocompromised and diabetes mellitus. *P* value significant at <.05.

[a]Hospital mortality is not available for 9 patients.

an independent variable for mortality in patients >50 years of age.[2] The females in the present cohort were significantly older than males. This raised a question of whether the observed mortality difference was attributed to sex or the fact that obese females were older. After adjusting for age between the groups, the observed mortality difference was no longer significant. This showed age is an independent predictor of hospital mortality. This can be helpful while risk-stratifying obese patients upon admission. Furthermore, we found a higher prevalence for chronic liver, respiratory, renal, and cardiac diseases among obese females than males. These same diseases were also independent predictors of hospital mortality, which explains the higher mortality in obese females in the cohort. In a similar study by Li et al, there was an increase in mortality from cardiac causes in obese males.[4] Their findings and ours, suggest that comorbid diseases in critically ill obese patients, and not sex, are associated with higher mortality. The clinical implications of these findings are important in outcome prediction upon admission and when discussing patient care with family members.

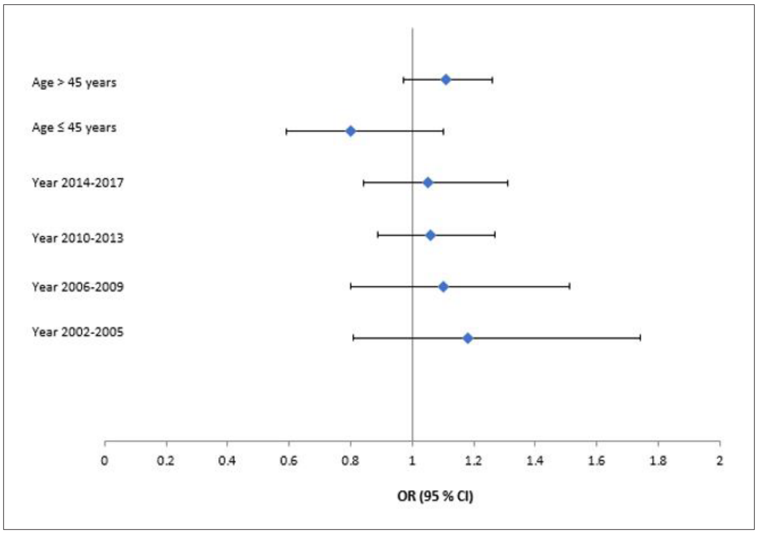

Figure 1. Odds ratios and confidence intervals of hospital mortality among different time periods and age groups using a cut-off of 45 years in multivariate logistic regression analysis. Co-variables included age, sex, BMI, trauma, chronic respiratory, chronic renal, chronic liver disease; chronic cardiac, chronic Immunocompromised.

For secondary outcomes, obese females required more renal replacement therapy than males, which, again, is probably related to older age and higher prevalence of underlying kidney disease and diabetes. This was also seen in the study of Todorov et al, which found that females regardless of weight, required more renal replacement therapy if they were <45 years of age.[12] This trend, however, was not seen in the older population, where the overall need for renal replacement therapy was higher in males vs females.[12] In their study, males required more vasoactive support and mechanical ventilation, which aligns with our findings. Given the prevalence of obesity of Saudi Arabia, the number of obese patients from both sexes is substantial as shown in our study. Our study suggests that sex alone does not influence mortality, and provides evidence for equity of care. Strengths of the study include a large sample size and the adjustment to key comorbid conditions. The study is limited by its single-center retrospective design.

CONCLUSION

In Saudi Arabia, critically ill obese females have a higher crude hospital mortality rate than critically obese males and this difference can be explained by older age, reasons for admission and number of comorbid conditions.

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request as per King Abdullah International Medical Research Center (KAIMRC) regulations.

Research ethics and patients' consent

The study was approved by the Institutional board review of the Ministry of National Guard Health Affairs (IRBC/1755/21). The need for written informed consent was waived due to the non-interventional design of the study.

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