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The Obesity Paradox Revisited

Is Obesity Still a Protective Factor for Patients With High Comorbidity Burden or High-Complexity Procedures?

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Objective: To investigate the relationship between obesity and postoperative mortality in the context of high procedural complexity and comorbidity burden.

Background: The "obesity paradox" suggests better postoperative outcomes in patients with higher body mass index (BMI), despite obesity's associated health risks. Research remains scarce on the influence of procedural complexity and comorbidities on the obesity–postoperative mortality relationship.

Methods: We performed an observational study of adult patients undergoing major surgery using the 2016 to 2019 National Surgical Quality Improvement Program database. The outcome was 30-day mortality. We first estimated the risk-adjusted effects of BMI on mortality across the full cohort via multivariable regression and restricted cubic spline models. Then, we investigated the subgroups stratified by procedural complexity and comorbidity burden using a modified Charlson Comorbidity Index (mCCI) and mortality probability.

Results: Among 3,085,582 patients, 47% had obesity. There was a reverse J-shaped relationship between BMI and mortality in the full cohort, consistent with the obesity paradox. However, no difference in odds of mortality was observed in patients with obesity who underwent high-complexity procedures compared with normal BMI counterparts (BMI 30–34.9: odds ratio, 0.93 [95% confidence interval: 0.86–1.01]; BMI 35–39.9: 0.92 [0.83–1.03]; BMI ≥ 40: 0.94 [0.83–1.07]), and in patients with obesity with high comorbidity burden (mCCI ≥ 8 [BMI 30–34.9: 0.95 (0.77–1.16); BMI 35–39.9: 0.78, (0.60–1.02); BMI ≥ 40: 0.84 (0.63–1.12)] and top 3% mortality probability [BMI 30–34.9: 0.96 (0.90–1.02); BMI ≥ 40: 0.94 (0.86–1.01)]).

Conclusion: Our findings suggest the existence of an obesity paradox in most adult surgical patients, yet the trend dissipates with high procedural complexity and comorbidity burden.

Keywords: comorbidity, obesity, postoperative mortality, procedure complexity

INTRODUCTION

Obesity has become a widespread and escalating public health issue, affecting individuals across all demographics in both developed and emerging nations. The World Health Organization reported a near tripling in the prevalence of obesity since 1975, projecting a 20% obesity rate by 2030.[1] Meanwhile, it is estimated that almost half of the adult population in the United States will have obesity by that same year.[2] In parallel, there is an observable surge in obesity among surgical patients, necessitating a critical analysis of its impact on surgical outcomes. Obesity contributes to a spectrum of medical comorbidities, such as coronary artery disease, hypertension, diabetes, and hyperlipidemia, alongside an elevated risk for specific malignancies.[3] These conditions, concomitant with obesity, predispose patients to increased metabolic demands, which can precipitate cardiac failure, hemodynamic instabilities, and airway compromise during surgical interventions.[4]

Counterintuitively, a body of research suggests that patients with obesity experience superior outcomes compared with their normal-weight counterparts in the face of critical illness or surgical stress.[5–7] This phenomenon is described as the obesity paradox and refers to the observation that despite the long-term health risks associated with obesity, a higher body mass index (BMI) may confer a survival advantage in certain acute medical conditions.[8] This paradoxical relationship challenges preconceived notions linking obesity unequivocally with poorer clinical prognoses postsurgery.

While previous studies have investigated the effect of increased BMI on postoperative outcomes, much of the existing literature is circumscribed by single-institution studies, with a narrowed focus on isolated surgical procedures and limited patient cohorts.[9–12] There is a dearth of research accounting for the intricate interplay of increased comorbidity burden and the added technical challenges of performing surgery on patients with obesity. During surgical procedures, particularly those necessitating abdominal access, increased intra-abdominal adiposity may elongate operative times, complicate organ access, augment bleeding risks, and precipitate a transition from

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minimally invasive techniques to open surgery.[13,14] Additionally, anesthetic management can become challenging due to altered airway anatomy and physiology as well as difficulties in establishing intravenous access and appropriate pharmacological dosing.[15,16] It is thus imperative to thoroughly evaluate the influence of obesity on postoperative outcomes within this multifactorial landscape.

The veracity of the obesity paradox in patients undergoing high-complexity procedures and those with significant comorbidities remains uncertain. This study aims to elucidate the relationship between obesity, as quantified by BMI, and 30-day postoperative mortality, adjusting for surgical procedure complexity and comorbidity burden. With the demographic of surgical patients with obesity expanding, understanding this relationship is paramount for tailoring perioperative care and informing clinical decision-making processes.

METHODS

We performed a retrospective observational cross-sectional study of adult patients who underwent surgery using the 2016 to 2019 American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database. This study was approved by the University of Toronto Research Ethics Board (protocol # 00042883) (Toronto, Ontario, Canada).

Data Source and Subjects

We used the 2016 to 2019 NSQIP Participant Use Data Files (PUF), a validated database of patient demographics, preoperative risk factors, intraoperative variables, and 30-day postoperative outcomes from more than 600 hospitals. Data reliability and quality are maintained through data abstractor training and inter-rater reliability audits.[17] We did not include NSQIP PUF from other years because our study cohort of over 3 million patients provided sufficient statistical power to address our study's primary objective, and we did not anticipate significant temporal changes in the trends in the relationship between obesity and postoperative outcomes. Adult patients (≥18 years) who underwent surgical procedures under general, epidural, or spinal anesthesia, in the inpatient setting, were included. We excluded patients with missing demographic factors, preoperative variables, and postoperative outcome data. Also, patients over 80 years old were excluded as previous studies[18] using the NSQIP database demonstrated a significant difference in postoperative mortality in this group compared with those aged 18 to 80 years.

Outcome

The outcome was mortality within 30 days after index surgery.

Exposure

Patient BMI was stratified into the World Health Organization[19] specified categories: underweight (BMI <18.5 kg/m^2), normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obesity class I (BMI 30–34.9 kg/m^2), class II (BMI 35–39.9 kg/m^2), and class III (BMI ≥ 40 kg/m^2).

Covariates

We included baseline patient characteristics such as age, sex, race (White, Asian, African American, Native American, and Pacific Islander), functional status (totally dependent, partially dependent, and independent), American Society of Anesthesiologists classification, smoking status, ventilator dependence, preoperative transfusion history, weight loss exceeding 10%, dialysis status, steroid use, and presence of sepsis or septic shock, disseminated cancer, open wound infection, diabetes, dyspnea, bleeding disorders, severe chronic obstructive pulmonary disorder (COPD), congestive heart failure (CHF), hypertension (HTN), and ascites. We also included intraoperative factors such as work Relative Value Units (RVU), emergency case status, and operative time.

Study Cohort Stratification

We stratified the study cohort to examine the effects of procedural complexity and patient comorbidity burden in the relationship between BMI and mortality.

Procedural Complexity

Due to a lack of well-established measures of procedural complexity, we relied on previously published guidelines and classifications, as well as clinical judgment from expert surgeons. We first organized all of the procedures reported in the NSQIP using published guidelines and classification criteria including the Johns Hopkins Surgical Classification System[20] and the National Institute for Clinical Excellence Specific Surgery Grades.[21] Additionally, procedure complexity was stratified based on mortality[22,23] and blood transfusion risk.[24] Current Procedural Terminology codes were used to identify the specific procedures. We used clinician judgment from 3 practicing surgeons (D.W.G, D.G., J.J.J.) with over 10 years of clinical experience who independently examined the list of procedures and stratified them into high, moderate, and low complexity. Once consensus was reached, the list of procedures was compiled (Table 1). For our analysis, we examined patients who underwent high and low procedure complexity.

Comorbidity Burden

We used the predicted 30-day mortality probability provided by NSQIP and a modified Charlson Comorbidity Index (mCCI) as measures of comorbidity burden. The NSQIP-derived mortality probabilities are calculated using regression models based on patient preoperative characteristics, including comorbidities. Several studies have used the 30-day mortality probability as a surrogate measure of the burden of patient comorbidities.[25–27] In our study, high comorbidity burden was defined as patients with top 3% mortality probabilities as established by Parkin et al.[28] This provided a relevant benchmark with similar mortality probability thresholds, in addition to clinical judgment considering the practical implications of defining high-risk patients in a clinical setting and a statistically derived method based on distribution. In addition, the severity of comorbidity was assessed using the Charlson Comorbidity Index (CCI), modified (mCCI) to fit the available data and patient sample.[29] Previous studies have shown that mCCIs were similar in efficiency and prognosis to the original CCI.[30,31] Specifically, mCCIs exhibited similar prevalence and prognostic association with mortality as well as discrimination ability to the original CCI.[30,31] The available comorbidities in the NSQIP dataset that were used to determine the mCCI included (corresponding point values): COPD (1), CHF (1), diabetes (2), dialysis or end-stage renal disease (2), ascites or end-stage liver disease (3), and metastatic cancer (6). The point values were summed for a total mCCI score, according to the scoring system established by Charlson et al.[29] Scores were stratified into 3 groups: low comorbidity burden (mCCI scores 0–2), moderate comorbidity burden (mCCI scores 3–7), and high comorbidity burden (mCCI scores ≥8). For the analysis, we examined patients with high comorbidity burden defined as patients with top 3% mortality probabilities and mCCI scores ≥8.

TABLE 1.

List of Procedures by Procedural Complexity

		CPT Code
Low-complexity procedures (n = 1,239,958)		
Cardiovascular	Varicose vein excision	36475–36479, 37700, 37718, 37722, 37780, 37785, 37500, 37735, 37760
Neurosurgery	Discectomy	63075, 63076
Abdominal	Hernia, hernia (L), cholecystectomy (L), appendectomy, appendectomy (L), fundoplication (L), adrenal (L), gastric (L) procedure, hemorrhoidectomy	49500–49590, 49650–49659, 47562–47579, 44970, 44979, 44950–44960, 43280, 60650, 43644–43659, 46221, 46250, 46255, 46257, 46258, 46260, 46261, 46262, 46320, 46930, 46945, 46946, 46999
Genitourinary/ gynecologic	Hysterectomy, salpingectomy, salpingo-oophorectomy, TURP, fallopian tube ligation, breast abscess drainage, endometrial ablation by thermal balloon, renoscopy, hydrocele and varicocele excision	58150–58294, 58552, 58700, 58720, 52601, 52648, 58600, 58605, 58611, 58615, 58670, 58671, 58661, 58700, 19020, 58353, 52353, 52351, 52352, 52354, 52355, 52356, 55040, 55041, 55500, 55530, 55535, 55540
Endocrine/ dermatologic	Breast surgery (lump, mastectomy), superficial surgery (lymph node dissection, vein ligation, soft tissue excision), thyroid, parathyroid	19300–19396, 38720–38745, 38760–38765, 37700–37785, 36475–36478, 21555, 21557, 60200–60281, 60500–60502
Orthopedic	Arthroscopy	29800–29999
Head and neck	Tonsillectomy, adenoidectomy, middle ear surgery	42821, 42826, 42831, 42836, 42821, 42870, 69420–69450, 69501–69554, 69601–69676, 69700–69799
Plastic	Reduction mammoplasty and other surgery for benign breast disease	19318, 88305
High-complexity procedures (n = 257,723)		
Cardiovascular	Abdominal aortic aneurysm (ruptured, nonruptured) repair, aortic aneurysm repair (including thoracic), surgical embolectomy/ thrombectomy, cardiac valve replacement, coronary artery bypass graft, vascular bypass, amputation	35082, 35092, 35103, 35081, 35091, 35102, 33860, 33863, 33864, 33870, 33875, 33877, 34830, 34831, 34832, 35081, 35082, 35091, 35092, 35102, 35103, 34001–34490, 33405, 33406, 33410, 33410, 33411, 33412, 33413, 33430, 33465, 33475, 33510, 33511, 33512, 33513, 33514, 33515, 33516, 33533, 33534, 33535, 33536, 33537, 35539, 35540, 35637, 35638, 35646, 35647, 35521, 35533, 35621, 35654, 35556, 35566, 35656, 35666, 27590–27598, 27880–27889, 28800–28825
Thoracic	Pulmonary resection, esophagectomy (partial or total), decortication (partial or total), major tracheal/bronchial, major larynx (complete laryngectomy)	32440, 32442, 32445, 32480, 32482, 32486, 32488, 32491, 43107, 43108, 43112, 43113, 43116, 43117, 43118, 43121, 43122, 43123, 43124, 32220, 32225, 32651, 32652, 32320, 31750, 31755, 31760, 31770, 31775, 31780, 31781, 31785, 31786, 31800, 31805, 31360, 31365
Neurosurgery	Craniectomy or craniotomy, brain lobectomy, brain excision and incision, intracranial vessel incision, partial excision of pituitary gland (trans frontal approach)	61304, 61305, 61312, 61313, 61314, 61314, 61320, 61321, 61322, 61323, 61537, 61538, 61539, 61540, 61500, 61526, 61530, 61546, 61548, 61563, 61564, 61518, 61519, 61520, 61521, 61575, 61576, 61600, 61601, 61605, 61606, 61607, 61608, 61615, 61616, 61750, 61751, 61680, 61682, 61684, 61686, 61690, 61692, 61697, 61698, 61700, 61702, 61703, 61705, 61708, 61710, 61711, 61546, 61548, 62165
Abdominal	Abdominal/retroperitoneal tumor excision > 10 cm, pancreatectomy (partial or total), liver resection (hepatic lobectomy, partial hepatectomy), perforated bowel repair, bile duct surgery, total proctocolectomy, total colectomy, total colectomy (L), partial colectomy with lower pelvic anastomosis, transabdominal proctectomy, pelvic exenteration, nephrectomy (partial or total), nephrectomy (partial or total) (L), open adrenal resection (partial or complete), gastrectomy (partial or complete)	49205, 48140, 48145, 48156, 48150, 48152, 48153, 48154, 48155, 47120–47130, 47120, 47122, 47125, 47130, 471209, 44602–44605, 47760–47999, 44155–44157, 44211, 44212, 44150, 44151, 44155, 44156, 44157, 44158, 44160, 44210, 44211, 44212, 44145, 44146, 44207–44208, 45110–45113, 45119–45121, 45395, 45397, 45126, 58240, 50220, 50225, 50230, 50234, 50236, 50240, 50340, 50300, 50320, 50547, 50543, 50545, 50546, 50549, 60540, 60545, 43620, 43621, 43622, 43631, 43632, 43633, 43634
Orthopedic	Major orthopedic/spinal reconstruction	63051, 63295

CPT indicates Current Procedural Terminology; L, laparoscopic procedure; TURP, transurethral resection of the prostate.

Statistical Analyses

Descriptive statistics were performed to characterize the study cohort. Continuous variables were summarized using means and SD or medians with interquartile ranges (IQRs) as appropriate, depending on the normality of the data distribution. Categorical variables were expressed as frequencies and percentages (%). The standardized mean difference served as our metric for comparing baseline characteristics across BMI categories, considering a threshold of ≤0.1 to denote insignificant differences. Several prespecified associations were investigated between patient and procedure level variables and the outcome. We adhered to the generally accepted statistical practice of considering no more than one explanatory variable for 5–10 events for multivariable regression model selection. We performed univariable logistic regression models to investigate the relationship between explanatory variables and postoperative death within 30 days. BMI and each explanatory factor with $P < 0.05$ on univariate testing were entered into a multivariable model using forward selection, and then confirmed using backward elimination. To account for nonlinearity in the BMI and mortality relationship, we implemented restricted cubic spline models with risk adjustments as described by Harrell.[32] The optimal number of spline knots was determined by computing the fit of each model using the Akaike information criteria. Ultimately, 7 knots placed at equidistant percentiles over the range of the BMI variable were used for the final model.

We performed sensitivity analyses to assess model stability and the validity of our findings. First, we used operation time, categorized into top percentile groups (1%, 2%, 3%), instead of our procedure complexity category, to analyze its influence on the BMI–mortality relationship. Second, variations in the threshold for defining high comorbidity burden were examined using the top 1%, 2%, and 4% predicted mortality probabilities instead of the top 3% and mCCI score ranges (7–15, 9–15, or 10–15) in lieu of our initial mCCI range of 8–15. Finally, we included preoperative albumin level, a surrogate variable of nutritional status, as a covariable in the models to account for the prevalence of malnutrition in patients with obesity. Hypoalbuminemia was defined as albumin levels less than 3.5 g/dL with normal levels ranging from 3.5 to 5g/dL. Model

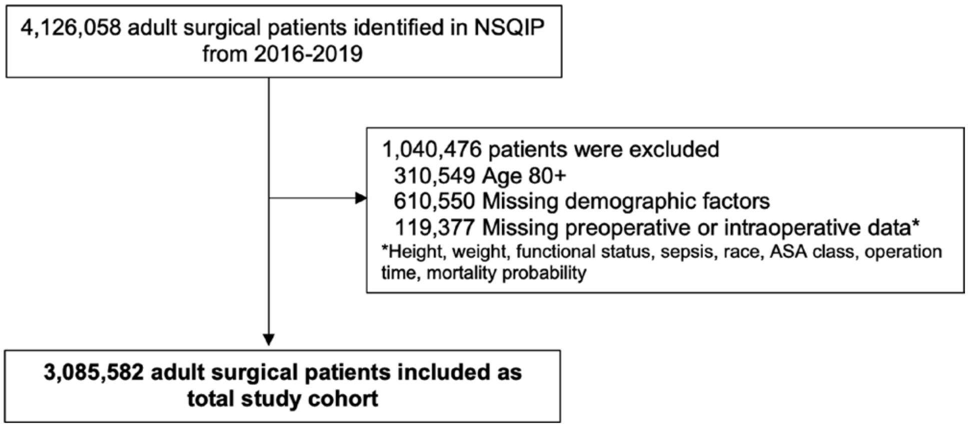

FIGURE 1. Flow diagram depicting the patient selection criteria for the study cohort.

validation was executed through fivefold cross-validation procedures, ensuring model stability. Calibration was gauged by comparing observed to predicted probabilities. Confidence interval (CI) and *P* values reported reflected a two-tailed α-level of 0.05. For all statistical computations, R 4.3.3 (R Foundation) was used as the analytical software.

RESULTS

Baseline Characteristics of the Study Cohort

The study cohort consisted of 3,085,582 patients after exclusion criteria were applied (Fig. 1). The cohort had a mean age of 54.7 years (SD: 15.3 years) and 42.7% were male (Table 2). Patients with obesity (BMI ≥ 30 kg/m^2) comprised 47.0% of the cohort with an increasing proportion of females compared with males in higher BMI categories. In contrast to other racial groups, there was a higher prevalence of patients with obesity in the African American population. Patients with higher BMI were more likely to have hypertension and diabetes whereas underweight patients were more prone to smoking, COPD, metastatic cancer, blood transfusion, and wound infections. Majority of the operations were elective cases (93.3%) with underweight patients significantly more likely to undergo emergent cases compared with normal-weight patients. Overall, the median (IQR) for operation time and work RVU in the entire study cohort were 88 (53–145) minutes and 15.4 (10.2–20.7) units, respectively. Compared with normal-weight patients, there was no significant difference in work RVU and operation time among those with obesity.

Multivariable Regression Models Predicting Postoperative Mortality

Across the total cohort, there were 18,979 patients (0.6%) who died within 30 days of surgery. Compared with normal BMI, patients with overweight BMI (odds ratio [OR]: 0.78, 95% CI: 0.75–0.81), obesity class I (OR: 0.73, 95% CI: 0.70–0.77), class II (OR: 0.68, 95% CI: 0.65–0.73), and class III (OR: 0.75, 95% CI: 0.70–0.80) had lower odds of postoperative mortality (Table 3). On the other hand, patients with underweight BMI had higher odds of postoperative mortality (OR: 1.58, 95% CI: 1.47–1.70) (Table 3). Using restricted cubic spline curves to examine the relationship between the OR of mortality across patient BMI, there was a reverse J-shaped relationship between BMI and postoperative mortality, with the highest odds of mortality in underweight BMI and lowest odds of mortality in the obesity class II category (Fig. 2).

The study cohort was stratified by procedural complexity. We identified 257,723 patients (8.4%) who underwent high-complexity procedures with a mortality rate of 2.2% and 1,239,958 patients (40.2%) who underwent low-complexity procedures with a mortality rate of 0.1%. In the low-complexity procedure cohort, high BMI was associated with lower odds of mortality compared with the normal BMI (BMI 30–34.9: OR: 0.78, 95% CI: 0.65–0.93; BMI 35–39.9: OR: 0.80, 95% CI: 0.65–0.98), following a similar relationship as the total cohort (Table 3). However, in the high-complexity procedure cohort, we did not observe the difference in the odds of mortality (BMI 30–34.9: OR: 0.93, 95% CI: 0.86–1.01; BMI 35–39.9: OR: 0.92, 95% CI: 0.83–1.03; BMI ≥ 40: OR: 0.94, 95% CI: 0.83–1.07) (Fig. 2 and Table 3). Also, the cohort was stratified by comorbidity burden, first by top 3% mortality probability and separately, by mCCI ≥ 8. In the top 3% mortality probability group, 92,568 patients (3% of the total) were identified, and they had a mortality rate of 13.2% and 13,794 patients (0.4% of the total) were identified to have mCCI ≥ 8 with a mortality rate of 7.9%. We did not observe a difference in the odds of mortality due to BMI in the subgroups with high comorbidity burden of mCCI ≥ 8 (BMI 30–34.9: OR: 0.95, 95% CI: 0.77–1.16; BMI 35–39.9: OR: 0.78, 95% CI: 0.60–1.02; BMI ≥ 40: OR: 0.84, 95% CI: 0.63–1.12) and of top 3% mortality probability (BMI 30–34.9: OR: 0.96, 95% CI: 0.90–1.02; BMI ≥ 40: OR: 0.94, 95% CI: 0.86–1.01) (Fig. 2 and Table 3).

Model Validation and Sensitivity Analysis

We assessed the goodness of fit of the multivariable logistic regression models by visually scrutinizing the calibration plots, in which the models followed the predicted samples (Supplemental Figure 1, see http://links.lww.com/AOSO/A443). We ran fivefold cross--validation on all our multivariable regression models for 30-day postoperative mortality and calculated OR and c-statistics to ensure consistency across the models (Supplemental Table 1, see http://links.lww.com/AOSO/A443). Moreover, our findings were robust to sensitivity analyses where different cutoff values for high-complexity procedures (ie, top 1%–3% operation time) and criteria for comorbidity burden – (ie, mortality probabilities top 1%, 2%, and 4% as cutoffs and high mCCI ranges 7–15, 9–15, and 10–15) were adopted (Supplemental Table 2a–c, see http://links.lww.com/AOSO/A443). Our findings were robust when hypoalbuminemia, an indicator of malnutrition was added as a covariable in the multivariable logistic regression models (Supplemental Table 3, see http://links.lww.com/AOSO/A443).

DISCUSSION

In this retrospective observational study of more than 3 million adult surgical patients from a large multicenter surgical

TABLE 2.

Pairwise Comparisons of Baseline Characteristics Between Normal BMI and Other BMI Categories

	Normal	Underweight		Overweight		Obesity Class I		Obesity Class II		Obesity Class III		
	BMI 18.5–24.9 (Ref)	BMI < 18.5		BMI 25–29.9		BMI 30–34.9		BMI 35–39.9		BMI ≥ 40		Overall
Variable	(n = 654,176)	(n = 41,841)	SMD	(n = 939,025)	SMD	(n = 710,381)	SMD	(n = 395,958)	SMD	(n = 344,201)	SMD	(n = 3,085,582)
Demographic												
Age (yr), mean (SD)	53.5 (16.9)	54.3 (17.6)	0.04	55.8 (15.4)	0.14	55.8 (14.4)	0.15	54.6 (14.0)	0.07	51.1 (14.0)	0.16	54.7 (15.30)
Male, sex, n (%)	268,662 (39.5)	13,911 (33.2)	0.13	476,481 (50.7)	0.23	327,929 (46.2)	0.13	146,917 (37.1)	0.05	92,852 (27.0)	0.27	1,316,752 (42.7)
Race, n (%)			0.11		0.14		0.25		0.33		0.40	
White	536,791 (82.1)	32,895 (78.6)		79,102 (84.2)		595,227 (83.8)		325,735 (82.3)		273,113 (79.3)		2,554,782 (82.8)
Native American	3368 (0.5)	265 (0.6)		5265 (0.6)		4711 (0.7)		2970 (0.8)		2582 (0.8)		19,161 (0.6)
Asian	46,321 (7.1)	3039 (7.3)		37,647 (4.0)		15,133 (2.1)		4974 (1.3)		2659 (0.8)		109,773 (3.6)
African American	65,252 (10)	55.39 (13.2)		101,264 (10.8)		91,999 (13.0)		60,242 (15.2)		63,779 (18.5)		388,075 (12.6)
Pacific Islander	2444 (0.4)	103 (0.2)		3828 (0.4)		3311 (0.5)		2037 (0.5)		2068 (0.6)		13,791 (0.4)
Preoperative conditions												
Functional status, n (%)			0.23		0.06		0.07		0.07		0.05	
Independent	638,767 (97.6)	38,801 (92.7)		924,742 (98.5)		700,243 (98.6)		389,836 (98.5)		337,496 (98.1)		3,029,885 (98.2)
Partially dependent	12,108 (1.9)	2164 (5.2)		11,864 (1.3)		8699 (1.2)		5322 (1.3)		5897 (1.7)		46,054 (1.5)
Totally dependent	3301 (0.5)	876 (2.1)		2419 (0.3)		1439 (0.2)		800 (0.2)		808 (0.2)		9643 (0.3)
Sepsis <48 h, n (%)			0.19		0.06		0.07		0.07		0.04	
Sepsis	15,393 (2.4)	1868 (4.5)		17,469 (1.9)		12,739 (1.8)		7185 (1.8)		7096 (2.1)		61,750 (2.0)
Septic shock	2698 (0.4)	446 (1.1)		2646 (0.3)		1996 (0.3)		1238 (0.3)		1587 (0.5)		10,611 (0.3)
SIRS	22,631 (3.5)	2560 (6.1)		25,421 (2.7)		18,591 (2.6)		10,208 (2.6)		9720 (2.8)		89,131 (2.9)
Diabetes, n (%)	51,327 (7.8)	2764 (6.6)	0.10	116,725 (12.5)	0.16	127,441 (17.9)	0.31	91,204 (23.0)	0.43	92,786 (26.9)	0.52	482,247 (15.6)
Dyspnea, n (%)	25,697 (4.0)	3411 (8.1)	0.18	35,688 (3.8)	0.02	33,865 (4.7)	0.05	24,791 (6.3)	0.11	32,567 (9.5)	0.23	156,019 (5.1)
Transfusion, n (%)	6198 (0.9)	1097 (2.6)	0.13	5489 (0.6)	0.04	3748 (0.5)	0.05	1905 (0.5)	0.06	1895 (0.6)	0.05	20,332 (0.7)
ASA class, n (%)			0.47		0.13		0.32		0.53		0.93	
1	89,659 (13.7)	3089 (7.4)		95,617 (10.2)		35,694 (5.0)		8137 (2.1)		2613 (0.8)		234,809 (7.6)
2	322,605 (49.3)	14,067 (33.6)		493,897 (52.6)		367,349 (51.7)		174,262 (44.0)		79,876 (23.2)		1,452,056 (47.1)
3	207,928 (31.8)	19,457 (46.5)		311,273 (33.1)		278,947 (39.3)		197,136 (49.8)		240,576 (69.9)		1,255,317 (40.7)
4	32,904 (5.0)	5039 (12.0)		37,123 (4.0)		27,611 (3.9)		15,999 (4.0)		20,691 (6.0)		139,367 (4.5)
5	1080 (0.2)	189 (0.5)		1115 (0.1)		780 (0.1)		424 (0.1)		445 (0.1)		4033 (0.1)
Current smoker < 1 yr, n (%)	147,411 (22.5)	15,804 (37.8)	0.34	163,951 (17.5)	0.13	113,869 (16.0)	0.17	59,163 (14.9)	0.20	47,894 (13.9)	0.23	548,092 (17.8)
Ventilation, n (%)	2040 (0.3)	338 (0.8)	0.07	2072 (0.2)	0.02	1609 (0.2)	0.02	979 (0.2)	0.01	1106 (0.3)	0.002	8144 (0.3)
Hx of COPD, n (%)	29,937 (4.6)	4943 (11.8)	0.27	33,315 (3.5)	0.05	26,695 (3.8)	0.04	16,024 (4.0)	0.03	14,951 (4.3)	0.01	125,865 (4.1)
Ascites, n (%)	3028 (0.5)	366 (0.9)	0.05	2558 (0.3)	0.03	1501 (0.2)	0.04	723 (0.2)	0.05	563 (0.2)	0.05	8739 (0.3)
Hx of CHF, n (%)	4265 (0.7)	444 (1.1)	0.04	5469 (0.6)	0.01	4651 (0.7)	<0.001	3019 (0.8)	0.01	3571 (1.0)	0.04	21,419 (0.7)
Hx of HTN, n (%)	192,016 (29.4)	12,317 (29.4)	0.002	379,149 (40.4)	0.23	350,489 (49.3)	0.42	216,902 (54.8)	0.53	193,169 (56.1)	0.56	134,4042 (43.6)
Renal failure, n (%)	2290 (0.4)	234 (0.6)	0.03	2654 (0.3)	0.01	2021 (0.3)	0.01	1264 (0.3)	0.01	1284 (0.4)	0.004	9747 (0.3)
Dialysis, n (%)	10,167 (1.6)	1014 (2.4)	0.06	11,295 (1.2)	0.03	8281 (1.2)	0.03	4786 (1.2)	0.03	4018 (1.2)	0.03	39,561 (1.3)
Metastatic cancer, n (%)	21,219 (3.2)	2508 (6.0)	0.13	21,318 (2.3)	0.06	12,646 (1.8)	0.09	5735 (1.4)	0.12	3767 (1.1)	0.15	67,193 (2.2)
Wound infection, n (%)	19,047 (2.9)	2978 (7.1)	0.19	20,532 (2.2)	0.05	15,022 (2.1)	0.05	8950 (2.3)	0.04	9894 (2.9)	0.002	76,423 (2.5)
Chronic steroid use, n (%)	29,549 (4.5)	3297 (7.9)	0.14	33,399 (3.6)	0.05	24,459 (3.4)	0.06	13,402 (3.4)	0.06	10,763 (3.1)	0.07	114,869 (3.7)
Recent weight loss >10%, n (%)	15,885 (2.4)	4989 (11.9)	0.37	8702 (0.9)	0.12	3942 (0.6)	0.16	1655 (0.4)	0.17	1030 (0.3)	0.18	36,203 (1.2)
Bleeding disorder, n (%)	23,944 (3.7)	2535 (6.1)	0.11	32,630 (3.5)	0.01	24,365 (3.4)	0.01	12,945 (3.3)	0.02	10,803 (3.1)	0.03	107,222 (3.5)
Operative details												
Work RVU, units, median (IQR)	15 (9.5–20.9)	17.4 (10.5–22.8)	0.17	15.04 (9.8–20.8)	0.003	15.37 (10.5–20.7)	0.02	15.6 (10.5–20.7)	0.04	16.84 (11.2–20.7)	0.07	15.4 (10.2–20.7)
Emergent operation, n (%)	57,091 (8.7)	5337 (12.8)	0.13	62,942 (6.7)	0.08	41,348 (5.8)	0.11	21,003 (5.3)	0.13	18,736 (5.4)	0.13	206,457 (6.7)
Operation time, min, median (IQR)	85 (49–145)	88 (50–153)	0.06	87 (52–145)	0.01	90 (54–146)	0.02	91 (56–144)	0.02	91 (57–142)	0.01	88 (53–145)

ASA indicates American Society of Anesthesiologists; SIRS, systemic inflammatory response syndrome; SMD, standardized mean difference.

TABLE 3.

Adjusted Odds Ratios for Mortality in the Total Study Cohort and Subcohorts Stratified by Patient Comorbidity Burden and Procedural Complexity

	BMI < 18.5			BMI 25–29.9			BMI 30–34.9			BMI 35–39.9			BMI ≥ 40		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Total study cohort	1.58	(1.47–1.70)	<0.001	0.78	(0.75–0.81)	<0.001	0.73	(0.70–0.77)	<0.001	0.68	(0.65–0.73)	<0.001	0.75	(0.70–0.80)	<0.001
Low-complexity procedures	1.54	(1.06–2.22)	<0.05	0.88	(0.74–1.04)		0.78	(0.65–0.93)	<0.01	0.80	(0.65–0.98)	<0.05	1.07	(0.88–1.31)	
High-complexity procedures	1.44	(1.25–1.65)	<0.001	0.84	(0.78–0.90)	<0.001	0.93	(0.86–1.01)		0.92	(0.83–1.03)		0.94	(0.83–1.07)	
Top 3% mortality probability	1.17	(1.08–1.27)		0.96	(0.91–1.01)		0.96	(0.90–1.02)		0.89	(0.83–0.97)	<0.01	0.94	(0.86–1.01)	
High mCCI ≥ 8	1.50	(1.05–2.16)	<0.05	0.97	(0.81–1.17)		0.95	(0.77–1.16)		0.78	(0.60–1.02)		0.84	(0.63–1.12)	

database, we examined the relationship between patients' BMI categories and their 30-day postoperative mortality. In keeping with previous accounts of the "obesity paradox," there was an inverse association between obesity and postoperative mortality in a broad cohort of surgical patients. Nevertheless, upon stratification by procedural complexity and comorbidity burden, the apparent protective effect of obesity dissipated. This finding challenges the universality of the obesity paradox, particularly among those subjected to high-complexity procedures and among patients with compounded comorbidities. Prior investigations on the relationship between obesity and mortality were performed on various patient populations ranging from critically ill patients[33] to those undergoing cardiac[34] and various noncardiac surgeries.[35,36] Our study adds to this corpus of literature by meticulously examining how nuanced differences in surgical complexity and patient comorbidity burden might affect the impact of obesity on postoperative mortality.

Conventionally, obesity has been posited to portend poorer postoperative outcomes due to its association with a multitude of comorbidities and the attendant operative challenges arising from body habitus.[37] However, we found in our study that for the entire cohort of adult patients undergoing surgery, overweight and patients with obesity have a lower risk of postoperative mortality compared with normal-weight patients. The mechanisms underlying the observed obesity paradox may be rooted in the altered metabolic and immunological states of patients with obesity.[38] Patients with obesity are in a state of low-grade, chronic inflammation with the secretion of adipose tissue-derived macrophages, adipokines, cytokines, tumor necrosis factor-alpha, interleukin (IL)-1, and IL-6.[39] This inflammatory state may prime the adaptive host response, facilitating the appropriate inflammatory and immune response for injury and tissue repair during the postoperative phase.[38] Additionally, the endotoxin-lipoprotein hypothesis postulates that elevated levels of lipoproteins, commonly observed in overweight and individuals with obesity, may provide a survival advantage in chronic diseases.[40] These lipoproteins can actively bind to and neutralize circulating endotoxins, resulting in an anti-inflammatory effect.

Using stratified cohorts, our study delineates how high procedure complexity and high patient comorbidity burden negate the mortality advantage otherwise observed in individuals with obesity. During high-complexity procedures, increased adiposity in the surgical field may pose augmented intraoperative risks leading to increased risk of intraoperative bleeding,[41] longer operation time[41] and postoperative complications, such as postoperative bleeding[42] and anastomotic leaks.[43] Increase in intraoperative adverse events can lead to longer operations and worse postoperative outcomes.[44–46] These factors may overshadow any protective effect attributable to obesity. Consequently, the discernment of obesity as a protective factor is not applicable in scenarios marked by significant comorbidities or surgical complexity.

Regarding the effect of comorbidity burden on the relationship between BMI and health outcomes, our study adds to the prospective study by Narumi et al,[47] where the impact of obesity on the cardiac prognosis (eg, cardiac death, myocardial infarction, stroke) in chronic heart failure patients, stratified by normal weight, obesity with metabolic syndrome (eg, dyslipidemia, diabetes, hypertension), and obesity without metabolic syndrome was studied. Here, metabolic syndrome could be interpreted as a high comorbidity burden due to its characteristic association with multiple metabolic comorbidities. The results indicated that in comparison to normal-weight patients, favorable cardiac prognosis was observed among patients with obesity without metabolic syndrome, but not among those with metabolic syndrome.

Our study builds on the findings from a nationwide study by Hirano et al,[48] contributing to the understanding of how surgical complexity influences the relationship between BMI and health outcomes. Hirano et al explored the association of BMI and mortality in patients who underwent oncologic esophagectomy, a notably invasive gastrointestinal procedure. Results showed that compared with normal weight, both high BMI ($\geq 27.5\,kg/m^2$) and low BMI ($\leq 18.4\,kg/m^2$) were associated with significantly higher mortality risk. This adds to our understanding that the obesity paradox may not be applicable to cases of high surgical complexity.

Our study also highlights the consistently elevated risk of mortality for underweight patients compared with those of normal weight. Underweight patients are more likely to have higher comorbidity burden including metastatic cancer, steroid use, and COPD. Previous studies also corroborate this relationship between underweight status and increased mortality across several surgical domains, including coronary artery bypass graft surgery,[34] intra-abdominal cancer surgery,[36] and critical illness.[33] The pathophysiology underlying this heightened mortality risk in underweight individuals may involve protein-energy malnutrition playing a central role in compromising immune function, wound healing, and infection resistance, thereby exacerbating postoperative mortality.[49]

Our study has several strengths. We used a large, multicenter, high-quality database across over 600 institutions in the United States and Canada to enable appropriate risk adjustments in the analyses examining the relationship between obesity and postoperative mortality. To our knowledge, we used the largest and the most contemporary study cohort to examine this relationship. It also allowed us to stratify the cohort by procedural complexity and comorbidity burden.

There are limitations in our study. First, surgeon and hospital-specific variables, such as experience and institutional infrastructure were unavailable in the database.[50] Second, obesity was defined only by the BMI in the present study, rather

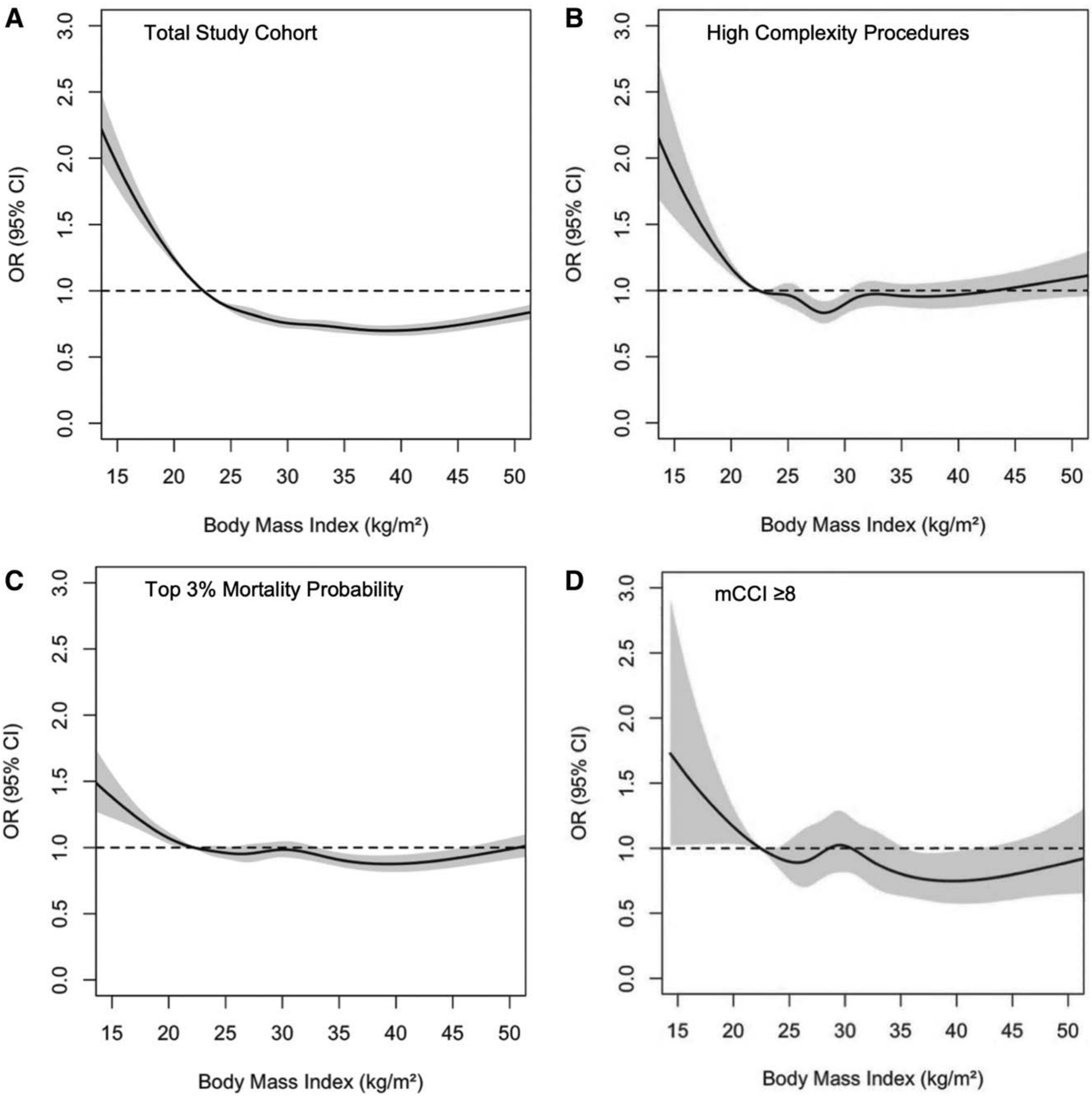

FIGURE 2. Distribution of odds ratios of 30-day postoperative mortality across patient BMI (reference BMI of 22kg/m²) using restricted cubic spline curves for (A) all patients, (B) patients who underwent high-complexity procedures, (C) patients with top 3% mortality probability, and (D) patients with mCCI ≥8.

than measures of adiposity. Alternative parameters that may be more reliable include waist circumference and waist-to-height ratio.[51] Third, there are constraints in the applicability of the mortality probability cutoff value derived from our cohort, warranting caution in extrapolating these findings across diverse populations. For our study, the chosen threshold and tested range of thresholds in the sensitivity analyses served as practical and clinically relevant markers for identifying patients with high comorbidity burden and surgical complexity. Fourth, we did not investigate the relationship between obesity and other postoperative outcomes, such as complications, readmissions, and reoperations. We chose to study only the relationship between obesity and postoperative mortality because previous studies on the obesity paradox in the surgical context focused on mortality only as well. Fifth, we did not compare between open and minimally invasive surgical procedures due to the lack of diversity in specialties among the cases for comparison. However, this distinction may serve as a factor for stratifying outcomes based on procedure complexity in future studies. Sixth, we recognize that for stratification of procedural complexity, a single surgeon's expertise may not cover all surgical domains. However, we believed that practicing surgeons in the study were able to make informed decisions on which procedures were of high versus low complexity. This was further supported by consensus discussions to reach an agreement, in addition to utilizing published guidelines and objective classification systems for risk stratification. Finally, the exclusion of postoperative mortality beyond 30 days constrains our understanding of the long-term effects of BMI on survival.

CONCLUSION

Our study corroborates the existence of the obesity paradox in a general cohort of adult patients undergoing surgery, where obesity is inversely associated with postoperative mortality. However, this relationship does not persist in the presence of high-complexity surgical cases or high comorbidity burden.

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