



# The Impact of Disease Severity on Paradoxical Association between Body Mass Index and Mortality in Patients with Acute Kidney Injury Undergoing Continuous Renal Replacement Therapy

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## INTRODUCTION

Association between high body mass index (BMI) and survival benefit is confounded by comorbid conditions such as nutritional status and inflammation. Patients with acute kidney injury (AKI), particularly those receiving continuous renal replacement therapy (CRRT), are highly catabolic and more susceptible to loss of energy. Herein, we evaluated whether disease severity can modify the relationship between BMI and mortality.

## METHODS

We conducted an observational study in 1144 patients who had undergone CRRT owing to various causes of AKI between 2010 and 2014. Patients were categorized into four groups; underweight (<18.5 kg/m<sup>2</sup>), normal (18.5-22.99 kg/m<sup>2</sup>), overweight (23.0-24.99 kg/m<sup>2</sup>), and obesity (≥25 kg/m<sup>2</sup>) according to BMI classification by the Committee of Clinical Practice Guidelines and Korean Society for the Study of Obesity. More severe disease was defined as sepsis-related organ failure assessment (SOFA) score of ≥ a median value of 12. The study endpoint was death that occurred within 30 days after the initiation of CRRT.

## RESULTS

Table 1. Baseline characteristics of patients according to BMI classification

	BMI classification				Total	P-value
	Underweight	Normal	Overweight	Obesity		
Number	99	403	220	422	1144	
BMI (kg/m <sup>2</sup> )*	16.9 (15-17.8)	21.1 (20.1-22.2)	24.1 (13.5-24.5)	27.5 (25.9-29.2)	23.6 (20.9-26.3)	<0.001
Age (yr)	62.3±17.2	65.0±13.6	63.9±14.0	61.3±14.5	63.2±14.4	0.002
Sex (Female, %)	38 (38.4)	162 (40.2)	65 (29.5)	174 (41.3)	439 (38.4)	0.03
DM (n, %)	27 (27.6)	140 (34.7)	79 (35.9)	153 (36.3)	399 (34.9)	0.42
HTN (n, %)	40 (40.4)	217 (53.8)	110 (50.0)	233 (55.3)	600 (52.5)	0.05
MI (n, %)	10 (10.1)	14 (11.7)	17 (7.7)	37 (8.8)	111 (9.7)	0.37
CHF (n, %)	20 (20.2)	71 (17.6)	37 (16.8)	57 (13.5)	185 (16.2)	0.26
CVA (n, %)	7 (7.1)	50 (12.4)	25 (11.4)	35 (8.3)	113 (9.9)	0.08
PVD (n, %)	6 (6.1)	15 (3.7)	12 (5.5)	13 (3.1)	46 (4.0)	0.35
COPD (n, %)	11 (11.0)	33 (8.2)	13 (5.9)	23 (5.5)	80 (7.0)	0.15
Cancer (n, %)						
Solid tumor	18 (18.4)	96 (23.8)	51 (23.3)	93 (22.1)	258 (22.6)	
Metastasis	5 (5.1)	19 (4.7)	18 (8.2)	26 (6.2)	68 (6.0)	0.77
Leukemia	3 (3.1)	19 (4.7)	13 (5.9)	51 (4.5)	51 (4.5)	
Lymphoma	12 (12.2)	37 (9.2)	21 (9.6)	38 (9.0)	108 (9.5)	
CCI score	3.1±2.4	3.2±2.2	3.1±2.2	3.2±2.3	3.2±2.2	0.94
Sepsis (n, %)	74 (74.7)	294 (73.0)	149 (67.7)	280 (66.5)	797 (69.7%)	0.13
Postop AKI (n, %)	3 (3.0)	13 (3.2)	9 (4.1)	26 (6.2)	51 (4.5)	0.18
Cause of CRRT						
Volume overload	8 (8.1)	62 (15.3)	26 (11.8)	64 (15.2)	160 (13.9)	
Metabolic acidosis	26 (26.3)	85 (21.1)	43 (19.5)	88 (20.8)	242 (21.2)	
Hyperkalemia	2 (2.0)	19 (4.7)	12 (5.4)	25 (5.9)	58 (5.1)	0.86
Uremia	13 (13.1)	35 (8.7)	21 (9.5)	46 (10.9)	115 (10.1)	
Oliguria	35 (35.4)	112 (27.5)	54 (24.5)	93 (22.0)	294 (25.7)	
Others	15 (15.2)	90 (22.4)	64 (29.1)	106 (25.1)	275 (24.0)	
CRRT dose (mL/kg)	46.2±16.4	44.6±19.4	41.3±15.1	40.0±15.0	43.4±16.9	<0.001
MAP (mmHg)	76.6±17.5	77.4±14.2	77.3±14.3	77.7±14.5	77.5±14.6	0.92
Creatinine (mg/dL)	2.6±1.5	2.5±1.3	2.9±1.9	2.9±1.7	2.7±1.6	0.001
eGFR (mL/min/1.73m <sup>2</sup> )	33.2±18.0	33.1±22.3	32.7±24.4	29.0±18.8	31.5±21.4	0.03
Albumin (g/dL)	2.5±0.5	2.6±0.6	2.6±0.6	2.6±0.6	2.6±0.6	0.47
Total cholesterol (mg/dL)	111.9±55.9	107.6±48.5	98.1±46.5	108.1±68.9	106.2±57.3	0.56
WBC (x10 <sup>3</sup> /mm <sup>3</sup> )	15.3±25.9	13.8±11.7	14.7±12.8	13.7±9.9	14.1±13.2	0.64
Hemoglobin (g/dL)	9.7±2.4	9.7±2.1	9.4±2.4	9.6±2.3	9.6±2.3	0.56
CRP (mg/L)*	37.1 (10.6-213.8)	87.3 (17.7-171.7)	72.9 (18.6-255.7)	56.7 (14.2-151.8)	67.5 (15.4-164.1)	0.06
Vasopressor (n, %)	68 (68.9)	270 (67.0)	165 (75.3)	314 (74.4)	817 (71.4)	0.15
Ventilator (n, %)	80 (81.0)	345 (85.7)	184 (83.7)	352 (83.5)	961 (84.0)	0.74
SOFA	11.3±3.4	11.8±3.7	12.0±3.5	12.5±3.5	12.1±3.6	0.005
APACHE II	26.4±8.3	27.4±8.0	27.5±9.1	26.7±8.4	27.1±8.4	0.44

\*Data were expressed as a median and interquartile range and compared by Kruskal-Wallis test.

Abbreviations: DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular attack; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; AKI, acute kidney injury; BMI, body mass index; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; WBC, white blood cell; SOFA, sepsis-related organ failure assessment.

Table 2. Length of stay, survival, and mortality according to BMI classification and disease severity

Disease severity	Variables	BMI classification				Total	p-value
		Underweight (N=99)	Normal (N=403)	Overweight (N=220)	Obesity (N=422)		
Low	ICU LOS (d)*	5 (2-14)	12 (5-26)	6.5 (3-14.5)	8 (3-15)	8 (3-18)	0.001
	Hospital LOS (d)*	9.5 (2.3-44.5)	28 (14-63.5)	25.5 (10-48)	22 (9-42)	23 (10-48)	0.002
	Mortality 30 <sup>th</sup> day (n, %)	38 (61.3)	93 (43.5)	66 (53.2)	97 (48.5)	294 (49.0)	0.06
High	ICU LOS (d)*	4 (1-12)	5 (2-14)	5 (3-18)	8 (3-18)	7 (2.5-17)	0.61
	Hospital LOS (d)*	5 (2-18.5)	10 (2-27)	16 (3-37)	18.5 (6-40.8)	15 (4-35)	0.002
	Mortality 30 <sup>th</sup> day (n, %)	32 (86.5)	163 (86.2)	70 (72.9)	142 (64.3)	407 (74.9)	<0.001
Total	ICU LOS (d)*	5 (2-14)	9 (3-20)	6 (3-15)	8 (3-16)	8 (3-17.5)	0.03
	Hospital LOS (d)*	8 (2-30)	20 (7-46)	23 (6.5-45.5)	21 (8-41)	20 (6-43)	0.006
	Mortality 30 <sup>th</sup> day (n, %)	70 (70.7)	256 (63.5)	136 (61.8)	239 (56.8)	701 (61.3)	0.04

\*Data are expressed as a median and interquartile range and compared by Kruskal-Wallis test.

Abbreviations: ICU, intensive care unit; LOS, length of stay.

Table 3. Multivariable Cox regression analyses for 30-day mortality

Disease severity	BMI classification	Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Low	Underweight	1.57 (1.07-2.30)	0.02	1.66 (1.13-2.45)	0.01	1.74 (1.16-2.60)	0.007		
	Normal	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)			
	Overweight	1.44 (1.05-1.99)	0.03	1.48 (1.07-2.04)	0.02	1.41 (1.02-1.94)	0.04	0.99 (0.96-1.01)	0.36
	Obesity	1.31 (0.98-1.76)	0.07	1.35 (1.01-1.82)	0.04	1.28 (0.95-1.72)	0.11		
High	Underweight	1.07 (0.73-1.56)	0.74	1.03 (0.70-1.51)	0.9	1.04 (0.70-1.53)	0.86		
	Normal	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		0.96 (0.94-0.98)	<0.001
	Overweight	0.79 (0.60-1.05)	0.11	0.81 (0.61-1.07)	0.14	0.78 (0.58-1.03)	0.08		
	Obesity	0.63 (0.50-0.79)	<0.001	0.64 (0.51-0.80)	<0.001	0.61 (0.48-0.76)	<0.001		
Total	Underweight	1.27 (0.97-1.66)	0.08	1.27 (0.97-1.67)	0.08	1.28 (0.97-1.68)	0.08		
	Normal	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		0.97 (0.96-0.99)	<0.001
	Overweight	1.02 (0.83-1.26)	0.87	1.02 (0.83-1.27)	0.83	0.99 (0.80-1.22)	0.89		
	Obesity	0.84 (0.70-1.01)	0.06	0.86 (0.72-1.03)	0.1	0.81 (0.68-0.97)	0.03		

Model 1: age, sex, CCI score, septic AKI, MAP, eGFR, 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

The mean age was 63.2 years and 439 (38.4 %) were females. The median BMI was 23.6 (20.9-26.2) kg/m<sup>2</sup>. The obese group were younger and higher SOFA score than normal BMI group. In a multivariable Cox regression analysis, we found a significant interaction between BMI and SOFA score (P < 0.001). Furthermore, obese patients were significantly associated with a lower risk of death as compared to normal BMI group after adjusting confounding factors [hazard ratio (HR), 0.81; 95% confidence interval (CI), 0.68-0.97; P = 0.03]. This association was only evident among patients with high severity (HR, 0.61; 95% CI, 0.48-0.76, P < 0.001). In contrast, in those with low severity, survival benefit of high BMI was lost, whereas underweight was associated with an increased risk of death (HR, 1.74; 95% CI, 1.16-2.60; P = 0.007).

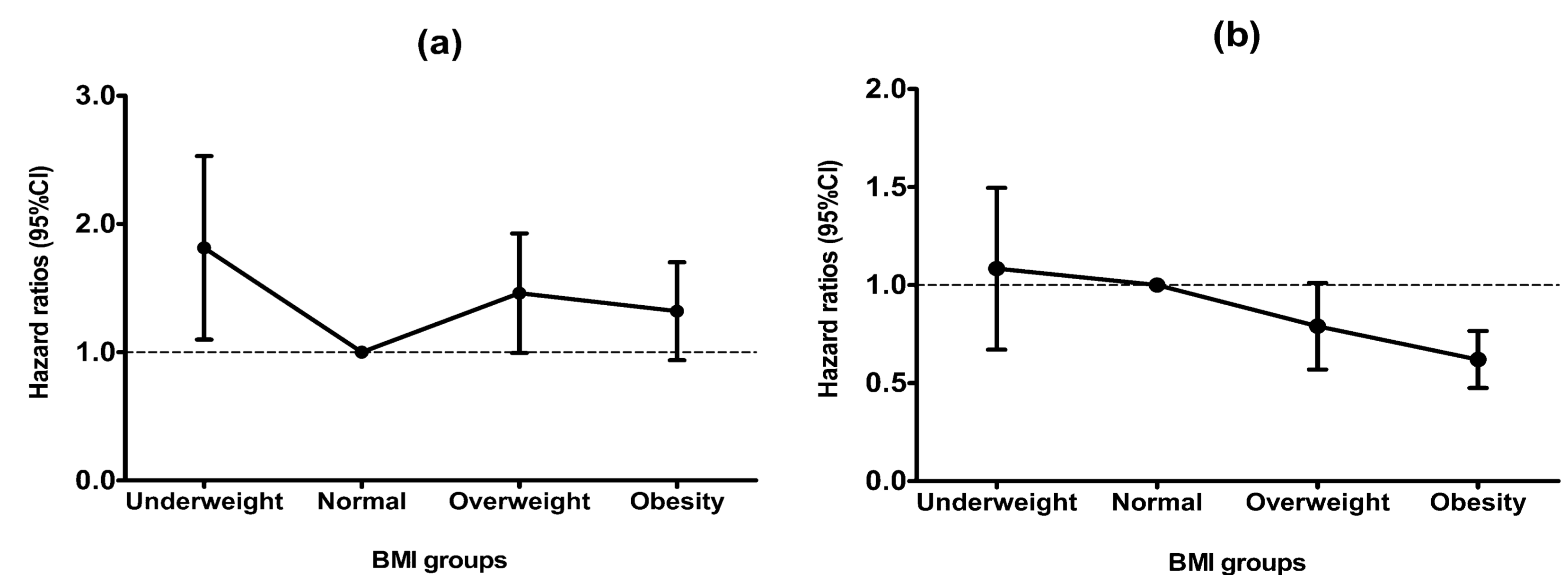


Figure 3. The hazard ratio plot of BMI for 30-day mortality in each subgroup by fully adjusted Cox regression model. BMI was analyzed as a continuous variable. (a) low severity, (b) high severity.

Abbreviations: DM, diabetes mellitus; CVD, cardiovascular disease; BMI, body mass index.

## CONCLUSION

In this study, we found a survival benefit of high BMI in AKI patients undergoing CRRT, particularly in those with more disease severity; the effect was not observed in those with less disease severity.

