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CLINICAL STUDY



## The effect of body mass index on the development of acute kidney injury and mortality in intensive care unit: is obesity paradox valid?

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### ABSTRACT

**Background:** The conflicting results of studies on intensive care unit (ICU) mortality of obese patients and obese patients with acute kidney injury (AKI) reveal a paradox within a paradox. The aim of this study was to determine the effects of body mass index and obesity on AKI development and ICU mortality.

**Methods:** The 4,459 patients treated between January 2015 and December 2019 in the ICU at a Tertiary Care Center in Turkey were analyzed retrospectively.

**Results:** AKI developed more in obese patients with 69.8% (620). AKI development rates were similar in normal-weight (65.1%; 1172) and overweight patients (64.9%; 1149). The development of AKI in patients who presented with cerebrovascular diseases was higher in obese patients (81; 76.4%) than in normal-weight (158; 62.7%) and overweight (174; 60.8%) patients ( $p < 0.05$ ). The risk of developing AKI was approximately 1.4 times (CI 95% = 1.177–1.662) higher in obese patients than in normal-weight patients. Dialysis was used more frequently in obese patients (24.3%,  $p < 0.001$ ), who stayed longer in the ICU ( $p < 0.05$ ). It was determined that the development of AKI in normal-weight and overweight patients increased mortality ( $p < 0.001$ ) and that there was not a difference in mortality rates between obese patients with and without AKI.

**Conclusion:** The risk of AKI development was higher in obese patients but not in those who were in serious conditions. Another paradox was that the development of AKI was associated with a higher mortality rate in normal-weight and overweight patients, but not in obese patients. Cerebrovascular diseases as a cause of admission pose additional risks for AKI.

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Acute kidney injury; body mass index; obesity; mortality; intensive care unit; obesity paradox; mechanical ventilation

### Introduction

Overweight and obesity occur as a result of the increase in the amount of body-fat to a degree that can negatively affect health [1]. The prevalence of obesity among adults is increasing significantly [2,3]. Obesity is recognized as an important public health problem. It has been shown to be associated with increased morbidity and mortality risks due to cardiovascular diseases, diabetes mellitus, respiratory tract diseases, some types of cancer, and all causes [2–4].

In parallel with the increase in obesity prevalence, there has been an increase in the number of obese patients admitted to intensive care units (ICUs) in recent years [5]. Previous studies have revealed that the rate of patients with a body mass index (BMI) of  $\geq 30$  in

ICUs is between 17.5 and 28.0%, and nearly 7% have a BMI of  $\geq 40$  [6–9]. Obesity can be the cause of disorders in cardiovascular, respiratory, and metabolic functions in the ICU. Depending on the lipophilicity of the molecule administered, drug administration can be implemented. The capability to obtain vascular access is often damaged as a result of large body habitus, and it ought to be supported by ultrasound guidance. The quality of blood pressure monitoring can also be negatively influenced, requiring the utilization of direct intra-arterial monitoring [10]. There is a strong relationship between obesity and ICU length of stay [7–10]. However, studies on the mortality impact of obesity on critically ill patients have yielded contradictory results [7,11–14]. Some studies have reported an increase in

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mortality [11–13], and, in the same way, other studies [7,14] have disclosed that obesity correlated with a longer period of mechanical ventilation and ICU length of stay; however, there is no association between mortality and obesity. Some studies stated that due to the fact that a high BMI provides nutritional reserves, exhibits protective hemodynamic effects of hypertension, which is common in obese patients, and, during circulatory failure, reduces the need for fluid or vasopressor support and the increased use of heparin prophylaxis among obese patients, effects such as inhibiting systemic inflammatory responses and coagulation phenomena have revealed that the obesity paradox is not harmful to patients but can be protective [15,16].

Another paradox associated with obesity is the development of acute kidney injury (AKI). Hospital-acquired AKI is a multifaceted and potentially reversible syndrome. Using the current diagnostic and grading criteria (increased serum creatinine levels and decreased urination), it was observed that more than 50% of ICU patients developed AKI. Renal replacement therapy is applied to 10–15% of ICU patients with severe AKI. AKI in obese patients includes all AKI stages from tubular dysfunction with mild to moderate increases in serum creatinine concentrations, to anuric acute renal failure requiring RRT [17]. Some of the previous studies that researched the relationship between AKI and mortality in obese patients followed in the ICU have reported conflicting results [18–24].

In addition to the complex results described regarding the ICU mortality of obese patients, the conflicting results of studies on obese patients who develop AKI reveal a paradox within a paradox. Our study was planned to evaluate the effects of BMI and obesity on AKI development and mortality in a large, single-center sample to elucidate this paradox.

## Materials and methods

### Data extraction center

This retrospective cohort study was conducted in the ICU of a training and research hospital with a bed capacity of 652, in Istanbul, Turkey. The ICU, which consists of 27 patient beds, accepts an average of 1440 medical, surgical, or trauma patients per year. The nurse-patient ratio is 1:2 in this center, which provides IC care as a closed unit controlled by a clinical decision support system (CDSS), where extracorporeal treatments (extracorporeal membrane oxygenation, hemodialysis, plasmapheresis) can be applied 24 h a day 7 days a week by intensive care (IC) specialists, IC minor

assistants, and Anesthesiology and Reanimation specialists and assistants.

When a patient is admitted to the ICU, after removing the clothes and jewelry on the patient, height and weight are measured and recorded in the CDSS by the nurse. Treatments such as intravenous fluid and diuretics administered before the patient's admission are not considered during this measurement. After the weight and height information is entered into the system, the system automatically calculates and saves the BMI. BMIs of the patients are evaluated only when they are admitted to the ICU. The patient's urine output is monitored hourly and noted in the CDSS. In addition, the results of laboratory tests such as creatine requested during follow-up are automatically uploaded to the system. The CDSS monitors hourly urine output and creatine values by using data with AKI algorithm prepared according to Kidney Disease: Improving Global Outcomes (KDIGO) (Clinical Practice Guideline for Acute Kidney Injury) [25] criteria. If the AKI criteria defined in KDIGO are met by following the increases in creatine and the decreases in urinary output, the CDSS generates an alert and determines the stage. The system records the AKI alert and warns the user with an alarm. In this way, the development of AKI is detected immediately and precisely in the patients followed in the ICU.

In all patients who develop AKI according to the KDIGO criteria, nephrotoxic drugs are removed from the treatment, or if the treatment cannot be halted, the dose is modified consistent with glomerular filtration rate (GFR). The fluid status of the patient is assessed with dynamic tests, and suitable fluid treatment is regulated. The potential factors that could instigate the development of AKI are eradicated. The interventions were introduced in a protocolized manner (Furosemide Stress Test, Gambro and Kalmar Hospital protocols). Diuretics were administered to facilitate ventilation protocolized in oliguric patients with acute kidney injury when fluid overload and consequently respiratory parameters were affected. Renal replacement therapy (RRT) was initiated immediately upon the observation of life-threatening changes in fluid-electrolyte and acid-base equilibrium such as metabolic acidosis (potential hydrogen (pH) <7.15), hyperkalemia (potassium >6.5 mEq/l or ECG changes), anuria (urine output <100 ml/24 h), respiratory failure causing pulmonary edema, uremia with altered mental status (BUN >100 mg/dl). In addition, for solute control, fluid elimination, and correction of acid-base abnormalities, renal replacement therapy was introduced and implemented as continuous venovenous hemodiafiltration or continuous

venovenous hemodialysis. Citrate was first used as an anticoagulant (based on Gambro and Kalmar Hospital protocols). The heparin was administered to patients who were not suitable for the use of citrate for anticoagulation. Furthermore, in the AKI algorithm in the CDSS, if the patient has a chronic renal failure (CRF) and is receiving RRT, this information is recorded in the relevant area in the CDSS so that the CDSS does not generate an AKI alert in these patients. Therefore, the system does not generate AKI alerts for the patients with CRF and for those receiving RRT. AKI data were acquired after these patients were excluded.

### Data collection

The data of patients followed up between 1 January 2015 and 31 December 2019 were obtained by EMRall-Qlin ICU Imd Soft Metavision CDSS with Structured Query Language (SQL) queries used in ICUs, and they were evaluated retrospectively. According to the anonymized age, gender, height, weight, BMI, diagnosis of comorbid diseases, ICU length of stay, and AKI alerts and AKI stages developed during the ICU stay; Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score III (SAPS III) scores measured in the ICU within the first 24 h were evaluated.

Mean Sequential Organ Failure Assessment score (SOFA) values calculated in the ICU, mean pH values obtained from blood gas samples taken in the ICU, partial pressure of oxygen (pO<sub>2</sub>) values, partial pressure of carbon dioxide (pCO<sub>2</sub>) values, bicarbonate anion (HCO<sub>3</sub><sup>-</sup>) and lactate values, treatments (vasoactive agent, antibiotic) and interventions (arterial catheter, central venous catheters [CVC], mechanical ventilation, tracheostomy, hemodialysis) applied in the ICU, one of the mechanical ventilation parameters FiO<sub>2</sub> (Fraction of inspired oxygen), minute respiratory rate, positive end-expiratory pressure (PEEP), P peak, tidal volume, compliance and work of breathing provided by a ventilator (WOBv) data, mechanical ventilation duration, and mortality data were evaluated.

### Study population

During the study period, a total of 7227 patients were admitted to the ICU. Four thousand four hundred fifty-nine patients who remained after the patients were excluded according to the exclusion criteria constituted the first study population.

According to the criteria of the World Health Organization [26], patients were classified according to

their BMI. Eighty-seven patients with a BMI of <18.5 (underweight), 1801 patients with a BMI between 18.5 and 24.9 (normal weight), 1770 patients with a BMI between 25 and 29.9 (pre-obesity), 566 patients with a BMI between 30 and 34.9 (obesity class I), 187 patients with a BMI between 35 and 39.9 (obesity class II), and 135 patients with a BMI of ≥ 40 (obesity class III) were determined. Eighty-seven patients with a BMI of <18.5 were excluded from the study population to avoid large differences in sample sizes among the groups. In addition, the BMIs of all obese patients were combined into a single group of ≥30. Consequently, a total of 4459 patients were decided as the final study population, in which 1,801 patients had a BMI between 18.5 and 24.9 (normal weight), 1770 patients a BMI between 25 and 29.9 (overweight), and 888 patients a BMI of ≥30 (obesity).

### Inclusion criteria

All patients over the age of 18 and staying in the ICU longer than 24 h were planned to be included in the study.

### Exclusion criteria

For this study, we excluded patients who were younger than 18 years of age (*n*: 53), those who had a BMI of <18.5 (*n*: 87), those who were transferred to hospital wards within the first 24 h of ICU admission (*n*: 815), those with mortality within the first 24 h in the ICU (*n*: 621), and those who had missing data (*n*: 1192).

### Primary outcome

According to the BMI of patients followed in the ICU, the primary aim of the study was to evaluate the effect of obesity on AKI development in these patients.

### Secondary outcomes

Secondary objectives of the study were to compare patients' BMI with comorbidities, admission diagnoses, scores calculated after admission to the ICU, laboratory values, interventions and treatments, mechanical ventilator data, AKI development and stages, and ICU mortality.

### Ethical issues

Before starting the research, institutional permission and ethics committee approval (Protocol code: 2020/232 -Decision number: 2020-08-06) was obtained from

Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee. The study conforms to the provisions of the 1995 Declaration of Helsinki (as revised in Brazil, 2013).

### Statistical analysis

The data collected in the study were evaluated with the SPSS 22.00 program (SPSS Inc., Chicago, IL). The Shapiro–Wilk test was used to check the normality of the data distribution. Categorical variables are given as frequency (*n*) and percentage (%), and numerical variables as mean  $\pm$  standard deviation or median and interquartile intervals (IQR). One-way ANOVA test was used for the comparison of numerical data and Tukey test for *post hoc* analysis. When one-way ANOVA assumptions could not be achieved, the Kruskal–Wallis test was used, and the Mann–Whitney *U* test was used to determine the group that caused the difference. The Chi-square test was used in categorical variables, and Fisher’s exact test was used when the conditions of the chi-square test were not met. A logistic regression model covering all patients was created in order to determine the differences in the risk of developing AKI between the groups determined according to BMI. It was thought that the severity of acute illness and chronic health conditions of the patients may be different and may affect the results. To avoid these differences and provide better randomization, patients were divided into four quarters according to their APACHE II scores ( $\leq 13$ , 13–20, 21–26,  $\geq 27$ ). Logistic regression models were created for the patients in each quarter to determine the differences in the risk of developing AKI between the groups determined according to BMI. Kaplan–Meier analysis was used to determine the effect of BMI on ICU mortality. A *p*-value of  $<0.05$  was used to determine the significance.

### Results

A total of 4459 patients were analyzed. Forty-four percent of the study population were female, and the mean age was  $60.08 \pm 19.46$ . The mean BMI was determined as  $27.05 \pm 5.56 \text{ kg/m}^2$  (min–max= 18.52–78.12). The most common comorbid disease was hypertension (1638; 36.7%), and the most common admission diagnosis was sepsis (991; 22.2%). The mean APACHE II score was  $19.9 \pm 8.9$ , the mean SAPS III score was  $45.1 \pm 14.2$ , and the mean SOFA score was  $6 \pm 4$ . Mechanical ventilation was applied to 3056 (68%) patients. The mean duration of ICU stay was  $9.7 \pm 13.8$ .

AKI development was observed in 2941 (66%) patients. The mortality rate was 31.6%.

### Comparison of clinical features according to BMI

General characteristics of the patients according to BMI are given in Table 1. Of the 4459 patients, 1801 (40.4%) were normal-weight, 1170 (39.7%) overweight, and 888 (19.9%) obese. The mean age of obese patients was  $64.69 \pm 15.53$ , and it was higher than those of normal-weight and overweight patients ( $57.88 \pm 21.53$ ,  $61.16 \pm 18$  years, respectively,  $p < 0.001$ ). It was determined that the male gender was more common in normal-weight and overweight patients, while the female gender (630; 70.9%) was more common in obese patients ( $p < 0.001$ ). Mean BMI values were  $22.93 \pm 1.62$ ,  $27.19 \pm 1.30$ , and  $35.44 \pm 6.80$  for normal-weight, overweight, and obese patients, respectively. Comorbid diseases were more prevalent in obese patients than in other groups ( $p < 0.001$ ). The frequency of hypertension, diabetes mellitus, and COPD was higher in obese patients ( $p < 0.05$ ). Cancer was more prevalent as a comorbid disease in normal-weight patients than in other groups ( $p < 0.05$ ). Considering the patients’ admission diagnoses to the ICU, the most common admission diagnosis in all groups was sepsis. In the comparison between groups, sepsis (236; 26.2%) was more common in obese patients than in normal-weight and overweight patients ( $p < 0.001$ ). The most common source of sepsis in obese patients was intra-abdominal sepsis (119; 13.4%). Other common diagnoses in obese patients were pulmonary diseases (pneumonia, COPD, and other causes) (146; 16.4%), cerebrovascular diseases (due to stroke and intracranial hemorrhage) (106; 11.9%), and postoperative follow-up (97; 10.9%). Cerebrovascular diseases were most prevalent in overweight patients (286; 16.2%), while trauma (224; 12.4%) and malignancy (151; 8.4%) were most prevalent in normal-weight patients ( $p < 0.05$ ) (Table 1).

The AKI stages, interventions, and treatments are shown in Table 2. The number of arterial catheters applied to the patients was similar in all groups. More central venous catheters were used in obese patients (502, 56.5%,  $p < 0.05$ ). There was no difference between the groups in terms of TPN and antibiotic and vasoactive agent use ( $p > 0.05$ ). APACHE II scores were lower in normal-weight patients (24 [17–29]) than in overweight (25 [19–30]) and obese (26 [19–31]) patients ( $p < 0.05$ ). The highest APACHE II scores were determined to be in obese patients ( $p < 0.05$ ). SAPS III scores were higher in obese patients (48 [37–60]) than in overweight (50 [39–60]) and normal-weight (49 [41–61])

**Table 1.** Characteristics of patients according to BMI groups and admission diagnosis.

Parameters	Normal weight, n: 1801 (40.4%), n (%)	Overweight, n: 1770 (39.7%), n (%)	Obese, n: 888 (19.9%), n (%)	p-value
Body mass index (kg/m <sup>2</sup> ) median (IQR)	23.37 (22.03–24.22)	27.34 (26.12–27.77)	33.20 (31.25–36.73)	
Age (year) mean ± SD	57.88 ± 21.53	61.16 ± 18.0 <sup>a</sup>	64.69 ± 15.53 <sup>b,c</sup>	<0.001
Gender				<0.001
Female	648 (36)	682 (38.5) <sup>a</sup>	630 (70.9) <sup>b,c</sup>	
Male	1153 (64)	1088 (61.5)	258 (29.1)	
Comorbidity	1265 (70.2)	1321 (74.6) <sup>a</sup>	752 (84.7) <sup>b,c</sup>	<0.001
Hypertension	495 (27.5)	662 (37.4) <sup>a</sup>	481 (54.2) <sup>b,c</sup>	<0.001
Diabetes	270 (15.0)	397 (22.4) <sup>a</sup>	326 (36.7) <sup>b,c</sup>	<0.001
Cerebrovascular disease	134 (7.4)	126 (7.1)	63 (7.1)	0.917
CAD	206 (11.4)	267 (15.1) <sup>a</sup>	121 (13.6)	0.006
COPD	157 (8.7)	181 (10.2)	126 (14.2) <sup>b,c</sup>	<0.001
CRF	147 (8.2)	157 (8.9)	99 (11.1) <sup>b</sup>	0.038
Malignancy	256 (14.2) <sup>a,b</sup>	211 (11.9)	92 (10.4)	0.011
Hepatic disease	32 (1.8)	28 (1.6)	18 (2)	0.706
Psychiatric disorder	43 (2.4)	36 (2)	13 (1.5)	0.283
Dementia	93 (5.2) <sup>a</sup>	621 (35.1)	34 (3.8)	0.038
Other	195 (10.8)	168 (9.5)	66 (7.4) <sup>b</sup>	0.019
Admission diagnosis				
Cerebrovascular disease	252 (14)	286 (16.2) <sup>c</sup>	106 (11.9)	0.011
Cardiac	89 (4.9)	102 (5.8)	58 (6.5)	0.220
Pulmonary	205 (11.4)	199 (11.2)	146 (16.4) <sup>b,c</sup>	<0.001
Pneumonia	130 (7.2)	120 (6.8)	65 (7.3)	0.830
COPD	48 (2.7)	56 (3.2)	53 (6) <sup>b,c</sup>	<0.001
Pulmonary, other	27 (1.5)	23 (1.3)	28 (3.2) <sup>b,c</sup>	0.002
Renal-metabolic	108 (6)	82 (4.6)	61 (6.9) <sup>c</sup>	0.042
Hepatic cirrhosis	19 (1.1)	20 (1.1)	12 (1.4)	0.792
Trauma	224 (12.4) <sup>b</sup>	208 (11.8) <sup>c</sup>	57 (6.4)	<0.001
Sepsis	383 (21.3)	373 (21.1)	236 (26.2) <sup>b,c</sup>	0.002
Pneumosepsis	91 (5.1)	77 (4.4)	38 (4.3)	0.524
Intra-abdominal sepsis	164 (9.1)	177 (10)	119 (13.4) <sup>b,c</sup>	0.002
Urosepsis	41 (2.3)	29 (1.6)	18 (2)	0.388
Sepsis, other	87 (4.8)	89 (5.0)	61 (6.9) <sup>b</sup>	0.067
Intoxication	87 (4.8) <sup>a,b</sup>	49 (2.8)	16 (1.8)	<0.001
Malignancy	151 (8.4)	134 (7.6)	46 (5.2) <sup>b,c</sup>	0.011
Postoperative	150 (8.3)	186 (10.5) <sup>a</sup>	97 (10.9) <sup>b</sup>	0.035
GIB-hemorrhage	53 (2.9)	57 (3.2)	18 (2)	0.215
Other	80 (4.4)	75 (4.2)	35 (3.9)	0.831

CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; GIB: gastrointestinal bleeding.

<sup>a</sup>Normal weight versus overweight  $p < 0.05$ .

<sup>b</sup>Normal weight versus obese  $p < 0.05$ .

<sup>c</sup>Overweight versus obese  $p < 0.05$ .

**Table 2.** AKI stages, interventions, and treatments during the ICU stay.

Parameters	Normal weight, n: 1801 (40.4%), n (%)	Overweight, n: 1770 (39.7%), n (%)	Obese, n: 888 (19.9%), n (%)	p-value
AKI	1172 (65.1)	1149 (64.9)	620 (69.8) <sup>b,c</sup>	0.025
Stage 1	98 (5.4)	118 (6.7)	57 (6.4)	0.286
Stage 2	156 (8.7)	185 (10.4)	101 (11.4)	0.054
Stage 3	918 (51.0)	846 (47.8)	462 (52.0)	0.062
Percentage of stages in AKI patients				
Stage 1	98 (8.4)	118 (10.3)	57 (9.2)	0.284
Stage 2	156 (13.3)	185 (16.1)	101 (16.3)	0.105
Stage 3	918 (78.3) <sup>a</sup>	846 (73.6)	462 (74.5)	0.023
Interventions				
Arterial catheter	1224 (68)	1253 (70.8)	613 (69)	0.183
Central catheter	858 (47.6)	903 (51) <sup>a</sup>	502 (56.5) <sup>b,c</sup>	<0.001
MV	1191 (66.1)	1230 (69.5) <sup>a</sup>	635 (71.5) <sup>b</sup>	0.010
Tracheostomy	307 (17)	345 (19.5)	165 (18.6)	0.164
Dialysis	295 (16.4)	329 (18.6)	216 (24.3) <sup>b,c</sup>	<0.001
Treatments				
TPN	618 (34.3)	655 (37)	318 (35.8)	0.243
Antibiotics	1534 (85.2)	1506 (85.1)	773 (87)	0.346
Vasoactive agents	985 (54.7)	1005 (56.8)	520 (58.6)	0.142

AKI: acute kidney injury; MV: mechanic ventilation; TPN: total parenteral nutrition.

<sup>a</sup>Normal weight versus overweight  $p < 0.05$ .

<sup>b</sup>Normal weight versus obese  $p < 0.05$ .

<sup>c</sup>Overweight versus obese  $p < 0.05$ .

**Table 3.** The average of ICU scores, mechanical ventilator values, and blood parameters of the patients during ICU follow-up.

Parameters	Normal weight Median (IQR)	Overweight Median (IQR)	Obese Median (IQR)	P-value
APACHE 2	24 (17–29)	25 (19–30) <sup>a</sup>	26 (19–31) <sup>b</sup>	<0.001
SAPS 3	48 (37–60)	50 (39–60)	49 (41–61) <sup>b,c</sup>	<0.001
SOFA	5 (3–9)	6 (3–9)	6 (3–9) <sup>b</sup>	0.019
MV (day)	4.81 (2.74–11.14)	5.73 (2.51–12.16)	5.89 (2.75–12.47)	0.242
LOS ICU (day)	5.45 (3–12.72)	6.54 (2.84–13.58) <sup>a</sup>	6.81 (3.32–13.88) <sup>b</sup>	0.004
FiO <sub>2</sub> (%)	42.2 (39.4–46.6)	42.2 (39.9–46.1)	42.6 (39.9–46.6) <sup>b,c</sup>	<0.001
PEEP (cmH <sub>2</sub> O)	5.4 (5.1–5.9)	5.4 (5.1–5.9)	5.6 (5.1–6.1) <sup>b,c</sup>	<0.001
P peak (cmH <sub>2</sub> O)	13.94 (12.13–15.86)	14.06 (12.64–15.87) <sup>a</sup>	15.17 (13.52–17.02) <sup>b,c</sup>	<0.001
Tidal volume (ml)	481 (427–541)	497 (442–569) <sup>a,c</sup>	476 (423–534)	<0.001
Tidal volume /IBW (ml/kg)	6.72 (5.98–7.58)	6.83 (6.08–7.68) <sup>a</sup>	7.05 (6.30–7.99) <sup>b,c</sup>	<0.001
Respiratory rate (min)	16.7 (14.8–19.6)	16.3 (14.7–19.1)	16.8 (14.7–19.2)	0.590
Compliance (ml/cm H <sub>2</sub> O)	41.2 (31.4–51.3) <sup>b</sup>	41 (32.8–51.3) <sup>c</sup>	35.5 (29.8–43.9)	<0.001
WOBv (j/l)	1.03 (0.91–1.20)	1.06 (0.92–1.21) <sup>a</sup>	1.17 (1–1.32) <sup>b,c</sup>	<0.001
Mechanical power (J/min)	9.35 (7.64–11.03)	9.37 (7.87–11.23)	9.61 (7.89–11.52)	0.066
pH	7.39 (7.33–7.43) <sup>b</sup>	7.39 (7.32–7.43)	7.38 (7.30–7.42)	0.002
pO <sub>2</sub> (mmHg)	94.9 (72.3–118.4) <sup>b</sup>	95 (75.5–116.3) <sup>c</sup>	91.5 (71.3–107.4)	<0.001
pCO <sub>2</sub> (mmHg)	42.2 (37.1–49.5)	42.9 (38.3–48.9)	44.8 (40.7–54.5) <sup>b,c</sup>	<0.001
HCO <sub>3</sub> (mEq/l)	24.9 (21.6–28.7)	25.1 (21.7–28.1)	24.7 (21.1–29)	0.820
Lactate (mmol/l)	1.78 (1.32–3.05)	1.96 (1.46–3.19)	1.98 (1.43–3.44)	0.297
Glucose (mg/dl)	137 (118–163)	149 (125–178) <sup>a</sup>	157 (132–197) <sup>b</sup>	<0.001
Nutrition (kcal/day)	1795 (1560–2086) <sup>b</sup>	1763 (1539–2082) <sup>c</sup>	1615 (1442–1865)	<0.001

APACHE: acute physiology and chronic health evaluation; SAPS: simplified acute physiology; SOFA: sequential organ failure assessment; MV: mechanic ventilation; LOS: length of stay; FiO<sub>2</sub>: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; IBW: ideal body weight; pCO<sub>2</sub>, partial pressure of carbon dioxide; pO<sub>2</sub>, partial pressure of oxygen; HCO<sub>3</sub>: bicarbonate; WOBv: work of breathing ventilator; IQR: inter quartile range.

<sup>a</sup>Normal weight versus overweight  $p < 0.05$ .

<sup>b</sup>Normal weight versus obese  $p < 0.05$ .

<sup>c</sup>Overweight versus obese  $p < 0.05$ .

**Table 4.** Logistic regression of the risk of AKI development according to the BMI.

Group	p-value	OR	CI 95
All patients			
Normal weight	Reference		
Overweight	0.823	1.016	0.887–1.163
Obese	<0.001	1.398	1.177–1.662
APACHE II GROUP 1 ( $\leq 13$ )			
Normal weight	Reference		
Overweight	0.606	1.069	0.829–1.379
Obese	0.024	1.476	1.054–2.068
APACHE II GROUP 2 (13–20)			
Normal weight	Reference		
Overweight	0.246	1.179	0.893–1.559
Obese	0.008	1.625	1.138–2.321
APACHE II GROUP 3 (21–26)			
Normal weight	Reference		
Overweight	0.130	0.795	0.591–1.070
Obese	0.759	1.059	0.733–1.530
APACHE II GROUP 4 ( $\leq 27$ )			
Normal weight	Reference		
Overweight	0.650	1.065	0.811–1.398
Obese	0.114	1.309	0.938–1.826

APACHE: acute physiology and chronic health evaluation; OR: odds ratio; CI: confidence interval.

patients ( $p < 0.05$ ). Obese patients' SOFA scores (6 [3–9]) were higher ( $p < 0.05$ ) than those of normal-weight patients (5 [3–9]) and similar to those of overweight patients (6 [3–9]) (Table 3).

### Mechanical ventilator and blood gas parameters

When the patients who received invasive mechanical ventilator support during the IC follow-up were

examined, it was seen that the need for mechanical ventilators increased as the BMI increased. While 66.1% (1,191) of normal-weight patients needed mechanical ventilator support, this rate increased to 69.5% (1,230) in overweight patients and to 71.5% (635) in obese patients ( $p < 0.05$ ). Considering the mechanical ventilator parameters, the values of FiO<sub>2</sub> (42.6 [39.9–46.6]), PEEP (5.6 [5.1–6.1]), peak pressure (15.17 [13.52–17.02]), and WOBv (1.17 [1–1.32]) were higher in obese patients, while compliance (35.5 [29.8–43.9]) and tidal volumes (476 [423–534]) were lower. When tidal volume is analyzed in ml/kg according to ideal body weight, it was higher in obese patients (7.05 [6.30–7.99]) than in overweight (6.83 [6.08–7.68]) and normal-weight (6.72 [5.98–7.58]) patients (Table 3). Minute Respiratory Rate and duration of mechanical ventilation were higher in obese patients, but this difference was not statistically significant. When looking at blood gas parameters, pH and pO<sub>2</sub> were lower in obese patients, while pCO<sub>2</sub> was higher ( $p < 0.05$ ). HCO<sub>3</sub> and lactate levels were found similar among the groups ( $p > 0.05$ ) (Table 3).

### Nutrition

Obese patients were given fewer daily calories than other groups (1615 [1442–1865];  $p < 0.05$ ). Despite the low-calorie input, the mean blood sugar was found to be higher in obese patients than in other groups (157 [132–197];  $p < 0.05$ ) (Table 3).

**Table 5.** AKI development according to the diagnosis of admission to the ICU and mortality rates to BMI groups.

Admission diagnosis	Normal weight, <i>n</i> (%)	Overweight <i>n</i> (%)	Obese, <i>n</i> (%)	<i>p</i> -value
Cerebrovascular disease	158 (62.7)	174 (60.8)	81 (76.4) <sup>a,b</sup>	0.014
Cardiac	55 (61.8)	63 (61.8)	41 (70.7)	0.465
Pulmonary	151 (73.7)	140 (70.4)	108 (74.0)	0.685
Pneumonia	99 (76.2)	88 (73.3)	49 (75.4)	0.872
COPD	34 (70.8)	39 (69.6)	37 (69.8)	0.990
Pulmonary, other	19 (67.9)	13 (56.5)	22 (78.6)	0.241
Renal-metabolic	51 (47.2)	50 (61)	32 (52.5)	0.170
Hepatic cirrhosis	133 (59.4)	126 (60.6)	37 (64.9)	0.747
Trauma	30 (56.6)	31 (54.4)	8 (44.4)	0.667
Sepsis	14 (73.7)	17 (85.0)	7 (58.3)	0.244
Pneumosepsis	291 (76)	272 (73.1)	173 (73.3)	0.619
Intra-abdominal sepsis	76 (83.5)	61 (79.2)	29 (76.3)	0.596
Urosepsis	131 (79.9)	130 (73.4)	99 (83.2)	0.113
Sepsis, other	22 (53.7)	14 (48.3)	6 (33.3)	0.354
Intoxication	50 (57.5)	45 (50.6)	37 (60.7)	0.322
Malignancy	36 (41.4)	23 (46.9)	10 (62.5)	0.286
Postoperative	101 (66.9)	89 (66.4)	32 (69.6)	0.924
GIB-hemorrhage	96 (64)	118 (63.4)	68 (70.1)	0.503
Other	57 (71.3)	46 (61.3)	23 (65.7)	0.425
Mortality				
All patient	548 (30.4)	556 (31.4)	307 (34.6)	0.091
AKI patient	388 (33.1)	399 (34.7)	223 (36.0)	0.198
AKI–mortality relationship				
AKI yes	388 (33.1)			<0.001
AKI no	160 (25.4)			
AKI yes		399 (34.7)		<0.001
AKI no		157 (25.3)		
AKI yes			223 (36.0)	0.183
AKI no			84 (31.3)	

COPD: chronic obstructive pulmonary disease; GIB: gastrointestinal bleeding; AKI: acute kidney injury.

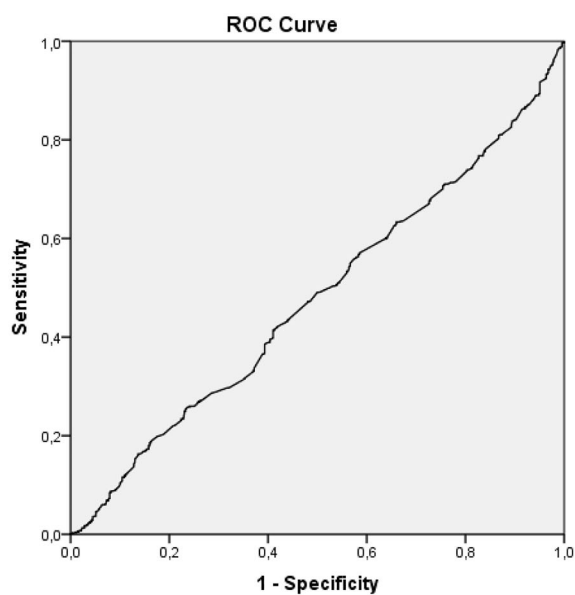
<sup>a</sup>Normal weight versus obese  $p < 0.05$ .

<sup>b</sup>Overweight versus obese  $p < 0.05$ .

### AKI development and dialysis

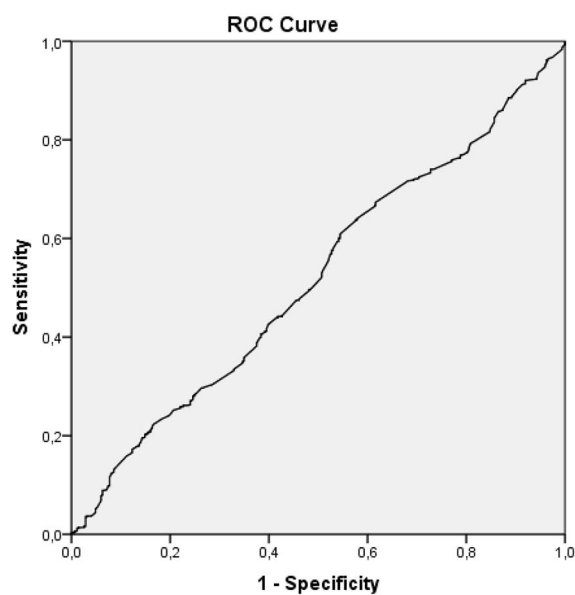
According to AKI alerts generated by the CDSS, most alerts were delivered for obese patients with 69.8% (620) ( $p < 0.05$ ). The rate of AKI development was similar in normal-weight (65.1%; 1172) and overweight patients (64.9%; 1149). Regarding the stages of the patients who received an AKI alert, patients who received Stage 1 and Stage 2 AKI alert did not show a statistically significant difference among the groups, while the rate of Stage 3 AKI alert in normal-weight patients (918; 78.3%) was higher than that of overweight patients (46; 73.6%) ( $p < 0.05$ ) and similar to that of obese patients (462; 74.5%) (Table 2). Logistic regression to determine the risk of AKI development according to patients' BMI revealed that the risk of developing AKI was approximately 1.4 times higher (OR: 1.398; CI95% = 1.177–1.662) in obese patients than in normal-weight patients. Considering that the clinical weights of the patients may differ, the disease severity was divided into four quarters according to the APACHE II group, and logistic regression was performed in patients with similar disease severity for the effect of BMI on the AKI development. The risk of developing AKI was found to be higher in obese patients in all groups. However, a statistically significant difference emerged in

low APACHE II scores. Obese patients with an APACHE II score in the first quarter ( $\leq 13$ ) had a 1.47 times higher risk of developing AKI (OR: 1.476 CI 95% = 1.054–2.068), and it was determined that the risk of developing AKI was 1.62 times higher in obese patients with an APACHE II score in the second quarter (13–20) (OR: 1.625 CI 95% = 1.138–2.321) than in normal-weight patients in the same quarter. Patients with an APACHE II score in the third (21–26) and fourth quarters ( $\leq 27$ ) showed no significant difference in terms of AKI development (Table 4). In the subgroup analysis performed according to the admission diagnosis, it was determined that the development of AKI in patients who were admitted with cerebrovascular diseases was higher in obese patients (81; 76.4%) than in normal-weight (158; 62.7%) and overweight (174; 60.8%) patients ( $p < 0.05$ ). There was no statistically significant difference between the groups in terms of the development of AKI in other admission diagnoses (Table 5). When looking at the patients who developed a need for dialysis, obese patients (216; 24.3%) needed significantly more dialysis than normal-weight (295; 16.4%) and overweight (329; 18.6%) patients ( $p < 0.001$ ). ROC analyses performed to determine cutoff values in the relationship of BMI with AKI development in different APACHE II groups did not yield significant results (Figure 1).



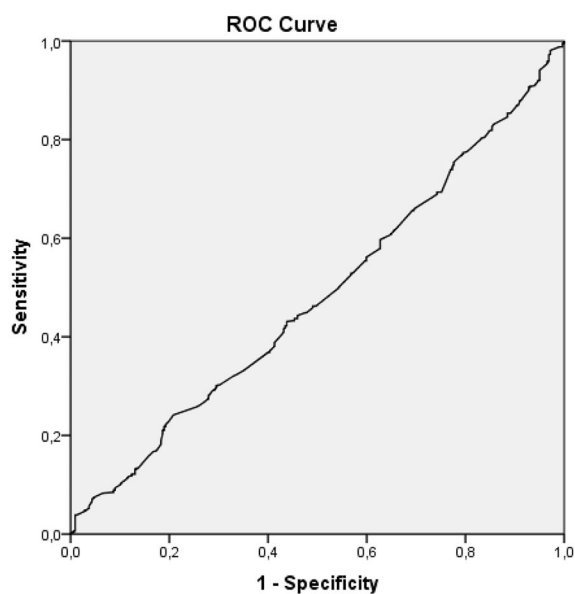
Diagonal segments are produced by ties.

APACHE II GROUP 1 ( $\leq 13$ ); AUC=0.477



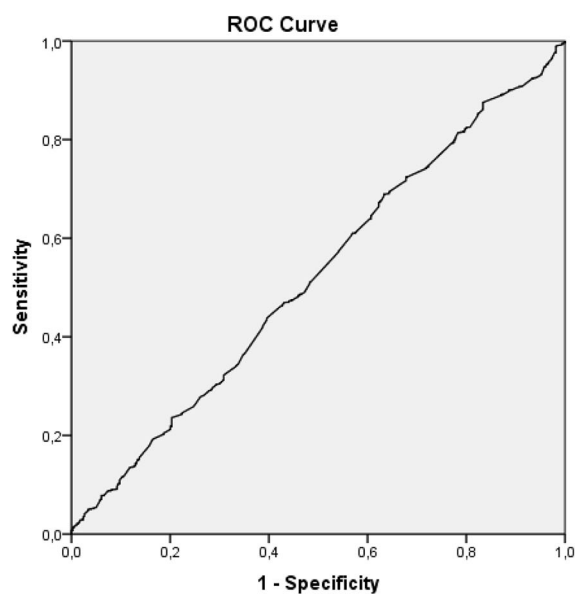
Diagonal segments are produced by ties.

APACHE II GROUP 2 (13-20); AUC=0.519



Diagonal segments are produced by ties.

APACHE II GROUP 3 (21-26); AUC=0.482



Diagonal segments are produced by ties.

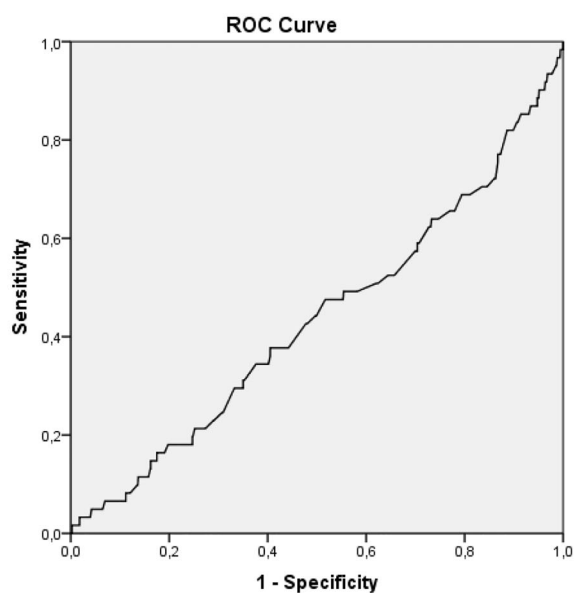
APACHE II GROUP 4 ( $\leq 27$ ); AUC=0.521

Figure 1. ROC analysis curves of BMI and AKI according to four different APACHE groups.

### AKI and mortality

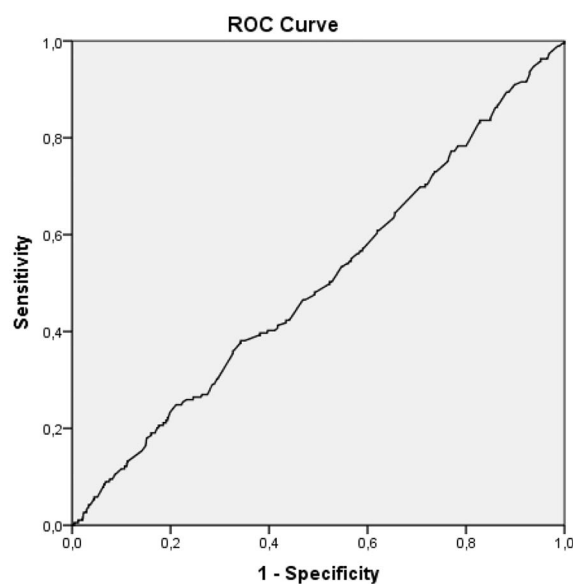
Patients who developed AKI needed more mechanical ventilator support in all three groups than patients without AKI and stayed longer in the ICU ( $p < 0.001$ ). There was no difference in mortality between obese, normal-weight, and overweight patients who developed AKI. While it was determined that the

development of AKI in normal-weight and overweight patients increased mortality ( $p < 0.001$ ), there was no significant difference between the mortality of obese patients who developed AKI (223; 36.0%) and the mortality of obese patients without AKI (84; 31.3%). The results of ROC analyses performed to determine cutoff



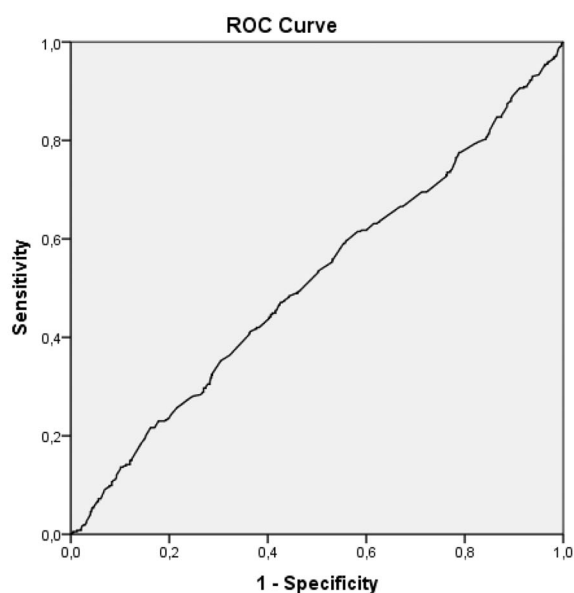
Diagonal segments are produced by ties.

APACHE II GROUP 1 ( $\leq 13$ ); AUC=0.435



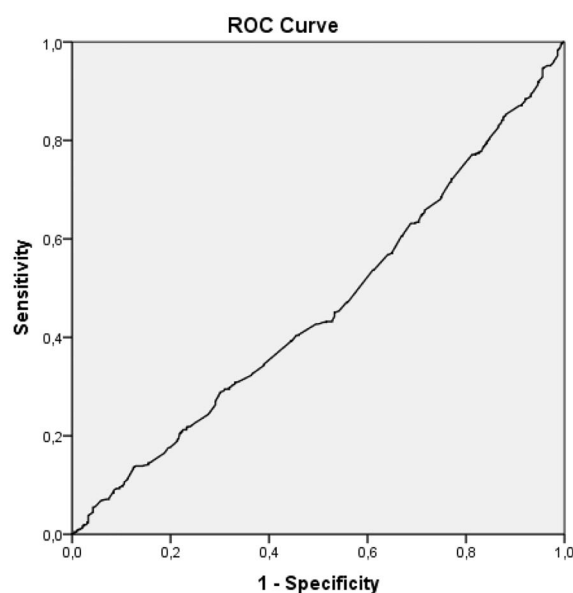
Diagonal segments are produced by ties.

APACHE II GROUP 2 (13-20); AUC=0.502



Diagonal segments are produced by ties.

APACHE II GROUP 3 (21-26); AUC=0.513



Diagonal segments are produced by ties.

APACHE II GROUP 4 ( $\leq 27$ ); AUC=0.460

**Figure 2.** ROC analysis curves of BMI and mortality according to four different APACHE groups.

values in the relationship of BMI with mortality in different APACHE II groups were not significant (Figure 2).

### ICU length of stay and mortality

Obese patients (6.81 [3.32–13.88]) had longer ICU length of stay ( $p < 0.05$ ) than normal-weight (5.45 [3–12.72]) and overweight (6.54 [2.84–13.58]) patients.

Mortality rates did not differ significantly among the groups. Even though the patients were grouped according to their admission diagnoses, there was no difference in mortality between any of the admission groups ( $p > 0.05$ ) (Table 2). As a result of ROC analysis performed to determine the relationship between BMI and mortality, the area under the curve was found to be only 51.6% (0.516).

## Discussion

As a result of this study, which investigated the effect of BMI on AKI and mortality, it was determined that as the BMI increased, the rate of AKI development also increased. Especially obese ICU patients with low APACHE II scores were found to have a higher risk of developing AKI. Consistent with the results of our study, it has been shown in previous studies that the prevalence of AKI in the ICU is higher in obese patients than in non-obese, critically ill patients and that the prevalence of AKI in critically ill patients increases with BMI [17]. Danziger et al. [23] retrospectively evaluated the relationship between obesity, AKI, and AKI severity in 14,986 critically ill patients in the United States and found that obese patients developed more AKI than non-obese patients. Again, in a retrospective study conducted with 751 American ICU patients, Soto et al. [22] determined that obesity was associated with increased AKI development and that each 5 kg/m<sup>2</sup> increase in BMI was associated with a 20% increased risk for developing AKI. In a large study conducted in Austria, it was determined that the risk of developing AKI increased more than two times in severely obese patients compared to normal-weight patients [18]. In a study conducted with 11,736 patients in Australia, Yap et al. found that obesity and morbid obesity were associated with an increased risk for AKI [27]. In a Danish study with 56,420 patients evaluating the effect of BMI on AKI risk retrospectively, Pedersen et al. reported that obese patients (BMI  $\geq 30$ ) showed an increased risk of developing AKI compared to patients with normal weight (BMI 18.5–24.9) [21].

Although the pathophysiology of increased AKI development in obesity is not fully understood, increased renal blood flow and GFR due to altered renal hemodynamics may increase the filtration fraction and increase the sensitivity to damage [28,29]. In addition to increased inflammatory mediators in response to acute diseases, increased production of leptin, an adipocyte-derived cytokine that controls energy metabolism and appetite and is metabolized in the kidney, and a significant decrease in the production of adiponectin, a hormone that regulates glucose and lipid metabolism, have been associated with an increased risk of AKI in obesity [30–32]. Obesity is associated with high HDL levels that bind bacterial lipopolysaccharide endotoxins [33]. In addition, autophagy, an important protection system in which damaged cells are eliminated, is impaired in obesity [34]. Obese ICU patients are at risk for increased intra-abdominal pressure, which may result in renal dysfunction due to both venous occlusion and poor arterial perfusion [35,36]. As determined

in our study in obese patients, the effects of more common comorbid diseases on kidney physiology should not be ignored. Glance et al. [37] found that obese patients with metabolic syndrome faced a 3–7 times higher risk of AKI. Another factor that may contribute to the impact of obesity on AKI is the difficulty in assessing intravascular volume status and determining adequate fluid therapy or the dose of vasoactive agents.

In our study, mechanical ventilation durations of obese patients were found to be higher than those of normal-weight and overweight patients, but this difference was not statistically significant. Previous studies have revealed conflicting results for the impact of obesity on mechanical ventilation duration [6,16,38]. In a study [6], while the duration of mechanical ventilation was longer in obese patients than in non-obese patients, there was no difference in another similar study [16,38]. Obesity triggers changes in respiratory function, particularly a decline in respiratory capacity and an upsurge in airway resistance [39]. When looking at mechanical ventilator parameters, obese patients had higher PEEP and peak pressures as well as lower compliances. The ventilator workload increased. These results are consistent with previous research. During mechanical ventilation, obese patients are more inclined to atelectasis and require higher PEEP support to prevent it [40]. Moreover, studies have stated that obese patients require higher inspiratory pressure and plateau pressures [41,42]. Despite the exposure of higher pressures [43,44] on the mechanical ventilator that obese patients underwent, they tend to have a lower functional residual capacity and lung volume [45]. The lower compliance of obese patients can be explained by the reduction in the lung and chest wall compliance caused by obesity and making the lungs more susceptible to atelectasis or increased alveolar wall tension [46]. Abdominal visceral fat accumulation can increase the respiratory workload by causing an increase in intra-abdominal pressure [43,44]. In addition, studies have determined that obese patients consume more oxygen and produce more carbon dioxide [47,48]. In obese patients, increased respiratory workload and ventilation/perfusion mismatched as a result of early airway closure may clarify this situation [45]. In the present study, the ICU follow-up period was found to be significantly longer in obese patients than in non-obese patients. While some similar studies reported an increase in the ICU length of stay for obese patients [49,50], others could not find a difference between the ICU length of stay of obese patients and other patient groups [16,24,51]. This situation can be explained by

the differences occurring among obese patients. There is no single obesity type in the ICU: obese patients vary according to their obesity class and comorbid disease burden. Also, some clinicians tend to think that obese patients have potentially worse outcomes [17]. Therefore, the increased acceptance of obese patients who can be treated more easily in the ICU and who are not very critical may shorten the follow-up period in the ICU. On the other hand, vascular access problems are common in obese patients, and the frequency of using central catheters is increased, as determined in our study. This may lead to infection development and catheter-related complications, prolonging the ICU stay. Nursing care of obese patients is more challenging due to their high body weight and large body surface area. Difficulty in changing the patient's position brings the risk of pressure sores and increased skin lacerations [52]. Deterioration of the skin barrier may increase complications such as infection or bleeding and might prolong the ICU stay.

### **Mortality**

In the present study, no difference was found between the groups in terms of ICU mortality. The phenomenon called the obesity paradox (associating obese patients with better survival in the ICU) could not be statistically confirmed. In addition, the ROC analysis performed to find a cutoff value where BMI affected mortality showed that determining such a cutoff value was almost indistinguishable from coin-tossing. However, despite the fact that obese patients had higher APACHE II scores, higher frequency of comorbid diseases, and higher ages in our study, the absence of a difference in mortality supports this paradox. In similar studies [14,53], the results on ICU mortality indicated that mortality was either lower in obese patients or was not any different [15,54,55]. In fact, Falagas et al. obtained higher mortality results [56] in a subgroup of obese patients. Even when the effect of the development of AKI [17] on ICU mortality in our study is considered, the development of AKI increased mortality in normal-weight and overweight patient groups, but interestingly, not in obese patients. The fact that mortality does not change even when the AKI table is added appears as another finding that supports the obesity paradox. Similar studies have obtained different results regarding the effect of AKI development on mortality in obese patients followed in the ICU. While some studies determined a decrease in mortality [18–20], some others did not find a difference in mortality [21–24]. Some studies determined that there was a U or J-shaped relationship between

mortality and BMI [18,19]. In another study [57], while there was no difference in low disease scores, it was determined that higher disease scores differed in mortality and that obese patients had a survival advantage in higher disease scores. The timing of AKI and the importance of early diagnosis were emphasized in another study [58]. These complex results may have arisen due to the use of arbitrary obesity definitions (such as BMI > 28, BMI > 31) or due to differences in obese patient profiles and comorbid disease burdens. In addition, the fact that BMI measurement does not consider fat distribution and lean muscle mass may cause the misinterpretation of obesity. A patient with metabolic and clinical risks of obesity due to increased visceral fat mass cannot be classified as obese, while a patient with a high muscle mass and preserved visceral fat ratio can be classified as obese. Therefore, the BMI measurement used in obesity determination can also cause these contradictory results.

Our study has some strengths such as minimizing the data loss as a result of receiving our study data by electronic query by the CDSS and preventing human errors. However, it also has some limitations. First of all, having a single-center cohort prevents the results from being generalized. The retrospective design of the study may cause confounding factors affecting the results and may lead to the risk of bias. In addition, the fact that obesity is defined according to BMI and the absence of additional data to support, such as waist circumference and waist-hip ratio, may have affected the accuracy of the groups formed according to BMI. Lack of registration of IV fluids and diuretic treatments given before the ICU follow-up may have affected BMI and AKI data by changing the weight and urine amount measured in the ICU. Also, the use of diuretic therapy during follow-up in the ICU may have changed the AKI stage of the patients.

In conclusion, it was determined that the risk of developing AKI was higher in obese patients, but not in those who are in serious conditions. Another paradox was that the development of AKI was associated with a higher mortality rate in normal-weight and overweight patients, but not in obese patients. In addition, cerebrovascular diseases pose an additional risk of AKI as a reason for hospitalization. The lack of difference in mortality between patients with and without AKI supports the obesity paradox in the ICU. However, further research in a larger cohort is required to better determine the effect of obesity in the ICU. Doing so may help identify patients who would most likely benefit from early AKI prevention and treatment.

## Disclosure statement

The authors declare they have no conflict of interest.

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