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The paradox prevails: Outcomes are better in critically ill obese patients regardless of the comorbidity burden

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ABSTRACT

During critical illness, obese patients have better outcomes compared to patients with normal BMI, and this is known as the obesity paradox. The difference in comorbidity burden have been implied to be responsible for the paradox. We performed a retrospective review from 2001 to 2012 of critically ill patients from the Medical Information Mart for Intensive Care database. We included 11,433 patients and classified them according to body mass index (BMI) and comorbidity burden (Elixhauser comorbidity measure). The odds of inpatient mortality were lower in obese patients compared to patients with normal BMI; in group with the least comorbidity score (Elixhauser <0) [OR: 0.47, CI (0.28–0.80), p-value 0.006] and higher comorbidity scores, (Elixhauser 1–5) [(OR: 0.66, CI (0.46–0.95), p-value 0.02)] and (Elixhauser 6–13) [OR: 0.69, CI (0.53–0.92), p-value 0.01]. 30-day mortality was also significantly lower in obese patients, in groups with the lowest (Elixhauser <0) [OR:49, CI (0.31–0.77), p-value 0.002] as well as the highest comorbidity burden (Elixhauser >14) [OR:0.59, CI (0.45–0.77), p-value <.001]. Subgroup analysis in patients with various comorbidities showed better outcomes in obese patients. These findings show that the decreased odds of mortality in critically ill obese patients is independent of the comorbidity burden or type of comorbidity.

1. Introduction

Positive energy balance in individuals leads to weight gain, mainly an increase in the adiposity in the body. Excess fat in adipose tissues impairs health and is termed obesity. Prevalence of obesity has been increasing and is ~13% in the world and up to 40% in developed countries [1]. Obese individuals constitute about 20% of all ICU patients [2-4]. Body mass index (BMI) is a universally accepted tool (has served as the classical proxy) for population-level measure of obesity. In the year 2000, WHO classified overweight and obesity in adults based on the BMI (underweight <18.5, normal 18.5–24.9, overweight ≥25–29.9, obese 30–40 and severely obese≥40) [3]. This graded classification is valuable as it allows for the identification of individuals and groups at increased risk of morbidity and mortality providing a firm basis for evaluating interventions.

The effect of obesity on long-term health is well understood [5,6]. However, its impact on acute illness remains unclear. Obesity poses a challenge to landmark identification complicating basic resuscitative procedures like the placement of an airway or intravenous lines and has adverse physiologic changes such as hyperglycemia [7]. There is evidence to suggest that this translates into worse outcomes for obese patients in Intensive Care Units (ICUs) [8-14]. On the contrary, there is growing data supporting a protective effect of obesity in critically ill patients. Several studies have shown a lower mortality rate for critically ill obese patients as compared to normal weight individuals [15-20]. Others have shown an increased risk for complications such as acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) in obese patients but nonetheless, better outcomes when compared to normal weight individuals [21,22]. This protective effect of obesity during critical illness has been termed the 'Obesity Paradox.'

It is prudent to include herein, the concept of metabolically healthy obese (MHO) individuals. This term has been used to denote obese individuals who do not have chronic pathologic stigmata associated with

Abbreviations: AKI, Acute kidney injury; ARDS, Acute respiratory distress syndrome; BMI, Body mass index; CCU, Coronary care unit; CI, Confidence interval; COPD, Chronic obstructive pulmonary disease; ICU, Intensive care unit; MHO, Metabolically healthy obese; MICU, Medical intensive care unit; MIMIC, Medical information mart for intensive care; NSTEMI, Non-ST elevation myocardial infarction; OR, Odds ratio; OSA, Obstructive sleep apnea; SICU, Surgical intensive care unit; SOFA, Sequential organ failure assessment; STEMI, ST Elevation myocardial infarction; WHO, World health organization.

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excess adiposity, namely insulin resistance, unfavorable cholesterol levels, and hypertension [23,24]. It has been stipulated that the associated comorbidities, rather than the excess weight, were responsible for the adverse outcomes. This leads to the assumption that MHO individuals' health risk should be comparable to that of lean people. This was supported by studies showing better outcomes in the MHO individuals than the unhealthy obese and comparable outcomes to those of lean individuals [25-29].

Hence, it is possible that improved outcomes in MHO individuals could influence the overall outcomes in critically ill obese patients and play a significant role in creating the obesity paradox. If this holds true, the presence of obesity paradox would be expected to be determined by the comorbidity burden of patients. We conducted our study to evaluate the effect of comorbidity burden in critically ill patients of different BMI classes, with an expectation that unhealthy obese individuals should not manifest the obesity paradox.

2. Methodology

2.1. Database description

Medical Information Mart for Intensive Care (MIMIC-III) database is a large, single-center database comprising information relating to patients admitted to critical care units at a large tertiary care hospital [30,31]. It contains data associated with 61,532 distinct intensive care unit admissions admitted to critical care units at Beth Israel Deaconess hospital between 2001 and 2012. Available data include patient demographics, height, weight, vital signs, medications, laboratory measurements, procedure codes, diagnostic codes, hospital length of stay and survival data. Specific ITEM ID is assigned to an individual procedure and medication. Individual comorbidities to calculate the Elixhauser score can be determined using the International Classification of DiseasesNinth Revision (ICD-9), Clinical Modification code. The data has been de-identified in accordance with Health Insurance Portability and Accountability Act (HIPAA) standards using structured data cleansing and date shifting [32].

2.2. Patient population

We included all adult patients over the age of 16 who were admitted to the MICU, CCU and SICU units. Patients admitted to the cardiac and thoracic surgical service and who stayed in the ICU for less than a day were excluded. Patients without either height or weight data on admission were also excluded. (Fig. 1). A sensitivity analysis was performed comparing the characteristics of patients included in the study and those excluded due to lack of height or weight data. If the patient is older than 89, the database sets the age to 300 at their first admission. The median age of these patients was 91.4 years; hence 1602 patients who met the inclusion criteria had their age replaced by 91.4 [32]. BMI is classified according to the WHO classification(<18.5, 18.5–24.9, 25–29.9 and 30–40 and ≥ 40) [3].

Comorbidity burden is assessed by computing the Elixhauser comorbidity measure. It is a set of thirty comorbidities that impact patient outcome including mortality [33]. A scoring system developed by van Walraven assigns a score to each comorbidity group that reflects the strength of association of each comorbidity with hospital death. The composite of all these score forms the Elixhauser score. The Elixhauser score can be further classified into five categories (<0, 0, 1–5, 6–13 and ≥ 14) [34]. We have named these groups as Group A (Elixhauser <0), Group B (Elixhauser = 0), Group C (Elixhauser 1–5), Group D (Elixhauser 6–13), Group E (Elixhauser ≥14) henceforth.

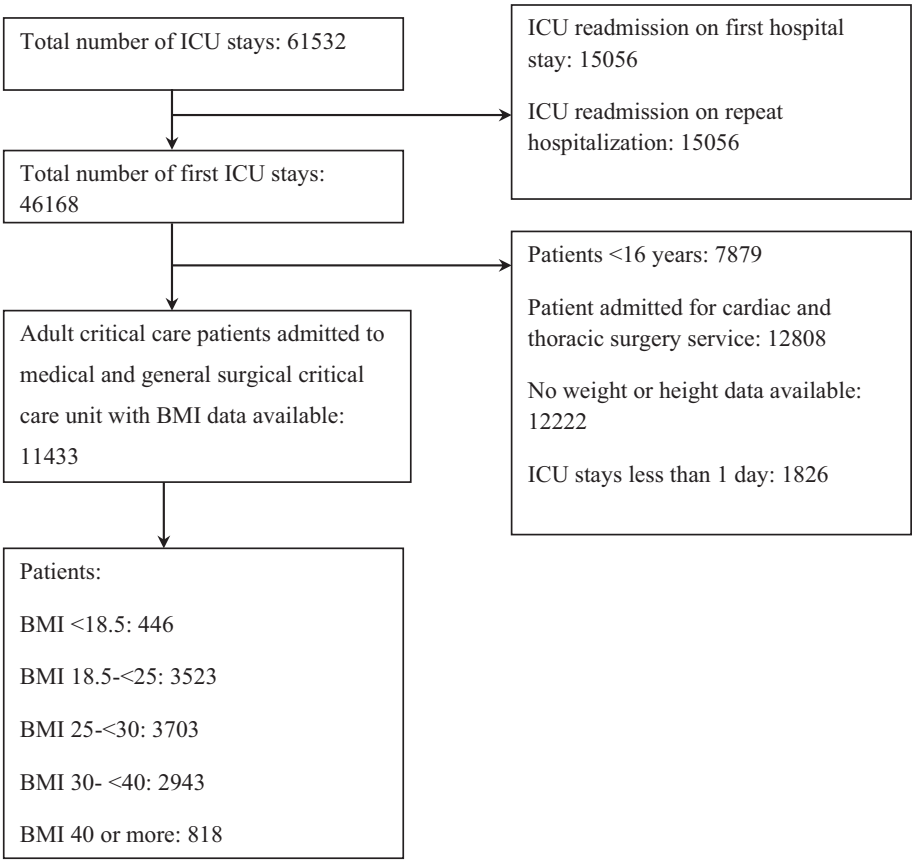

Fig. 1. Selection of the patient cohort.

2.3. Statistical analysis

Critical illness in patients with varying BMI and co-morbidity burden was the main exposure, and inpatient mortality was the primary outcome. Secondary outcomes include ICU length of stay, hospital length of stay, ICU readmission and 30-day mortality.

The difference in patient characteristics, comorbidities, and ICU interventions were assessed using one-way ANOVA test, two-way

Table 1
Characteristics of patient in different BMI classes.

Variables	Total	Normal BMI, 18.5–24.9	Underweight, < 18.5	Overweight,25–29.9	Obese, ≥30	Severe obesity, ≥40	p-value
n (%)	11,433	3523 (30.8)	446(3.9)	3703(32.4)	2943 (25.7)	818(7.15)	
Age (median years)	67	71.5	69.2	68.2	64.3	60.1	<0.001
Inter quartile (25%–75%)	54.3–78.8	55.6–82.3	53.4–81.7	55.1–78.9	53.9–74.8	50.4–69.5	
Female sex n (%)	45.3	48.2	61.2	38.3	44.9	56.9	<0.001
Ethnicity n (%)							
Blacks	1047(9.2)	298(8.5)	51(11.5)	302(8.2)	276(9.5)	120(14.8)	<0.001
Hispanic	328(2.9)	87(2.5)	6(1.4)	113(3.1)	104(3.6)	18(2.2)	
White	8182(72.2)	2499(71.6)	315(70.8)	2695(73.5)	2109 (72.3)	564(69.7)	
Unknown	1229(10.9)	373(10.7)	35(7.9)	415(11.3)	321(11)	85(10.5)	
Others	544(4.8)	234(6.7)	38(8.5)	142(3.9)	108(3.7)	22(2.7)	
Insurance type n (%)							
Government	297(2.6)	99(2.8)	10(2.2)	90(2.4)	76(2.6)	22(2.7)	<0.001
Medicaid	943(8.3)	290(8.2)	46(10.3)	278(7.5)	229(7.8)	100(12.2)	
Medicare	6586(57.6)	2202(62.5)	283(63.4)	2126(57.4)	1607 (54.6)	368(44.9)	
Private	3513(30.7)	879(25.5)	106(23.8)	1181(31.9)	1007 (34.2)	322(39.4)	
Self-Pay	94(0.8)	35(1)	1(0.3)	28(0.8)	24(0.8)	6(0.7)	
Admission type n (%)							
Elective	852(7.5)	248(7)	17(3.8)	268(7.2)	246(8.4)	73(8.9)	0.10
Emergency	10,215 (89.4)	3174(90.1)	419(93.9)	3303(89.2)	2601 (88.4)	718(87.8)	
Urgent	366(3.1)	101(2.9)	10(2.2)	132(3.6)	96(3.3)	27(3.3)	
ICU first service n (%)							
CCU	3598(31.5)	1093(31)	97(21.8)	1256(33.9)	947(32.2)	205(25.1)	0.004
MICU	5472(47.8)	1692(48)	257(57.6)	1675(45.2)	1386 (47.1)	462(56.5)	
SICU	2363(20.7)	738(21)	92(20.6)	772(20.9)	610(20.7)	151(18.5)	
Primary diagnosis n (%)							
Acute myocardial infarction (STEMI and NSTEMI)	1507(13.2)	442 (12.6)	24(5.4)	581(15.7)	403(13.7)	57(6.9)	0.88
Sepsis	1009(8.83)	299(8.5)	45(10.1)	299(8.1)	272(9.2)	94(11.5)	0.06
Cerebrovascular event (ischemic stroke/ intracranial hemorrhage)	699(6.11)	252(7.2)	20(4.5)	240(6.5)	162(5.5)	25(3.1)	<0.001
Acute heart failure	499(4.4)	149(4.2)	16(3.6)	155(4.2)	122(4.2)	57(6.9)	0.09
Acute respiratory failure	370(3.24)	99(2.8)	17(3.8)	99(2.7)	101(3.4)	54(6.6)	<0.001
Arrhythmia	314(2.75)	104(2.9)	9 (2.0)	98(2.7)	81(2.8)	22(2.7)	0.60
Pneumonia	299(2.62)	112(3.2)	16(3.6)	82(2.2)	69(2.3)	20(2.4)	0.02
Comorbidities n (%)							
Congestive heart failure	4071(35.6)	1234(35)	156(34.9)	1266(34.2)	1068 (36.3)	347(42.4)	<0.001
Cardiac arrest	439(3.9)	133(3.8)	10(2.3)	137(3.8)	131(4.5)	28(3.5)	0.16
Valvular heart disease	1503(13.2)	540(15.3)	72(16.14)	492(13.29)	334(11.4)	65(7.9)	<0.001
Arrhythmia	4425(38.7)	1384(39.3)	138(30.9)	1488(40.2)	1122 (28.1)	293(35.8)	0.001
Hypertension	6149(53.8)	1732(49.2)	180(40.4)	2032(54.9)	1718 (58.4)	487(59.5)	<0.001
DM	3156(27.6)	699(19.8)	71(15.9)	945(25.5)	1078 (36.6)	368(44.9)	<0.001
Chronic kidney disease	1942(16.9)	568(16.1)	79(17.7)	646(17.5)	505(17.2)	146(17.9)	0.55
Chronic respiratory illness (COPD/ Asthma/OSA)	2694(23.6)	818(23.2)	134(30)	756(20.4)	719(24.4)	267(32.6)	<0.001
HIV	87(0.8)	43(1.2)	8(1.8)	24(0.7)	11(0.37)	1(0.12)	<0.001
Chronic liver disease	1466(12.8)	431(12.2)	44(9.9)	466(12.6)	428(14.5)	97(11.9)	0.01
Cancer	1280(11.2)	469(13.3)	69(15.5)	436(11.8)	263(8.9)	43(5.3)	<0.001
Severity score							
Mean SOFA (SD)	4.36 (3.3)	4.28(3.2)	4.1(2.9)	4.3(3.3)	4.49(3.5)	4.82(3.5)	<0.001
ICU intervention n (%)							
Transfusion of blood products	5477(48.2)	1692(48.3)	214(48.1)	1814(49.2)	1388 (47.4)	369(45.2)	0.28
Use of antibiotics	2696(23.7)	813(23.2)	109(24.5)	836(22.7)	713(24.4)	225(27.6)	0.04
Hemodialysis	230(2)	51(1.5)	8(1.8)	82(2.2)	70(2.4)	19(2.3)	0.06
Mechanical ventilation	1313(11.5)	381(10.9)	35(7.9)	390(10.6)	376(12.9)	131(16.1)	<0.001
Total parenteral nutrition	745(6.6)	245(7)	44(9.9)	206(5.6)	198(6.8)	52(6.4)	0.004

Table 2
Odds of inpatient and 30-day mortality among different BMI classes compared to patients with normal BMI.

	Inpatient mortality			30-day mortality		
BMI	Odds ratio	Confidence interval	p-value	Odds ratio	Confidence interval	p-value
Group A (Elixhauser <0)						
Underweight	1.25	0.46–3.40	0.66	1.49	0.68–3.29	0.31
Overweight	0.76	0.47–1.22	0.25	0.77	0.51–1.14	0.19
Obese	0.47	0.28–0.80	0.006	0.49	0.31–0.77	0.002
Severe obesity	0.96	0.51–1.80	0.9	0.89	0.51–1.57	0.69
Group B (Elixhauser = 0)						
Underweight	1.16	0.45–2.98	0.76	1.21	0.52–2.79	0.65
Overweight	0.93	0.61–1.42	0.75	0.92	0.63–1.34	0.65
Obese	0.83	0.52–1.34	0.46	0.78	0.50–1.21	0.27
Severe obesity	1	0.45–2.23	0.99	1.11	0.53–2.29	0.79
Group C (Elixhauser 1–5)						
Underweight	1.47	0.79–2.73	0.22	1.41	0.79–2.51	0.25
Overweight	0.72	0.52–0.99	0.04	0.71	0.53–0.96	0.02
Obese	0.66	0.46–0.95	0.02	0.58	0.41–0.81	0.002
Severe obesity	0.66	0.38–1.14	0.14	0.70	0.42–1.18	0.18
Group D (Elixhauser 6–13)						
Underweight	1.34	0.85–2.11	0.20	1.49	0.98–2.29	0.06
Overweight	0.79	0.62–1.02	0.07	0.79	0.63–0.99	0.04
Obese	0.69	0.53–0.92	0.01	0.59	0.45–0.77	<0.001
Severe obesity	0.79	0.48–1.30	0.35	0.61	0.37–1.02	0.06
Group E (Elixhauser ≥14)						
Underweight	1.38	0.64–2.97	0.41	1.36	0.66–2.79	0.41
Overweight	0.87	0.56–1.34	0.52	0.71	0.47–1.08	0.11
Obese	0.82	0.49–1.37	0.45	0.62	0.38–1.01	0.06
Severe obesity	0.86	0.32–2.31	0.77	0.55	0.19–1.52	0.25

ANOVA and chi-square test. Univariate and Multivariate regression analysis was conducted to estimate the association between exposure and outcome. Logistic regression was conducted to estimate the odds of mortality and readmission. Linear regression was conducted to estimate the difference in length of stay. The odds ratio and corresponding 95% CIs were calculated after controlling for covariates including demographic variables (age, sex, ethnicity, admission type, insurance), comorbidities, severity score (SOFA score) and ICU interventions (transfusion, antibiotic use, hemodialysis, mechanical ventilation, and total parenteral nutrition). All reported statistical tests were two-sided and p value of 0.05 was considered statistically significant. All the analysis was performed using Stata 14.0 (Stata Corp, College Station, TX).

2.4. Ethical consideration

The use of MIMIC III database for any research is pre-approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA). Hence, a formal IRB clearance was not sought. The requirement for individual patient consent was waived because all health information was de-identified.

3. Results

There were 61,532 ICU stays, out of which 11,433 patients met the study inclusion criteria between 2001 and 2012. (Fig. 1) The demographic and clinical characteristics of our patient population is shown in Table 1. Median age was 67 years [Inter-quartile (IQ) 25–75%: 54.3–78.8 years]. About 45% of the total study population was female, 72.2% was white and 57.6% was insured by Medicare. Acute myocardial infarction (13.2%), sepsis (8.8%) and cerebrovascular event (ischemic stroke and intra-cerebral hemorrhage) (6.1%) were the most common primary diagnosis. Mean SOFA score on admission was 4.36 [Standard deviation (SD): 3.3]. Among the ICU interventions, the rate of mechanical ventilation, use of antibiotics and total parenteral nutrition was significantly different among the different BMI classes whereas the rate of transfusion of blood products and hemodialysis were similar.

Compared to patients with normal BMI, the adjusted odds of inpatient mortality were lower in overweight patients for all the Elixhauser groups but was statistically significant only for Group C [(OR: 0.72, CI (0.52–0.99), p-value 0.04)]. For obese patients, the odds of inpatient mortality was significantly decreased for Group A (Elixhauser <0) [OR: 0.47, CI (0.28–0.80), p-value 0.006], Group C (Elixhauser 1–5) [(OR: 0.66, CI (0.46–0.95), p-value 0.02)] and Group D (Elixhauser 6–13) [OR: 0.69, CI (0.53–0.92), p-value 0.01] (Table 2). The odds of 30-day mortality was significantly lower in overweight patients in Group C [OR: 0.71, CI (0.53–0.96), p-value 0.02] and Group D [OR:0.79, CI (0.63–0.99), p-value 0.04]. Similarly, the odds of 30-day mortality were decreased in obese patients in Elixhauser Group A [OR:49, CI (0.31–0.77), p-value 0.002], Group C [OR:0.58, CI (0.41–0.81), p-value 0.002] and Group D [OR:0.59, CI (0.45–0.77), p-value <0.001]. The odds of inpatient mortality and 30-day mortality were lower in severely obese patients but were not statistically significant (Table 2). In the subgroup of patients with congestive heart failure (CHF) and chronic kidney disease (CKD), both overweight [CHF - OR:0.75, CI (0.59–0.96), p-value 0.02; CKD – OR:0.73, CI (0.56–0.95), p-value 0.02] and obese patients [CHF - OR:0.64, CI (0.45–0.76), p-value 0.01; CKD – OR:0.50, CI (0.34–0.76), p-value 0.001] had decreased odds of inpatient mortality. In subgroups of patients with diabetes and hypertension, the odds of inpatient mortality were significantly lower in overweight, obese and severely obese patients (Table 3).

The length of ICU stay was longer for severely obese patients in Elixhauser groups A [0.89 days, CI (0.29–1.51), p-value 0.004], Group C [1.49 days (0.34–2.63, p-value 0.01], Group D [1.77 days (0.68–2.85,

Table 3
Subgroup analysis of inpatient mortality in patients with various comorbidities.

	Inpatient mortality compared to patients with normal BMI		
BMI class	Odds ratio	Confidence interval	p-value
Congestive heart failure			
Underweight	0.91	0.55–1.49	0.69
Overweight	0.75	0.59–0.96	0.02
Obese	0.73	0.56–0.95	0.02
Severe obesity	0.82	0.55–1.24	0.35
Diabetes			
Underweight	0.52	0.19–1.39	0.19
Overweight	0.57	0.41–0.78	0.001
Obese	0.50	0.36–0.69	<0.001
Severe obesity	0.60	0.38–0.97	0.04
Hypertension			
Underweight	0.89	0.53–1.47	0.64
Overweight	0.71	0.58–0.89	0.002
Obese	0.59	0.47–0.76	<0.001
Severe obesity	0.59	0.39–0.89	0.01
Chronic kidney disease			
Underweight	0.96	0.48–1.92	0.90
Overweight	0.64	0.45–0.91	0.01
Obese	0.50	0.34–0.76	0.001
Severe obesity	0.85	0.47–1.53	0.58
Chronic respiratory illness			
Underweight	1.57	0.94–2.59	0.08
Overweight	0.89	0.65–1.21	0.45
Obese	0.72	0.51–1.01	0.06
Severe obesity	0.85	0.52–1.41	0.53
Chronic liver disease			
Underweight	2.21	1.02–4.79	0.04
Overweight	0.92	0.64–1.33	0.66
Obese	0.77	0.52–1.14	0.19
Severe obesity	1.17	0.64–2.13	0.61

Table 4
Length of ICU stay and length of hospitalization among different BMI class compared to patients with normal BMI.

ICU length of stay (days)				Hospital length of stay (days)		
BMI	Coefficient	Confidence interval	p-value	Coefficient	Confidence interval	p-value
Group A (Elixhauser <0)						
Underweight	−0.34	−1.34 - 0.66	0.51	0.69	−1.33–2.70	0.51
Overweight	−0.05	−0.49 - 0.39	0.83	−0.42	−1.33–0.48	0.36
Obese	0.27	−0.19 - 0.73	0.25	0.28	−0.65–1.20	0.55
Severe obesity	0.89	0.29–1.51	0.004	0.96	−0.27–2.19	0.12
Group B (Elixhauser = 0)						
Underweight	−0.52	−1.68 - 0.64	0.38	−0.92	−3.05–1.20	0.39
Overweight	0.27	−0.19 - 0.73	0.25	−0.34	−1.18–0.51	0.43
Obese	0.42	−0.09 - 0.93	0.10	−0.16	−1.08–0.78	0.74
Severe obesity	−0.02	−0.95–0.90	0.96	0.61	−1.09–2.31	0.48
Group C (Elixhauser 1–5)						
Underweight	0.11	−1.38–1.59	0.89	−0.04	−2.85–2.78	0.98
Overweight	−0.02	−0.72–0.67	0.95	−0.43	−1.74–0.88	0.52
Obese	0.85	0.10–1.60	0.03	0.67	−0.75–2.09	0.36
Severe obesity	1.49	0.34–2.63	0.01	2.19	0.30–4.36	0.04
Group D (Elixhauser 6–13)						
Underweight	−1.41	−2.48 - -0.33	0.01	−1.03	−3.13–1.08	0.34
Overweight	0.28	−0.28–0.84	0.33	0.49	−0.59–1.58	0.38
Obese	0.55	−0.07–1.16	0.08	1.40	0.20–2.59	0.02
Severe obesity	1.77	0.68–2.85	0.001	0.84	−1.27–2.96	0.43
Group E (Elixhauser ≥14)						
Underweight	−1.21	−3.43–1.02	0.29	0.28	−4.99–5.54	0.92
Overweight	0.75	−0.50–1.99	0.24	−0.23	−3.19–2.74	0.88
Obese	0.41	−1–1.94	0.57	1.05	−2.31–4.42	0.54
Severe obesity	3.32	0.52–6.12	0.02	1.53	−5.10–8.16	0.65

p-value 0.001] and Group E [3.32 days (0.52–6.12, p-value 0.02]. Obese patients in group C [0.85 days (0.10–1.60, p-value 0.03] also had a longer length of ICU stay. The hospital length of stay longer for severely obese patients in Group C [2.19 days (0.30–4.36, p-value 0.04] and obese patients in Group D [1.40 days (0.20–2.59, p-value 0.02] (Table 4). There was no significant difference in the odds of ICU readmission in various BMI groups among different Elixhauser classes (Table 5).

Table 5
Odds of ICU readmission among different BMI class compared to patients with normal BMI.

ICU readmission			
BMI	Odds ratio	Confidence interval	p-value
Group A (Elixhauser <0)			
Underweight	1.43	0.57–3.55	0.45
Overweight	0.95	0.60–1.50	0.84
Obese	1.07	0.68–1.69	0.76
Severe obesity	1.02	0.56–1.85	0.94
Group B (Elixhauser = 0)			
Underweight	0.58	0.13–2.52	0.47
Overweight	1.03	0.65–1.64	0.91
Obese	0.72	0.42–1.24	0.23
Severe obesity	1.77	0.83–3.78	0.14
Group C (Elixhauser 1–5)			
Underweight	1.31	0.66–2.62	0.44
Overweight	0.81	0.56–1.15	0.23
Obese	0.75	0.51–1.10	0.15
Severe obesity	0.54	0.25–1.05	0.07
Group D (Elixhauser 6–13)			
Underweight	1.03	0.59–1.79	0.92
Overweight	0.79	0.59–1.06	0.12
Obese	0.86	0.62–1.17	0.33
Severe obesity	0.73	0.40–1.31	0.29
Group E (Elixhauser ≥14)			
Underweight	1.87	0.85–4.12	0.12
Overweight	1.01	0.62–1.64	0.98
Obese	0.62	0.34–1.13	0.12
Severe obesity	0.64	0.19–2.05	0.45

A sensitivity analysis was performed comparing the characteristics and outcomes between patients included in the study and those excluded due to lack of height or weight measurements. The two population were similar in terms of age and ethnicity, but the excluded population had higher percentage of females. The patients included in the study had higher percentage of CCU admissions, cardiac diagnoses of admission and comorbidities. However, the mean Elixhauser score and the percentage of population in different Elixhauser classes were similar. The occurrence of primary outcome of inpatient mortality was similar in both the groups. (Supplement 1).

4. Discussion

In our study, we classified critically ill patients according to their comorbidities burden using the Elixhauser score. Subsequently, we compared outcomes between the different BMI classes within the various Elixhauser Groups while adjusting for individual comorbidities. We found that obese and overweight individuals had decreased risk of inpatient and thirty-day mortality when compared to normal weight individuals, regardless of the difference in comorbidity burden. Underweight patients on the other hand, consistently had worse outcomes when compared to any other weight class. If MHO individuals were influencing the manifestation of the obesity paradox, we would expect to see the paradox only in the lower comorbid groups (groups A, B and C). Notwithstanding that expectation, our study showed a consistent trend of lower mortality with increasing BMI regardless of the comorbidity burden.

Several hypotheses have been proposed to explain this unanticipated mortality benefit of obesity in critically ill patients. First, obesity may be protective by altering the immune milieu in the body which helpful during critical illness. This phenomenon is referred to as preconditioning. Obese patients have higher levels of adipokines and inflammatory mediators, such as leptin and interleukin-10 secreted by fat cells. These cytokines may attenuate the inflammatory response and thus improve survival during critical illness [35,36]. In addition, it has

been shown that during critical illness, the adipose tissues macrophages shift from the proinflammatory M1 to anti-inflammatory M2 phenotype [37].

Additionally, obese individuals are thought to have a survival benefit because these patients have additional nutritional reserves, which can provide substrate during critical illness [38]. In a study by Harris et al., the survival disadvantage for BMI categories <25.0 kg/m2 was minimal or unobservable when compared to higher BMI categories when enteral nutrition was provided early in their critical illness. Among the cohort that did not receive early enteral nutrition, obese patients had a significant survival benefit [39]. This study supports the hypothesis that presence of additional nutritional reserves in the obese may also be responsible for the obesity paradox. Also, disparities in processes of care may explain better outcomes in obese patients. Obese patients have higher physical care requirements and diminished physiologic reserve. This may lead practitioners to triage obese patients to higher levels and standards of personal care [40].

The strength of our study is that we conducted our comparison only among individuals with similar comorbidity burden and performed adjustment for wide array of confounders. The sensitivity analysis showed no significant difference in the comorbidity burden as well as the primary outcome between the patients included in the study and those excluded because of lack of height or weight measurement. This further suggests the robustness of our findings. Our study has several limitations. Similar to prior studies, we were unable to adjust for the effect of fluid retention on BMI classification and for the selection bias of triaging similarly ill obese patients to higher level of care than non-obese patients [18,40]. Also, the use of BMI as a measure of obesity has been called into question [41-45]. However BMI, even with its limitations, continues to be the most widely used measure of obesity and was utilized in our study. Additionally, we used ICD-9 codes to determine the comorbidities for calculation of Elixhauser score. The fact that these codes are generated for reimbursement purposes could impact its precision in reflecting the comorbidities. Despite this limitation, Elixhauser has been shown to outperform other comorbidity indexes when used with an administrative data and was used in our study [46].

5. Conclusion

Our study demonstrates that a higher than normal BMI is associated with decreased mortality in critically ill patients, regardless of the type of comorbidity or the comorbidity burden. The presence of the mortality benefit in patients with the least comorbidity burden, similar to those with higher comorbidity burden, helps refute the hypothesis that metabolically health obese patients contribute to the obesity paradox. There is a need of prospective studies, with defined patient selection and treatment protocols, to further delineate the effect of BMI on the outcomes of critically ill patients.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.05.004.

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