Obesity is associated with improved early survival but increased late mortality in surgical patients with Sepsis: A propensity matched analysis

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BACKGROUND: While obesity is a risk factor for postoperative complications, its impact following sepsis is unclear. The primary objective of this study was to evaluate the association between obesity and mortality following admission to the surgical intensive care unit (SICU) with sepsis.

METHODS: We conducted a single center retrospective review of SICU patients grouped into obese (n = 766, body mass index ≥30 kg/m^2) and nonobese (n = 574; body mass index, 18–29.9 kg/m^2) cohorts. Applying 1:1 propensity matching for age, sex, comorbidities, sequential organ failure assessment, and transfer status, demographic data, comorbidities, and sepsis presentation were compared between groups. Primary outcomes included in-hospital and 90-day mortality, ICU length of stay, need for mechanical ventilation (IMV) and renal replacement therapy (RRT). $p < 0.05$ was considered significant.

RESULTS: Obesity associates with higher median ICU length of stay (8.2 vs. 5.6, $p < 0.001$), need for IMV (76% vs. 67%, $p = 0.001$), ventilator days (5 vs. 4, $p < 0.004$), and RRT (23% vs. 12%, $p < 0.001$). In-hospital (29% vs. 18%, $p < 0.0001$) and 90-day mortality (34% vs. 24%, $p = 0.0006$) was higher for obese compared with nonobese groups. Obesity independently predicted need for IMV (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.2–2.1), RRT (OR, 2.2; 95% CI, 1.5–3.1), in-hospital (OR, 2.1; 95% CI, 1.5–2.8), and 90-day mortality (HR, 1.4; 95% CI, 1.1–1.8), after adjusting for sequential organ failure assessment, age, sex, and comorbidities. Comparative survival analyses demonstrate a paradoxical early survival benefit for obese patients followed by a rapid decline after 7 days (logrank $p = 0.0009$).

CONCLUSION: Obesity is an independent risk factor for 90-day mortality for surgical patients with sepsis, but its impact appeared later in hospitalization. Understanding differences in systemic responses between these cohorts may be important for optimizing critical care management. (*J Trauma Acute Care Surg.* 2024;97: 233–241. Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic and Epidemiological; Level III.

KEY WORDS: Emergency general surgery outcomes; obesity; sepsis.

While obesity is a known predictor of all-cause mortality in hospitalized patients, its impact on outcomes following sepsis is poorly characterized.[1] It is estimated that over 25% of patients admitted with sepsis have obesity as a comorbidity, which can rise to 60% within patients presenting with intra-abdominal sepsis.[2–5] Obesity is associated with significant end-organ complications, including insulin resistance and type 2 diabetes, hypertension, obstructive sleep apnea, and peripheral vascular disease.[6–9] Both murine and human studies have shown that obesity is associated with chronic low-grade inflammation, which disrupts adaptive and innate immune function, endothelial integrity, glycemic control, and the normal gut microbiota.[6,8,10–15] These impairments are thought to exacerbate proinflammatory responses in obese versus lean mice in the setting of sepsis, with a resultant increase in mortality.[16,17]

Clinically, the association between obesity and sepsis outcomes is unclear. Several meta-analyses and systematic reviews report conflicting data, some supporting an "obesity paradox" whereby increasing body mass index is protective, while others demonstrate increased morbidity and mortality.[18–21] Review of the Vasopressin and Septic Shock Trial cohort demonstrates lower mortality for obese patients with septic shock, as well as lower initial IL-6 response.[22] In addition, large retrospective analyses support the observation that obese individuals exhibit lower short term mortality in patients with sepsis.[23] Furthermore, human translational data confirm that while obese individuals have higher levels of circulating inflammatory cytokines at baseline, they exhibit a blunted response to infectious stimuli.[24–26] Importantly, many of these studies either combine medical and surgical causes of sepsis or exclude surgical patients altogether. This is an important distinction for surgical patients, where obesity and its related complications are known independent predictors of surgical morbidity and mortality.[27–29]

While there appears to be a relationship between obesity and short-term mortality, the long-term combinatorial effects of obesity and sepsis are poorly understood. Given these findings, the primary objective of this study is to evaluate the association between obesity and 90-day mortality in surgical patients admitted to the ICU with sepsis. Secondary objectives evaluated included inpatient critical care needs, including ventilator and renal replacement therapy requirement, ICU and overall length of stay (LOS), and discharge disposition. We hypothesized that obesity would be associated with increased 90-day mortality and end organ dysfunction for surgical patients admitted with sepsis.

METHODS

Patients and Study Design

All patients admitted to a large quaternary surgical ICU were retrospectively reviewed in a 5-year period from January 1, 2014, to July 1, 2019. All data were maintained and collected in an institutionally approved and reviewed database. Inclusion criteria were (1) surgical patients admitted to the surgical ICU 2) age ≥18 years and (3) diagnosis of sepsis (sequential organ failure assessment (SOFA) ≥ 2). Patients were excluded if they were prisoners, pregnant, or did not have complete mortality data up to 90 days from the index admission. In addition, readmissions were removed from analysis. Patients were subsequently categorized by whether they

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were obese (body mass index [BMI], ≥30 kg/m^2) or nonobese (BMI, 18.5–29.9 kg/m^2). Patients who were underweight (BMI, <18.5 kg/m^2) were excluded from this analysis, as underweight BMI was considered a surrogate for cachexia and malnutrition, which is a known risk factor for mortality following sepsis.[30–32] The overall sample size included 1340 patients, of which 766 were obese and 574 were nonobese.

Data Collection and Outcome Measures

The Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) guidelines were used to ensure proper reporting of methods, results, and discussion (Supplemental Digital Content, http://links.lww.com/TA/D649). All variables reported were retrieved using the electronic medical record. Our institutional medical record is linked to most hospitals located within the state, allowing us to capture data for patients transferred from outside hospitals. This feature was utilized to document presenting laboratory data and diagnoses for hospital transfers. Baseline characteristics reported included demographic data (age, sex, race [non-Hispanic white, Black, other, or unknown]), and transfer status (yes/no). Selected pre-hospitalization comorbidities were documented based on admission documentation and included congestive heart failure (CHF), type 2 diabetes (T2DM), moderate to severe liver disease, chronic obstructive pulmonary disease (COPD), stage III and above chronic kidney disease (CKD), metastatic cancer, and median Charlson Comorbidity index. Baseline laboratory data and sepsis data were obtained for the patient's initial presentation. This included median SOFA score, vasopressor use on admission, median lactate (mmol/L), white blood cell count (K/m, WBC), hemoglobin (g/dL, Hgb), and creatinine (mg/dL). The initial source of sepsis was determined based on in-depth chart review and included the following: line-associated sepsis, respiratory, intra-abdominal (hepatobiliary, foregut, small and large bowel, ob/gyn), skin and soft tissue (burn, soft tissue infection), renal/urologic, orthopedic, and head and neck and thoracic. Additionally, we catalogued the index procedure for all patients in this study.

The primary outcome for this study was in-hospital and cumulative 90-day mortality. Additional outcomes evaluated included overall and ICU LOS, need for invasive mechanical ventilation and days on ventilator, renal failure and need for renal replacement therapy (RRT). Discharge disposition for patients who survived was categorized as home, skilled nursing facility or long term acute care hospital (SNF/LTACH), and discharge to home or inpatient hospice.

Statistical Analyses

Patients were grouped into nonobese (BMI, 18–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) cohorts. Baseline characteristics and comorbidities, and sepsis presentation were compared between groups. Student's *t* tests or Wilcoxon Rank sum tests were run for continuous parametric and nonparametric values, respectively, and χ^2 and Fischer's exact tests were utilized for categorical variables. Next, we performed 1:1 greedy propensity score matching between groups, with a caliper of 0.2, using SOFA, age, sex, transfer status, and Charlson Comorbidity Index. We elected to utilize transfer as a variable in this matching, as we have previously shown that transfer status is associated with a significant, independent risk of mortality following admission to our surgical ICU.[4] This yielded two cohorts, each containing 528 patients. These variables were chosen based on significant differences we observed in unmatched bivariate analyses and to mitigate known confounders that are implicated in sepsis mortality. All baseline analyses were then repeated with our

TABLE 1. Baseline Demographics and Comorbidities of Patients Admitted to the Surgical ICU in Unmatched and Matched Cohorts

	Unmatched: Obesity			Matched: Obesity		
Variables	**No (n = 574)/**	**Yes (n = 766)**	***p***	**No (n = 528)**	**Yes (n = 528)**	***p***
Transferred yes/no, n (%)	238 (41.5)	393 (51.3)	<0.0005	226 (43.0)	254 (48.0)	0.10
Age (years): mean SD	59.8 (16.4)	60.9 (14.2)	0.22	60.4 (15.6)	58.9 (14.1)	0.0516
Geriatric population (*n*, %)						
65–74 y	123 (21.4)	207 (27.0)	0.05	118 (52.44)	124 (64.25)	0.0490
75–84 y	92 (16.0)	106 (13.8)		88 (39.11)	58 (30.05)	
85 y	25 (4.4)	21 (2.7)		19 (8.44)	11 (5.70)	
Female, n (%)	211 (36.8%)	382 (50.0)	<0.0005	209 (39.58)	190 35.98)	0.2279
Antecedent trauma, n (%)	61 (10.6)	46 (6.01)	0.002	47 (8.9)	37 (7.0)	0.24
Race, n (%)						
Non-Hispanic White	480 (83.6)	668 (87.2)	0.19	454 (85.98)	449 (85.04)	0.9679
Black	63 (11.0)	69 (9.0)		52 (9.85)	57 (10.80)	
Other	21 (3.7)	23 (3.0)		16 (3.03)	16 (3.03)	
Unknown	10 (1.7)	6 (0.8)		6 (1.14)	6 (1.14)	
Selected comorbidities, *n* (%)						
CHF	39 (6.8)	80 (10.4)	0.02	34 (6.44)	47 (8.90)	0.1328
T2DM	115 (20.0)	270 (35.3)	<0.005	106 (20.08)	201 (38.07)	<0.0001
Moderate/severe liver disease	42 (7.3)	43 (5.6)	0.21	40 (7.58)	33 (6.25)	0.3958
COPD	110 (19.2)	173 (22.6)	0.13	106 (20.08)	124 (23.48)	0.1796
Stage III to IV CKD	59 (10.3)	92 (12.0)	0.32	50 (9.47)	67 (12.69)	0.0956
Metastatic cancer	34 (5.9)	0 (5.2)	0.58	31 (5.87)	29 (5.49)	0.7903
Charlson Comorbidity Index: p50 (IQR)	4 (2–6)	4 (2–6)	0.24	4 (2–6)	4 (2–5)	0.5369

matched cohorts. Primary and secondary outcomes were compared using both unmatched and matched cohorts. Cox Proportional Hazards regression models were utilized to determine baseline predictors of in-hospital and 90-day mortality, using both matched and unmatched cohorts. To assess the implications of obesity on mortality, we adjusted for clinically relevant variables, including admission SOFA, age, sex, congestive heart failure, and liver dysfunction, as well as baseline comorbidities that remained statistically different between cohorts, such as type 2 diabetes. In addition, we performed multiple logistic regression to model predictors of respiratory and renal failure, using all variables of interest to the outcome. No backwards or forwards selection was carried out on the final models presented. Finally, Kaplan-Meier 90-day survival curves were compared between matched obese and nonobese cohorts. A p value of <0.05 was considered statistically significant.

RESULTS

Comparative Baseline Demographic and Comorbidity Data Between Obese and Nonobese Cohorts

Over half of the study cohort was obese (n = 766, 57.2%). In the unmatched bivariate analyses, patients with obesity were significantly more likely to be female, have been transferred from an outside hospital, and were more likely to have type 2 diabetes and congestive heart failure at baseline (Table 1). Patients with obesity were less likely to present with sepsis following a trauma. There were no differences in race. Selected comorbidities such as liver disease, COPD, stage III or higher chronic kidney disease, cancer or Charlson Comorbidity Index were comparable between groups. After 1:1 propensity matching, each cohort retained 528 patients. Comparative baseline characteristics for our matched cohort are summarized in Table 1. The distribution of baseline characteristics and comorbidities was comparable between cohorts following matching, with the exception of lower median age ($p = 0.05$) and higher prevalence of type 2 diabetes ($p < 0.001$) in the cohort with obesity.

Comparison of Sepsis Severity and Source and Index Procedure in Obese and Nonobese Patients

Admission SOFA score, use of vasopressor, serum lactate, white blood cell count, hemoglobin, and creatinine were compared (Table 2). Using unmatched cohorts, patients with obesity presented with a higher median white blood cell count and creatinine compared with nonobese patients. Overall, 65% of the patients included in this cohort underwent emergency general surgery (inclusive of intra-abdominal surgery, soft tissue debridements), while the remainder represent sepsis secondary to

TABLE 2. Laboratory and Admission Characteristics for Patients Admitted to the SICU With sepsis in Unmatched and Matched Cohorts

	Unmatched: Obesity			Matched: Obesity		
Variables	**No (n = 574)**	**Yes (n = 766)**	***p***	**No (n = 528)**	**Yes (n = 528)**	***p***
Clinical presentation						
SOFA: median (IQR)	5 (3–8)	6 (4–8)	0.33	5 (3–8)	6 (4–8)	0.4693
Vasopressor use on admission, *n* (%)	200 (34.8)	303 (39.6)	0.08	185 (35.04)	202 (38.26)	0.2776
Lactate on presentation, median (IQR)	2.3 (1.5–3.8)	2.0 (1.4–3.6)	0.17	2.3 [1.5, 3.8]	2.0 [1.4, 3.6]	0.2310
WBC on admission, median (IQR)	12.8 (6.8–19.4)	13.9 (8.5–20.3)	0.007	12.8 (7–19.4)	13.7 (8.5–20.8)	0.04
Hgb on admission, median (IQR)	9.7 (8.3–11.5)	9.8 (8.5–11.4)	0.67	9.7 (8.2–11.4)	9.9 (8.5–11.7)	0.25
Creatinine on admission, median (IQR)	1.1 (0.8–1.7)	1.3 (0.9–2.3)	<0.0005	1.12 (0.75–1.7)	1.35 (0.89–2.4)	<0.0005
Sepsis source						
0. Other/unknown/line-associated	27 (4.7)	38 (5.0)	0.35	24 (4.6)	31 (5.8)	0.35
1. Respiratory	64 (11.2)	73 (9.6)	55 (10.5)	53 (10.0)		
2. Intra-abdominal (HPB, foregut, small and large bowel, other, and ob/gyn)	350 (61.1)	464 (60.7)	328 (62.5)	323 (61.2)		
3. Skin/soft tissue (burn and NSTI)	64 (11.2)	116 (15.2)	57 (10.9)	77 (14.6)		
4. Renal/urologic	36 (6.3)	40 (5.2)	33 (6.3)	23 (4.4)		
5. Orthopedic	15 (2.6)	17 (2.2)	12 (2.3)	9 (1.7)		
6. Head and neck, thoracic	17 (3.0)	16 (2.1)	16 (3.1)	12 (2.3)		
Procedure category						
0. None	105 (18.3)	103 (13.5)	0.01	94 (17.9)	68 (12.88)	0.10
1. Exploratory laparotomy/laparoscopy (including urology, gyn, bowel)	299 (52.2)	423 (55.4)	281 (53.5)	298 (56.4)		
2. Soft tissue debridement (including Burn)	51 (8.9)	105 (13.7)	45 (8.6)	69 (13.1)		
3. IR procedure (when the sole intervention): including therapeutic embolization, perc drainage (not included if accompanied by invasive procedure otherwise described)	28 (4.9)	43 (5.6)	27 (5.1)	24 (4.6)		
4. Therapeutic endoscopy (when the sole intervention, not included if accompanied by invasive procedure otherwise described)	35 (6.1)	43 (5.6)	31 (6.1)	32 (6.1)		
5. Thoracic and head and neck (excluding foregut)	20 (3.5)	14 (1.8)	19 (3.6)	13 (2.5)		
6. Neurosurgery	11 (1.9)	9 (1.2)	7 (1.3)	9 (1.7)		
7. Orthopedic/vascular	24 (4.2)	24 (3.1)	20 (3.8)	15 (2.8)		

other surgical sources. There were no significant differences in sepsis source between groups, with intra-abdominal sources being most common, followed by skin and soft tissue. The type of index procedure was statistically different between groups, with a higher proportion of soft tissue debridements in the obese cohort and increased head and neck operations in the nonobese group. These analyses were performed in the matched cohorts and are summarized in Table 2.

Hospital Outcomes for Obese and Nonobese Surgical Patients With Sepsis

Comparative outcomes are summarized between unmatched and matched cohorts in Table 3. In unmatched analyses, patients with obesity demonstrated higher median ICU LOS but lower overall LOS, excluding in-hospital mortalities. The incidence of respiratory and renal failure was significantly higher in the obese cohort, with a near doubling in the incidence of renal failure. Median days spent receiving renal replacement therapy (RRT) or on mechanical ventilation were not statistically different between unmatched cohorts. Both in-hospital and cumulative 90-day mortality were significantly higher in the obese versus nonobese cohort. We performed a subgroup analysis to characterize comparative mortality across obesity classifications (see Table 3). There was no statistical difference in mortality across obesity classifications for both in-hospital and cumulative 90-day mortality. Discharge disposition was comparable between groups. Within matched groups, median ICU LOS was significantly longer for patients with obesity but was not significant when excluding in-hospital deaths. Overall LOS was comparable. In-hospital and cumulative 90-day mortality remained significantly higher in the obese versus the control cohort after matching.

Predictors of Mortality, Respiratory, and Renal Failure

Baseline characteristics predictive of mortality, respiratory, and renal failure were modeled in Table 3 and Table 4. Following matching, in-hospital mortality was independently predicted by increasing admission SOFA and age, having COPD or baseline moderate to severe liver dysfunction, being transferred from an outside hospital, antecedent trauma, and obesity, with an associated hazards ratio (HAZ. ratio) of 2.1 (95% confidence interval [CI], 1.5–2.9). Undergoing an exploratory laparotomy (compared with nonoperative management) was associated with a significant increase in the hazards ratio of in-hospital mortality (HAZ ratio, 1.64; 95% CI, 1.03–2.64). Obesity was an independent predictor of 90-day mortality (HAZ. ratio, 1.6; 95% CI, 1.2–2.2), with severe liver dysfunction, transfer status, COPD, antecedent trauma, increasing age and SOFA score remaining significant. Procedurally, undergoing a soft tissue debridement (compared with nonoperative management) was associated reduction in the hazards ratio for cumulative 90-day mortality (HAZ. ratio, 0.45; 95% CI, 0.24–0.86). Next, we modeled predictors of respiratory failure in this patient population in both matched and unmatched cohorts. Following matching, obesity was an independent predictor of respiratory failure requiring mechanical ventilation, along with increasing baseline SOFA scores. Covariates chosen to model predictors of renal failure included admission SOFA, obesity, age,

TABLE 3. Comparative Outcomes Following Admission to the Surgical ICU in Matched Cohorts

	Matched: obesity		
Variables	**No (n = 528)**	**YES (n = 528)**	***p***
ICU LOS (days): p50 (IQR)	5.6 (2.6–13.3)	8.2 (3.6–18.1)	<0.0001
LOS (excluding in-house deaths): p50 (IQR)	19.0 (11.0–33.0)	18.5 (10.0–31.0)	0.9100
Overall LOS (days): p50 (IQR)	20.0 (12.0–33.0)	19.0 (12.0–32.0)	0.4091
LOS (excluding in-house deaths): p50 (IQR)	19 (11–33)	20 (12–32)	0.34
Respiratory failure, *n* (%)	354 (67.3)	303 (76.4)	0.001
Time on vent (days): p50 (IQR)	4 (2–9)	5 (2–12)	0.006
Renal failure, *n* (%)	61 (11.6)	123 (23.3)	<0.0005
Days on renal replacement therapy (days): p50 (IQR)	6 (3–12)	7 (3–16)	0.26
In-house mortality	96 (18.18)	154 (29.17)	<0.0001
90-d Mortality	129 (24.43)	180 (34.09)	0.0006
In-house mortality by BMI classification within obese patients			
Class I obesity: BMI 30–35		57 (27.5)	0.76
Class II obesity: BMI 35–40		40 (31.3)	
Class III obesity: >40-		57 (29.4)	
Cumulative 90-d mortality by BMI classification with obese patients			
Class I obesity: BMI 30–35		72 (34.8)	1.0
Class II obesity: BMI 35–40		45 (35.2)	
Class III obesity: >40		68 (35.1)	
Discharge disposition, n (%)			
Home	137 (31.93)	104 (27.96)	0.4727
SNF/LTACH	268 (62.47)	246 (66.13)	
Hospice	24 (5.59)	22 (5.91)	

TABLE 4. Cox Proportional Hazards Model for In-House and 90-Day Mortality in Matched and Unmatched Cohorts

	In-Hospital Mortality				Cumulative 90-Day Mortality			
	Matched Cohort				Matched Cohort			
Covariates	**HAZ. Ratio**	**Std. Error**	**95% CI**	***p***	**HAZ. Ratio**	**Std. Error**	**95% CI**	***p***
SOFA	1.15	0.028	1.10–1.21	<0.0001	1.13	0.025	1.08–1.18	<0.0001
Obese vs. nonobese	2.11	0.35	1.52–2.92	<0.0001	1.61	0.24	1.20–2.16	0.001
Age	1.04	0.006	1.027–1.052	<0.0001	1.035	0.0056	1.024–1.046	<0.0001
Female sex	0.961	0.162	0.697–1.345	0.85	1.0	0.15	0.74–1.34	0.994
COPD	1.97	0.36	1.38–2.81	<0.0005	1.84	0.31	1.31–2.60	<0.005
CHF	1.04	0.19	0.62–1.85	0.800	0.72	0.19	0.42–1.21	0.22
Diabetes (controlled and complicated)	1.04	0.18	0.73–1.48	0.818	1.13	0.185	0.82–1.56	0.44
Moderate to severe liver dysfunction	2.43	0.68	1.40–4.21	0.002	2.48	0.66	1.47–4.2	0.001
Procedure (compared with no operation)								
Exploratory laparotomy	1.64	0.40	1.03–2.64	0.04	1.37	0.29	0.91–2.08	0.13
Soft tissue debridement	0.58	0.21	0.28–1.19	0.14	0.45	0.15	0.24–0.86	0.015
IR procedure	1.14	0.49	0.49–2.65	0.77	0.91	0.35	0.43–1.95	0.82
Therapeutic endoscopy	1.07	0.44	0.47–2.42	0.87	0.75	0.28	0.36–1.56	0.44
Thoracic/head and neck	1.07	0.61	0.35–3.28	0.90	0.54	0.30	0.19–1.58	0.26
Neurosurgery	0.90	0.67	0.21–3.89	0.78	0.85	0.55	0.24–3.04	0.80
Orthopedic/vascular	1.16	0.62	0.41–3.31	0.78	0.68	0.34	0.25–1.82	0.44
Trauma	3.04	0.91	1.70–5.48	<0.005	2.17	0.61	1.24–3.77	0.006
Transfer (yes vs. no)	1.94	0.31	1.41–2.66	<0.0005	1.73	0.25	1.30–2.30	<0.0001

sex, COPD, diabetes, moderate to severe liver dysfunction, stage III or higher CKD, CHF, and transfer status (Table 5).

Impact of Obesity on Survival Following Admission to the Surgical ICU

Kaplan Meier survival curves for 90-day survival were generated and compared between matched obese and nonobese cohorts (Fig. 1A). Overall survival curves were significantly different between obese and nonobese patients, with overall survival significantly lower in the obese cohort at 90 days. However, the survival curve for the obese cohort exhibited a paradoxical increase in survival during the first 7 days from admission, which was also statistically significant from the nonobese cohort. This survival difference is magnified in Figure 1B. Following this time point, the survival curve for the obese cohort demonstrates a steep decline in survival, which is carried out to the 90-day time point.

DISCUSSION

The objective of this study was to evaluate the obesity paradox within a surgical cohort of patients with sepsis. To our knowledge, this is the first study to examine the implications of obesity in sepsis in a large cohort of surgical patients, of which the majority underwent emergency general surgery. Within surgical patients with sepsis, we demonstrated that obesity was independently associated with increased overall 90-day and in-hospital mortality compared with nonobese patients. Furthermore, obesity remained an independent predictor of respiratory and renal failure during the index admission.

TABLE 5. Predictors of Respiratory and Renal Failure

Respiratory Failure Requiring Mechanical Ventilation					Renal Failure Requiring RRT				
	Matched Cohort					Matched Cohort			
Covariates	**OR**	**Std. Error**	**95% CI**	***p***	**Covariates**	**OR**	**Std. Error**	**95% CI**	***p***
SOFA	1.137	0.0240	1.085–1.192	<0.0001	SOFA	1.1	0.27	1.05–1.16	<0.005
Obese vs. Nonobese	1.561	0.1446	1.176–2.072	0.0021	Obese vs. nonobese	2.18	0.39	1.54–3.1	<0.005
Age	0.998	0.00474	0.989–1.008	0.7054	Age	0.99	0.006	0.98–1.00	0.20
Female sex	0.949	0.1464	0.712–1.264	0.7182	Female sex	0.62	0.11	0.44–0.90	0.01
COPD	1.316	0.1816	0.922–1.878	0.1309	COPD	1.27	0.25	0.85–1.87	0.24
Diabetes	0.869	0.1604	0.634–1.189	0.3798	Diabetes	1.14	0.21	0.80–1.63	0.46
Moderate to severe liver dysfunction	1.296	0.3005	0.719–2.336	0.3878	Moderate to severe liver dysfunction	1.4	0.43	0.77–2.54	0.26
CHF	1.205	0.2829	0.692–2.097	0.5103	CKD Stage III or higher	2.26	0.54	1.42–3.60	0.001
Transfer (yes vs. no)	1.255	0.1425	0.949–1.660	0.1110	CHF	0.94	0.29	0.51–1.72	0.835
					Transfer (yes vs. no)	0.87	0.15	0.62–1.21	0.42

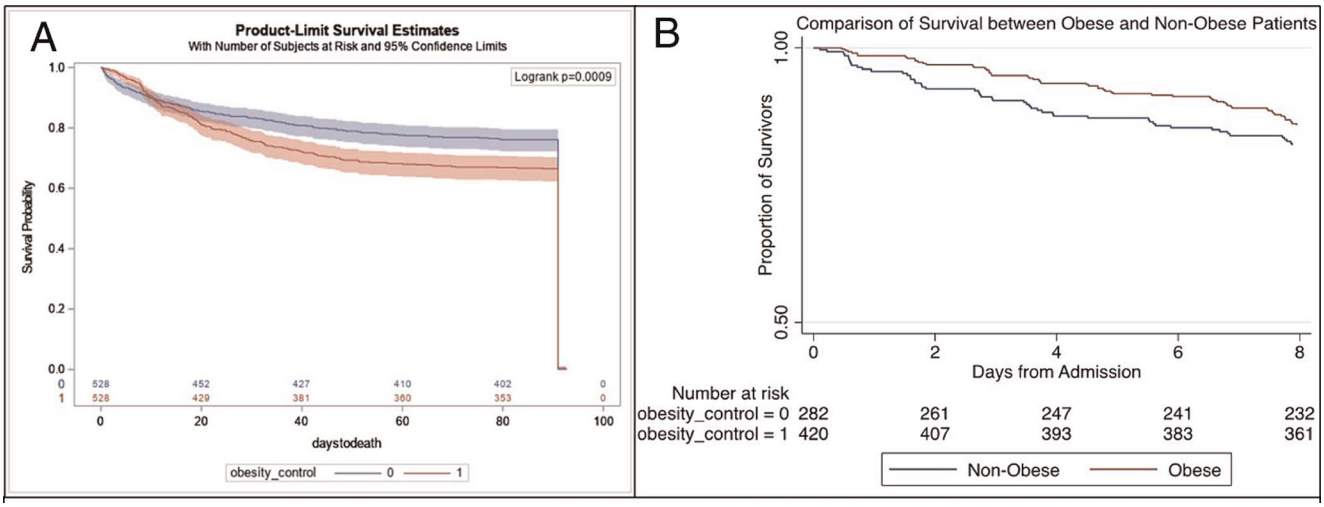

Figure 1. Comparative adjusted Kaplan-Meier curves for obese and nonobese patients using matched cohorts for overall 90-day (*A*) and early survival within 8 days of admission (*B*). (*A*) Biphasic distribution of survival in obese versus lean cohorts, with an initial survival benefit in the early period. Shaded areas include 95% CIs. This survival benefit is magnified in panel *B*.

Interestingly, when comparing survival curves between both cohorts, patients with obesity exhibited two distinct phases compared with lean patients. The first 7 days following hospitalization was characterized by a statistically significant improvement in survival compared with the nonobese cohort, reflecting a 33% reduction in early mortality among obese patients. A precipitous drop in survival followed this time point, resulting in a higher cumulative 90-day mortality compared with nonobese patients. Overall, using robust statistical analyses including propensity matching, these data support the conclusion that obese surgical patients had a significantly higher in-hospital and cumulative 90-day mortality, while also exhibiting a paradoxical survival benefit in the early period following their septic insult.

While there are many conflicting studies on the obesity paradox in critically ill patients, the majority of these utilize nonsurgical cohorts. This is an important distinction, as sepsis is not one unique phenomenon, and operative interventions likely have significant implications for modulating the sepsis phenotype. The closest study to ours evaluated the impact of BMI on 60-day mortality in over 12,000 patients admitted to a surgical ICU.[33] Notably, their data suggested improved survival with higher BMI. However, when analyzing the cohort for this study, nearly 10% of these admissions were medical and more than 70% were elective surgical cases.[33] This contrasts significantly to our cohort, the majority of which were urgent surgical admissions with intra-abdominal sepsis. Therefore, one plausible explanation for the divergence of results between these two studies is that the impact of obesity has differential effects based on the type of patient (medical vs. surgical), the disease process (sepsis vs. other organ failure), and the sepsis source (intra-abdominal, skin and soft tissue, trauma).

To this point, previously published data from our own institution demonstrated significant variability in outcomes based on sepsis source, with mortality being highest in patients with intra-abdominal sepsis and lowest in those with urologic sources of infection.[34] In another study analyzing the impact of obesity for outcomes following necrotizing soft tissue infections, class II obesity was associated with decreased adjusted in-hospital and 90-day mortality compared with other weight categories.[35] Conversely, Arbabi et al. noted that rising BMI was associated with decreased injury severity score in trauma patients but a paradoxical increase in adjusted mortality.[28] Thus, despite a protective "cushion effect" that reduced presenting injury severity, obese patients demonstrated worsened systemic outcomes following traumatic insults.[28,36] These findings may be particularly relevant when considering our own study, as traumatic injury is associated with significant immune disruption, comparable in many ways to sepsis.[37] Secondly, trauma patients often require emergent surgical intervention, a characteristic our study cohort shares. Taken together, these data suggest that the implications of obesity vary significantly based on the specific surgical population and obesity classification. Unfortunately, our current data set was not powered to detect nuances in comparative mortality by procedure category between obese and nonobese patients. Future studies will focus on elucidating this interaction more comprehensively.

A particularly notable finding from this study is the biphasic trend in survival exhibited by obese surgical patients compared with the lean cohort. Septic surgical patients with obesity demonstrated a paradoxical improvement in survival compared with lean patients in the first 7 days of their hospitalization, followed by a rapid decline between Days 7 and 90. While the mechanism behind this is likely multifactorial, the immunologic dysregulation associated with obesity undoubtedly plays an important role in this initial "obesity paradox." Although obesity is associated with chronic, low-grade inflammation, immune cell functionality can be impaired under these circumstances. Cichon et al. demonstrated that while neutrophils from obese mice were more likely to be chronically activated and spontaneously form neutrophil extracellular traps (NETs), they formed less NETs in response to LPS compared with lean mice.[38] This suggests that obese neutrophils may be chronically exhausted and less responsive in the setting of a septic insult.[39] Given the importance of neutrophil function in pathogen clearance and wound

healing, this consequence likely has significant ramifications for surgical patients with sepsis. Baseline neutrophil dysfunction may contribute to a relative immunologic anergy that reduces the overwhelming proinflammatory cascade in the early phase of sepsis, while leaving the patients more susceptible to longer term morbidity, including secondary infections, surgical complications, and the development of persistent inflammation immunosuppression catabolism syndrome.[40] Obesity is associated with regulatory T cell exhaustion, as well as polarization of macrophages to proinflammatory M1 subtypes. These changes are associated with downstream systemic consequences, such as peripheral vascular disease and type II diabetes. Given the systemic immune changes associated with sepsis, it is likely that there are significant derangements associated with exposing chronically inflamed immune cells to a new septic insult. This may explain the rapid decline patients with obesity exhibited in this study further along in their hospitalization after a septic insult.

LIMITATIONS

This study is limited by its retrospective nature and represents data from a single institution. Given the heterogeneity of surgical patients, we acknowledge that there are many other factors in the surgical course of these patients that may impact mortality. To this point, we included details about sepsis source and index procedure to alleviate some of these concerns. However, the number of reoperations and the impact of specific abdominal pathologies on morbidity and mortality are clearly relevant to this study and will need to be analyzed in future studies. For example, the type of intervention, length of operation, and modality (minimally invasive vs. open) are known procedural variables that can modify morbidity and mortality in surgical patients. Unfortunately, this study cohort was not powered to statistically elucidate nuances in mortality across these procedural considerations. Another important confounder that we were unable to adjust for is malnutrition. While this is often underrecognized in obese patients, malnutrition has been demonstrated to be a significant predictor of surgical outcomes. Furthermore, given its implications for frailty, understanding the interplay between obesity and malnutrition will be an important area of research in future studies. Our current database does not include robust data on prehospital nutritional status and could not be included for this analysis. Prior studies have found that mortality may not be equally distributes across weight classification.[41,42] In our study, subgroup analysis did not reveal any statistical difference in mortality across obesity category (see Table 3). One reason for this discrepancy may be that nuances in mortality by obesity classification are procedurally dependent or vary across different sepsis sources. This study was not powered to evaluate these interactions, representing another limitation in our conclusions. Similarly, diabetes has been associated with worsening surgical outcomes and mortality. Our data set did not reveal that diabetes was a significant predictor of mortality within our cohort, although granular data regarding degree of pre-admission control, medication versus insulin therapy, and time with diagnosis were not available for this study. This represents an area for future investigations. fFinally, additional laboratory surrogates for inflammation, such as cytokine data, c-reactive protein, and erythrocyte sedimentation rate, are not included in this data set and would add important insight into differences in immunologic responses between these cohorts.

CONCLUSION

Despite the above limitations, this is a robust evaluation of the implications of obesity on morbidity and mortality following sepsis in surgical patients. We think these data convincingly demonstrate that obesity is associated with a paradoxical improvement in early survival after a septic insult and a rapid increase in mortality later in the index hospitalization. This study provides novel insight into the obesity paradox within surgical patients with sepsis. Future studies evaluating the immunologic impact of obesity on sepsis-induced immune dysregulation will be paramount, both in exploring the immediate survival benefit and understanding the pathophysiology of increased later mortality. Understanding the physiologic differences that may mediate these outcome disparities may ultimately provide crucial insight into new treatment strategies for obese and lean septic surgical patients.

AUTHORSHIP

A.J., W.W., J.W., S.S., and R.T. contributed in the conception and study design. A.J., C.C., W.K., and W.W. helped in literature review. A.J., M.I., C.C., W.K., and J.W. managed data acquisition. A.J., M.I., W.K., C.C., S.S., R.T., W.W., and J.W. performed data analysis and interpretation. A.J., C.C., W.K., W.W., and J.W. helped in the drafting of the manuscript. A.J., W.W., and J.W. performed critical revision.

DISCLOSURE

Conflict of Interest Disclosure Statement: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D650).
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