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Perioperative Outcomes among Patients with the Modified Metabolic Syndrome Who Are Undergoing Noncardiac Surgery

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ABSTRACT

Background: Previous studies have demonstrated that obesity is paradoxically associated with a lower risk of mortality after noncardiac surgery. This study will determine the impact of the *modified* metabolic syndrome (defined as the presence of obesity, hypertension, and diabetes) on perioperative outcomes.

Methods: This study is based on data from 310,208 patients in the American College of Surgeons National Surgical Quality Improvement Program database. We estimated separate multivariate logistic regression models for 30-day mortality and for 30-day complications.

Results: Patients with the modified metabolic syndrome who are super obese had a 2-fold increased risk of death (adjusted odds ratio [AOR] 1.99; 95% CI 1.41–2.80). As stratified by body mass index, patients with the modified metabolic syndrome had a 2- to 2.5-fold higher risk of cardiac adverse events (CAE) compared with normal-weight patients: obese (AOR 1.70; 95% CI 1.40–2.07), morbidly obese (AOR 2.01; 95% CI 1.48–2.73), and super obese (AOR 2.66; 95% CI 1.68–4.19). In addition, the risk of acute kidney injury (AKI) was 3- to 7-fold higher in these patients: obese (AOR 3.30; 95% CI 2.75–3.94), morbidly obese (AOR 5.01; 95% CI 3.87–6.49), and super obese (AOR 7.29; 95% CI 5.27–10.1).

Conclusion: Patients with the modified metabolic syndrome undergoing noncardiac surgery are at substantially higher risk of complications compared with patients of normal weight.

What We Already Know about This Topic

- Obesity is associated with a paradoxically lower risk of mortality after noncardiac surgery.
- Whether risk differs between metabolically healthy obese patients and patients with the metabolic syndrome is unknown.

What This Article Tells Us That Is New

- Compared with patients of normal weight, patients with the modified metabolic syndrome undergoing noncardiac surgery are at substantially higher risk of postoperative complications, including death, adverse cardiac events, and acute kidney injury.

MANY studies have shown that obesity is associated with lower mortality after noncardiac surgery,[1–6] percutaneous coronary intervention,[7] heart failure,[8] acute coronary syndromes,[9] and admission to the intensive care unit.[10] The "obesity paradox" is surprising given the evidence that obesity is associated with decreased life expectancy.[11,12] One possible explanation is that obese persons consist of two distinct subsets. One group is "the metabolically healthy but obese," whereas the other group are the "metabolically obese." These are the patients with the metabolic syndrome (MetS).[13] The MetS is characterized by central obesity, hypertension, hyperglycemia, dyslipidemia, and prothrombotic and proinflammatory states.[14] The apparent protective effect of obesity may be due to the large number of metabolically healthy but obese patients included in cohorts of obese patients receiving medical care.

Although many studies have examined the association between obesity and perioperative outcomes, very few studies

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have distinguished between metabolically healthy obese patients and patients with the MetS. However, recent studies have shown increased operative mortality,[15] stroke, and acute renal failure[16] in patients with the MetS undergoing coronary artery bypass grafting. To date, the largest study examining the association between obesity and outcomes in patients undergoing noncardiac surgery demonstrates a "paradoxically" lower risk of mortality in overweight and moderately obese patients.[6] That study, based on the American College of Surgeons National Surgical Quality Improvement (ACS NSQIP) database, also showed an increased incidence of overall complications, mostly attributable to wound infections, in patients with increasing obesity. Researchers did not look at the subset of obese patients with the MetS.

The goal of our study is to determine the impact of the modified MetS (mMetS; *i.e.*, obesity, hypertension, and diabetes) on perioperative outcomes in patients undergoing noncardiac surgery. The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) defined the MetS as the presence of three or more of the following risk factors: (1) abdominal obesity, (2) increased triglycerides, (3) reduction of high-density lipoprotein cholesterol, (4) increased blood pressure, and (5) glucose intolerance (*e.g.*, diabetes).[17,18] Because the ACS NSQIP database does not include information on waist circumference or dyslipidemia, we used obesity as a proxy for abdominal obesity and did not include dyslipidemia as a criterion for the present investigation. As recognized by the NCEP-ATP III Expert Panel, "most persons with the MetS are overweight or obese."[17] Therefore, in this investigation, we have defined patients with obesity, hypertension, and diabetes as having the mMetS. Using this *modified* definition of the MetS, our goal was to explore whether "metabolically obese" patients were at higher risk for mortality and complications after major surgery compared with patients of normal weight. Given the high prevalence of obesity in the United States, our findings may have important implications for risk stratification and the perioperative management of obese patients with the mMetS undergoing noncardiac surgery.

Materials and Methods

Data Source

This study is based on the ACS NSQIP database, a prospective validated outcomes registry designed to provide feedback to member hospitals on 30-day risk-adjusted surgical mortality and complications.[19] The ACS NSQIP database includes deidentified data on patient demographics, functional status, admission source, preoperative risk factors, intraoperative variables, and 30-day postoperative outcomes for patients undergoing major surgery in more than 200 participating hospitals.[19] A systematic sampling strategy is used to avoid bias in case selection and to ensure a diverse surgical case mix. Trained surgical clinical reviewers collect patient data from medical records, operative log, anesthesia record, interviews with the attending surgeon, and postoperative telephone interviews with the patient.[19] Data quality is ensured through comprehensive training of the nurse reviewers and an interrater reliability audit of participating sites.** The University of Rochester School of Medicine Institutional Review Board (Rochester, NY) approved this study after expedited review.

Study Population and Outcomes

Using Current Procedural Terminology (CPT) codes, we identified 351,572 patients who underwent general, vascular, or orthopedic surgery between 2005 and 2007. We excluded patients who received no anesthesia, local anesthesia, or monitored anesthesia care (22,056); patients whose records were missing demographic information (10,450); and patients whose records had procedures with work relative value units (RVUs) equal to zero (8,836).†† The study cohort consisted of 310,208 patients (fig. 1).

We focused on 30-day mortality and major 30-day complications: (1) cardiac (acute myocardial infarction or cardiac arrest); (2) pulmonary (pneumonia, ventilatory support for greater than 48 h, or unplanned intubation); (3) renal (progressive renal insufficiency or acute renal failure); (4) central nervous system (cerebrovascular accident or coma lasting more than 24 h); (5) sepsis (sepsis or septic shock); (6) wound infection (deep incisional surgical site infection, organ or space surgical site infection, or wound dehiscence); and (7) thromboembolic (deep venous thrombosis or pulmonary embolism). Patients who required mechanical ventilation any time during the 48 h preceding surgery were excluded from the analysis of pulmonary complications. In addition, patients with acute or chronic renal failure preoperatively were excluded from the analysis of renal complications. Patients with preoperative paraplegia, hemiplegia, quadriplegia, cerebrovascular accident with neurologic deficit, and coma were excluded from the analysis of central nervous system complications. Patients with preoperative sepsis or septic shock were excluded from the analysis of septic complications. Patients with superficial wound infections were not included in the definition of the wound infection outcome.

Statistical Analysis

The goal of this study was to examine the impact of the mMetS on 30-day mortality and morbidity in patients undergoing major noncardiac surgery. The mMetS was identified using a modification of the criteria used by the NCEP-ATP III[14]: (1) obe-

** ACS NSQIP User Guide for the 2008 Participant Use Data File. American College of Surgeons. https://acsnsqip.org/puf/docs/ACS_NSQIP_Participant_User_Data_File_User_Guide.pdf. Accessed June 4, 2010.

†† An RVU is used as a measure of surgical complexity. Many of the CPT codes assigned a work relative value equal to zero were procedures where the procedure description is nonspecific. For example, CPT codes with procedure descriptions such as breast surgery procedure, musculoskeletal surgery, head surgery procedure, spine surgery procedure are all assigned a workrvu of zero.

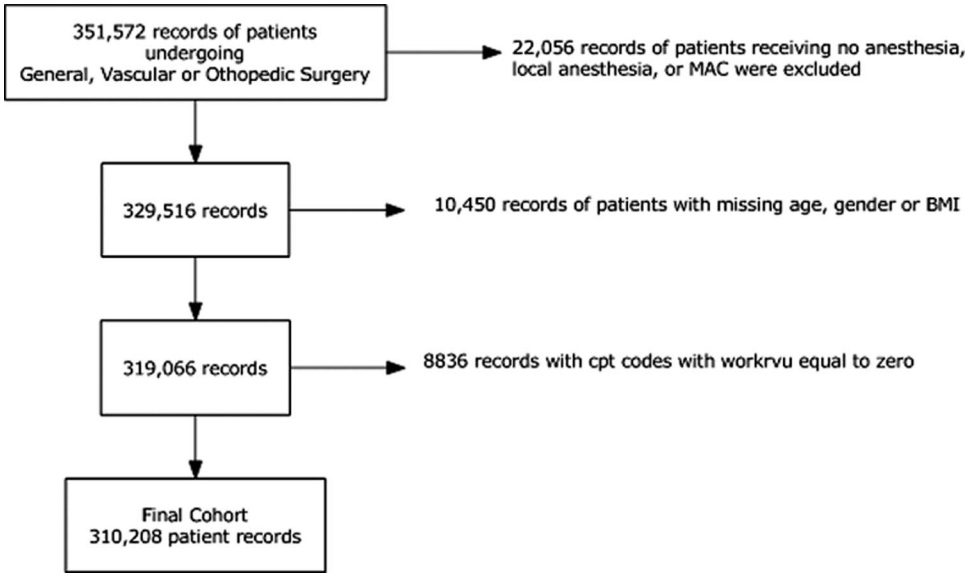

Fig. 1. A total of 351,572 patients undergoing general, vascular, or orthopedic surgery were identified. After applying the study exclusion criteria, the study cohort consisted of 310,208 patients. BMI = body mass index; workrvu = work relative value unit.

sity, defined as a body mass index (BMI) of 30 kg/m^2 or higher, (2) treatment with an oral hypoglycemic or insulin (*i.e.*, instead of glucose intolerance), and (3) hypertension. As noted, we did not use waist circumference as a criterion for obesity because waist circumference is unavailable in the ACS NSQIP database. Likewise, we did not include dyslipidemia as a criterion for the mMetS for the same reason.

Patients were classified by weight categories according to BMI: (1) underweight (less than 18.5 kg/m^2), (2) normal (18.5 to 24.9 kg/m^2), (3) overweight (25 to 29.9 kg/m^2), (4) obese (30 to 39.9 kg/m^2), (4) morbidly obese (40 to 49.9 kg/m^2), and (5) super obese (greater than 50 kg/m^2).

We first explored the distribution of risk factors across weight categories. We performed chi-square tests for categorical variables and regression analyses for continuous variables. We then estimated separate multivariate logistic regression models for 30-day mortality and for each of the major 30-day complications. The primary exposure variable was the presence of the mMetS, as stratified by BMI: (1) obesity, (2) morbid obesity, and (3) super obesity. By construction, patients without the mMetS classified as obese, morbidly obese, or super obese did not have both diabetes and hypertension. Because the definition of the mMetS includes diabetes and hypertension, patients with the mMetS were assigned a zero value for the covariates diabetes and hypertension in each of the multivariate models. This decision was made so that patients with the mMetS would receive "full credit" for the impact of each of the clinical components included in the mMetS, ensuring unbiased estimates of the impact of the mMetS on outcomes. The reference population consisted of patients with normal weights. We adjusted for age, sex, surgical complexity, admission source, functional status, wound classification, preoperative hematocrit, and comorbidities. In addition to RVUs as a measure of surgical complexity, we included separate intercept terms for the type of procedure by CPT code group: (1) integumentary; (2) musculoskeletal; (3) vascular; (4) hemic and lymphatic system; (5) mouth, palate, salivary glands, pharynx, adenoids, and esophagus; (6) stomach, intestines, appendix and mesentery, rectum and anus, liver, biliary tract, pancreas, abdomen, peritoneum, and omentum (nonhernia); (7) endocrine system; and (8) hernia repair (reference group). To avoid underestimating the impact of the mMetS on surgical outcomes, we did not include intraoperative process variables as covariates, such as operative times and intraoperative packed red cell transfusion.

Fractional polynomials were used to explore alternative transformations for age and RVUs.[20] Backward stepwise selection and clinical judgment were used to select covariates for inclusion in the regression models. We did not drop variables that were related to our primary hypothesis. Multiple imputation was used to impute missing values[21] for the preoperative serum creatinine and the preoperative hematocrit using the STATA (SE/MP version 11; STATA Corp., College Station, TX) implementation of the multiple imputation by chained equations method of multiple imputation[22] described by van Buuren *et al.*[23] We specified the imputation model using nonparsimonious linear regression. Simpler approaches for handling missing data, such as deleting observations with missing data or using the missing-indicator method, may produce biased results.[24–26] Rubin's rule was used to combine parameter estimates across the five imputed data sets obtained by multiple imputation.[22] Robust variance estimators were used to account for the nonindependence of observations within hospitals.[27] The effect of the mMetS, stratified by obesity level, was assessed using estimated adjusted odds ratios (AOR).

The data set was divided randomly into a development and a validation data set (50:50). Each model was first estimated in the development data set and subsequently validated in the validation set using measures of discrimination and goodness of fit. Model discrimination was assessed using the C statistic; model calibration was evaluated using the Hosmer-Lemeshow statistic. The final models were reesti-

Table 1. Categories of Procedures (N = 310,208)

CPT Range	Procedure Type	Operations, No. (%)
10000–19999	Integumentary	29,633 (9.55)
20000–29999	Musculoskeletal	16,545 (5.33)
34000–37799	Vascular	36,997 (11.93)
38000–38999	Hemic and lymphatic system	3,329 (1.07)
40000–43499	Mouth, palate, salivary glands, pharynx, adenoids, and esophagus	5,359 (1.73)
43500–49429, 49900–49999	Stomach, intestines, appendix and mesentery, rectum and anus, liver, biliary tract, pancreas, abdomen, peritoneum, and omentum (nonhernia)	159,387 (51.38)
49490–49659	Hernia	41,186 (13.28)
60000–60999	Endocrine system	17,772 (5.73)

CPT = Current Procedural Terminology.[28]

mated using the entire data set. All statistical analyses were performed using STATA SE/MP version 11.

Results

Between 2005 and 2007, the ACS NSQP database included data on 310,208 patients undergoing general, vascular, or orthopedic surgery. The distribution of procedures classified by CPT codes[28] is shown in table 1. More than half of the procedures were in the CPT code range for gastrointestinal surgery. The next two highest CPT groups were hernia repair (13.3%) and vascular procedures (11.9%).

Of the 310,208 patients included in this study, 20,845 (6.7%) patients met the modified criteria for the MetS. Of those patients with the mMetS, 13,092 (62.8%) were obese; 5,360 (25.7%), morbidly obese; and 2,393 (11.5%), super obese. A total of 98,036 patients that did not meet the criteria for the mMetS were obese (70,140), morbidly obese (20,560), or super obese (7,336).

Patient demographics are shown in table 2. Compared with patients of normal weight, patients with the mMetS were less likely to have emergency surgery. They were more likely to have dependent functional status, a history of congestive heart failure, angina, percutaneous coronary intervention, ventilator dependence, and dyspnea at rest or on exertion.

Risk-adjustment models are shown in appendix 1. The statistical performance of the models in the development, validation, and full data are shown in appendix 2. All models exhibited very good to excellent discrimination. The C statistic for the 30-day mortality model, based on the full data, was 0.93. The C statistic for the 30-day morbidity models, based on the full data, ranged between 0.78 and 0.89. Model calibration, assessed using the Hosmer-Lemeshow statistic, is acceptable given the test's well-known sensitivity to sample size and the size of our cohort.[29]

Patients with the mMetS and super obesity had a 2-fold increased risk of mortality (AOR 2.28; 95% CI 1.61–3.22) compared with normal-weight patients (table 3 and fig. 2a). With the exception of patients with the mMetS and super obesity, the mMetS was not associated with increased mortality.

The incidence of CAE in patients with obesity, morbid obesity, and super obesity was not significantly different from that for patients of normal weight, after adjusting for preoperative factors. However, the mMetS was an important risk factor among these patients for CAE. As stratified by body mass index, patients with the mMetS had a nearly 2- to 3-fold higher risk of CAE compared with normal-weight patients: (1) obese (AOR 1.70; 95% CI 1.40–2.07), (2) morbidly obese (AOR 2.01; 95% CI 1.48–2.73), and (3) super obese (AOR 2.66; 95% CI 1.68–4.19) (table 3 and fig. 2a).

Although the risk of pulmonary adverse events among patients with obesity (AOR 1.15; 95% CI 1.07–1.23), morbid obesity (AOR 1.21; 95% CI 1.08–1.36), and super obesity (AOR 1.42; 95% CI 1.20–1.68) was significantly higher than in normal-weight patients, these risks were substantially higher when accompanied by the mMetS. Such patients had an approximately 1.5- to 3-fold higher risk of pulmonary adverse events compared with normal-weight patients: (1) obese (AOR 1.50; 95% CI 1.35–1.66), (2) morbidly obese (AOR 1.61; 95% CI 1.38–1.89), and (3) super obese (AOR 2.73; 95% CI 2.26–3.30) (table 3 and fig. 2b).

The risk of AKI was dramatically increased across all obesity strata regardless of the mMetS. The incidence of AKI among patients with obesity was nearly 2- to 3-fold higher than in normal-weight patients: (1) obese (AOR 1.64; 95% CI 1.43–1.87), (2) morbidly obese (AOR 1.98; 95% CI 1.58–2.50), and (3) super obese (AOR 3.08; 95% CI 2.27–4.17). Among patients with the mMetS, the risk of AKI was 3- to 7-fold higher than in normal-weight patients: (1) obese (AOR 3.30; 95% CI 2.75–3.94), (2) morbidly obese (AOR 5.01; 95% CI 3.87–6.49), and (3) super obese (AOR 7.29; 95% CI 5.27–10.1) (table 3 and fig. 2b).

The incidence of CNS adverse events in patients with obesity, morbid obesity, and super obesity was not significantly different from that for patients of normal weight after adjusting for preoperative factors. Among patients with the mMetS, the risk of CNS adverse events was approximately 2-fold higher than in patients with normal weight: (1) obese (AOR 1.60; 95% CI 1.18–2.16), (2) morbidly obese (AOR 1.86; 95% CI 1.15–3.03), and (3) super obese (AOR 2.30; 95% CI 1.15–4.64) (table 3 and fig. 2c).

There was no clear association between obesity, with or without the mMetS, and thromboembolic complications (table 3 and fig. 2c). There was also no clear association between postoperative sepsis and septic complications in patients with obesity, morbid obesity, and super obesity without the mMetS (table 3 and fig. 2d). However, the mMetS

Table 2. Descriptive Statistics

	Under	Normal	Over	Obese	MO	SO	Obese-mMetS	MO-mMetS	SO-mMetS	*P* Value
Total, n	8,090	88,270	95,010	70,140	20,560	7,336	13,092	5,360	2,393	
Age, yr	57	55	57	53	47	44	63	56	52	<0.001
Men	66.0	58.7	47.6	59.5	77.9	76.3	53.5	68.6	70.3	<0.001
Emergency	20.3	15.8	13.2	11.6	7.52	7.05	10.9	8.54	8.40	<0.001
Admission Source										
Home	91.8	96.0	96.7	97.6	98.2	97.9	94.1	95.8	96.5	<0.001
Hospital	4.28	2.16	1.92	1.62	1.25	1.44	3.01	2.46	2.13	<0.001
Chronic Care	3.46	1.45	0.96	0.47	0.38	0.57	2.32	1.38	1.21	<0.001
DNR Status	1.99	0.94	0.61	0.37	0.26	0.25	1.05	0.43	0.38	<0.001
Dependent	18.8	8.45	6.35	4.36	3.25	4.42	13.5	9.50	11.0	<0.001
Cardiac										
CHF	1.83	1.12	0.99	0.64	0.53	0.74	3.13	2.78	1.50	<0.001
MI	1.22	0.83	0.74	0.44	0.25	0.20	2.09	1.03	0.33	<0.001
PCI	4.46	4.74	6.14	4.33	2.15	1.43	15.0	9.96	5.60	<0.001
CV Surgery	5.60	6.27	7.61	4.47	1.69	1.21	17.0	7.84	3.38	<0.001
Angina, Previous 30 d	1.10	0.81	0.89	0.73	0.44	0.30	2.53	1.66	0.79	<0.001
Hypertension	38.3	35.6	44.5	42.7	41.8	44.4	100	100	100	<0.001
Peripheral Vascular Surgery	9.26	5.70	4.79	2.43	0.89	0.85	13.3	5.37	3.01	<0.001
Rest Pain/Gangrene	6.22	3.54	2.75	1.18	0.59	0.52	8.08	3.04	1.59	<0.001
Pulmonary										
Ventilator	2.35	1.01	0.96	0.93	0.78	1.05	1.85	1.62	2.05	<0.001
COPD	11.3	4.98	4.09	3.53	2.60	2.70	8.40	6.60	7.44	<0.001
Pneumonia	1.76	0.69	0.55	0.38	0.35	0.34	0.98	0.82	1.13	<0.001
Dyspnea Rest	3.21	1.41	1.26	1.19	1.13	1.53	3.17	2.78	4.01	<0.001
Dyspnea Exertion	10.6	6.97	7.73	9.59	18.8	29.6	18.8	27.7	38.2	<0.001
Tobacco Use	34.3	24.2	20.8	20.1	18.0	16.4	17.2	14.4	12.8	<0.001
Renal										
Mild	28.9	31.2	34.2	28.2	11.1	5.04	31.5	22.1	13.1	<0.001
Moderate	27.4	22.9	22.7	11.3	2.81	1.48	25.6	9.51	4.59	<0.001
Severe	4.77	2.95	2.18	0.78	0.21	0.05	2.72	1.03	0.17	<0.001
Failure	4.09	2.75	2.05	1.22	0.87	0.71	6.03	3.81	2.59	<0.001
Acute Failure	1.15	0.60	0.62	0.44	0.35	0.48	1.50	1.08	1.00	<0.001
CNS										
Impaired Sensorium	2.55	1.16	0.85	0.60	0.42	0.35	1.60	1.14	1.21	<0.001
Coma	0.23	0.08	0.07	0.06	0.06	0.07	0.14	0.11	0.08	<0.001
Hemiplegia	1.82	1.23	1.05	0.68	0.38	0.30	2.40	1.12	0.84	<0.001
Paraplegia	0.90	0.45	0.36	0.32	0.25	0.30	0.56	0.39	0.46	<0.001
Quadriplegia	0.44	0.15	0.09	0.07	0.05	0.07	0.08	0.07	0.00	<0.001
CVA										
Neurodeficit	3.93	2.81	2.65	1.65	0.90	0.64	6.10	3.10	1.92	<0.001
No neurodeficit	2.82	2.18	2.15	1.40	0.80	0.46	4.66	2.46	1.30	<0.001
Transient Ischemic Attack	3.30	3.11	3.39	2.31	1.14	0.76	5.59	3.17	2.09	<0.001
CNS Tumor	0.17	0.11	0.11	0.10	0.09	0.05	0.09	0.09	0.04	0.444
Hepatobiliary										
Ascites	4.87	2.35	1.64	1.18	0.81	0.56	1.79	1.08	0.92	<0.001
Varices	0.25	0.15	0.19	0.14	0.08	0.05	0.28	0.11	0.08	<0.001
Nutrition/Endocrine										
Diabetes, Oral	5.12	3.93	4.74	1.42	1.87	2.07	39.8	38.9	37.9	<0.001
Diabetes, Insulin	3.70	4.59	7.33	2.58	4.46	5.67	60.2	61.1	62.1	<0.001
Alcohol	3.88	3.13	3.15	2.40	0.90	0.65	1.63	0.78	0.21	<0.001
Metastatic Cancer	4.47	2.86	2.39	1.82	0.89	0.53	2.03	1.10	0.71	<0.001
Steroid use	7.64	4.21	3.32	2.69	2.06	1.83	4.51	3.34	2.55	<0.001
Weight Loss	16.0	4.74	2.13	1.17	0.61	0.49	2.10	0.80	0.50	<0.001
Chemotherapy	2.41	1.74	1.27	1.09	0.65	0.42	0.97	0.41	0.29	<0.001
Radiotherapy	1.58	1.11	0.95	0.73	0.35	0.18	0.67	0.41	0.25	<0.001
Systemic Infection										
Systemic Inflammatory Response Syndrome	11.6	7.78	6.78	6.30	4.44	4.87	7.13	5.60	5.60	<0.001
Sepsis	3.42	1.78	1.46	1.19	1.15	1.20	2.92	1.96	2.93	<0.001
Septic Shock	2.52	1.08	0.89	0.86	0.77	1.00	1.81	1.70	1.63	<0.001

(*continued*)

Table 2. Continued

	Under	Normal	Over	Obese	MO	SO	Obese-mMetS	MO-mMetS	SO-mMetS	*P* Value
Hematology										
Hematocrit	0.367	0.385	0.396	0.400	0.398	0.398	0.374	0.383	0.386	<0.001
Bleeding Disorder	9.04	6.41	6.29	4.78	3.34	3.56	13.4	8.23	7.02	<0.001
Preoperative Transfusion	0.79	0.50	0.46	0.41	0.18	0.31	0.51	0.47	0.37	<0.001
Operation, Previous 30 d	4.67	3.17	2.85	2.47	2.13	2.18	5.26	2.93	2.97	<0.001
Wound infection	10.7	5.49	4.52	3.37	3.20	4.10	13.7	8.90	9.15	<0.001

All data are percentages, unless otherwise specified. Complete definitions for risk factors unless otherwise specified are those used in the ACS NSQIP database: http://www.acsnsqip.org/puf/docs/ACS_NSQIP_Participant_User_Data_File_User_Guide.pdf.

CHF = congestive heart failure within 30 d of surgery; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; CV = cardiovascular (*i.e.*, any major cadiac surgery, such as coronary artery bypass, valve replacement or repair); CVA = cerebrovascular accident; DNR = do-not-resuscitate status; mMetS = modified metabolic syndrome; MO = morbidly obese; MI = myocardial infarction within 6 mo of surgery; Normal = normal weight; Over = overweight; PCI = percutaneous coronary intervention; preoperative transfusion = more than four units packed red blood cells in 72 h before surgery; Renal = criteria based on National Kidney Foundation Practice Guidelines[40]; SO = super obese; Under = underweight.

was associated with an approximately 25–50% higher risk of postoperative sepsis after adjusting for preoperative risk factors: (1) obese (AOR 1.46; 95% CI 1.32–1.61), (2) morbidly obese (AOR 1.25; 95% CI 1.08–1.46), and (3) super obese (AOR 1.36; 95% CI 1.11–1.67) (table 3 and fig. 2d).

Patients with obesity (AOR 1.35; 95% CI 1.26–1.45) and morbid obesity (AOR 1.17; 95% CI 1.05–1.31), without the mMetS, were at increased risk of wound infection compared with normal-weight patients. Patients with the mMetS also had a higher risk of serious wound infections compared with normal-weight patients: (1) obese (AOR 1,41; 95% CI 1.25–1.59), (2) morbidly obese (AOR 1.26; 95% CI 1.05–1.50), and (3) super obese (AOR 1.39; 95% CI 1.10–1.76) (table 3 and fig. 2d). Finally, underweight patients were at significantly higher risk for mortality (AOR 1.48; 95% CI 1.30–1.68), pulmonary morbidity (AOR 1.34; 95% CI 1.21–1.50), and septic complications (AOR 1.20; 95% CI 1.08–1.33).

Discussion

Patients with the mMetS undergoing noncardiac surgery are at increased risk for mortality, CAE, pulmonary complications, AKI, stroke and coma, wound complications, and postoperative sepsis. Increasing levels of obesity in patients with the mMetS was generally associated with worse postoperative outcomes. These findings are present after adjusting for clinical and demographic factors associated with increased risk of postoperative morbidity and mortality.

The magnitude of the increase in risk is dramatic for some complications. In particular, compared with normal-weight patients, patients with the mMetS have a nearly 2- to 3-fold higher risk of cardiac complications, a 1.5- to 2.5-fold higher risk of pulmonary complications, a 2-fold higher risk of coma and stroke, and a nearly 3- to 7-fold higher risk of AKI.

It is estimated that 22% of the adult population in the United States has the MetS.[30] Obesity, a central component of the MetS, can lead to a metabolically triggered low-grade inflammatory state,[31] which may augment the proinflammatory response caused by surgery.[32] Inflammation can be an adaptive response to infection and injury, allowing the body to fight off infection and promote tissue repair.[31] Chronic inflammation, on the other hand, is maladaptive and is not beneficial.[31] A recent meta-analysis shows that the MetS is associated with a 35% increase in the risk of all-cause mortality, a 50% increase in the risk of cardiovascular disease, and a 75% increase in the risk of stroke.[32] Patients with the MetS also have a 2.6-fold increased risk of chronic kidney disease[34] and are more likely to have impaired lung function.[35]

Recent studies have shown that patients with the MetS are at increased risk of operative morality, postoperative stroke, and acute renal failure after undergoing coronary artery bypass grafting.[15,16] However, both of these studies were relatively small single-center investigations and are restricted to cardiac surgical patients.

Several studies have examined the independent impact of obesity on surgical mortality and morbidity after noncardiac surgery. Yet, most have failed to show that obesity is associated with increased morbidity and mortality after noncardiac surgery.[1–5] The largest study to date, by Mullen *et al.*[6]—and also based on the ACS NSQIP database—showed a mild protective effect of BMI on mortality for overweight and obese patients undergoing general surgery. In our current study, based on general, orthopedic, and vascular surgery patients, we also found that being overweight was "protective"—but that obesity and morbid obesity were not independently associated with decreased mortality. Differences between study populations, and in statistical model selection may have led to these divergent findings. Mullen *et al.*[6] also found that obesity increased the incidence of overall complications, which they attributed to wound infections; they did not examine the impact of BMI on individual postoperative complications. In contrast to the study by Mullen *et al.*,[6] the main focus of our study was to examine the impact of the MetS, as opposed to the independent effect of obesity, on perioperative outcomes. We hypothesized that "metabol-

Table 3. Results of Bivariate and Multivariate Analyses

Variable by Weight Category	Incidence, %	Odds Ratio	
		Unadjusted	Adjusted
Mortality			
Underweight	5.88	2.72 (2.46, 3.02)	1.48 (1.30, 1.68)
Normal Weight	2.25	Reference	Reference
Overweight	1.56	0.69 (0.64, 0.74)	0.85 (0.78, 0.92)
Obese	1.09	0.48 (0.44, 0.51)	0.90 (0.81, 1.00)
Morbidly Obese	0.67	0.29 (0.25, 0.35)	0.84 (0.69, 1.03)
Super Obese	0.95	0.42 (0.33, 0.53)	1.32 (0.98, 1.77)
+ Comorbid mMetS			
Obese	2.77	1.24 (1.11,1.39)	1.04 (0.90,1.21)
Morbidly Obese	1.77	0.79 (0.64,0.97)	1.12 (0.86, 1.45)
Super Obese	2.34	1.04 (0.80, 1.35)	1.99 (1.41, 2.80)
Cardiac Complications			
Underweight	1.46	1.88 (1.58, 2.18)	1.07 (0.87, 1.32)
Normal Weight	0.78	Reference	Reference
Overweight	0.67	0.85 (0.76, 0.95)	0.99 (0.88, 1.11)
Obese	0.39	0.50 (0.44, 058)	0.91 (0.79,1.06)
Morbidly Obese	0.27	0.34 (0.26, 0.45)	0.98 (0.73, 1.32)
Super Obese	0.34	0.43 (0.29, 0.65)	1.23 (0.79, 1.91)
+ Comorbid mMetS			
Obese	1.44	1.86 (1.58, 2.18)	1.70 (1.40, 2.07)
Morbidly Obese	1.01	1.29 (0.98, 1.70)	2.01 (1.48, 2.73)
Super Obese	1.04	1.34 (0.90, 2.00)	2.66 (1.68, 4.19)
Pulmonary Complications			
Underweight	8.25	2.29 (2.10, 2.50)	1.34 (1.21, 1.50)
Normal Weight	3.78	Reference	Reference
Overweight	3.08	0.81 (0.77, 0.85)	0.95 (0.90,1.01)
Obese	2.50	0.65 (0.62, 0.69)	1.15 (1.07, 1.23)
Morbidly Obese	2.01	0.52 (0.47, 0.58)	1.21 (1.08, 1.36)
Super Obese	2.44	0.64 (0.54, 0.74)	1.42 (1.20, 1.68)
+ Comorbid mMetS			
Obese	5.43	1.46 (1.35, 1.59)	1.50 (1.35, 1.66)
Morbidly Obese	3.96	1.05 (0.91, 1.21)	1.61 (1.38, 1.89)
Super Obese	5.97	1.62 (1.36, 1.93)	2.73 (2.26, 3.30)
Renal Complications			
Underweight	1.10	1.43 (1.14, 1.80)	0.81 (0.63, 1.03)
Normal Weight	0.77	Reference	Reference
Overweight	0.73	0.95 (0.85, 1.06)	1.10 (0.98, 1.23)
Obese	0.65	0.85 (0.75,0.96)	1.64 (1.43, 1.87)
Morbidly Obese	0.52	0.67 (0.55, 0.83)	1.98 (1.58, 2.50)
Super Obese	0.76	0.99 (0.75, 1.30)	3.08 (2.27, 4.17)
+ Comorbid mMetS			
Obese	1.97	2.61 (2.24, 3.03)	3.30 (2.75, 3.94)
Morbidly Obese	1.63	2.14 (1.70, 2.69)	5.01 (3.87, 6.49)
Super Obese	1.95	2.57 (1.90, 3.49)	7.29 (5.27, 10.1)
CNS complications			
Underweight	0.63	1.96 (1.44, 2.66)	1.22 (0.88, 1.68)
Normal Weight	0.32	Reference	Reference
Overweight	0.27	0.82 (0.69,0.98)	0.90 (0.75, 1.07)
Obese	0.20	0.61 (0.50, 0.76)	0.99 (0.80, 1.24)
Morbidly Obese	0.13	0.41, (0.28, 0.61)	1.02 (0.67, 1.55)
Super Obese	0.17	0.51 (0.29,).91)	1.27 (0.69, 2.34)
+ Comorbid mMetS			
Obese	0.55	1.71 (1.31, 2.23)	1.60 (1.18, 2.16)
Morbidly Obese	0.39	1.20 (0.76, 1.90)	1.86 (1.15, 3.03)
Super Obese	0.39	1.20 (0.62, 2.33)	2.30 (1.15, 4.64)
Sepsis Complications			
Underweight	8.06	2.02 (1.85, 2.21)	1.20 (1.08, 1.33)
Normal Weight	4.15	Reference	Reference
Overweight	3.44	0.82 (0.78, 0.86)	0.95 (0.90, 1.01)

(*continued*)

Table 3. Continued

Variable by Weight Category	Incidence, %	Odds Ratio	
		Unadjusted	Adjusted
Obese	2.97	0.71 (0.67, 0.75)	1.10 (1.04, 1.17)
Morbidly Obese	2.66	0.63 (0.57, 0.69)	1.00 (0.91, 1.11)
Super Obese	2.70	0.64 (0.55, 0.74)	0.88 (0.75, 1.03)
+ Comorbid mMetS			
Obese	5.97	1.47 (1.35, 1.59)	1.46 (1.32, 1.61)
Morbidly Obese	4.30	1.04 (0.90, 1.19)	1.25 (1.08, 1.46)
Super Obese	5.04	1.22 (1.01, 1.48)	1.36 (1.11, 1.67)
Thromboembolic Complications			
Underweight	1.61	1.57 (1.31, 1.89)	1.05 (0.87, 1.27)
Normal Weight	1.03	Reference	Reference
Overweight	1.00	0.97 (0.89, 1.06)	1.08 (0.99, 1.19)
Obese	0.97	0.94 (0.85, 1.04)	1.28 (1.15, 1.42)
Morbidly Obese	0.69	0.67 (0.56, 0.80)	1.00 (0.83, 1.21)
Super Obese	0.74	0.71 (0.54, 0.94)	0.99 (0.74, 1.32)
+ Comorbid mMetS			
Obese	1.25	1.22 (1.03, 1.45)	1.03 (0.86, 1.24)
Morbidly Obese	1.59	1.55 (1.24, 1.94)	1.64 (1.30, 2.08)
Super Obese	1.04	1.02 (0.68, 1.52)	1.04 (0.69, 1,57)
Wound Complications			
Underweight	4.07	1.66 (1.47, 1.88)	1.13 (0.99, 1.30)
Normal Weight	2.49	Reference	Reference
Overweight	2.43	0.98 (0.92, 1.04)	1.09 (1.02, 1.16)
Obese	2.56	1.03 (0.97, 1.10)	1.35 (1.26, 1.45)
Morbidly Obese	2.41	0.97 (0.87, 1.07)	1.17 (1.05, 1.31)
Super Obese	2.35	0.94 (0.80, 1.11)	0.97 (0.82, 1.15)
+ Comorbid mMetS			
Obese	3.41	1.38 (1.25. 1.54)	1.41 (1.25, 1.59)
Morbidly Obese	2.95	1.19 (1.00, 1.41)	1.26 (1.05, 1.50)
Super Obese	3.73	1.52 (1.21, 1.90)	1.39 (1.10, 1.76)

The mMetS was identified using a modification of the criteria used by the NCEP-ATP III: (1) obesity, defined as a body mass index of 30 kg/m^2 or higher, (2) treatment with an oral hypoglycemic or insulin, and (3) hypertension.

CNS = central nervous system; mMetS = modified metabolic syndrome; NCEP-ATP III = National Cholesterol Education Program-Adult Treatment Panel III.[14]

ically obese" patients were qualitatively different from "metabolically healthy but obese" patients, and would therefore be at greater risk for adverse outcomes after noncardiac surgery.

This study has several potential limitations. First, although the ACS NSQIP is a rich clinical registry, we had to adapt the NCEP-ATP III definition of the MetS to the data elements included in ACS NSQIP. In the NCEP-ATP III definition, the MetS is diagnosed when a patient has three or more of the following criteria: abdominal obesity, increased triglycerides, decreased high-density lipoprotein cholesterol, increased blood pressure, and glucose intolerance. We substituted obesity for central obesity and omitted the lipid profile in identifying patients with the MetS. This modified definition of the MetS may have classified some patients with obesity, who did not have abdominal obesity, as having the mMetS. But, as recognized by the NCEP-ATP III Expert Panel, "most persons with the mMetS are overweight or obese."[17] Some patients with the MetS may have been "missed" because we did not include the lipid profile in our definition—and because central obesity is not always captured by a high BMI.[36] Our results, therefore, are valid for our modified definition of the MetS. Moreover, the mMetS has biologic plausibility.[13] Furthermore, the results of this study empirically demonstrate that this syndrome, as defined here, is associated with significant morbidity.

Second, the retrospective nature of this study only allows us to conclude that there is an association between the mMetS and postoperative morbidity and mortality. We cannot conclude that the mMetS causes worse outcomes. Nevertheless, identifying patients with the mMetS as a high-risk group is an important step in improving care in this patient population. It is also possible that we failed to include potentially important confounders in our analyses. However, given the high quality of the data, the robustness of our findings, and the performance of our statistical models, we do not believe that this is likely.

Third, this study is not population based. Instead, it is based on the patient case mix of a self-selected group of hospitals that is not necessarily representative of the surgical case mix of hospitals in the United States. This factor may limit the generalizability of our findings.

Fourth, 11% of relevant patient records were missing values for serum creatinine or hematocrit. Missing data are fre-

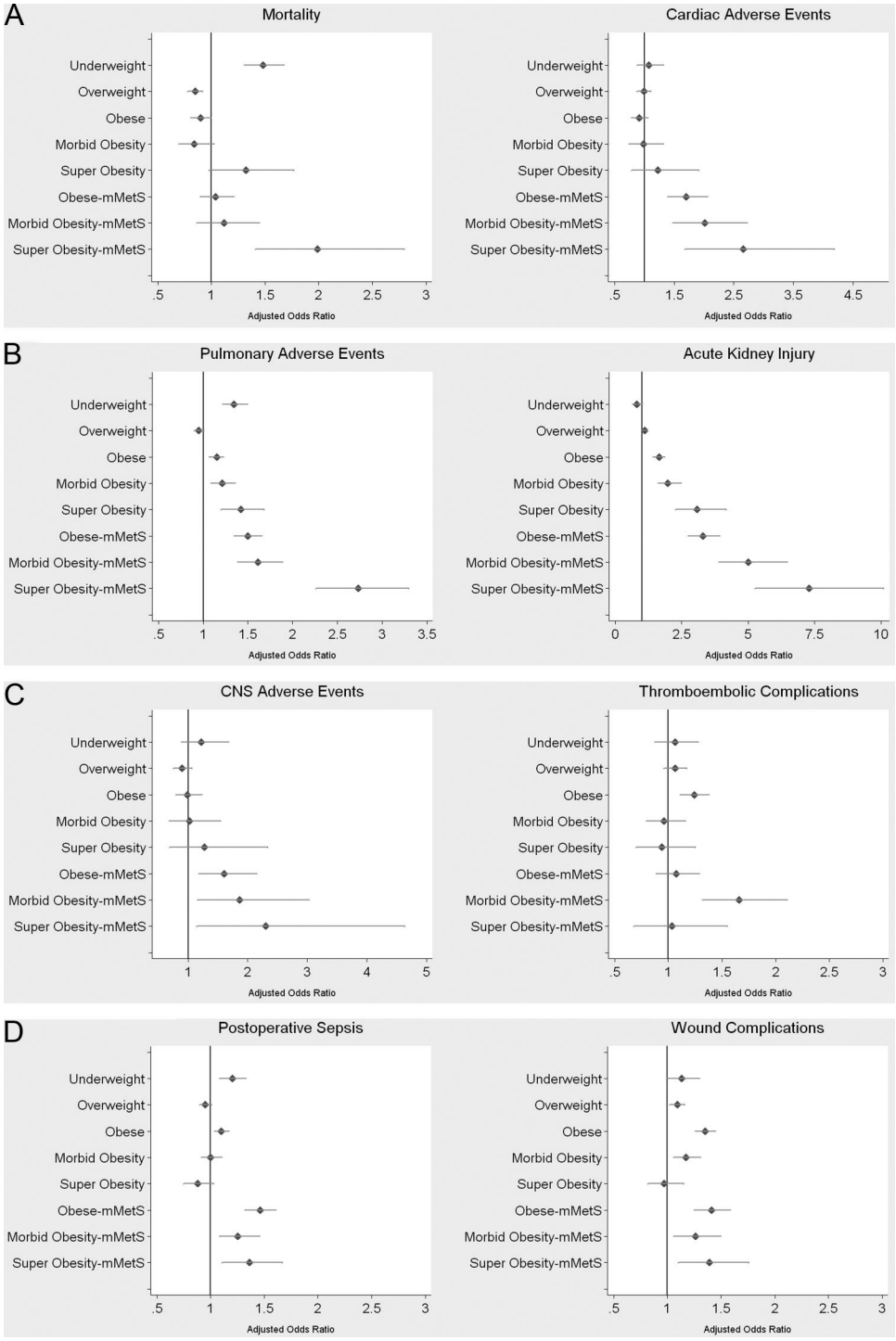

Fig. 2. (*A*) Multivariate analysis of the impact of metabolic syndrome on 30-day mortality and 30-day cardiac morbidity controlling for multiple patient risk factors (see appendix 1). The error bars represent 95% confidence intervals (CI). Patients with normal weight are the reference population. (*B*) Multivariate analysis of the impact of metabolic syndrome on 30-day pulmonary and 30-day renal morbidity controlling for multiple patient risk factors (see appendix 1). The error bars represent 95% CI. Patients with normal weight are the reference population. (*C*) Multivariate analysis of the impact of metabolic syndrome on 30-day stroke and coma complications and 30-day thromboembolic complications controlling for multiple patient risk factors (see appendix 1). The error bars represent 95% CI. Patients with normal weight are the reference population. (*D*) Multivariate analysis of the impact of mMetS on 30-day septic complications and 30-day wound complications controlling for multiple patient risk factors (see appendix 1). The error bars represent 95% CI. Patients with normal weight are the reference population abbreviation. mMetS = modified metabolic syndrome.

quently encountered in large outcome registries. There are many statistical approaches for handling missing data. The simplest approach, defined as complete case analysis, ignores observations with missing data, but this adjustment can lead to biased results if the excluded cases are systematically different from those included in analysis.[24,37] Multiple imputation has become widely accepted methodology for handling missing data[25,38] and was therefore used in our analyses.

One of the primary strengths of this study is that the number of patients with the mMetS was sufficiently large to explore the impact of this syndrome on 30-day mortality and on individual postoperative complications. Most prior studies have examined all-cause morbidity. By examining the impact of the mMetS on individual complications, we were able to detect a wide range in the magnitude of the increase in risk associated with the mMetS across potential complications. Another important strength of this study is the richness of the database on which it is based. Because of the large number of clinical variables collected on the patients in the ACS NSQIP, we were able to control for many important confounders. This feature is particularly important given the fact that patients with the mMetS have many comorbidities.

One of the striking findings of this study is that obese and morbidly obese patients without the mMetS had a 1.5- to 3-fold increased risk of renal complications whereas patients with the syndrome had a 3- to 7-fold increased risk of renal complications. To our knowledge, this is the first time that obese patients have been reported to have substantially higher risk of postoperative renal complications compared with nonobese patients. It is possible that clinicians are not adequately adjusting fluid administration upwards for obese patients, and that, as a result, obese patients are not receiving adequate intraoperative hydration. Future studies linking the ACS NSQIP data to intraoperative data collection may be able to examine this potential mechanism. Such a finding would have important clinical implications given the substantially increased risk of mortality associated with renal failure.[39]

Unlike previous studies, which have concluded that obesity is not associated with increased perioperative risk, our study identifies a subpopulation of "metabolically obese" patients, patients with the mMetS, who have a dramatically higher risk of complications after undergoing noncardiac surgery. In particular, patients with the mMetS experience a nearly 2- to 3-fold higher risk of CAE, a 1.5- to 2.5-fold higher risk of pulmonary complications, a 2-fold higher risk of neurologic complications, and a 3- to 7-fold higher risk of AKI. By identifying this very high–risk group of patients, we now have the opportunity to explore approaches that may improve outcomes in this patient population. This knowledge may also help to further drive public health efforts to control the obesity epidemic.

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Appendix 1. Impact of Obesity and the Modified Metabolic Syndrome on 30-d Mortality and Morbidity

Patient Risk Factors	Mortality	Cardiac	Pulmonary	Renal	CNS	Sepsis	Wound	Thromboembolic
Modified metabolic syndrome								
Obese	1.04	1.70§	1.50§	3.30§	1.60*	1.46§	1.41§	1.03
Morbidly Obese	1.12	2.01§	1.61§	5.01§	1.86†	1.25*	1.26§	1.64§
Super Obese	1.99§	2.66§	2.73§	7.29§	2.30†	1.36*	1.39§	1.04
No Metabolic Syndrome								
Underweight	1.48§	1.07	1.34§	0.81‡	1.22	1.20§	1.13‡	1.05
Normal Weight	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Overweight	0.85§	0.99	0.95‡	1.10	0.90	0.95‡	1.09*	1.08‡
Obese	0.90†	0.91	1.15§	1.64§	0.99	1.10*	1.35§	1.28§
Morbidly Obese	0.84‡	0.98	1.21*	1.98§	1.02	1.00	1.17*	1.00
Super Obese	1.32‡	1.23	1.42§	3.0§	1.27	0.88	0.97	0.99
Age	1.04§	1.02§	1.02§		1.02§	1.01§	1.01§	1.02
Men			0.84§		1.35§	0.83§	0.72	0.85§
Work Relative Value Units	1.03§	1.04§	1.06§	1.05§	1.03§	1.06§	1.05§	1.04§
Emergency	2.04§	1.75§	2.21§	1.79§		1.58§	1.61§	1.36§
Admission Source								
Chronic Care Facility				0.72†				
Hospital	1.44§	1.35§	1.52§	1.37§		1.35§		1.31§
Do-Not-Resuscitate Status	2.63§							
Dependent Functional Status	2.70§	1.88§	2.24§	1.70§	2.07§	2.15§	1.55§	1.56§
Cardiac								
Congestive Heart failure, Previous 30 d	1.27§		1.23*	1.16				
Myocardial Infarction, Previous 6 mo					1.93§			
Percutaneous Coronary Intervention		1.37§						1.13‡
Previous Cardiac Surgery		1.26§	1.11*		1.24†			0.76§
Angina, Previous 30 d		1.62§				1.20†	1.32*	1.39*
Hypertension	1.13*	1.29§	1.25§	1.60§	1.40§	1.17§	1.06†	1.04
Peripheral Vascular Disease		1.42§				1.14*	1.40§	
Rest Pain/Gangrene							1.84§	
Pulmonary								
Ventilator Dependent	1.85§	1.54§		1.47§	2.00§	1.59§		
Chronic Obstructive Pulmonary Disease	1.35§	1.26§	1.66§	1.32§		1.46§	1.18§	
Pneumonia, Current								
Dyspnea at Rest	1.50§		1.87§	1.33*	1.57*	1.39§		1.27*
Dyspnea on Exertion	1.33§	1.19*	1.36§	1.21*	1.30*	1.15§		1.17*
Tobacco Use	1.22§	1.41§	1.67§	1.24§	1.39§	1.38§	1.36§	
Renal								
Mild		1.54§	1.14§	2.06§	1.67§			
Moderate	1.49§	2.29§	1.49§	5.03§	2.17§	1.14§		
Severe	2.59§	3.77§	1.97§	12.1§	2.88§	1.31§		
Chronic Failure	3.83§	5.04*	2.00§	NA	2.88§	1.78§		
Acute Failure	2.68§	4.02§	2.20§	NA	3.41§	1.87§		
Central Nervous System								
Impaired Sensorium	1.38§	1.30*	1.42§					1.15
Coma	2.99§				NA			
Hemiplegia					NA			
Paraplegia	1.26				NA	1.33†		
Quadriplegia			1.93*		NA	2.05§		
Cerebrovascular accident								
Neurodeficit					NA			
No Neurodeficit	1.22*				1.67§			
Transient Ischemic Attack								
Tumor Involving CNS								1.67‡
Hepatobiliary								
Ascites	2.19§		1.83§	1.71§	1.84§	1.75§		1.29*
Esophageal Varices	3.47§		2.25§	4.58§	2.74*	2.24§		

(*continued*)

Appendix 1. Continued

Patient Risk Factors	Mortality	Cardiac	Pulmonary	Renal	CNS	Sepsis	Wound	Thromboembolic
Nutrition/Endocrine/Immune								
Diabetes, Oral	1.03	1.02	1.02	1.15‡	1.19	1.03	0.94	0.98
Diabetes, Insulin	1.08	1.22*	1.14*	1.40§	1.05	1.27§	1.11	0.86‡
Alcohol								
Disseminated Cancer	3.52§	1.41§	1.36§	1.67§	2.06§	1.52§	1.22§	1.78§
Steroid Use	1.52§		1.40§	1.26*		1.55§	1.73§	1.78§
Weight Loss	1.89§	1.66§	1.37§			1.39§	1.26§	1.37§
Chemotherapy	1.55§							
Radiotherapy							1.52§	
Systemic Infection								
Systemic Inflammatory Response Syndrome	1.91§	1.77§	2.10§	1.63§	1.83§	2.46§	1.75§	1.47§
Sepsis	1.89§	1.63§	2.55§	2.04§		NA	2.07§	2.00§
Septic Shock	2.79§	1.94§	4.96§	2.13§	2.02§	NA	1.46§	1.68§
Hematocrit								
<0.20	2.15§	1.81*	1.41†	2.18*	1.14	1.17	1.25	1.48
0.20–0.29	1.70§	1.50§	1.70§	2.12§	1.21	2.12§	1.66§	1.88§
0.30–0.39	1.35§	1.18*	1.28§	1.61§	1.15	1.38§	1.23§	1.30§
0.40–0.49	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
≥0.50	1.35‡	1.70*	1.65§	0.752	0.79	1.29*	1.12	1.05
Hematology								
Bleeding Disorder	1.28§		1.23§	1.25§		1.26§		1.26§
Preoperative Transfusion								
Previous Operation			1.13*			1.26§	1.45§	1.36
Wound Infection	1.08		1.22§			1.78§		NA
C Statistic	0.93	0.89	0.87	0.88	0.86	0.84	0.78	0.78

The modified metabolic syndrome was identified using a modification of the criteria used by the NCEP-ATP III: (1) obesity, defined as a body mass index of 30 kg/m^2 or higher, (2) treatment with an oral hypoglycemic or insulin, and (3) hypertension. The seven system-based medical complications analyzed are as follows: cardiac, pulmonary, renal, CNS, sepsis, wound infection, and thromboembolic. $P \leq 0.001$ unless otherwise specified. The intercept terms for surgery Current Procedural Terminology groups and wound classification are not shown (available on request).

§ $P \leq 0.001$.

* $P \leq 0.01$. † $P \leq 0.05$. ‡ $P \leq 0.10$.

CNS = central nervous system; CPT = Current Procedural Terminology[28]; NA, not available; NCEP-ATP III = National Cholesterol Education Program-Adult Treatment Panel III.[14]

Appendix 2. Results of the Cross-Validation of the 30-d Mortality and Morbidity Models

Model & Sample	C Statistic	Hosmer-Lemeshow Statistic
Mortality		
Development	0.93	76.5
Validation	0.93	73.4
Total	0.93	152
Cardiac Complications		
Development	0.89	37.3
Validation	0.88	34.6
Total	0.89	64.3
Pulmonary Complications		
Development	0.87	104
Validation	0.89	149
Total	0.87	203
Renal Complications		
Development	0.88	23.2
Validation	0.87	41.3
Total	0.88	46.5
Central Nervous System Complications		
Development	0.86	20.1
Validation	0.85	43.1
Total	0.86	40.9
Sepsis Complications		
Development	0.84	142
Validation	0.84	204
Total	0.84	301
Wound Complications		
Development	0.78	76.0
Validation	0.77	77.6
Total	0.78	139
Thromboembolic Complications		
Development	0.78	31.0
Validation	0.78	33.6
Total	0.78	66.9