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Body Mass Index and Acute Kidney Injury in the Acute Respiratory Distress Syndrome

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Abstract

Objectives—Obesity is increasingly encountered in the intensive care units (ICUs) but the relationship between obesity and acute kidney injury (AKI) is unclear. We aim to evaluate whether body mass index (BMI) was associated with AKI in the acute respiratory distress syndrome (ARDS) and to examine the association between AKI and mortality in patients with and without obesity.

Design, Setting, Patients—Retrospective study of a cohort of 751 patients with ARDS at Massachusetts General Hospital and Beth Israel Deaconess Medical Center.

Interventions—None

Measurements and Main Results—AKI was defined as meeting the "Risk" category according to modified Risk Injury Failure Loss End-stage (RIFLE) criteria based on Creatinine (Cr) and glomerular filtration rate (GFR) since urine output was only available on the day of ICU admission. BMI was calculated from height and weight on ICU admission. The prevalence of AKI increased significantly with increasing weight ($p = 0.01$). The odds of AKI were twice in obese and severely obese patients compared to normal BMI after adjusting for predictors of AKI (age, diabetes, APACHE III, aspiration, vasopressor use, and thrombocytopenia (platelets ≤ 80,000/mm^3)). After adjusting for the same predictors, BMI was significantly associated with AKI (OR_{adj} 1.20 per 5 kg/m^2 increase in BMI, 95%CI 1.07–1.33). On multivariate analysis, AKI was associated with increased ARDS mortality (OR_{adj} 2.76, 95%CI 1.72–4.42) while BMI was associated with decreased mortality (OR_{adj} 0.81 per 5 kg/m^2 increase in BMI, 95%CI 0.71–0.93) after adjusting for mortality predictors.

Conclusions—In ARDS patients, obesity is associated with increased development of AKI that is not completely explained by severity of illness or shock. While increased BMI is associated with decreased mortality, AKI remained associated with higher mortality even after adjusting for BMI.

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Keywords

body mass index; acute respiratory distress syndrome; acute kidney injury; mortality; obesity

INTRODUCTION

With the obesity epidemic in the US, an increasing number of obese and morbidly obese patients are admitted to the intensive care unit (ICU) (1). Overall, 30% of ICU patients are obese and 7% morbidly obese (2). Obesity seems to confer a higher risk for development of common conditions in critically ill patients such as the acute respiratory distress syndrome (ARDS) (3) (4).

Parallel to the obesity epidemic, multiple studies show that a high number of critically ill patients develop some degree of acute kidney injury (AKI) during their ICU stay (35–67%) (5, 6). Obese patients have distinct risk factors for AKI due to their high burden of comorbidities (e.g., chronic kidney disease (CKD)) and underlying renal damage (e.g., obesity-related glomerulopathy) (7). However, the incidence of AKI in critically ill obese patients is unknown since the largest epidemiological studies of AKI in the ICU did not examine the role of obesity in AKI. One study found increased incidence of AKI requiring renal replacement therapy (RRT) with increasing body mass (8) but patients with less severe AKI were not included even though small increases in creatinine (Cr) have been associated with excess morbidity and mortality (9).

AKI and obesity are associated with increased length-of-stay (LOS) and health-care costs (10, 11) (12); however, their combined effects in the critically ill are unclear. AKI in critically ill patients is associated with a very high mortality (50–60%) (13). However, several meta-analyses show that obesity may be associated with lower mortality in critically ill patients (2, 14, 15). The interactions between AKI, ARDS, and obesity are even less clear. Even though ARDS mortality is currently declining (25–40%) (16) (17), AKI increases mortality in ARDS to 50–80% and negatively affects clinical outcomes (18) (19). There is epidemiological and animal data suggesting a cross-talk between lung and kidney in ARDS with injury in one organ initiating and aggravating injury to the other and both AKI and ARDS synergistically worsening mortality in ICU patients (20). Clinical data indicate that mortality is unacceptably high when ARDS patients develop AKI and that the release of inflammatory mediators from lung injury can lead to end-organ renal damage through common pathophysiological pathways (18). Yet, recent studies that showed increased development of ARDS with BMI did not show increased mortality (3) (4) even though one of these studies found a significant increase in AKI with increasing BMI (4). This suggests that even though ARDS patients are at higher risk of worse clinical outcomes from AKI, obesity may have a protective effect in ARDS. Among CKD patients with or without dialysis, there seems to be a better survival with higher BMI (21) (22). Whether a similar association would be observed between BMI and AKI is not currently clear as there is limited data regarding the outcomes of obese patients with AKI.

Therefore, the purpose of this study was to assess the relationship between AKI, obesity, and mortality in a cohort of critically ill patients with ARDS. Specifically, we wanted to evaluate whether obesity is associated with AKI and to examine the relationship between AKI and 60-day all-cause mortality in patients with and without obesity.

MATERIALS AND METHODS

Study population

All study participants were enrolled into the Molecular Epidemiology of ARDS study as described previously (23). Briefly, the study was conducted at Massachusetts General Hospital (MGH) from September 1999 to August 2010 and at Beth Israel Deaconess Medical Center (BIDMC) (Boston, MA) from December 2000 to April 2010. All admissions to adult ICUs were eligible for the study if they were admitted with one or more risk factors for ARDS and no exclusion criteria. All patients were screened daily for ARDS defined similarly to the American European Consensus Committee (24): (1) hypoxemic respiratory failure requiring intubation and $PaO_2/FiO_2 \leq 200$ mmHg; (2) bilateral infiltrates on chest radiographs; and (3) absence of left atrial hypertension (e.g., pulmonary arterial occlusion pressure ≤ 18 mm Hg or lack of congestive heart failure in their clinical assessment that day). Patients were excluded if they had diffuse alveolar hemorrhage, chronic lung disease, neutropenia (not secondary to sepsis), advanced directives to withhold intubation, HIV^+, or immunosuppression other than from corticosteroid therapy. For this analysis, patients were also excluded if they had end-stage-renal-disease (ESRD) on dialysis, unavailable BMI, or if their height could not be determined (bilateral amputees, severe kyphoscoliosis or contractures). Only patients who developed ARDS during this hospitalization were included. Incidence and mortality of ARDS did not differ between the two sites ($p \geq 0.7$). The Human Subjects Committees of the MGH, BIDMC and Harvard School of Public Health approved the study, and informed consent was obtained from all participants.

Data Collection and Definitions

Baseline clinical and demographic data were collected. Data on organ failures as defined by the Brussels Organ Dysfunction Score (25), which included highest daily serum Cr, were also collected on days 0–28 of ARDS. The Acute Physiology and Chronic Health Evaluation (APACHE) III score was calculated as a measure of severity of illness using vital signs and laboratory values collected in the first 24 hours of ICU admission. Mechanical ventilation data were also available on the day of ICU admission, and on days 0, 3, 7, 14, 21 and 28 of ARDS.

BMI was calculated from height and weight recorded on ICU admission (BMI = weight (kg)/height $(m)^2$).

AKI was defined as a transition from normal Cr and glomerular filtration rate (GFR) to at least the Risk category (increased Cr x 1.5 from baseline or GFR decrease of > 25%) from the Risk Injury Failure Loss End-stage (RIFLE) classification (26). Modified RIFLE criteria were used based on Cr and GFR since the urine output was only available on the day of ICU admission. AKI was determined according to the change between baseline and the peak Cr or GFR value during the first 28 days after diagnosis of ARDS using a baseline Cr estimated from the Modification in Diet and Renal Disease (MDRD) equation assuming a GFR of 75 $ml/min/1.73m^2$ (27) (28). The most severe degree of AKI between the Cr and GFR criteria was assigned to every patient. Two different sensitivity analyses were performed to assess for possible misclassification of AKI from the use of MDRD-estimated baseline Cr as this may overestimate AKI in patients with CKD and elevated baseline Cr. First, we reviewed the medical records of a random subset of 202 patients (26.9%) of the cohort for baseline Cr prior to admission. Second, we also examined AKI that occurred more proximal to the onset of ARDS (within 4 days of diagnosis) such as published by Liu et al (29). using the highest Cr within the first 4 days after ARDS diagnosis.

Outcomes

All patients were followed-up until death or 60 days after diagnosis of ARDS for all-cause mortality. Survival in patients discharged before 60 days after ARDS was ascertained by follow-up phone calls. Only 18 patients (2.4%) were lost to follow-up and not included in the mortality analyses. As secondary outcomes, we also evaluated time-to-AKI, time-to-death, ICU and hospital length-of-stay (LOS), ICU-free days and ventilator-free-days (VFDs) in the first 28 days of ARDS.

Statistical analysis

Univariate analyses were performed with parametric and non-parametric tests as appropriate. We explored the relationship between BMI, AKI and all-cause 60-day mortality in two ways. We included BMI as a continuous variable in a logistic regression model and reported the odd ratios (ORs) for every 5 kg/m^2 change in BMI. We also categorized BMI according to the National Institutes of Health (NIH) definition of obesity (16) and reported the ORs using normal BMI as reference.

We examined the association between BMI and development of AKI with multivariate logistic regression models. Predictors related to AKI or BMI categories on univariate analysis ($p < 0.10$) were entered into the initial AKI model. A backward stepwise elimination algorithm was used with a $p < 0.05$ for predictors associated with AKI to remain in the final model (age, APACHE III, aspiration, and thrombocytopenia). Diabetes and vasopressor use were forced into the model from the outset due to their clinical relevance for development of AKI. We report two final AKI models with BMI: one with adjusted ORs per 5 kg/m^2 change in BMI and another with NIH categories of BMI entered as dummy variable and using normal BMI category as reference.

A similar model-building approach was used for the association between BMI and mortality. Covariates were entered into the initial mortality model if $p < 0.10$ on univariate analysis with mortality and remained in the final model on backward selection if the covariate had a $p < 0.05$ with mortality. Septic shock was forced into the final model from the outset as it is a well-established risk factor for ARDS mortality. Only the mortality model with BMI as continuous variable is reported given the reduced sample size in some of the BMI categories.

For all models, variables were included as continuous because the plot of the logit was linear. Interactions between BMI and other covariates were tested with the addition of an interaction term but no significant interaction was found ($p > 0.05$). Model discrimination was assessed using receiver operating characteristic curves (30). Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit (GOF) test with a nonsignificant value suggestive of absence of biased fit. GOF testing and standard regression diagnostics in all models indicated that the logistic regression models were adequate. All statistical analyses were done using STATA version 10.1 (StataCorp, College Station, TX). Two-tailed p-values < 0.05 were considered statistically significant for all analyses. However, we used the Bonferroni correction to adjust the p-value for our 3 main study questions: the association between AKI and BMI, AKI and mortality, and BMI and mortality on multivariate logistic regression analyses. Therefore, for these 3 associations a $p < 0.05/3$ or 0.016 was used for statistical significance.

RESULTS

From 3,128 patients enrolled in the Molecular Epidemiology of ARDS study, 848 (27.1%) developed ARDS. After excluding 97 subjects (11.4%), 751 were included for this analysis. In this cohort, 25% of ARDS patients were obese and 8% severely obese. The median time

to development of ARDS after ICU admission was very short (1 day, interquartile range (IQR) = 0–3) and 39.4% of the cohort was diagnosed with ARDS on the day of ICU admission.

The median BMI was 27.3 kg/m^2 (IQR = 23.4–32 kg/m^2). At baseline, obese patients were younger and the proportion of patients who were female varied significantly by BMI category (Table 1). The proportion of patients with diabetes increased with BMI. On the day of ICU admission, obese patients had less acuity of illness and hemodynamic instability as evidenced by less shock on admission. There were no differences between BMI categories in race, comorbidities, and other organ failures. Of note, a larger proportion of underweight patients had septic shock, shock on ICU admission, liver disease, and a higher severity of illness compared to the other BMI categories. The rate of metastatic solid tumor was also higher in the underweight but not significant given the small number of patients. The underweight were also more likely to have ARDS on the day of ICU admission and the largest tidal volume (TV) per ideal body weight (IBW) on the day of ARDS diagnosis.

Development of AKI

In our cohort, 61.9% (N = 465) of ARDS patients developed AKI. The prevalence of AKI increased significantly with increasing BMI category (p = 0.01). Most patients with AKI met the Failure criteria (except in the underweight) and the proportion of patients with Failure was higher once BMI ≥ 25 kg/m^2 (Table 2). After adjustment for predictors of AKI, increasing BMI was significantly associated with development of AKI (OR_{adj} 1.20 per 5 kg/m^2 increase in BMI, 95% CI 1.07–1.33, p = 0.001). The odds of AKI were twice in obese and severely obese ARDS patients compared to normal BMI (Table 3). Excluding underweight patients did not change the association between BMI and AKI on univariate or multivariate analyses.

When the medical records of a random subset of 202 patients were reviewed for baseline Cr, there were 10 (4.9%) patients with CKD and only 2 (1%) were misclassified as AKI by assuming a GFR of 75 ml/min/1.73m^2. Using Liu's criteria, over half of the cohort (53.7%) developed AKI during the first 4 days of study with a similar increased prevalence in AKI by increasing BMI category (underweight 51.6%, normal 49%, overweight 53.4%, obese 59.3%, and severely obese 56.7%, p = 0.04). On multivariate analysis, the association between BMI and AKI remained unchanged (Table 3).

In regards to time-to-AKI, the great majority of patients (70%) developed AKI on the day of ICU admission (median = 0, IQR = 0–1), 20% during the next seven days after ARDS diagnosis, and the remaining 10% after the first week. There were no significant differences in the median time to AKI among the BMI categories (Table 6).

Outcomes in ARDS patients with AKI

ARDS patients with AKI had significantly higher 60-day mortality than those without AKI (44.7% vs. 15%, p < 0.001) and mortality significantly increased with increasing AKI severity (Risk = 30.8%, Injury = 43.8%, and Failure = 54.6%, p < 0.001). The proportion of ARDS patients with AKI who died decreased as BMI increased (Table 4). But, within each weight category, patients with AKI had a significantly increased mortality except in the underweight in which the association had borderline significance (p = 0.06) most likely due to the limited sample size. Furthermore, obese and severely obese patients with Failure had significantly higher mortality than those with Injury or Risk (Table 4). After adjustment for predictors of ARDS mortality, BMI was associated with a significant 19% decrease in 60-day mortality per 5 kg/m^2 increase in BMI (p = 0.002) while AKI was associated with increased odds of death (p < 0.001) (Model 4, Table 5).

Excluding underweight patients did not change the association between BMI and mortality (OR_{adj} 0.87, 95%CI 0.75–0.99), or AKI and mortality (OR_{adj} 2.62, 95%CI 1.59–4.32). Using Liu's criteria showed similar findings for mortality and BMI (OR_{adj} 0.83 per 5 kg/m^2 increase in BMI, 95%CI 0.73–0.95) but a more attenuated but still significant effect of AKI on mortality (OR_{adj} 1.64, 95% CI 1.06–2.51).

Underweight patients had the highest ICU mortality, shorter hospital LOS and died sooner than obese or severely obese patients (Table 6). Obesity was associated with more ICU-free and VFDs but longer hospital LOS despite obese and severely obese patients having much lower PaO2/FiO2 ratios and similar or higher plateau pressures on the day of ARDS diagnosis than patients with normal BMI (Table 1).

DISCUSSION

This study examined the relationship between obesity, AKI, and ARDS mortality. In our cohort, obesity was an independent risk factor for AKI not explained by greater severity of illness or shock. Increasing BMI was significantly associated with increased development of AKI but decreased all-cause 60-day ARDS mortality. ARDS patients with AKI had a higher mortality even after adjusting for BMI and other mortality predictors. Consistent with the rapid onset of end-organ failures in critically ill patients, most of the cohort had AKI on the day of ICU admission. There were no differences on the time to development of AKI by BMI categories. Obesity was associated with more ICU-free days and VFDs but longer hospital LOS compared to normal BMI.

This study has several strengths. First, it had a large sample size and included medical and surgical patients with common ICU conditions that are known causes of ARDS. Second, since the worst Cr was available daily in all patients for the entire study period, development of AKI could be assessed for all patients. Lastly, we examined 60-day mortality instead of ICU or hospital mortality since this outcome parameter is more clinically relevant to the critically ill population with AKI (31).

A prior study using data from the first NHLBI ARDS Network trials found a much lower prevalence of AKI in ALI patients (24%) than in our cohort (61.9%) (18). This could be explained by different diagnostic criteria used for AKI. In our study the baseline Cr was estimated from the MDRD equation while Liu's study used the lowest Cr on day 0 as baseline which may represent already existing renal dysfunction on ICU admission and would underestimate the true change in Cr and the extent of AKI. Using similar AKI criteria as Liu's in our cohort, we still found a higher prevalence of AKI (53.7%) with the same association between BMI and AKI and a protective effect of BMI on mortality.

The use of GFR to determine RIFLE criteria for AKI might overestimate AKI in patients with higher BMI because of higher muscle or bone mass. We did not correct for body surface area (BSA) in the GFR equation which may overestimate the renal excretory function among the obese (32). However, the BSA equations have not been validated in obese patients because of their lack of accuracy and performance in these patients and the lack of proof that using actual BSA improves the accuracy of the MDRD equation (33) (34). Therefore, it is not standard practice to correct the GFR for the patient's BSA and we did not perform such correction in this study. Furthermore, in our cohort, AKI was associated with higher mortality rates in every BMI category and obese and severely obese patients with Failure had higher mortality than those with less severe renal dysfunction. Therefore, it is unlikely that the higher prevalence of AKI in our obese and severely obese patients may be attributed to an overestimation of renal function from a BSA-uncorrected GFR and our results suggest that AKI may represent true organ dysfunction.

There is limited data on the possible pathophysiological mechanisms for the observed relationship between obesity and AKI. Animal studies have shown a possible link between leptin and renal injury. In humans with obesity, leptin levels may be inappropriately high due to hyporesponsiveness to leptin (35) but the levels decline rapidly during fasting (36). In patients with CKD, leptin is elevated due to decreased plasma clearance and increased production (37). A clinical study found normal plasma leptin levels prior to first dialysis in patients with AKI and no significant differences in leptin levels between survivors and non-survivors with AKI (38). In this study, AKI and CKD patients had similar mean BMI (26 kg/m^2 vs. 26.3 kg/m^2). In a leptin-deficient animal model of obesity (ob/ob mice), leptin-deficient obese mice were much more susceptible to endotoxin-related AKI than their lean littermates (39). Ob/ob mice had a significant decrease in GFR and exhibited histological evidence of acute tubular necrosis after endotoxin (LPS) administration. These pathological changes were mild as observed in human AKI. When ob/ob mice developed shock with a higher dose of LPS, leptin replacement offered protection against AKI with significant improvement in mean arterial pressure and decrease in serum Cr. These beneficial effects suggest a leptin-mediated effect on peripheral vascular resistance.

Interleukin (IL)-18, a pro-inflammatory cytokine, is systemically elevated in obesity (40) and directly correlates with BMI (41) (42). Urinary IL-18 is associated with increased development of AKI in critically ill patients (43, 44), but it is not clear whether IL-18 is a causal factor or merely an early marker of AKI. In the ARDS Network trials, urinary IL-18 was elevated earlier than plasma Cr and the urinary IL-18 values were also significantly different between survivors and non-survivors. Furthermore, urine IL-18 on day of ARDS diagnosis was an independent predictor of ARDS mortality (44). It is unclear whether increasing BMI is related to AKI by an IL-18 mediated mechanism. However, the limited data available suggest that there may be a biological factor related to leptin- or IL-18 mediated effects that may be associated with AKI.

Our results show that critically ill patients with AKI have worse prognosis as documented in other studies (6, 13, 45, 46). Yet, we found a much higher mortality by RIFLE category than the study by Hoste (Risk = 8.8%, Injury = 11.4%, Failure = 26.3%) (6) probably because our study examined patients at higher risk of death (ARDS) and Hoste's study included an unselected group of critically ill patients. Even if AKI was associated with higher mortality in each weight group, BMI was associated with lower mortality. This is supported by prior studies in ALI/ARDS that showed either a trend for a protective mortality effect by obesity (3) or a significantly lower mortality in obese patients (47). However, our study differed from others that reported either a higher ICU mortality (48) or no association with 28-day mortality with obesity (49). This may be explained by differences in sample size, study design, or patient characteristics. The study by Gong included 547 ARDS patients with a trend towards less mortality in univariate analysis and a non-significant protective effect on multivariate analysis (3). With the larger sample size in our study, this protective effect of BMI on mortality became statistically significant. Bercault included 170 pairs of patients from a single ICU who were matched on 8 clinical criteria which could have biased the results due to overmatching. O'Brien excluded underweight patients, who have higher mortality, and the most likely cause of ALI in overweight and obese patients was trauma which is the risk factor for ALI with the best outcomes (50). In our cohort, the underweight had a higher mortality and died sooner than obese patients most likely because they were older, had a higher severity of illness, had more shock and ARDS on the day of ICU admission, more chronic liver disease, and were exposed to the highest TV per IBW on the day of ARDS diagnosis. Further research to elucidate the mechanisms behind the paradoxical survival benefit in the obese critically ill is needed. One possible explanation is that since acute illness is associated with a high catabolic state, the increasing adipose tissue

in obese patients could be used as nutritional and energy support during highly catabolic conditions.

There are several limitations to this study. First, because the parent study focused on risk factors for development and mortality of ARDS, we lack data on blood urea nitrogen, volume status, fluid resuscitation, daily urine output, or new dialysis. However, the highest daily Cr during the 28 days of the study period was available. Second, although we had data on diabetes, we did not have information on other relevant comorbidities (e.g., hypertension and peripheral vascular disease), or other risks factors for AKI (e.g., contrast dye, aminoglycosides, or other nephrotoxic drugs). Third, BMI was examined in this study rather than other potentially more reliable measures of body composition such as the waist-to-hip ratio (51) (52). Fourth, although weight was determined on ICU admission, we cannot exclude the possibility that fluids given prior to admission may have affected BMI as well as the volume of distribution of Cr which may affect its measurement. Additionally, we determined baseline Cr from the MDRD equation which could overestimate the prevalence of AKI in CKD. However, we did exclude ESRD patients and a sensitivity analysis of 202 random patients indicated minimal (1%) misclassification of AKI using MDRD-estimated Cr. Also, this study did not include an assessment of processes of care (e.g., criteria for RRT initiation) that could account for some of the observed differences in the results among BMI groups. Lastly, this study was limited to patients with ARDS who were predominantly Caucasian and the results may not be generalizable to other populations of critically ill patients or other racial groups.

CONCLUSIONS

In ARDS, obesity is associated with increased development of AKI that cannot be explained by differences in shock or severity of illness. ARDS mortality decreased with increasing BMI. However, after adjusting for BMI, AKI remained significantly associated with higher all-cause 60-day mortality. The results of this study should foster further research into the role of body mass in the development of AKI in critically ill patients and the mechanisms associated with the lower mortality observed among obese patients with AKI.

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Table 1

Baseline characteristics by body mass index categories

Characteristic	Underweight (N=31)	Normal (N=233)	Overweight (N=238)	Obese (N=189)	Severely Obese (N=60)	p-value
Age, mean (SD)	65.3 (17.5)	58.8 (18.8)	59 (18.7)	56.7 (16.9)	50.2 (13.9)	<0.001
Females, n (%)	19 (51%)	86 (37%)	74 (31%)	65 (34%)	34 (57%)	<0.001
Whites, n (%)	29 (94%)	215 (92%)	221 (93%)	164 (87%)	57 (95%)	0.12
Alcohol abuse, n (%)	4 (13%)	43 (18%)	45 (19%)	25 (13%)	7 (12%)	0.35
Smoking, n (%)	19 (68%)	142 (71%)	127 (66%)	107 (66%)	43 (61%)	0.68
Diabetes, n (%)	2 (6%)	35 (15%)	45 (19%)	50 (27%)	29 (45%)	<0.001
Liver disease, n (%)	3 (10%)	18 (8%)	10 (4%)	14 (7%)	5 (8%)	0.47
Steroids (prior to ICU admission), n (%)	2 (6%)	23 (10%)	15 (6%)	9 (5%)	8 (13%)	0.12
Immunosuppression, n (%)	2 (6%)	24 (11%)	12 (5%)	11 (6%)	8 (13%)	0.08
Lymphoma, n (%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.5%)	0 (0%)	0.85
Solid tumor with metastasis, n (%)	1 (3.2%)	8 (3.5%)	3 (1.3%)	1 (0.5%)	0 (0%)	0.11
Bacteremia, n (%)	9 (29%)	42 (18%)	40 (17%)	28 (15%)	11 (18%)	0.41
Sepsis without Shock, n (%)	1 (3%)	54 (23%)	60 (25%)	46 (24%)	12 (20%)	0.09
Septic Shock, n (%)	29 (94%)	145 (62%)	144 (61%)	111 (59%)	45 (75%)	0.001
Pneumonia, n (%)	28 (90%)	171 (73%)	167 (70%)	131 (69%)	43 (72%)	0.17
Trauma, n (%)	0 (0%)	16 (9%)	22 (9%)	14 (7%)	3 (5%)	0.37
Aspiration, n (%)	6 (19%)	22 (9%)	22 (9%)	18 (10%)	2 (3%)	0.18
Multiple transfusions, n (%)	1 (3%)	19 (8%)	24 (10%)	21 (11%)	3 (5%)	0.41
ICU presentation						
APACHE III, mean (SD)	80.9 (20.1)	75.4 (22.5)	75.7 (25.7)	70.4 (21.1)	69.1 (21.3)	0.02
Vasopressor use in last 24 hours, n (%)	28 (90%)	158 (68%)	163 (68%)	128 (68%)	44 (73%)	0.11
Shock[a], n (%)	30 (97%)	191 (82%)	189 (79%)	141 (75%)	47 (78%)	0.05
Creatinine ≥ 2.0 mg/dl, n (%)	4 (13%)	52 (22%)	67 (28%)	55 (29%)	19 (32%)	0.14
Platelets ≤ 80,000/mm^3, n (%)	6 (19%)	42 (18%)	44 (18%)	26 (14%)	7 (12%)	0.51
Bilirubin ≥ 2.0 mg/dl, n (%)	6 (19%)	42 (18%)	43 (15%)	31 (16%)	10 (17%)	0.98
Day 0 of ARDS[b]						
Time-to-ARDS (days), median, IQR	0 (0, 1)	1 (0, 3)	1 (0, 3)	1 (0, 3)	1 (0, 3)	0.35
ARDS on ICU admission, n (%)	18 (58%)	89 (38%)	92 (38.6%)	75 (39.7%)	22 (36.7%)	0.29

Characteristic	Underweight (N=31)	Normal (N=233)	Overweight (N=238)	Obese (N=189)	Severely Obese (N=60)	p-value
LIS, mean (SD)	2.94 (0.53)	2.99 (0.51)	3.01 (0.48)	3.00 (0.48)	3.03 (0.55)	0.94
Tidal volume (TV) ≤ 8cc/kg ideal body weight[c], n (%)	10 (33%)	124 (54%)	106 (45%)	93 (50%)	28 (47%)	0.13
TV (cc/kg by ideal body weight), median (IQR)	8.99 (7.07, 11.09)	7.88 (6.57, 9.72)	8.21 (7.08, 9.96)	7.98 (6.57, 9.97)	8.18 (7.04, 10.7)	0.08
TV (cc), median (IQR)	505.6 (414.3, 610)	507.8 (426.5, 600)	550 (472.7, 650)	514 (440, 650)	520 (450, 614.3)	0.009
PaO_2/FiO_2, median (IQR)	113 (72, 137)	115 (79, 140)	110 (77, 140)	108 (74, 148)	93.5 (65.5, 134.5)	0.45
Plateau Pressure (cm H_2O)[d], mean (SD)	25.2 (4.4)	27.9 (7.3)	28.2 (6.8)	27.8 (6.4)	29.5 (8.1)	0.32

[a] Shock defined as systolic blood pressure < 90 mmHg or vasopressor use on ICU admission.

[b] Day 0 ARDS represents the day when ARDS criteria was met.

[c] 15 patients were missing tidal volume.

[d] 306 patients were missing plateau pressure.

ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; LIS, lung injury score; IQR, interquartile range.

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Table 2

Development of acute kidney injury by body mass index categories

AKI by RIFLE	Underweight (< 18.5 kg/m^2)	Normal (18.5–24.9 kg/m^2)	Overweight (25–29.9 kg/m^2)	Obese (30–39.9 kg/m^2)	Severely Obese (≥ 40 kg/m^2)
Risk	4 (13%)	35 (15%)	39 (16%)	35 (18%)	10 (17%)
Injury	9 (29%)	46 (20%)	41 (17%)	45 (24%)	14 (23%)
Failure	5 (16%)	52 (22%)	63 (27%)	51 (27%)	16 (27%)
Any AKI[a]	18 (58%)	133 (57%)	143 (60%)	131 (69%)	40 (67%)
No AKI	13 (42%)	100 (43%)	95 (40%)	58 (31%)	20 (33%)
Total	31	233	238	189	31

[a]The Chi^2 test for trend is significant for the association between development of AKI and increasing BMI category (p = 0.01).

Table 3

Multivariate logistic regression analysis for acute kidney injury

Acute Kidney Injury[a]	Model A[b] [OR (95% CI)]	Model B[b] [OR (95% CI)]
Underweight	0.93 (0.38–2.26)	0.89 (0.37–2.15)
Overweight	1.20 (0.77–1.87)	1.21 (0.78–1.87)
Obese	2.65 (1.63–4.29)	2.23 (1.40–3.54)
Severely Obese	2.24 (1.09–4.59)	2.16 (1.08–4.31)

[a]The reference group is the normal BMI category.

[b]Model A shows the adjusted results for AKI as defined in the current study (within 28 days of ARDS) and Model B for AKI as defined by Liu and colleagues (within 4 days of ARDS). Both models are adjusted for diabetes, vasopressor use within 24 hours of ICU admission, risk factors of ARDS (aspiration), age, acute physiology and chronic health evaluation (APACHE) III, and thrombocytopenia (platelets ≤ 80,000/mm^3).

Table 4

All-cause 60-day ARDS mortality and acute kidney injury by body mass index category

BMI category [a]	No AKI [b]	Any AKI [c]	p-value[d]	Risk [c]	Injury [c]	Failure [c]	p-value[e]
Underweight (N = 18)	5/13 (38.5%)	13/18 (72.2%)	0.06	4/4 (100%)	5/9 (55.6%)	4/5 (80%)	0.16
Normal (N = 83)	18/100 (18%)	65/133 (48.8%)	<0.001	15/35 (42.8%)	20/46 (43.5%)	30/52 (57.7%)	<0.001
Overweight (N = 90)	16/94 (17%)	74/143 (51.8%)	<0.001	12/39 (30.8%)	28/41 (68%)	34/63 (54%)	<0.001
Obese (N = 44)	4/58 (6.9%)	40/131 (30.5%)	<0.001	6/35 (17%)	10/45 (22%)	24/51 (47%)	<0.001
Severely Obese (N = 16)	0/20 (0%)	16/40 (40%)	0.001	1/10 (10%)	5/14 (35.7%)	10/16 (62.5%)	<0.001

[a] The number in parenthesis represents the number of deaths within each BMI category.

[b] The values and percentages in each cell represent the number of patients without AKI who died divided by the total number of patients without AKI in each BMI category.

[c] The values and percentages in each cell represent the number of patients with any AKI, Risk, Injury, or Failure who died divided by the total number of patients with any AKI, Risk, Injury, or Failure respectively in each BMI category.

[d] The p-value is for the association between mortality and AKI vs. No AKI in each BMI group (Chi^2 test).

[e] The p-value is for the association between mortality and No AKI, Risk, Injury, and Failure in each BMI group (Chi^2 test for trend).

Table 5

Multivariate logistic regression analysis for all-cause 60-day ARDS mortality

All-cause 60-day mortality	Model 1 [a] [OR (95% CI)]	Model 2[a] [OR (95% CI)]	Model 3[b] [OR (95% CI)]	Model 4[c] [OR (95% CI)]
BMI (per 5 kg/m^2)	0.82 (0.74–0.91)	--	0.77 (0.69–0.87)	0.81 (0.71–0.93)
AKI	--	4.55 (3.14–6.61)	5.02 (3.43–7.34)	2.76 (1.72–4.42)

[a]Models 1 and 2: Unadjusted ORs for the association with 60-day mortality.

[b]Model 3: ORs for the AKI-associated risk for mortality adjusting for BMI and for the BMI-associated risk for mortality after adjusting for AKI.

[c]Model 4: ORs for the ARDS mortality after adjusting for age, APACHE III, etiology of ARDS (septic shock, trauma), comorbidities (chronic liver disease), steroid use prior to ICU admission, bilirubin ≥ 2mg/dl on ICU admission, lung injury score, peak airway pressure on the day of ARDS diagnosis, and number of packed red cells transfused.

OR, odds ratio; BMI, body mass index; AKI, acute kidney injury; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit.

Table 6

Secondary outcomes

Outcome	Underweight (N=31)	Normal (N=233)	Overweight (N=238)	Obese (N=189)	Severely Obese (N=60)	p-value
ICU mortality	13 (44.8%)	64 (28.8%)	68 (29.8%)	33 (18.4%)	14 (24.1%)	0.01
Time-to-death (days), median (IQR) (N=251)[a]	15 (5, 43)	31 (12, 60)	23 (9, 52)	34 (14, 60)	40 (11.5, 60)	0.005
Time-to-AKI (days), median (IQR) (N=465)[b]	0 (0, 3)	0 (0, 2)	0 (0, 1.5)	0 (0, 0)	0 (0, 0)	0.33
Ventilator-free days[c], median (IQR)	3 (0, 14)	5 (0, 11)	4 (0, 10)	5 (0, 14)	8 (0, 13)	0.18
ICU-free days [b], median (IQR)	0 (0, 15)	3 (0, 18)	2.5 (0, 19)	11 (1, 20)	4.5 (0, 18)	0.005
ICU LOS, median (IQR)	11 (5, 19)	13 (7, 22)	11 (6, 20.5)	12 (7, 24)	13 (8.5, 25)	0.18
Hospital LOS, median (IQR)	13 (5, 60)	20 (10, 60)	16 (9, 60)	21 (11, 60)	21 (11.5, 60)	0.05

[a]This is reported for the patients who died.

[b]This is reported for patients who developed AKI.

[c]In the first 28 days of ARDS.

ICU, intensive care unit; IQR, interquartile range; AKI, acute kidney injury; LOS, length-of-stay