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Body mass index is inversely associated with mortality in patients with acute kidney injury undergoing continuous renal replacement therapy

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Background: Many epidemiologic studies have reported on the controversial concept of the obesity paradox. The presence of acute kidney injury (AKI) can accelerate energy-consuming processes, particularly in patients requiring continuous renal replacement therapy (CRRT). Thus, we aimed to investigate whether obesity can provide a survival benefit in this highly catabolic condition.

Methods: We conducted an observational study in 212 patients who had undergone CRRT owing to various causes of AKI between 2010 and 2014. The study end point was defined as death that occurred within 30 days after the initiation of CRRT.

Results: Patients were categorized into three groups according to tertiles of body mass index (BMI). During 30 days after the initiation of CRRT, 39 patients (57.4%) in the highest tertile died, as compared with 58 patients (78.4%) in the lowest tertile (P = 0.02). In a multivariable analysis adjusted for cofounding factors, the highest tertile of BMI was significantly associated with a decreased risk of death (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.37–0.87; P = 0.01). This significant association remained unaltered for 60-day (HR, 0.64; 95% CI, 0.43–0.94; P = 0.03) and 90-day mortality (HR, 0.66; 95% CI, 0.44–0.97; P = 0.03).

Conclusion: This study showed that a higher BMI confer a survival benefit over a lower BMI in AKI patients undergoing CRRT.

Keywords: Acute kidney injury, Body mass index, Continuous renal replacement therapy, Mortality, Obesity

Introduction

The prevalence of obesity has been gradually increasing worldwide during the past few decades. Obese persons are more likely to have hypertension, dyslipidaemia, and diabetes mellitus (DM) than non-obese persons, which are important causes of cardiovascular and cerebrovascular diseases. Accordingly, mortality rates are higher in this population [1]. It is also highly associated with the development of chronic kidney disease (CKD),

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microalbuminuria, and overt proteinuria [2]. With such increasing prevalence, many critically ill patients who require treatment in the intensive care unit (ICU) also have obesity. A previous meta-analysis from the United States showed that approximately 30% of ICU patients had a body mass index (BMI) of ≥ 30 kg/m^2, and these patients had prolonged durations of mechanical ventilation and lengths of ICU stay [3].

Acute kidney injury (AKI) occurs in many hospitalized and ICU patients, and is significantly associated with adverse outcomes such as high mortality, increased length of hospital stay, and progression to CKD [4]. Given the high burden of comorbidities accompanying obesity, it can be inferred that obese patients are prone to the development of AKI and thus experience more serious complications than non-obese patients with critical conditions. However, this assumption has not yet been clearly proven, and there has been much controversy on the relationship between AKI, obesity, and mortality. In fact, several studies have shown that obesity is associated with a high incidence and severity of AKI [5–7], as well as increased mortality in ICU patients [6]. In contrast, an inverse or null relationship between obesity and mortality has also been reported in other studies [5,8–12].

This phenomenon, called the 'obesity paradox', has been observed in patients with chronic diseases . In particular, in CKD patients, a higher BMI is associated with a lower risk of all-cause mortality [13], than a normal or lower BMI. Furthermore, recent evidence has shown that obese patients undergoing ICU and ventilator therapy have a survival benefit over non-obese patients [5]. Although the physiologic mechanism is not yet established, fat tissue as an energy reservoir has been suggested to explain this beneficial effect of obesity [14]. Of note, sepsis is characterized by increased protein catabolism and high energy consumption. It can be presumed that this process can be more deteriorated particularly when complicated by AKI in patients requiring renal replacement therapy. Therefore, we aimed to delineate the relationship between obesity and mortality in critically ill patients with AKI who were treated with continuous renal replacement therapy (CRRT).

Methods

Patients

We conducted an observational study in 212 adult patients who were treated with CRRT in the ICU of our institution between January 2010 and December 2014. A total of 573 patients were initially assessed for study eligibility. Patients were excluded if they were ≤ 18 or ≥ 75 years old, had end-stage renal disease (ESRD) on dialysis, or had stage 4 malignancy. Patients who had no BMI data were also excluded (Fig. 1). The study was approved by the Institutional Review Board of Yonsei University Severance Hospital (4-2010-0440). Since current study was a retrospective observational study and the study subjected de-identified, the IRB waived the need for written consent from the patients.

Data collection

Demographic factors and comorbid conditions were obtained from electronic medical records. The Charlson comorbidity index (CCI) was used to evaluate the severity of the patients' comorbidities [15], and BMI was calculated by using the height and weight data obtained on ICU admission (weight [kg]/height [m^2]). The causes of AKI were classified into five categories: (i) sepsis, (ii) nephrotoxin, (iii) hypovolemic ischemia, (iv) surgery, and (v) others. Blood samples were collected immediately after ICU admission. The measured laboratory data included white blood cell (WBC) count, haemoglobin, haematocrit, platelet, prothrombin time, partial thromboplastin time, cholesterol, albumin, blood urea nitrogen, and creatinine. The estimated glomerular filtration rate (eGFR)

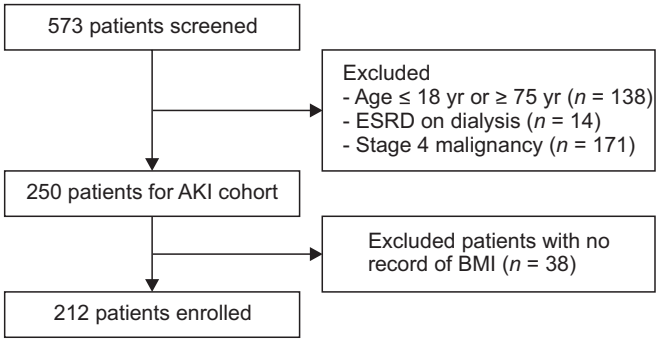

Figure 1. Flowchart of participants in the cohort. AKI, acute kidney injury; BMI, body mass index; ESRD, end stage renal disease.

was determined by using the Modification of Diet in Renal Disease equation [16]. The average vital signs, PaO_2, FiO_2, and Glasgow coma scale score in the first 24 hours of ICU admission were collected to calculate the sepsis-related organ failure assessment (SOFA) score.

Outcomes

The primary outcome was death from any cause that occurred at 30 days after CRRT initiation. Secondary outcomes included death from any cause occurred at 60 and 90 days after CRRT initiation, and weaning from CRRT due to renal recovery.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation, and compared with *t*-test and one-way ANOVA. The normality of the distribution of parameters was analysed by using the Kolmogorov-Smirnov test. If data did not show a normal distribution, these were presented as median and interquartile range and compared

Table 1. Baseline characteristics of patients according to BMI tertiles

Characteristic	BMI (kg/m^2) tertiles			*P*
	Tertile 1 (13.5–21.8)	Tertile 2 (21.9–25.4)	Tertile 3 (25.5–37.1)	
Patient (*n*)	74	70	68	
Age (yr)	61.8 ± 13.2	64.0 ± 11.8	60.5 ± 14.1	0.29
Sex (female)	23 (31.1)	26 (37.1)	25 (36.8)	0.69
Diabetes mellitus	16 (21.9)	16 (22.9)	26 (38.2)	0.06
Hypertension	31 (41.9)	35 (50.0)	34 (50.0)	0.53
Myocardiac infarction	1 (1.4)	3 (4.3)	0 (0.0)	0.17
Congestive heart failure	7 (9.5)	4 (5.7)	7 (10.3)	0.59
Cerebrovascular attack	4 (5.6)	5 (7.1)	2 (2.9)	0.80
Peripheral vascular disease	1 (1.4)	2 (2.9)	0 (0.0)	0.36
COPD	2 (2.7)	4 (5.7)	6 (8.8)	0.29
Cancer	46 (62.2)	42 (60.9)	35 (51.5)	0.2
CCI score	2.9 ± 1.9	2.9 ± 2.1	3.0 ± 2.5	0.96
AKI cause				0.30
Sepsis	57 (77.0)	59 (84.3)	49 (72.1)	
Nephrotoxin	1 (1.4)	0 (0.0)	1 (1.5)	
Ischemia	2 (2.7)	0 (0.0)	0 (0.0)	
Surgery	1 (1.4)	0 (0.0)	0 (0.0)	
Others	13 (17.6)	11 (15.7)	18 (26.5)	
BMI (kg/m^2)	19.4 ± 2.0	23.6 ± 1.1	28.6 ± 2.8	<0.001
MAP (mmHg)	79.8 ± 14.3	79.6 ± 15.8	77.4 ± 13.5	0.55
BUN (mg/dL)	54.2 ± 26.8	67.4 ± 29.0	66.0 ± 39.4	0.03
Creatinine (mg/dL)	2.5 ± 1.2	3.6 ± 2.2	3.2 ± 1.6	0.001
eGFR (mL/min/1.73m^2)	32.8 ± 31.0	23.2 ± 18.1	22.5 ± 10.5	0.008
WBC (× 10^3/mm^3)	13.8 ± 13.5	13.3 ± 11.2	13.7 ± 10.1	0.96
Hemoglobin (g/dL)	9.7 ± 1.8	9.3 ± 1.8	9.2 ± 2.2	0.24
Albumin (g/dL)	2.5 ± 0.6	2.4 ± 0.6	2.5 ± 0.5	0.33
Potassium (mmol/L)	4.4 ± 0.8	4.4 ± 1.0	4.5 ± 1.0	0.70
Mechanical ventilation	66 (89.2)	56 (80.0)	55 (80.9)	0.26
Vasopressor	57 (76.5)	57 (81.4)	58 (85.2)	0.42
SOFA	14.1 ± 3.0	14.1 ± 3.3	14.4 ± 3.0	0.87

Data are presented as number only, number (%), or mean ± standard deviation.

AKI, acute kidney injury; BMI, body mass index; BUN, blood urea nitrogen; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; SOFA, sepsis-related organ failure assessment; WBC, white blood cell.

Table 2. Length of stay, survival, and mortality according to body mass index tertiles

Variable	BMI tertiles			*P*
	Tertile 1	Tertile 2	Tertile 3	
ICU LOS (d)	5 (2–12.5)	5.5 (3–15.3)	9 (4–18)	0.17
Hospital LOS (d)	7.5 (2–20)	12 (3–34.25)	4 (14–34)	0.28
Mortality (d)				
30	58 (78.4)	44 (62.9)	39 (57.4)	0.02
60	60 (81.1)	50 (71.4)	47 (69.1)	0.22
90	60 (81.1)	51 (72.9)	49 (72.1)	0.38
Weaning from CRRT				
30	13 (17.6)	16 (22.9)	18 (26.5)	0.15
60	9 (12.2)	14 (20.0)	14 (20.6)	0.83
90	10 (13.5)	13 (18.6)	12 (17.6)	0.67

Data are expressed as median (interquartile range) or number (%).

CRRT, continuous renal replacement therapy; ICU, intensive care unit; LOS, length of stay.

by using the Mann-Whitney test or Kruskal-Wallis test. Categorical variables were expressed as percentages and compared with the chi-square test. Cumulative survival curves were derived using the Kaplan-Meier method, and differences between curves were analysed by log-rank test. To evaluate the relationship of BMI, covariables, and mortality, a Cox-proportional hazard model was used, and the results were presented as a hazard ratio (HR) and 95% confidence interval (CI). In addition, receiver operating characteristic (ROC) curve analysis was conducted and the cut-off value of BMI for the outcome was derived by Youden index, which is the maximum vertical distance between ROC curve and chance line. Statistical significance was defined as $P < 0.05$. All analyses were conducted by using IBM SPSS Statistics, version 20.0 (IBM Co., Armonk, NY, USA) and R language (version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

The baseline characteristics of the patients and the CRRT prescription are presented in Tables 1 and 2, respectively. We classified patients into tertiles according to BMI: Q1, 13.5–21.8 kg/m^2; Q2, 21.9–25.4 kg/m^2; and Q3, 25.5–37.1 kg/m^2. The average BMI was 23.9 ± 4.3 kg/m^2. The mean age was 62.1 years, and 74 patients (34.9%) were women. The prevalence of hypertension, DM, and other comorbidities did not significantly differ between groups. The mean age-adjusted CCI score was 4.6 ± 2.6 and was similar in the three groups. Sepsis was a predominant cause of AKI (77.8%), and occurred less frequently in high tertiles; however, the difference did not reach statistical significance ($P = 0.3$). The mean eGFR at the time of starting CRRT was 26.3 ± 22.3 mL·min^{-1}·1.73 m^{-2}, and the initial kidney function of lowest tertile was significantly higher than those of other two quartiles ($P = 0.008$). The average SOFA score was 14.2 ± 3.1, and the severity of illness was not significantly different between groups ($P = 0.54$).

ICU and hospital stay durations and mortality rates according to BMI tertiles

The ICU and hospital stay durations, survival days, and 30, 60 and 90-day mortality rates are presented in Table 2. The mean ICU and hospital stay was 6 (3–15) and 11 (3–32) days, respectively. Patients with a higher BMI stayed longer in the ICU and hospital than those with a lower BMI; however, the differences did not reach statistical significance. A total of 141 deaths (66.5%) occurred during 30 days after CRRT initiation. Most patients died of sepsis and there was no difference in cause of death between groups (data not shown). Thiry-nine patients (57.4%) in the highest tertile died as compared with 58 patients (78.4%) in the lowest tertile ($P = 0.02$). The Kaplan-Meier curve of the 30-day shows that the cumulative survival of the highest BMI tertile group was significantly higher than those of the lowest BMI group (Fig. 2, $P = 0.04$). An additional 19 deaths occurred between 30 and 90 days. When we analysed the 90-day mortality rate, there were

49 deaths (72.1%) in the highest tertile as compared with 60 deaths (81.1%) in the lowest tertile (P = 0.37). There were no differences of renal survival at all time points.

Relationship between BMI and mortality in multivariable-adjusted models

We further analysed the association between BMI and mortality by using multivariable-adjusted Cox models. To this end, we constructed four different models (Table 3). In model 1, in which sex, age-adjusted CCI score, septic AKI, and SOFA score were entered, the highest tertile of BMI was significantly associated with a decreased risk of death (HR, 0.58; 95% CI, 0.38–0.88; P = 0.01). In model 2, we additionally adjusted WBC and albumin as inflammatory and nutritional markers, and found that the survival benefit of a high BMI persisted. Finally, in model 3, CRRT prescription was added to model 2. In this fully adjusted model, patients in the highest tertile had a significantly decreased risk of death compared with those in the lowest tertile (HR, 0.57; 95% CI, 0.37–0.87; P = 0.01). When BMI was analysed as a continuous variable, a high BMI was still independently associated with a decreased risk of death (HR, 0.94 per 1 kg/m^2 increase; 95% CI, 0.90–0.99; P = 0.007). We further analysed the 60-day and 90-day mortality in these patients, and obtained similar results. In subgroup analyses according to presence of sepsis and cancer, survival benefit of high BMI was seen in only patients with sepsis (Fig. 3). In addition, to evaluate the cut-off value of BMI as a prognostic marker for outcome, ROC analysis was conducted. The area under

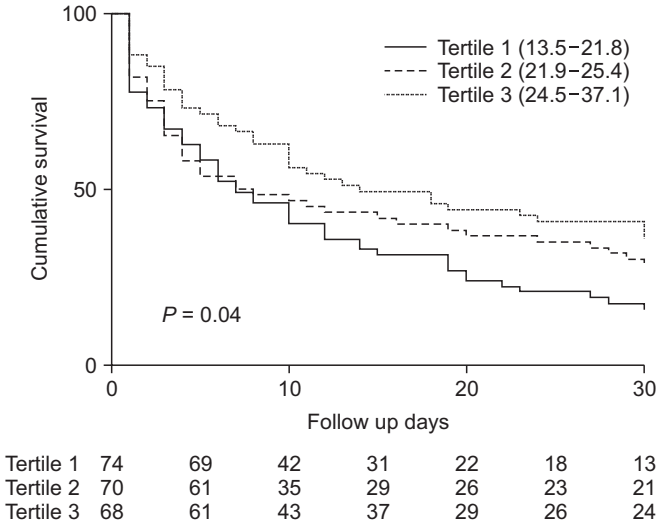

Figure 2. Kaplan-Meier curves of the 30-day mortality according to body mass index tertiles.

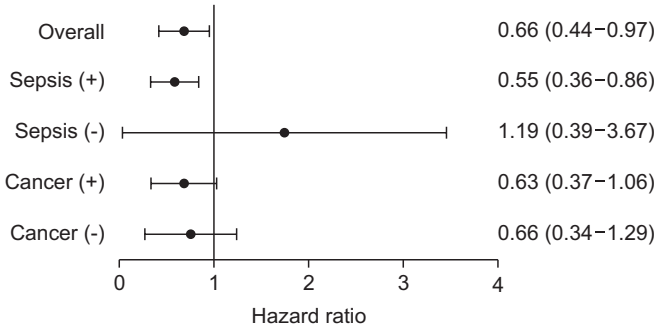

Figure 3. Hazard ratio for mortality according to presence of sepsis and cancer in fully adjusted model.

Table 3. Multivariable Cox regression analyses for mortality

Follow-up	BMI tertiles	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
30-day	Tertile 1	1.00 (reference)		1.00 (reference)		1.00 (reference)		0.94 (0.90–0.98)	0.01
	Tertile 2	0.77 (0.52–1.16)	0.21	0.76 (0.51–1.16)	0.21	0.77 (0.51–1.15)	0.2		
	Tertile 3	0.58 (0.38–0.88)	0.01	0.58 (0.38–0.87)	0.01	0.57 (0.37–0.87)	0.01		
60-day	Tertile 1	1.00 (reference)		1.00 (reference)		1.00 (reference)		0.96 (0.92–0.99)	0.03
	Tertile 2	0.87 (0.59–1.28)	0.48	0.85 (0.58–1.26)	0.43	0.85 (0.58–1.26)	0.43		
	Tertile 3	0.65 (0.44–0.95)	0.03	0.64 (0.43–0.94)	0.02	0.64 (0.43–0.94)	0.03		
90-day	Tertile 1	1.00 (reference)		1.00 (reference)		1.00 (reference)		0.96 (0.92–0.99)	0.03
	Tertile 2	0.88 (0.60–1.29)	0.51	0.86 (0.59–1.27)	0.45	0.86 (0.58–1.27)	0.45		
	Tertile 3	0.67 (0.46–0.98)	0.03	0.66 (0.45–0.97)	0.03	0.66 (0.44–0.97)	0.03		

Model 1, sex, age-adjusted CCI score, septic AKI, and SOFA score; Model 2, Model 1 + WBC and albumin; Model 3, Model 2 + CRRT prescription (total effluent volume); Model 4, Model 3 + BMI as a continuous variable.

AKI, acute kidney injury; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; CRRT, continuous renal replacement therapy; HR, hazard ratio; SOFA, sepsis-related organ failure assessment; WBC, white blood cell.

ROC curve for BMI was 0.616, and optimal point of BMI derived from Youden index was 22.9 kg/m^2.

Discussion

In this study, we showed that a higher BMI is associated inversely with mortality in AKI patients undergoing CRRT. By using different multivariable-adjusted models, we found a consistent survival advantage of a higher BMI over a lower BMI, even though patients with lower BMI had a superior initial kidney function than patients with higher BMI. With ROC curve, we showed that patients with BMI over 22.9 kg/m^2, which is defined as overweight and obesity in Asian population by World Health Organization criteria, had low risk of mortality. Thus, our findings are robust and can add evidence to the recently prevailing concept of the 'obesity paradox', even in critically ill patients undergoing renal replacement therapy.

We particularly paid attention to AKI patients treated with CRRT. Critical ill patients are generally hypercatabolic, and have substantial energy expenditure in proportion to the amount of stress [17]. In addition, patients with AKI have a high prevalence of malnutrition [18], and protein can be excessively degraded in uraemia caused by AKI [19]. Especially, loss of protein can be accelerated in AKI with CRRT, since protein and other nutritional elements are lost through CRRT [20]. Previous studies showed that 17% of centrally infused protein losses into CRRT effluent [21]. Accordingly, the American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient recommend that patients receiving hemodialysis or CRRT should receive increased protein, up to a maximum of 2.5 g/kg/day, and protein should not be restricted in patients with renal insufficiency [22]. In this regard, AKI patients on CRRT are more susceptible to a loss of energy reserve. To our knowledge, few studies have examined the relationship between obesity and adverse outcome in this exceptionally highly catabolic group. Considering this background, we sought to investigate whether obesity can exert protective effects against continuously energy-depleting conditions, and found that the obesity paradox indeed exists in these patients.

In general, obesity portends a high risk of developing adverse cardiovascular outcomes. However, contrary to this concept, many epidemiologic studies revealed an inverse relationship between obesity and mortality not only in chronic diseases [23,24] but also in the general population [25]. Recent evidence also indicates that this opposite relationship may hold true for acutely and seriously ill patients under various conditions [5,7,10,26]. In fact, obesity has been considered a significant predictor of AKI. A recent observational cohort study also found that obese patients were at high risk of developing AKI than patients with normal BMI [6]. Conversely, obesity plays a different role in acutely ill patients, even in those having AKI. A previous meta-analyses involving a large number of ICU patients have suggested that patients with a higher BMI are more likely to survive than those with a lower BMI [3,9,11,27]. However, these studies require cautious interpretation because their meta-analyses were statistically heterogeneous and detailed adjustments were not made. Our study has the merit of applying three different multivariable models, taking all potential factors into account. Our database included demographic and laboratory data, comorbidity index, vital sign monitoring, scoring system for the severity of illness, and CRRT prescription. Thus, we adjusted all these factors and found an inverse relationship between BMI and mortality, in agreement with previous studies [5,7–11].

A possible mechanistic link between obesity and a low death rate is largely presumptive. It is generally accepted that fat tissue can function as an energy reservoir; thus, obese patients can tolerate stressful and damaging conditions better than non-obese patients [28]. A recent study by Robinson et al [29] investigated the relationship among obesity, nutritional status, and mortality. In accordance with our study, they showed that high BMI was significantly associated with survival benefit in critical ill patients. Of note, they found malnutrition is less prevalent in obese patients than in underweight and normal patients, suggesting nutrition as a potential factor to explain survival advantage of obesity. Short-term protective cytokine profiles in obese patients [30,31] and other protective effects conferred by higher muscle mass [32] and fat tissue [33] have also been suggested as possible mechanisms responsible for this phenomenon. In aggregates, it can be presumed that obesity provides substantial energy resources and protective effects, and negates the harmful effects caused by inflammation, infection, and cardiovascular events.

Experimental evidence can also explain the favourable effects of obesity in AKI animal models. In a study by Sleeman et al [34], AKI was prevented by feeding a high-fat diet to adult swine that underwent cardiopulmonary bypass. The authors suggested a 'pre-conditioning' effect of obesity against abrupt bursts of hyper-inflammation, which can attenuate pro-inflammatory redox signalling and help maintain renal vascular and tubular homeostasis. Altered adipokine and cytokine profiles from adipose tissue can also play a role. Adiponectin and tumour necrosis factor-α receptors are produced by adipose tissue and can exert protective effects by decreasing inflammation [31].

Several shortcomings should be discussed. First, although we created multivariable models adjusted for many potential factors, this is an observational study with a relatively small sample size. Hence, unknown bias cannot be entirely excluded and our findings need to be interpreted with caution. Second, we used only BMI to evaluate obesity. BMI is easily measured and is the most widely used measure of obesity. However, it does not accurately reflect body composition [35]; thus, BMI is limited in assessing obesity. Other parameters such as abdominal diameter can be added to increase the diagnostic accuracy for obesity. Third, WBC and serum albumin were entered as inflammatory and nutritional markers in this study. Our database had laboratory data for CRP, a better marker of inflammation. However, > 30% of the data were missing and thus cannot be used for analysis. In addition, serum albumin is a well-known nutritional marker [36]; however, it has a limited ability in reflecting nutritional status in critically ill patients because it is also a negative acute-phase reactant [37]. Nevertheless, many studies have shown that high WBC and low serum albumin level are independent predictors of mortality in critically ill patients [38,39]. For this reason, these two parameters were adjusted in a multivariable Cox model. Finally, area under ROC curve for BMI was less than 0.7 in our analysis, suggesting that BMI is not a powerful predictor of mortality. Our study had relatively small sample size and thus further large-scale investigations are needed to verify BMI as a useful predictor of mortality of AKI patients with CRRT.

In conclusion, this study showed that high BMI is associated with survival benefit in AKI patients undergoing CRRT. Although the causality is uncertain, our findings suggest that obesity can function as an energy reservoir in this continuously energy-depleting condition.

Conflicts of interest

All authors have no conflicts of interest to declare.

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