Association Between Body Mass Index and Mortality in Patients Requiring Cardiac Critical Care

Soo Jin Na, MD; Taek Kyu Park, MD; Joo Myung Lee, MD; Young Bin Song, MD; Jin-Oh Choi, MD; Joo-Yong Hahn, MD; Jin-Ho Choi, MD; Seung-Hyuk Choi, MD; Hyeon-Cheol Gwon, MD; Chi Ryang Chung, MD; Kyeongman Jeon, MD; Gee Young Suh, MD; Joong Hyun Ahn; Keumhee C Carriere, PhD; Jeong Hoon Yang, MD

Background: Data on the association between obesity and mortality in patients who require acute cardiac care are limited, so we investigated the effect of obesity on clinical outcomes in patients admitted to the cardiac intensive care unit (CICU).

Methods and Results: We reviewed 2,429 eligible patients admitted to the CICU at Samsung Medical Center between January 2012 and December 2015. After excluding 197 patients with low body mass index (BMI) to adjust for the possibility of frailty, patients were divided into 3 categories: normal BMI (n=822), 18.5–22.9 kg/m²; moderate BMI (n=1,050), 23–27.4 kg/m²; and high BMI (n=360), ≥27.5 kg/m². The primary outcome was 28-day mortality. Overall, 124 (2.6%) of 2,232 patients died during 28-day follow-up after CICU admission. The 28-day mortality was numerically lower in the moderate (4.5%) and high (5.3%) BMI groups than in the normal BMI group (7.1%), but the difference was not statistically significant (P=0.052). After multivariable adjustment, the moderate and high BMI categories were not significant predictors of primary outcome (adjusted hazard ratio [HR] 0.74, 95% CI 0.50–1.09, P=0.127 and adjusted HR 0.80, 95% CI 0.47–1.36, P=0.404, respectively). However, Acute Physiology and Chronic Health Evaluation II scores, liver cirrhosis, malignancy, history of cardiac arrest, and need for organ support treatment were independent predictors of 28-day mortality.

Conclusions: Obesity was not associated with short-term mortality in patients requiring cardiac critical care.

Key Words: Cardiac critical care; Death; Obesity

Obesity is a well-known major risk factor and is related to several comorbid conditions that predispose to cardiovascular disease, the number one cause of death globally. In the general population, obesity is associated with increased risk of death from all causes and cardiovascular disease regardless of sex or age. Although still controversial, some studies conducted in critically ill patients with conditions such as septic shock and acute respiratory distress syndrome have reported reduced mortality in overweight and/or obese patients, which is known as the ‘obesity paradox’. One possibility for inconsistent results regarding the obesity-mortality relationship may be that disease severity status is not properly controlled, particularly in intensive care unit (ICU) patients. In the field of cardiac critical care, previous studies of the clinical impact of obesity have focused on acute myocardial infarction and acute heart failure. To date, limited data on the association between obesity and mortality in the overall patients who require acute cardiac critical care are available. Therefore, we investigated the association of body mass index (BMI) with clinical outcomes in patients admitted to a cardiac ICU (CICU).

Methods

Study Population
We retrospectively reviewed 2,929 consecutive patients admitted to the CICU at Samsung Medical Center, a tertiary-care center in Seoul, Korea, between January 2012 and December 2015. Patients who had no diagnosis of cardiovascular disease and no available BMI were excluded. The 2,429 eligible patients were classified into 4 categories...
Results

Baseline Clinical Characteristics
The baseline characteristics of 2,232 patients according to BMI group are shown in Table 1. Patients in the normal BMI group were older than in the moderate and high BMI groups; the median age of each group was 68, 65, and 61 years, respectively (P<0.001). The normal BMI group also had higher incidences of chronic kidney disease, liver cirrhosis, malignancy, and acute heart failure as the reason for admission compared with the other groups. Acute coronary syndrome was the primary reason for CICU admission, accounting for 52.6% of admissions, followed by heart failure at 22.5%. The mean APACHE II score on the 1st day in the CICU in the normal BMI group was 11 (7–17) and was significantly higher than the moderate and high BMI groups, which were 8 (5–15) and 8 (5–14), respectively (P<0.001).
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Post-cardiac arrest, use of vasoactive drugs, mechanical ventilation, and continuous renal replacement therapy were independent predictors of 28-day mortality (Table 3). We also performed multivariable analysis using the logistic regression method for sensitivity analysis (Supplementary Table 1) and the results were similar with Cox regression analysis. The median hospital length of stay was 7, 5, and 5 days in the normal, moderate and high BMI groups, respectively (P<0.001).

In patients with acute heart failure, 28-day (10.8% vs. 10.4% vs. 8.6%, P=0.86), CICU (9.2% vs. 9.8% vs. 10.0%, P=0.06), and hospital (113.3% vs. 14.0% vs. 111.4%, P=0.86) mortality were not different among the 3 groups (Figure 2). Also, multivariable analysis demonstrated that the moderate and high BMI groups were not associated with 28-day mortality in any of the subgroups (Supplementary Table 2). There was no difference in 28-day (5.7% vs. 3.3% vs. 5.0, P=0.18), CICU (4.3%% vs. 3.5% vs. 4.0%, P=0.79), and hospital (7.0% vs. 3.8% vs. 5.0%, P=0.08) mortality according to BMI in patients with acute coronary syndrome.

### Table 1. Baseline Characteristics of Patients Admitted to CICU

| Variables                                      | Normal BMI (n=822) | Moderate BMI (n=1,050) | High BMI (n=360) | P value |
|------------------------------------------------|--------------------|------------------------|------------------|---------|
| Age, years                                      | 68 (56–76)         | 65 (55–74)             | 61 (49–71)       | <0.001  |
| Male                                           | 491 (59.7)         | 758 (72.2)             | 244 (67.8)       | <0.001  |
| Comorbidities                                   |                    |                        |                  |         |
| Body mass index, kg/m²                          | 21.4 (20.4–22.1)   | 24.8 (23.9–26.0)       | 29.4 (28.3–31.2) | <0.001  |
| Diabetes mellitus                               | 234 (28.5)         | 332 (31.6)             | 119 (33.1)       | 0.19    |
| Hypertension                                    | 388 (47.2)         | 554 (52.8)             | 207 (57.5)       | 0.003   |
| Cerebrovascular disease                         | 58 (7.1)           | 53 (5.0)               | 21 (5.8)         | 0.19    |
| Chronic kidney disease                          | 114 (13.9)         | 104 (9.9)              | 30 (8.3)         | 0.005   |
| Chronic kidney disease without dialysis         | 87 (76.3)          | 78 (75.0)              | 25 (83.3)        |         |
| Chronic kidney disease with dialysis            | 27 (23.7)          | 26 (25.0)              | 5 (16.7)         |         |
| Liver cirrhosis                                 | 32 (3.9)           | 21 (2.0)               | 6 (1.7)          | 0.02    |
| Malignancy                                      | 72 (8.8)           | 60 (5.7)               | 13 (3.6)         | 0.002   |
| Reason for admission                            |                    |                        |                  |         |
| Acute coronary syndrome                         | 370 (45.0)         | 606 (57.7)             | 199 (55.3)       | <0.001  |
| Heart failure                                   | 240 (29.2)         | 193 (18.4)             | 70 (19.4)        | <0.001  |
| Heart failure with reduced ejection fraction    |                    |                        |                  |         |
| Ischemic cardiomyopathy                         | 63 (35.6)          | 57 (41.9)              | 20 (40.0)        |         |
| Dilated cardiomyopathy                          | 65 (36.7)          | 45 (33.1)              | 16 (32.0)        |         |
| Valvular heart diseasea                         | 25 (14.1)          | 20 (14.7)              | 9 (18.0)         |         |
| Myocarditis with or without pericarditis        | 13 (7.3)           | 17 (12.5)              | 5 (10.0)         |         |
| Stress-induced cardiomyopathyb                  | 12 (6.8)           | 13 (9.6)               | 7 (14.0)         |         |
| Hypertrophic or restrictive cardiomyopathy      | 12 (6.8)           | 6 (4.4)                | 2 (4.0)          |         |
| Heart failure with preserved ejection fraction  | 50 (28.2)          | 35 (25.7)              | 11 (22.0)        |         |
| Arrhythmia                                      | 118 (14.4)         | 134 (12.8)             | 41 (11.4)        | 0.339   |
| Acute aortic syndrome, type B                   | 49 (6.0)           | 65 (6.2)               | 26 (7.2)         | 0.705   |
| Pericardial disease                             | 16 (1.9)           | 21 (2.0)               | 8 (2.2)          | 0.952   |
| Pulmonary thromboembolism                       | 14 (1.7)           | 21 (2.0)               | 14 (3.9)         | 0.052   |
| Infective endocarditis                          | 15 (1.8)           | 10 (1.0)               | 2 (0.6)          | 0.107   |
| Post-cardiac arrest                             | 47 (5.7)           | 68 (6.5)               | 25 (6.9)         | 0.68    |
| APACHE II score                                 | 11 (7–17)          | 8 (5–15)               | 8 (5–14)         | <0.001  |

Values are median with interquartile range or n (%). aValvular heart disease includes congenital heart disease. bStress-induced cardiomyopathy includes tachycardia-induced cardiomyopathy and peripartum cardiomyopathy. APACHE II, Acute Physiology and Chronic Health Evaluation II; CICU, cardiac intensive care unit.

### In-Hospital Management and Clinical Outcomes

In normal BMI group most frequently required inotropes or vaspressors (34.5% vs. 23.3% vs. 25.6%, P<0.001) (Table 2). There was no significant difference among the 3 BMI groups in the frequency of use of organ support devices, such as intra-aortic balloon pump, extracorporeal membrane oxygenation, mechanical ventilator, and continuous renal replacement therapy. Patients were followed for a median of 650 days (227–1,104) or until death. A total of 124 (5.6%) patients died during the 28-day follow-up. The 28-day mortality rates according to BMI were 7.1%, 4.5%, and 5.3% in the normal, moderate and high BMI groups, respectively (P=0.052). In-hospital death was also lower in the moderate and high BMI groups than in the normal BMI group, but the difference was not statistically significant (8.5% vs. 5.8% vs. 5.8%, P=0.051). Cox regression analysis revealed that the unadjusted HR of moderate and high BMI groups for 28-day mortality was 0.62 (95% CI, 0.41–0.94; P=0.024) and 0.80 (95% CI, 0.47–1.38; P=0.429), respectively, and the adjusted HR was 0.80 (95% CI, 0.52–1.21; P=0.291) and 0.95 (95% CI, 0.55–1.65; P=0.861) (Table 3). After multivariable adjustment, APACHE II scores, liver cirrhosis, malignancy, history of post-cardiac arrest, use of vasoactive drugs, mechanical ventilation, and continuous renal replacement therapy were independent predictors of 28-day mortality (Table 3).
Table 2. In-Hospital Management and Clinical Outcomes of Patients Admitted to CICU

| Variables                             | Normal BMI (n=822) | Moderate BMI (n=1,050) | High BMI (n=360) | P value |
|---------------------------------------|--------------------|------------------------|------------------|---------|
| In-hospital managements               |                    |                        |                  |         |
| Inotropes or vasopressors             | 284 (34.5)         | 245 (23.3)             | 92 (25.6)        | <0.001  |
| Intra-aortic balloon pump             | 46 (5.6)           | 40 (3.8)               | 12 (3.3)         | 0.10    |
| Extracorporeal membrane oxygenation   | 40 (4.9)           | 64 (6.1)               | 24 (6.7)         | 0.37    |
| Mechanical ventilation               | 153 (18.6)         | 153 (14.6)             | 61 (16.9)        | 0.06    |
| Continuous renal replacement therapy  | 81 (9.9)           | 77 (7.3)               | 27 (7.5)         | 0.12    |
| Clinical outcomes                     |                    |                        |                  |         |
| Mortality                             |                    |                        |                  |         |
| CICU mortality                        | 48 (5.8)           | 47 (4.5)               | 17 (4.7)         | 0.39    |
| Cardiac death                         | 30 (3.6)           | 36 (3.4)               | 15 (4.2)         | 0.811   |
| Non-cardiac death                     | 18 (2.2)           | 11 (1.0)               | 2 (0.6)          | 0.037   |
| Hospital mortality                    | 70 (8.5)           | 61 (5.8)               | 21 (5.8)         | 0.05    |
| Cardiac death                         | 42 (5.1)           | 43 (4.1)               | 18 (5.0)         | 0.543   |
| Non-cardiac death                     | 28 (3.4)           | 18 (1.7)               | 3 (0.8)          | 0.007   |
| 28-day mortality                      | 58 (7.1)           | 47 (4.5)               | 19 (5.3)         | 0.052   |
| Cardiac death                         | 39 (4.7)           | 36 (3.4)               | 17 (4.7)         | 0.299   |
| Non-cardiac death                     | 19 (2.3)           | 11 (1.0)               | 2 (0.6)          | 0.023   |
| Length of stay                        |                    |                        |                  |         |
| CICU length of stay                   | 2 (1–4)            | 2 (1–3)                | 2 (1–3)          | <0.001  |
| Hospital length of stay               | 7 (4–15)           | 5 (3–10)               | 5 (3–10)         | <0.001  |

Values are median with interquartile range or n (%). CICU, cardiac intensive care unit.

Table 3. Predictors of 28-Day Mortality in Patients According to Disease Severity

|                     | Univariable                  | Multivariable                 |
|---------------------|------------------------------|-------------------------------|
|                     | HR   | 95% CI | P value | HR   | 95% CI | P value |
| Body mass indexa    | –    | –      | –       | –    | –      | –       |
| Moderate (BMI 23–27.4 kg/m²) | 0.62 | 0.41–0.94 | 0.024 | 0.80 | 0.52–1.21 | 0.291 |
| High (BMI ≥27.5 kg/m²) | 0.80 | 0.47–1.38 | 0.429 | 0.95 | 0.55–1.65 | 0.861 |
| Age ≥65 years       | 1.49 | 1.01–2.19 | 0.044 | 1.16 | 0.77–1.75 | 0.481 |
| APACHE II score     | 1.16 | 1.13–1.18 | <0.001 | 1.04 | 1.01–1.07 | 0.020 |
| Liver cirrhosis     | 4.23 | 2.27–7.89 | <0.001 | 1.91 | 0.99–3.68 | 0.055 |
| Malignancy          | 2.25 | 1.31–3.89 | 0.003 | 1.73 | 0.99–3.01 | 0.055 |
| Main reason for admissionb | –    | –      | –       | –    | –      | –       |
| Acute heart failure | 2.79 | 1.85–4.21 | <0.001 | 1.54 | 1.00–2.37 | 0.050 |
| Other               | 0.90 | 0.52–1.56 | 0.702 | 0.88 | 0.50–1.55 | 0.663 |
| Post-cardiac arrest | 8.40 | 5.60–12.59 | <0.001 | 1.85 | 1.17–2.94 | 0.009 |
| Vasoactive drugs    | 24.85 | 13.33–46.32 | <0.001 | 6.48 | 3.22–13.03 | <0.001 |
| Mechanical ventilation | 13.27 | 8.82–19.95 | <0.001 | 2.04 | 1.22–3.42 | 0.007 |
| Continuous renal replacement therapy | 17.05 | 11.69–24.87 | <0.001 | 2.74 | 1.73–4.36 | <0.001 |

*Reference group is normal BMI (18.5–22.9 kg/m²). **Reference group is all other cardiovascular diseases except heart failure. APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; HR, hazard ratio.

Discussion

We investigated whether the obesity paradox exists in patients with cardiovascular disease requiring cardiac intensive care. The major findings of this study were: (1) the moderate and high BMI groups were relatively younger and had lower severity scores than the normal BMI group; (2) the 28-day mortality was not significantly different among the normal, moderate and high BMI groups. Furthermore, both moderate and high BMI were not prognostic predictors for 28-day mortality after adjusting for relevant factors; (3) Acute Physiology and Chronic Health Evaluation II scores, liver cirrhosis, malignancy, history of cardiac arrest, and need for organ support treatment were independent predictors of 28-day mortality.

In general, obese patients may be at a disadvantage in critical care because of procedural difficulties related to anatomy or altered drug doses in plasma resulting from changes in pharmacokinetics. However, as shown in patients with chronic illnesses such as chronic obstructive pulmonary disease, endstage renal disease, and chronic heart failure, several studies of patients in medical and surgical ICUs have suggested the existence of an obesity paradox in critically ill patients by demonstrating the
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There are some differences between our findings and results of previous studies (Supplementary Table 3). In this study, we only included non-surgical patients with cardiovascular disease, but previous studies included either only surgical patients or both medical and surgical patients. Furthermore, admission type was an independent factor associated with death in one study. Although direct comparison of severity of illness among patients included in each study is difficult because each study used different scoring systems, both the proportion of patients receiving organ support and mortality rates were much lower in our study than in previous studies. We consider that the differences in patient characteristics, interventions, and mortality are partly related to the obesity paradox, but further studies are needed to prove our assumption. Previous studies have suggested several theories for the obesity paradox in critically ill patients admitted to the ICU. One is that obese patients have a nutritional reserve that helps to overcome the severe catabolic state associated with critical illness. Stapleton et al demonstrated an altered inflammatory response with lower level pro-inflammatory cytokines in patients who were obese and had acute lung injury, the opposite to people who were healthy and obese. This might be related to the obesity paradox, although the mechanism is unclear.

Abdulla and colleagues performed a pooled analysis of 5 registries that included high-risk patients with myocardial infarction or chronic heart failure who had mortality rates greater than 50% and also did not show evidence of any protective effect of obesity. Conversely, a recent study in Japan showed better prognosis of overweight patients compared with normal and underweight patients who had severely decompensated acute heart failure and were admitted to ICU. Similar to other areas of critical illness, the presence of the obesity paradox in cardiac critical care remains contradictory. In previous studies, the overweight or obesity group was often relatively younger and had lower severity scores compared with the normal weight group, which may affect clinical outcomes. Recently published research has shown that the trend in observed unadjusted mortality in different obesity classes is similar to that of illness severity. In the present study, we identified that specific underlying diseases and organ support treatments were related to 28-day mortality, rather than BMI or diagnosis at admission. Overt organ dysfunction or failure to overwhelm the protective effect of obesity is based on nutritional support and anti-inflammatory cytokines in patients requiring acute cardiac critical care regardless of diagnosis.

Study Limitations
First, because this study was conducted as a retrospective cohort study, there is a potential risk of confounding and bias. Second, a heterogeneous group of patients requiring acute cardiac critical care was included, rather than selecting patients with specific cardiovascular diseases. Therefore, the APACHE II score was used as a severity scoring system in all included patients. Although the APACHE II score has been validated in ICU patients with various cardiovascular diseases, it remains to be determined whether it adequately reflects severity. Third, BMI is calculated with only height and weight and does not accurately reflect body composition. Therefore, BMI could be overestimated in the setting of volume overload in patients with acute decompensated heart failure. Novel methods that address these concerns are needed to more accurately elucidate the effect of BMI.

Conclusions
Obesity may be not associated with survival benefit in patients requiring acute cardiac critical care, particularly after adjusting for the relatively young age and low APACHE II score of the obese patients.

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sibility for both its integrity and the accuracy of its analysis. S.J.N., J.H.Y., C.R.C., K.J., and G.Y.S. contributed to study conception and design. S.J.N., J.H.Y., J.M.L., Y.B.S., J.C.C., J.Y.H., J.H.C., S.H.C., and H.C.G. contributed to acquisition of data; S.J.N., J.H.Y., J.H.A. and K.C.C. contributed to analysis and interpretation of data; S.J.N. and J.H.Y. drafted the manuscript; all authors participated in critical revision and approved the final version of the manuscript.

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Supplementary Files
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