Summary

Obesity is a well-known risk factor for cardiovascular diseases including heart failure (HF). However, some literatures suggested better clinical outcomes in obese patients with HF. Since higher body mass index (BMI) levels of HF patients were significantly associated with younger age, the impact of obesity on clinical outcomes in non-elderly HF patients should be elucidated.

Consecutive 155 non-elderly acute decompensated HF patients (< 60-year-old) who admitted to our institution between 2009 and 2013 were included. Those patients were divided into the two groups according to the BMI: the obesity group (BMI ≥ 25 kg/m², n = 81) and the non-obesity group (BMI < 25 kg/m², n = 74). The primary composite outcome of this study was defined as re-admission due to HF and all-cause death.

The primary composite outcome was less frequently observed in the obesity group as compared with the non-obesity group (Hazard ratio [HR] 0.50, 95% confidence interval [CI] 0.26-0.95, P = 0.03). Re-admission due to HF was significantly less in the obesity group than in the non-obesity group (HR 0.44, 95% CI 0.23-0.86, P = 0.02), whereas all-cause death was not significantly different between the groups (P = 0.44).

The mid-term outcomes in non-elderly HF patients with obesity were better as compared with non-elderly HF patients without obesity, which supports obesity paradox in this specific population.

Key words: Obesity paradox, Body mass index, Sleep disordered breathing, B-type natriuretic peptide

Methods

Study design and participants: This was a single-center, retrospective, observational study. Consecutive 155 non-elderly acute decompensated HF patients (< 60-year-old) who admitted to our institution between 2009 and 2013 were included. Those patients were divided into the two groups according to the BMI: the obesity group (BMI ≥ 25 kg/m², n = 81) and the non-obesity group (BMI < 25 kg/m², n = 74). We used BMI 25 kg/m² as a cut off for obesity according to the recommendation of the Japan Society for the Study of Obesity (JASSO). Clinical follow-up was performed via patients’ medical records. The primary composite outcome of this study was defined as re-admission due to HF and all-cause death. The event-free time was calculated from the date of admission until the end point or last follow-up date. This study was approved by the institutional review board. Written informed consent was waived because of the retrospective study design.

Definition of characteristics: We compared baseline characteristics between the two groups such as cause of HF, echocardiographic parameters, laboratory data, sleep-disordered breathing (SDB) data, and medications. The diagnosis of HF was performed by cardiologists based on the criteria of the Framingham study. The cause of HF was estimated from the medical records. Hypertension was defined as the recent use of antihypertensive drugs, a

O besity is a well-known risk factor for cardiovascular diseases including heart failure (HF). As compared with the normal body mass index population (BMI < 22.5 kg/m²), obesity (BMI > 30 kg/m²) in midlife had approximately 1.6 to 2.6 times greater risk for the development of future HF after adjusting other risk factors. However, the impact of obesity on long-term outcomes in HF patients remains controversial. Some literatures showed an inverse relationship between obesity and mortality in patients with HF, whereas most of these studies focused on elderly HF patients. Since higher BMI levels of HF patients were significantly associated with younger age, the impact of obesity on clinical outcomes in non-elderly HF patients should also be elucidated. Furthermore, clinical characteristics stratified by the presence of obesity in non-elderly HF patients have yet to be revealed. The purpose of this study was to investigate the clinical characteristics and the mid-term outcomes of obesity in patients with HF among Japanese non-elderly population.

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### Table 1. The Comparison of Baseline Characteristics between the Obesity Group and the Non-Obesity Group

| Demographics | All (n = 155) | Obesity group (n = 81) | Non-obesity group (n = 74) | P  |
|--------------|--------------|------------------------|---------------------------|----|
| Age, years (mean ± SD) | 47.4 ± 8.6 | 47.2 ± 8.4 | 47.7 ± 8.7 | 0.64 |
| Male, % | 79.4 | 86.4 | 71.6 | 0.02 |
| BMI, kg/m² (mean ± SD) | 26.8 ± 6.1 | 31.4 ± 4.5 | 21.7 ± 2.5 | <0.001 |
| Causes of heart failure, % | | | | 0.20 |
| Ischemic heart disease | 21.3 | 22.2 | 20.3 | |
| Hypertensive heart disease | 25.8 | 29.6 | 21.6 | |
| Valvular heart disease | 5.2 | 4.9 | 5.4 | |
| Dilated cardiomyopathy | 29.7 | 32.1 | 27.0 | |
| Others | 18.1 | 11.1 | 25.7 | |
| Comorbidities, % | | | | |
| History of heart failure admission | 33.5 | 30.9 | 36.5 | 0.11 |
| Hypertension | 76.1 | 87.7 | 63.5 | <0.001 |
| Diabetes mellitus | 29.0 | 35.8 | 21.6 | 0.91 |
| Dyslipidemia | 40.6 | 43.2 | 37.8 | 0.50 |
| Hemodialysis | 1.9 | 1.2 | 2.7 | 0.61 |
| Hyperuricemia | 73.5 | 74.1 | 73.0 | 0.63 |
| Atrial fibrillation | 16.1 | 16.0 | 16.2 | 0.98 |
| Coronary artery disease | 15.5 | 16.0 | 14.9 | 0.84 |
| Laboratory data at admission | | | | |
| Albumin, g/dL | 3.8 ± 0.6 | 3.8 ± 0.5 | 3.7 ± 0.6 | 0.26 |
| Bilirubin, mg/dL | 1.0 ± 0.6 | 1.1 ± 0.7 | 0.9 ± 0.6 | 0.23 |
| Hemoglobin, g/dL | 14.2 ± 2.3 | 14.5 ± 2.2 | 13.8 ± 2.3 | 0.04 |
| Urea nitrogen, mg/dL | 20.3 ± 10.3 | 19.2 ± 8.3 | 21.5 ± 12.0 | 0.36 |
| Total cholesterol, mg/dL | 180.2 ± 46.4 | 177.6 ± 45.4 | 183.0 ± 47.3 | 0.35 |
| LDL-cholesterol, mg/dL | 114.0 ± 35.5 | 113.9 ± 34.6 | 114.1 ± 36.5 | 0.77 |
| Triglyceride, mg/dL | 135.3 ± 105.3 | 132.3 ± 91.1 | 126.2 ± 105.2 | 0.38 |
| Total laboratory data at admission | | | | |
| Vital signs at admission | | | | |
| Systolic BP, mmHg | 131.3 ± 22.7 | 135.9 ± 22.2 | 126.4 ± 21.1 | 0.10 |
| Diastolic BP, mmHg | 86.5 ± 22.7 | 91.0 ± 22.2 | 81.6 ± 22.1 | 0.01 |
| Echocardiographic parameters | | | | |
| EF, % (mean ± SD) | 34.6 ± 14.8 | 34.1 ± 13.1 | 35.1 ± 16.4 | 0.46 |
| Sleep disordered breathing | | | | |
| Executive rate of apnea monitor, % | 64.9 | 75.3 | 53.4 | <0.01 |
| Apnea Hypopnea Index | 21.0 ± 17.9 | 25.5 ± 19.2 | 14.0 ± 13.1 | <0.01 |
| Central sleep apnea, % | 26.0 | 28.5 | 23.6 | 1.00 |
| Obstructive sleep apnea, % | 10.7 | 13.1 | 8.2 | 0.12 |
| Mixed sleep apnea, % | 6.9 | 7.9 | 6.0 | 0.25 |
| Medications use at hospital discharge | | | | |
| ACE-I, % | 54.8 | 60.5 | 48.6 | 0.14 |
| ARB, % | 25.8 | 28.4 | 23.0 | 0.44 |
| β blocker, % | 87.7 | 91.4 | 83.8 | 0.15 |
| Calcium antagonist blocker, % | 16.1 | 19.3 | 12.2 | 0.20 |
| Aldosterone antagonist, % | 50.7 | 63.0 | 54.1 | 0.42 |
| Diuretics, % | 78.7 | 84.0 | 73.0 | 0.06 |
| Dihydropyridine, % | 6.5 | 3.7 | 9.5 | 0.20 |
| Nitrate, % | 14.2 | 16.0 | 12.2 | 0.49 |
| Values are percentages or means ± SD. BMI indicates body mass index; EF, ejection fraction; HFrEF, heart failure with preserved ejection fraction; eGFR, estimated glomerular filtration rate; LDL-cholesterol, low-density lipoprotein cholesterol; BP, blood pressure; ACE-I, angiotensin converting enzyme inhibitor; and ARB, Angiotensin II receptor blocker.
systolic blood pressure >140 mmHg, and/or a diastolic pressure > 90 mmHg. Diabetes mellitus was defined on the basis of the diagnostic criteria of diabetes mellitus in Japan.10 Dyslipidemia was defined as the recent use of cholesterol lowering drugs, total cholesterol value of > 220 mg/dL, and/or a low-density lipoprotein cholesterol value of > 140 mg/dL. Hyperuricemia was defined as the recent use of blood uric acid lowering drugs and/or uric acid value of > 7.0 mg/dL defined by the Japanese Society of Gout and Nucleic Acid Metabolism.11 Coronary artery disease was defined as past history of old myocardial infarction, percutaneous coronary intervention, and/or coronary artery bypass grafting. Ejection Fraction (EF) was measured by Teichholz method using echocardiography. When the value of EF measured by Teichholz method was not obtained, the value of EF measured by left ventriculography or myocardial scintigraphy was used as a substitution. HF with preserved ejection fraction (HFpEF) was defined as EF ≥ 50%.

**Statistical analysis:** Data were expressed as mean ± standard deviation (SD). Patients’ characteristics and medications were compared between the groups using the Pearson chi-square test for categorical variables, Student’s t-test for normally distributed continuous variables, and the Mann-Whitney U-test for non-normally distributed continuous variables. Univariate Cox analyses were performed between all clinical variables and cardiac events in each group. Cardiac events were defined as re-admission due to HF and cardiac death. Multivariate Cox regression analysis was applied to the variables that had significant univariate predictive values (P < 0.05). The survival curves of the two groups were drawn using Kaplan-Meier methods, and log-rank test was used to calculate statistical differences. The Cox proportional hazard models were performed to assess the association between the obesity group and long-term outcomes even after controlling age and sex. Hazard ratios (HR) and the 95% confidence interval (CI) were calculated. P < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software version 18.0.0.

## Results

**Patient backgrounds of HF in non-elderly:** The comparison of baseline characteristics between the groups is shown in Table I. The mean age was not significantly different between the two groups (the obesity group: 47.2 ± 8.4 years, the non-obesity group: 47.7 ± 8.7 years, P = 0.64). The mean BMI of the obesity group and non-obesity group were 31.4 ± 4.5 kg/m² and 21.7 ± 2.5 kg/m², respectively. The prevalence of hypertension was significantly greater in the obesity group (87.7%) than in the non-obesity group (63.5%) (P < 0.001). The levels of plasma B-type natriuretic peptide (BNP) were significantly lower in the obesity group (758.4 ± 765.8 pg/mL) than in the non-obesity group (1099.2 ± 968.0 pg/mL) (P = 0.03). There was no statistical significance in the level of serum triglyceride between the two groups (the obesity group: 132.3 ± 91.1 mg/dL, the non-obesity group: 126.2 ± 105.2 mg/dL, P = 0.38). The median date of measurements for EF was the 8th hospital day. The mean EF and the proportion of HFpEF were not significantly different between the two groups. The apnea-hypopnea index (AHI) was greater in the obesity group (25.5 ± 19.2 /hour) than in non-obesity group (14.0 ± 13.1 /hour) (P < 0.01).

**Mortality and re-admission due to HF after discharge:** The mean follow-up period was 884 ± 684 days. During the follow-up period, there were 11 cardiac deaths (4 in the obesity group and 7 in the non-obesity group) and 2 non-cardiac deaths. The causes of them consisted of 8 pump failure (2 in the obesity group and 6 in the non-obesity group), 2 ventricular fibrillation (in each group), and 1 nocturnal sudden death (in the obesity group). The causes of non-cardiac deaths were 1 cancer (non-obesity group) and 1 sepsis (obesity group). There were 38 re-admissions due to HF. Multivariate Cox regression analyses were applied to the variables that had significant univariate predictive values (P < 0.05) in each group. In the obesity group, hypertension (HR 0.17, 95%CI 0.05-0.57, P < 0.01) and serum creatinine level (HR 1.10, 95%CI 1.03-1.18, P < 0.01) were the independent predictor of cardiac deaths. In the non-obesity group, hypertension (HR 0.40, 95% CI 0.17-0.95, P = 0.04) and hyperuricemia (HR 0.37, 95%CI 0.16-0.86, P = 0.02) were the predictors of cardiac events (Table II). The Kaplan-Meier curves of the two groups for the primary composite outcome, all-cause death, and re-admission due to HF are shown in the Figure. The primary composite outcome was significantly less in the obesity group than in the non-obesity group (log-rank, P = 0.047), and re-admission due to HF was also significantly less in the obesity group than in the non-obesity group (log-rank, P = 0.02). The Cox proportional hazard analysis showed that the primary composite outcome was less frequently observed in the obesity group as compared with the non-obesity group after controlling age and sex (HR 0.50, 95% CI 0.26-0.95, P = 0.03). Re-admission due to HF was significantly less in the obesity group than in the non-obesity group (HR 0.44, 95% CI 0.23-0.86, P = 0.02), whereas all-cause death was not significantly different between the groups (P = 0.16) (Table III).

**Discussion**

The present study focused on non-elderly population and compared the patients’ characteristics and the clinical outcomes between the obesity group and the non-obesity group. We showed that the prevalence of hypertension and the value of AHI were greater in the obesity group, whereas the levels of AHI and BNP were significantly lower in the
obesity group. The primary composite outcome was less frequently observed in the obesity group as compared with the non-obesity group, suggesting obesity paradox in this study population.

**Obesity paradox:** There have been some hypotheses explaining the mechanism of the obesity paradox in HF, but
The present study demonstrated that the levels of BNP were significantly lower in the obesity group. BNP levels were generally affected by extra-cardiac factors including renal disease, atrial fibrillation, and obesity. Iwanaga, et al. showed that obese patients had lower BNP levels compared with non-obese patients even with similar hemodynamic severities of HF. Since natriuretic peptides including BNP have some compensatory functions for HF including enhanced diuresis and decreasing vascular resistance, low BNP levels might contribute to the development of HF in obese patients. Furthermore, BNP has been shown to have some metabolic functions including activation of lipolysis, which might lead to weight loss or cachexia in advanced HF patients. Therefore, BNP may be associated with the mechanism of obesity paradox. Further studies are needed to understand the relationship between BNP and obesity patients with HF.

**Study limitations:** There are several limitations in the present study. First, as the present study was a single-center, retrospective, observational study, there is a risk of selection bias. Second, we divided study patients into only two groups because the total study population was small. In fact, the obese group included 3 extremely obese patients (BMI ≥ 40 kg/m²), whereas the non-obese group included 5 lean patients (BMI < 18.5 kg/m²). Since the U-shaped relationship between BMI and outcomes of HF patients was demonstrated, these extremely obese and lean patients might have a significant impact on outcomes in each group. Third, BMI at hospital admission might not reflect the patients’ usual body weight because patients with acute decompensated HF tend to have fluid retention at admission. Fourth, as the result of multivariate Cox regression analysis, there were only a few predictors of cardiac events in each group. The cause of this result might be the small sample size of this study. Larger sample size might be needed.

**Conclusion**

The mid-term outcomes in non-elderly HF patients with obesity were better as compared with non-elderly HF patients without obesity, which supports obesity paradox in this specific population.

**Disclosures**

**Conflicts of interest:** The authors declare that there is no conflict of interest.

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