# Obesity, Acute Kidney Injury, and Mortality in Critical Illness

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**Objectives:** Although obesity is associated with risk for chronic kidney disease and improved survival, less is known about the associations of obesity with risk of acute kidney injury and post acute kidney injury mortality.

**Design:** In a single-center inception cohort of almost 15,000 critically ill patients, we evaluated the association of obesity with acute kidney injury and acute kidney injury severity, as well as in-hospital and 1-year survival. Acute kidney injury was defined using the Kidney Disease Outcome Quality Initiative criteria.

**Measurements and Main Results:** The acute kidney injury prevalence rates for normal, overweight, class I, II, and III obesity were 18.6%, 20.6%, 22.5%, 24.3%, and 24.0%, respectively, and the adjusted odds ratios of acute kidney injury were 1.18 (95% CI, 1.06–1.31), 1.35 (1.19–1.53), 1.47 (1.25–1.73), and 1.59 (1.31–1.87) when compared with normal weight, respectively. Each 5-kg/m$^2$ increase in body mass index was associated with a 10% risk (95% CI, 1.06–1.24; $p < 0.001$) of more severe acute kidney injury. Within-hospital and 1-year survival rates associated with the acute kidney injury episodes were similar across body mass index categories.

**Conclusion:** Obesity is a risk factor for acute kidney injury, which is associated with increased short- and long-term mortality. (*Crit Care Med* 2016; XX:00–00)

**Key Words:** acute kidney injury; acute renal failure; body mass index; obesity; survival

As obesity grows as an epidemic, knowledge of its pathophysiologic complications is important. Many of the hallmark systemic abnormalities of obesity, including insulin resistance, hypertension, and cardiovascular disease, are known contributors to renal disease, and more recently, renal-specific pathways, including increased autophagy and fibrosis, have been described (1). In addition, the emerging importance of renal vein congestion as a determinant of renal function (2) raises questions whether the hemodynamic complications of obesity, including obesity hypoventilation, pulmonary hypertension and cor pulmonale, may contribute to renal dysfunction.

Although obesity has been associated with chronic kidney disease (CKD) (3–6), it is not widely accepted as a risk factor for acute kidney injury (AKI) (7, 8). The prevalence of AKI in obesity has been described in bariatric surgery (9, 10), cardiac surgery (11–14), and in the acute respiratory distress syndrome (15), and a more recent study focused on severe AKI requiring dialysis (16). However, to our knowledge, the association of body mass index (BMI) with AKI and AKI severity has not been well described in a large representative critically ill population. In addition, no study has described the long-term outcomes of AKI in critically ill obese patients. In CKD, obesity is paradoxically associated with an improved prognosis (17, 18). Thus, whereas an episode of AKI is typically associated with worse survival (19, 20), whether this association is also true for critically ill obese patients is unknown.

To address the simultaneous associations of obesity with prevalence and prognosis of AKI, we evaluated a large

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cohort of patients hospitalized in the ICU of a single large medical center.

## METHODS

### Study Population

We used the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-III) database, a joint venture managed by the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT) and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC) (21). MIMIC-III contains data from 37,305 unique adult critical care admissions between 2001 and 2012 at BIDMC, a 700-bed urban academic medical center with 77 adult ICU beds. The database contains high-temporal-resolution data from clinical systems, including laboratory results, electronic documentation, and bedside monitor trends and waveforms. Use of the MIMIC II database has been approved by the Institutional Review Boards of BIDMC and MIT.

A total of 22,073 individuals had a documented height within the BIDMC electronic medical record. Of these, 18,938 had a documented weight upon ICU admission, allowing calculation of BMI. After exclusion of 743 end-stage renal disease patients, 17,140 had documentation of renal function. To identify comorbidities and medication exposure, we included the 15,470 patients with an admission history and physical examination with admission medication lists. Of these, 484 were missing documentation of admission ICU vitals, leaving a primary complete case analysis of 14,986.

### Outcomes

The primary outcome was acute kidney injury during ICU admission, as defined by either a greater than or equal to 0.3 mg/dL increase within 48 hours or a greater than or equal to 50% increase within 7 days of ICU admission, or acute dialysis, in keeping with the Kidney Disease Outcome Quality Initiative guidelines (22). We also explored the association of BMI with severity of AKI. Stage I AKI was defined as 50–100% increase in admission serum creatinine within 7 days, stage II as greater than 100–200% increase, and stage III as greater than 200% increase, or the initiation of acute dialysis. Following best practice guidelines, we used the admission creatinine to define "baseline" (23).

To evaluate risk of death during hospitalization and within 1 year from hospital discharge, we linked medical records to the Social Security Death Index.

### Exposure

BMI was the primary exposure, categorized in standard World Health Organization groupings: less than 18.5 (underweight), greater than or equal to 18.5 to less than 25 (normal), greater than or equal to 25 to less than 30 (overweight), greater than or equal to 30 to less than 35 (class I obesity), greater than or equal to 35 to less than 40 (class II obesity), and BMI greater than or equal to 40 (class III obesity), and as a continuous variable per 5 units of BMI.

Because weight at the time of critical illness might not reflect usual body weight, we performed a validation study among 150 randomly selected subjects within the dataset to determine body weights measurements obtained during noncritical illness. A total of 86 individuals had documented weights during noncritical illness in the electronic medical record. The Spearman correlation coefficient between ICU and non-ICU body weights measurements was 0.93 ($p < 0.001$), with a median difference of –0.03 kg (interquartile range, –2.8 to 2.9).

### Covariates

Demographic information included age, sex, and race, coded as white, African-American, Asian, Hispanic, other, or unknown. We identified patients with heart failure through Natural Language Processing searching of the Past Medical History section of the admission examination or Elixhauser discharge coding (24). We also used oral diabetes medication or insulin usage, along with Elixhauser discharge coding, to identify diabetic patients. All additional Elixhauser discharge coding comorbidities except for "acute renal failure" and "obesity" were included as separate variables (24). ICU types included cardiac, surgical, cardiothoracic, and medical units. Sequential Organ Failure Assessment scores were used to indicate severity of illness. Because of the effect of hemodynamics on renal function, we also included systolic and diastolic blood pressure, heart rate, and temperature as independent variables. Admission creatinine, defined as the first available creatinine 24 hours prior to, or 6 hours after, ICU admission, was used as a determinant of "baseline" kidney function. Admission hemoglobin was also included. Because obesity is likely associated with increased diuretic, angiotensin-converting enzyme inhibitor (ACE-I), angiotensin-receptor blocker (ARB), and statin usage, we used Natural Language Processing searches of prehospital medication lists to identify these exposures. All admission values, except for creatinine, were taken from the first available laboratory data within 24 hours of ICU admission.

### Statistical Analysis

We present descriptive baseline characteristics stratified by BMI. We used logistic regression to examine the association between BMI, defined categorically and continuously, and odds of AKI, based on serum creatinine changes. We adjusted for age, gender, race, ICU type, Sequential Organ Failure Assessment score, history of diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease and 22 additional Elixhauser comorbidities, admission systolic and diastolic blood pressure, heart rate, temperature, creatinine and hemoglobin, and preillness diuretic, ACE-I, ARB, or statin use.

We describe the prevalence of AKI stages I to III per BMI classification. We used ordinal logistic regression to describe the adjusted risk of a one-step increase of AKI severity with an increase of BMI. In separate logistic regressions, we then examined the risk of having either stage II or III AKI when compared with that of having either no AKI or stage I AKI and the risk of having stage III AKI when compared with that of having no AKI, stage I, or stage II AKI.



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**TABLE 1. Baseline Characteristics Stratified by Body Mass Index Categories**

| | < 18.5 | ≥ 18.5 to < 25 | ≥ 25 to < 30 | ≥ 30 to < 35 | ≥ 35 to < 40 | > 40 | |
|---|---|---|---|---|---|---|---|
| | *n* = 431 | *n* = 4,271 | *n* = 5,047 | *n* = 2,908 | *n* = 1,292 | *n* = 1,037 | *p* |
| Demographics | | | | | | | |
| Age (yr), mean (SD) | 66. 42 (17.4) | 66.0 (17.8) | 65.2 (15.9) | 63.9 (14.5) | 62.3 (13.6) | 58.1 (13.9) | < 0.001 |
| Female, *n* (%) | 273 (63.3) | 1,972 (46.2) | 1,783 (35.3) | 1,091 (37.5) | 582 (5.1) | 578 (55.7) | < 0.001 |
| Race, *n* (%) | | | | | | | |
| White | 308 (71.38) | 3,078 (72.1) | 3,693 (73.7) | 2,080 (71.5) | 952 (73.7) | 724 (69.8) | < 0.001 |
| Black | 8 (8.8) | 308 (7.2) | 336 (6.7) | 239 (8.2) | 117 (9.1) | 123 (11.9) | |
| Hispanic | 7 (1.6) | 108 (2.5) | 177 (3.5) | 116 (4.0) | 49 (3.8) | 49 (3.8) | |
| Asian | 28 (6.5) | 183(4.3) | 107 (2.1) | 24 (0.8) | 7 (0.5) | 7 (0.5) | |
| Other | 12 (2.8) | 121 (2.8) | 129 (2.6) | 90 (3.1) | 37 (2.9) | 26 (2.5) | |
| Unknown | 38 (8.8) | 473 (11.1) | 605 (120.) | 359 (12.4) | 130 (10.1) | 123 (11.9) | |
| Cardiac care unit | 67 (15.5) | 808 (18.9) | 945 (19.1) | 555 (19.1) | 261 (20.2) | 184 (17.7) | < 0.001 |
| Medical care unit | 187 (43.4) | 1,416 (33.2) | 1,464 (29.0) | 842 (29.0) | 402 (31.1) | 378 (36.5) | < 0.001 |
| Surgical care unit | 177 (41.1) | 2,047 (48.0) | 2,638 (52.2) | 1,511 (52.0) | 629 (48.6) | 475 (45.8) | < 0.001 |
| Past medical history, *n* (%) | | | | | | | |
| Congestive heart failure | 46 (10.7) | 407 (9.5) | 460 (9.1) | 256 (8.8) | 155 (12.0) | 142 (13.7) | < 0.001 |
| Peripheral vascular disease | 48 (11.1) | 445(10.4) | 524 (10.4) | 256 (8.8) | 130 (10.1) | 90 (7.7) | 0.24 |
| Hypertension | 133 (30.9) | 1,461(34.2) | 1,983(39.2) | 1,240 (42.6) | 579 (44.8) | 442 (42.6) | < 0.001 |
| Chronic pulmonary disease | 111 (25.8) | 785 (18.4) | 765 (15.2) | 512 (17.6) | 287 (22.2) | 282 (27.9) | < 0.001 |
| Diabetes | 64 (14.9) | 921 (21.6) | 1,381 (27.4) | 1,071 (36.8) | 591 (45.7) | 467 (45.3) | < 0.001 |
| Diuretic use | 97 (22.5) | 1,183 (27.7) | 1,484 (29.4) | 1,011 (34.8) | 511 (39.6) | 460 (44.4) | < 0.001 |
| Ang. conv. inhibitor use | 93 (21.6) | 1,049 (24.6) | 1,444 (28.7) | 919 (31.7) | 401 (31.1) | 336 (32.4) | < 0.001 |
| Ang. receptor blocker use | 23 (5.3) | 269 (6.3) | 438 (8.7) | 299 (10.3) | 152 (11.8) | 108 (10.4) | < 0.001 |
| Admission vitals, mean (SD) | | | | | | | |
| Systolic blood pressure (mm Hg) | 123.7 (26.9) | 123.2 (24.8) | 123.1 (24.2) | 12,336 (14.5) | 124.0 (24.4) | 124.4(24.6) | 0.55 |
| Diastolic blood pressure (mm Hg) | 64.6 (17.9) | 63.1 (15.6) | 63.8 (15.7) | 64.1 (15.8) | 64.6 (15.4) | 64.8 (17.0) | 0.002 |
| Heart rate (bpm) | 89.8 (19.9) | 88.3 (19.2) | 87.1 (18.8) | 87.3 (18.7) | 88.8 (19.1) | 91.0 (19.4) | < 0.001 |
| Temperature (°C) | 36.3 (1.2) | 36.4 (1.0) | 36.5 (0.9 | 36.5 (0.9) | 36.6 (1.0) | 36.7 (0.9) | < 0.001 |
| Admission values, mean (SD) | | | | | | | |
| Hemoglobin (%) | 11.2 (2.1) | 11.7 (2.1) | 12.0 (2.2) | 12.2 (2.2) | 12.0 (2.2) | 11.8 (2.2) | < 0.001 |
| Creatinine (mg/dL) | 1.2 (1.2) | 1.1 (1.2) | 1.3 (1.3) | 1.2 (1.1) | 1.4 (1.3) | 1.4 (1.3) | < 0.001 |

Mean (standard deviation) for continuous variables and number (within column percentages) for categorical variables provided. P values across groups provided.

To contextualize the clinical significance of an episode of AKI in obesity, we used logistic regression to define the adjusted risk of an episode of AKI on within-hospital mortality within each BMI category. We also describe the effect of AKI on long-term survival according to BMI in hospital survivors. We used Cox regression analyses, censoring those who survived 365 days or more, and adjusting for the same variables as above, within each BMI category.

In sensitivity analyses, to further explore potential mechanisms for the observed strong association of increasing BMI with risk of AKI, we performed sequential logistic regressions examining how the addition of admission proteinuria, defined as trace or greater on urinary dipstick measurement, and admission central venous pressure (CVP), obtained within the first 6 hours of admission, changed the association of BMI



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with AKI. In addition, we used creatinine measurements obtained prior to 7 days from ICU admission as "baseline" in 7,000 patients with available measurements.

For all analyses, normal weight was considered the reference category. All analyses were performed using JMP Pro (SAS Institute, Cary, NC).

## RESULTS

### Baseline Characteristics

Of 14,986 critically ill patients admitted to a medical or surgical ICU with available data, 431 (3%) were underweight, 4,271 (28%) were normal weight, 5,047 (34%) were overweight, 2,908 (19%) had class I obesity, 1,292 (9%) had class II obesity, and 1,037 (7%) had class III obesity. Obesity was associated with a higher prevalence of heart failure, hypertension, and diabetes than those with normal BMIs, and greater exposure to diuretics, ACE-Is, ARBs, and statins prior to admission (**Table 1**). Admission blood pressure tended to be similar across BMI categories. Admission creatinines tended to be higher in obese patients.

### BMI and Prevalence and Severity of AKI

During the course of critical illness, 3,122 (21.1%) individuals developed AKI. As seen in **Table 2**, the prevalence and adjusted risk of AKI progressively increased with higher BMI. Each 5-kg/m$^2$ increment in admission BMI was associated with a 10% (95% CI, 1.06–1.24; $p < 0.001$) higher adjusted risk of AKI in a model that accounted for demographics, comorbidities, severity of critical illness, medication exposure, and admission creatinine. As a frame of reference, diabetes was associated with a 1.26 (95% CI, 1.15–1.38; $p < 0.001$) higher risk of AKI.

The prevalence of AKI severity according to BMI is illustrated in **Figure 1**. In adjusted analysis, a 5-kg/m$^2$ increment was associated with a 9% higher risk (95% CI, 1.06–1.22; $p < 0.001$) of having a higher stage of AKI. As seen in **Table 3**, the risk of having stage II or III AKI, when compared with that of having either no AKI or stage I AKI, or stage III AKI, compared with that of having no AKI, stage I, or stage II AKI, increased progressively with higher BMI relative to normal weight patients.

### AKI and Survival

There were 1,513 (10%) deaths during the critical illness hospitalization. The association of AKI with in-hospital mortality was modified by BMI (multiplicative interaction term $p < 0.01$). When stratified by BMI category, AKI was consistently associated with a significantly higher risk of death (**Table 4**). When stratified by AKI, a protective effect of obesity on hospital survival was observed in those without AKI, as has previously been reported. A 5-kg/m$^2$ BMI increase was associated with a 0.89 (95% CI, 0.85–0.94; $p < 0.001$) odds ratio (OR) of within-hospital death in those without AKI. However, in those with AKI, each 5-kg/m$^2$ BMI increase was associated with a 0.98 (95% CI, 0.96–1.09; $p = 0.59$) risk of within-hospital death.

Among 13,473 hospital survivors, 1,568 (12%) died within 1 year of hospital discharge. The association of AKI with subsequent 1-year mortality was not modified by BMI (multiplicative interaction term, 0.43). Similarly, an episode of AKI during critical illness was associated an increased risk of dying within the following 1 year across BMI categories (Table 4).

### Sensitivity Analyses

Among patients with available data, CVP ($n = 4,017$) and prevalence of admission proteinuria ($n = 5,753$) increased progressively with higher BMI (**Fig. 2**). Addition of CVP into the multivariate-adjusted model reduced the OR minimally (OR, 1.08; 95% CI, 1.02–1.14; $p = 0.003$, per 5-kg/m$^2$ BMI increase), and in 2,116 participant with both measurements, each 5-kg/m$^2$ increment was associated with a 1.08 (95% CI, 1.01–1.16; $p = 0.03$) increased risk of AKI.

Defining baseline renal function by a serum creatinine obtained more than 7 days prior to critical illness, rather than by the admission creatinine, did not meaningfully change the association between BMI and AKI. In 7,891 patients with available preillness serum creatinine measurements, the correlation between preillness and admission serum creatinine measurements was 0.68 ($p < 0.001$). Each 5-kg/m$^2$ increment remained associated with a 1.08 (95% CI, 1.01–1.16; $p = 0.02$) increased risk of AKI.

## DISCUSSION

Our findings highlight obesity as a risk factor for AKI during critical illness. In models that adjusted for comorbidities,

**TABLE 2. Adjusted Risk of Acute Kidney Injury According to Body Mass Index**

| | BMI Categories | | | | | | Per 5 kg/m$^2$ Positive |
|---|---|---|---|---|---|---|---|
| | < 18.5 | 18.5 ≥ BMI < 25 | 25 ≥ BMI < 30 | 30 ≥ BMI < 35 | 30 ≥ BMI < 35 | BMI ≥ 45 | |
| *n* (%) | 69 (16.0) | 796 (18.6) | 1,041 (20.6) | 653 (22.5) | 314 (24.3) | 249 (24.0) | |
| OR (95% CI); *p* | 0.81 (0.60–1.06), 0.13 | Ref. | 1.18 (1.06–1.31), 0.003 | 1.35 (1.19–1.53), < 0.001 | 1.47 (1.25–1.73), < 0.001 | 1.59 (1.31–1.87), < 0.001 | 1.10 (1.06–1.24), < 0.001 |

BMI = body mass index, OR = odds ratio.

Number of acute kidney injury episodes per body mass index category, within column percentages, and odds ratio provided. Adjusted for age, gender, race, ICU type, Sequential Organ Failure Assessment, history of diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease and 22 additional Elixhauser comorbidities, admission vitals (systolic and diastolic blood pressure, heart rate, and temperature) admission laboratories (hemoglobin and creatinine), and preillness medication usage (angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, statin, and diuretics).



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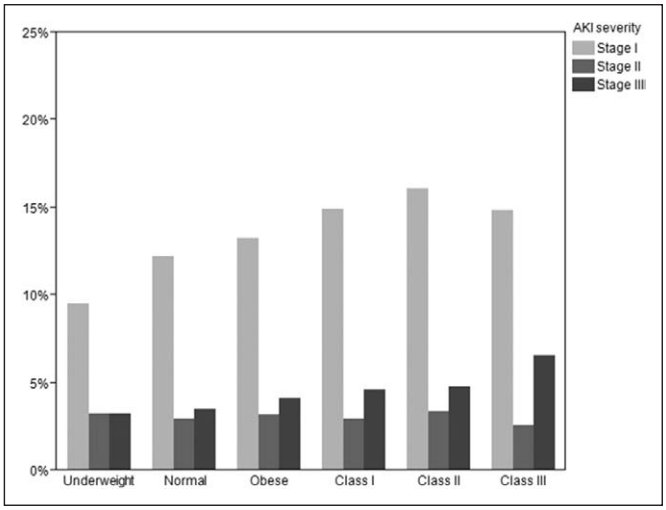


**Figure 1.** Percentage of patients stratified by body mass index who develop Stage I, II, and III AKI within seven days of ICU admission. AKI = acute kidney injury.

acuity of illness, preillness ACE, ARB, and diuretic use, each 5 kg/m$^2$ was associated with a 10% increased risk of AKI. Furthermore, these episodes of AKI were associated with worse short- and long-term survival.

Our findings supplement a growing awareness of the susceptibility to AKI in obesity. In a recent study of almost 500 critically ill patients with acute respiratory distress, each 5-kg/m$^2$ increase in BMI was associated with a 20% increased risk of AKI (15). In a large Austrian study, severely obese patients had a greater than two-fold increased risk of severe AKI than normal-weighted patients (16). Long-term survival was not available in either study. More recent studies, however, have not identified obesity as a significant risk factor for AKI (7).

Our observed association between obesity and AKI raise questions about potential pathophysiologic mechanisms (25). The hemodynamic perturbations associated with obesity could explain an increased susceptibility (26). Cor pulmonale, a result of hypoventilation, sleep apnea, and pulmonary hypertension, occurs frequently in obesity (27, 28) and leads to sodium avidity and peripheral venous congestion. Patients with obesity have higher right-sided filling pressures (29) and greater diuretic requirements (30) than those with normal weight. The role of venous congestion as a determinant of renal function has been known for over 80 years, with early physiology experiments highlighting that increased renal venous pressures decreased urine formation (31, 32). More recent clinical data have focused on peripheral venous congestion in heart failure (33), where CVPs, but not cardiac output or pulmonary artery pressures, are associated with renal dysfunction, highlighting the importance of the transrenal pressure gradient, a balance between renal arterial perfusion and venous drainage, as a determinant of renal function. Similarly, increasing CVP has been associated with AKI in sepsis (34).

In our analysis, increasing BMI was associated with higher CVPs obtained within 6 hours to the ICU. However, inclusion of CVP measures did not significantly attenuate or modify the association between BMI and AKI, suggesting that additional factors may exist.

Recent data have highlighted organ-specific abnormalities in obesity, with changes seen both within the kidney and the heart. Obesity leads to renal glomerular hypertrophy and hyperfiltration (35), which potentially contribute to renal susceptibility. More recently, an "adipose-renal" hormonal axis has emerged. Adiponectin, an insulin-sensitizing hormone that regulates glucose and lipid metabolism, and which is markedly decreased in visceral obesity, is protective in some models of renal ischemia reperfusion injury although considered pathogenic in others (36). Leptin, an adipocyte-derived cytokine that is metabolized in the kidney and controls energy metabolism and appetite modulates susceptibility to

**TABLE 3. Adjusted Association of Body Mass Index With Acute Kidney Injury Severity**

| | Body Mass Index Categories | | | | | | Per 5 kg/m$^2$ Positive |
|---|---|---|---|---|---|---|---|
| | < 18.5 | ≥ 18.5 to 25, Reference | ≥ 25 to 30 | ≥ 30 to 35 | ≥ 30 to 35 | ≥ 40 | - |
| AKI as defined by KDOQI stage II or stage III ($n$ = 1,092) | | | | | | | |
| OR (95% CI), $p$ | 0.94 (0.66–1.41), 0.78 | Ref. | 1.23 (1.04–1.47), 0.01 | 1.26 (1.04–1.54), 0.02 | 1.22 (0.94–1.55), 0.12 | 1.38 (1.06–1.80), 0.02 | 1.06 (1.02–1.10), 0.006 |
| AKI as defined by KDOQI stage III ($n$ = 636) | | | | | | | |
| OR (95% CI), $p$ | 0.91 (0.48–1.60), 0.77 | Ref. | 1.29 (1.03–1.62), 0.03 | 1.44 (1.11–1.87), 0.005 | 1.23 (0.87–1.75), 0.22 | 1.75 (1.25–2.42), < 0.001 | 1.08 (1.04–1.14), 0.007 |

AKI = acute kidney injury, KDOQI = Kidney Disease Outcome Quality Initiative, OR = odds ratio.

Adjusted for age, gender, race, ICU type, Sequential Organ Failure Assessment, history of diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease and 22 additional Elixhauser comorbidities, admission vitals (systolic and diastolic blood pressure, heart rate, and temperature) admission laboratories (hemoglobin and creatinine), and preillness medication usage (angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, statin, and diuretics).



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**TABLE 4. Association of Acute Kidney Injury Episode With Short- and Long-Term Mortality According to Body Mass Index Status**

| | Body Mass Index Categories | | | | | |
|---|---|---|---|---|---|---|
| | < 18.5 | ≥ 18.5 to 25 | ≥ 25 to 30 | ≥ 30 to 35 | ≥ 30 to 35 | ≥ 40 |
| Within-hospital mortality | | | | | | |
| OR (95% CI), *p* | 1.31 (0.55–2.98), 0.53 | 2.09 (1.66–2.62), < 0.001 | 2.13 (1.69–2.86), < 0.001 | 2.85 (2.08–3.92), < 0.001 | 4.26 (2.65–6.89), < 0.001 | 2.04 (1.21–3.42), 0.008 |
| One-year mortality in hospital survivors | | | | | | |
| OR (95% CI), *p* | 0.51 (–0.73 to 0.03), 0.07 | 1.29 (1.05–1.59), 0.02 | 1.16 (0.92–1.45), 0.19 | 2.85 (2.08–3.92), < 0.001 | 1.37 (0.76–2.42), 0.28 | 2.51 (1.18–5.76), 0.02 |

OR = odds ratio.

Odds ratio (95% CI) are provided for effect of acute kidney injury (AKI) episode on outcome per body mass index category. Reference is those without AKI within each category. Adjusted for age, gender, race, ICU type, Sequential Organ Failure Assessment, history of diabetes, congestive heart failure, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease and 22 additional Elixhauser comorbidities, admission vitals (systolic and diastolic blood pressure, heart rate, and temperature) admission laboratories (hemoglobin and creatinine), and preillness medication usage (angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, statin, and diuretics) and body mass index.

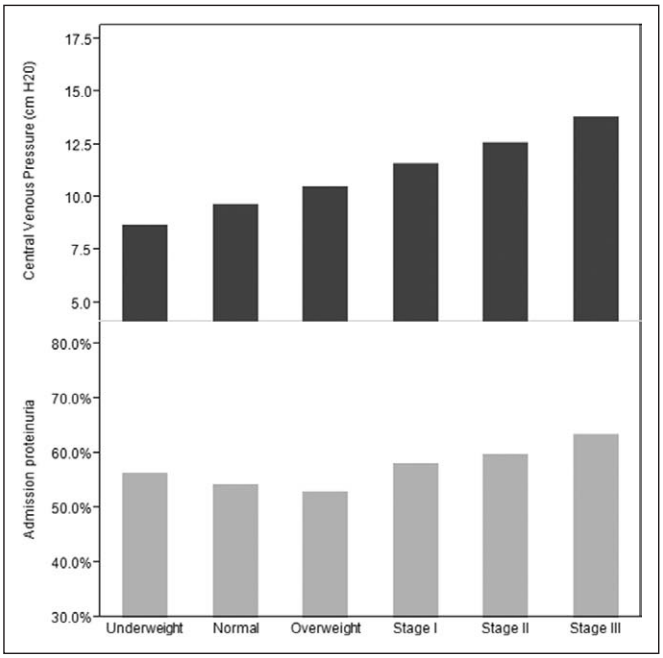


**Figure 2.** Mean admission central venous pressure and percentage of patients with admission proteinuria stratified by body mass index.

endotoxin-mediated renal failure and stimulates proliferation and fibrosis (37, 38). Autophagy, an important internal degradation system whereby cells can remove damaged proteins and organelles, is impaired in obesity (1). Cardiac changes associated with obesity also might affect renal perfusion. In addition to increased left ventricular hypertrophy, direct infiltration of the myocardium has been reported, termed "cardiomyopathy of obesity" (39–41). Thus, whether kidney or cardiac-specific changes associated with obesity contribute to the prevalence of AKI is plausible.

In addition to establishing obesity as a risk for AKI, our data highlight the associated short- and long-term outcomes associated with AKI. In our analysis, even though patients with obesity were more likely to develop AKI, these AKI episodes were not less significant. Rather, across BMI categories, AKI was associated with increased within-hospital mortality and 1-year mortality. In addition, whereas obesity has paradoxically been associated with an improved prognosis in critical illness, this protective association is absent in patients with AKI. Whether renal protective strategies, including minimizing radiographic contrast and potentially nephrotoxic medications, careful use of diuretics, and careful blood pressure management to minimize hypotension, might improve outcomes, remains speculative.

## Limitations

Although our study had a number of strengths, including an extremely large dataset with ample power and systematic assessment of mortality, the observational nature of our analysis limits any conclusions of causality. Furthermore, although the large number of patients and the multiple covariates allow for adjustment, it is plausible that confounding remains. Given the unaccounted effect of critical illness on weight, and the lack of information about weight changes prior to admission, confounding due to malnutrition, cachexia, and fluid retention likely remains although we would not expect nonadipose contributors to BMI such as fluid retention to be associated with improved 1-year mortality. In addition, our manual review of randomly selected charts suggests a strong correlation between critical and noncritical illness BMI values. In addition, we used admission serum creatinines to account for baseline function, which likely leads to misclassification. However, in a subset of patients with available creatinine measurements prior to critical illness, admission and baseline creatinines were highly correlated, and the association of BMI with AKI remained robust. Furthermore, because the baseline serum creatinine may be increased in obesity, our outcome of a



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relative change in creatinine should be conservative and hence this would bias our findings toward the null.

## CONCLUSIONS

AKI more likely to develop in patients with obesity , which is associated with increased short- and long-term mortality. Whether renal protective strategies during critical illness might improve outcomes will require further investigation.

## REFERENCES


1. Yamahara K, Kume S, Koya D, et al: Obesity-mediated autophagy insufficiency exacerbates proteinuria-induced tubulointerstitial lesions. *J Am Soc Nephrol* 2013; 24:1769–1781
2. Damman K, van Deursen VM, Navis G, et al: Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 2009; 53:582–588
3. Ting SM, Nair H, Ching I, et al: Overweight, obesity and chronic kidney disease. *Nephron Clin Pract* 2009; 112:c121–c127
4. Ix JH, Sharma K: Mechanisms linking obesity, chronic kidney disease, and fatty liver disease: The roles of fetuin-A, adiponectin, and AMPK. *J Am Soc Nephrol* 2010; 21:406–412
5. Othman M, Kawar B, El Nahas AM: Influence of obesity on progression of non-diabetic chronic kidney disease: A retrospective cohort study. *Nephron Clin Pract* 2009; 113:c16–c23
6. Hsu CY, McCulloch CE, Iribarren C, et al: Body mass index and risk for end-stage renal disease. *Ann Intern Med* 2006; 144:21–28
7. Kane-Gill SL, Sileanu FE, Murugan R, et al: Risk factors for acute kidney injury in older adults with critical illness: A retrospective cohort study. *Am J Kidney Dis* 2015; 65:860–869
8. Sileanu FE, Murugan R, Lucko N, et al: AKI in low-risk versus high-risk patients in intensive care. *Clin J Am Soc Nephrol* 2015; 10:187–196
9. McCullough PA, Gallagher MJ, Dejong AT, et al: Cardiorespiratory fitness and short-term complications after bariatric surgery. *Chest* 2006; 130:517–525
10. Sharma SK, McCauley J, Cottam D, et al: Acute changes in renal function after laparoscopic gastric surgery for morbid obesity. *Surg Obes Relat Dis* 2006; 2:389–392
11. Kumar AB, Bridget Zimmerman M, Suneja M: Obesity and post-cardiopulmonary bypass-associated acute kidney injury: A single-center retrospective analysis. *J Cardiothorac Vasc Anesth* 2014; 28:551–556
12. Wigfield CH, Lindsey JD, Muñoz A, et al: Is extreme obesity a risk factor for cardiac surgery? An analysis of patients with a BMI > or = 40. *Eur J Cardiothorac Surg* 2006; 29:434–440
13. Yap CH, Mohajeri M, Yii M: Obesity and early complications after cardiac surgery. *Med J Aust* 2007; 186:350–354
14. Billings FTt, Pretorius M, Schildcrout JS, Mercaldo ND, Byrne JG, Ikizler TA, et al. Obesity and oxidative stress predict AKI after cardiac surgery. *J Am Soc Nephrol*. 2012;23:1221–1228
15. Soto GJ, Frank AJ, Christiani DC, et al: Body mass index and acute kidney injury in the acute respiratory distress syndrome. *Crit Care Med* 2012; 40:2601–2608
16. Druml W, Metnitz B, Schaden E, et al: Impact of body mass on incidence and prognosis of acute kidney injury requiring renal replacement therapy. *Intensive Care Med* 2010; 36:1221–1228
17. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, et al: Survival advantages of obesity in dialysis patients. *Am J Clin Nutr* 2005; 81:543–554
18. Kalantar-Zadeh K, Anker SD, Coats AJ, et al: Obesity paradox as a component of reverse epidemiology in heart failure. *Arch Intern Med* 2005; 165:1797; author reply 1797–1797
19. Hoste EA, Kellum JA: Acute kidney injury: Epidemiology and diagnostic criteria. *Curr Opin Crit Care* 2006; 12:531–537
20. Hoste EA, Clermont G, Kersten A, et al: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. *Crit Care* 2006; 10:R73
21. Saeed M, Villarroel M, Reisner AT, et al: Multiparameter Intelligent Monitoring in Intensive Care II: A public-access intensive care unit database. *Crit Care Med* 2011; 39:952–960
22. Palevsky PM, Liu KD, Brophy PD, et al: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 2013; 61:649–672
23. Fliser D, Laville M, Covic A, et al; Ad-hoc working group of ERBP: A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: Part 1: Definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant* 2012; 27:4263–4272
24. Elixhauser A, Steiner C, Harris DR, et al: Comorbidity measures for use with administrative data. *Med Care* 1998; 36:8–27
25. Wickman C, Kramer H: Obesity and kidney disease: Potential mechanisms. *Semin Nephrol* 2013; 33:14–22
26. Chagnac A, Weinstein T, Korzets A, et al: Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol* 2000; 278:F817–F822
27. Marik PE, Desai H: The emergent malignant obesity hypoventilation syndrome: A new critical care syndrome. Author reply. *J Intensive Care Med* 2013; 28:200
28. Marik PE, Desai H: Characteristics of patients with the "malignant obesity hypoventilation syndrome" admitted to an ICU. *J Intensive Care Med* 2013; 28:124–130
29. Fishman AP, Maxwell MH, Crowder CH, et al: Kidney function in cor pulmonale; particular consideration of changes in renal hemodynamics and sodium excretion during variation in level of oxygenation. *Circulation* 1951; 3:703–721
30. de Louw EJ, Sun PO, Lee J, et al: Increased incidence of diuretic use in critically ill obese patients. *J Crit Care* 2015; 30:619–623
31. Winton FR: The influence of venous pressure on the isolated mammalian kidney. *J Physiol* 1931; 72:49–61
32. Winton FR: The influence of increase of ureter pressure on the isolated mammalian kidney. *J Physiol* 1931; 71:381–390
33. Mullens W, Abrahams Z, Francis GS, et al: Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 2009; 53:589–596
34. Legrand M, Dupuis C, Simon C, et al: Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: A retrospective observational study. *Crit Care* 2013; 17:R278
35. Chagnac A, Weinstein T, Herman M, et al: The effects of weight loss on renal function in patients with severe obesity. *J Am Soc Nephrol* 2003; 14:1480–1486
36. Cheng CF, Lian WS, Chen SH, Lai PF, Li HF, Lan YF, et al. Protective effects of adiponectin against renal ischemia-reperfusion injury via prostacyclin-PPARalpha-heme oxygenase-1 signaling pathway. *J Cell Physiol*. 2012; 227:239–249
37. Han DC, Isono M, Chen S, et al: Leptin stimulates type I collagen production in db/db mesangial cells: Glucose uptake and TGF-beta type II receptor expression. *Kidney Int* 2001; 59:1315–1323
38. Wolf G, Hamann A, Han DC, et al: Leptin stimulates proliferation and TGF-beta expression in renal glomerular endothelial cells: Potential role in glomerulosclerosis [seecomments]. *Kidney Int* 1999; 56:860–872
39. Alexander JK: The cardiomyopathy of obesity. *Prog Cardiovasc Dis* 1985; 27:325–334
40. Kasper EK, Hruban RH, Baughman KL: Cardiomyopathy of obesity: A clinicopathologic evaluation of 43 obese patients with heart failure. *Am J Cardiol* 1992; 70:921–924
41. McGavock JM, Victor RG, Unger RH, et al; American College of Physicians and the American Physiological Society: Adiposity of the heart, revisited. *Ann Intern Med* 2006; 144:517–524




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