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A reduction of BMI predicts the risk of rehospitalization and cardiac death in non-obese patients with heart failure

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ABSTRACT

Background: Low body mass index (BMI) has been associated with decreased survival in patients with heart failure (HF), although Obesity is an important risk factor for cardiovascular disease. HF patients with a relatively higher BMI tend to live longer, which is known as "Obesity Paradox". However, cardiac cachexia is another determinant of prognosis in HF patients. This study investigated whether a change in BMI is associated with either prognosis or frequency of hospitalizations in patients with HF.

Methods: We correlated changes in BMI to prognosis and frequency of hospitalizations in patients who were hospitalized for decompensated HF. A total of 971 HF patients were initially evaluated, and 81 patients with repeat HF admissions were included.

Results: The average change in BMI was -0.05 ± 0.15, -0.87 ± 0.56, -1.03 ± 0.34, and -1.97 ± 0.33 in patients who were hospitalized twice, three times, four times, and over five times, respectively. The reduction in BMI correlated with the frequency of hospitalizations ($P < 0.01$). We compared patients with increased BMI (group I, $n = 38$) versus decreased BMI (group D, $n = 43$) between the first and second discharge. The rate of hospitalization in group D was higher than in group I, and group D had a lower survival rate. The reduction of BMI was a significant and independent risk factor for cardiac death (HR, 4.17; 95% CI, 1.53 to 14.6).

Conclusions: Losing body weight in HF patients was a significant predictive factor of the frequency of hospitalizations and increased mortality.

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1. Introduction

Obesity is associated with the metabolic syndrome, which includes hypertension, diabetes, and dyslipidemia, and is associated with cardiovascular disease. Furthermore, several studies have shown that obesity is an important risk factor for heart failure (HF) [1,2]. Data from the Framingham Heart Study demonstrated that a higher Body Mass Index (BMI) increased the risk of HF; the risk of HF increased by 5% in men and by 7% in women for every 1 kg/m^2 increase in BMI [3]. On the other hand, the "Obesity Paradox" describes a phenomenon in which HF patients with a relatively high BMI have a better prognosis than those with a low BMI [4]. A previous study indicated that weight loss and leanness were important predictors of poor prognosis in chronic HF patients [5]. It remains unclear whether obesity itself is protective or adverse in HF. The objective of this study was to evaluate the impact of BMI changes on prognosis in HF.

2. Methods

2.1. Patients

We conducted a retrospective study of patients with repeated (≥2) hospitalizations due to decompensated HF at our institution between April 2009 and March 2013. On admission, all patients were diagnosed with acute decompensated HF based on the Framingham criterion, in addition to imaging and biochemical data. HF patients with both reduced and preserved ejection fractions were included in this study. All patients received the standard of care according to current guidelines. BMI was defined as weight in kilograms divided by the square of the height in meters. Weight assessed on admission may reflect some component of fluid overload. Therefore, the BMI on discharge, that is, after extensive diuresis, was used in this study. Laboratory data and echocardiography occurred within three months of the initial referral, and later values were excluded from the analysis. The nutritious status was measured at first discharge with the Controlling Nutritional Status (CONUT) score, which was composed of serum albumin concentration, total lymphocyte count, total cholesterol level. We excluded patients without BMI data available on admission and discharge. Other exclusion criteria included evidence of liver dysfunction (alanine aminotransferase level >100 IU/l or total bilirubin level >2.5 mg/dl), estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2, nephrotic syndrome, uncontrolled diabetes mellitus, cancer, hypothyroidism, lymphedema, alcohol abuse, and the use of steroids.

2.2. Study design and end points

Patients were classified into four categories based on frequency of hospitalization: twice, three times, four times, and more than five times during the study period. We then investigated the relationship between changes in BMI from the first discharge to

Abbreviations and acronyms: BMI, body mass index; HF, heart failure; eGFR, estimated glomerular filtration rate; CONUT, Controlling Nutritional Status; TNF-α, tumor necrosis factor (TNF)-α.

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the second discharge and the frequency of hospitalization due to decompensated HF. For each patient, baseline demographic information was obtained from the medical records after the first discharge. We then compared mortality between two groups; those patients in whom the BMI increased (group I) or decreased (group D) between the first and second discharge. The primary outcome was cardiovascular mortality, with a secondary outcome of hospitalization frequency due to decompensated HF. All follow-up assessments were performed by questionnaire, telephone interview, and review of the medical record.

2.3. Statistics

Baseline characteristics are presented as means and standard error of the mean for continuous variables with normal distribution. Statistically significant between-group differences in BMI changes from first to second hospitalization were calculated based on an analysis of variance. We conducted multiple regression analysis between BMI changes and frequency of hospitalization. The covariates considered in the analysis were age, ejection fraction, and BMI on first discharge. Categorical variables are expressed as numbers or percentages, which were compared using the χ^2 test and the Cochran-Armitage test for trend. The comparison of BMI changes between group I and D from first to second discharge were made with a Cox proportional hazards model with follow-up time to cardiac death as the primary outcome. Hazard ratio estimates with 95% CIs were calculated using the Cox proportional hazards regression model, adjusted for age, ejection fraction, and BMI at first discharge. The cumulative incidence of events and interval estimates were calculated using the Kaplan-Meier survival method. A log-rank test was used to assess the relationship between change in BMI from first to second discharge and the rate of cardiac death. In addition, survival rates were compared between patients with a BMI at first discharge ≥22 kg/m^2 versus <22 kg/m^2 to evaluate the influence of basal BMI (because BMI < 22 kg/m^2 is considered lean). Two-sided *P*-values were used in all analyses. We regarded a *P*-value under 0.05 as statistically significant and conducted all statistical analyses using SPSS software, version 21 (IBM, Chicago, IL, USA).

3. Results

3.1. Patient characteristics

Between April 1, 2009 and March 31, 2013, a total of 971 patients were hospitalized for acute decompensated HF in our hospital. Of these, 81 patients were hospitalized two or more times and were thus included in the study. Patients were divided into four categories based on the frequency of hospitalization during the study period: twice, three times, four times, of more than five times. Table 1 shows the baseline characteristics of the study population. Of the study subjects, 69.1% were male ($n = 56$), and the average age was 73.2 ± 11.2 years. There were no significant differences in primary diagnosis of HF and CONUT score among the four groups. Most patients had a low CONUT score, suggesting undernourishment at the first discharge. In addition, the average BMI at baseline was 20.9 ± 0.38 kg/m^2, which is lower than the standard value. There was no significant difference in the drugs used between the two groups.

3.2. Changes in BMI and frequency of hospitalization for decompensated HF

The reductions in BMI between the first and final discharge were −0.05 ± 0.15, −0.87 ± 0.56, −1.03 ± 0.34, and −1.97 ± 0.33 in patients who were hospitalized two, three, four, and greater than five times, respectively ($P < 0.01$). Greater decreases in BMI were associated with higher frequencies of HF hospitalization. In addition, the decrease from first to final discharge in BMI was a significant predictive factor for frequent hospitalization even after taking covariates into consideration, including age, ejection fraction, and BMI on first discharge (multiple regression analysis, $\beta = -0.42$, $P < 0.01$, 95% confidence interval (CI) −4.4 to −0.14). The explanatory variables were independent without multicollinearity. We then divided all patients into two groups: those in whom BMI increased (group I) and those in whom BMI decreased (group D) between the first and second discharge and evaluated the prognosis of each group and the parameters involved in prognosis. Group D consisted of 43 patients and group I consisted of 38 patients. Group D included a higher number of males (81.8% vs 54.1%, $P = 0.01$) and a lower ejection fraction (41.6 ± 2.5% vs 53.0 ± 2.7%, $P < 0.01$). Age, primary diagnosis of HF, baseline BMI, and nutrition indexes were similar in both

Table 1
Patient characteristics during the first hospitalization, grouped by the number of subsequent hospitalizations.

	All	2	3	4	5<	*P* value
n	81	49	13	14	5	
Age (years)	73.1 ± 1.3	74.0 ± 1.6	69.6 ± 3.5	73.5 ± 2.7	74.4 ± 5.4	0.66
Male no. (%)	56 (69.1)	31 (63.3)	8 (61.5)	13 (60.4)	4 (80.0)	0.17
Height (cm)	157.4 ± 1.2	156.1 ± 1.5	154.2 ± 3.4	163.0 ± 1.2	162.1 ± 6.2	0.07
Weight (kg)	51.2 ± 1.25	50.4 ± 1.51	48.1 ± 3.91	55.5 ± 2.92	55.5 ± 4.48	0.26
BMI at first discharge (kg/m^2)	20.9 ± 0.38	20.6 ± 0.49	20.9 ± 0.96	21.6 ± 0.92	22.0 ± 1.54	0.68
Primary disease no. (%)						0.98
Ischemic heart disease	31 (38.3)	18 (36.7)	6 (46.1)	5 (35.7)	1 (20.0)	
Idiopathic dilated cardiomyopathy	21 (25.9)	9 (18.4)	1 (7.7)	3 (21.4)	1 (20.0)	
Valvular heart disease	17 (21.0)	13 (26.5)	2 (15.4)	3 (21.4)	2 (40.0)	
Hypertensive heart disease	8 (9.9)	2 (4.1)	1 (7.7)	1 (7.2)	0 (0)	
Other	4 (4.9)	7 (14.3)	3 (23.1)	2 (14.3)	1 (20.0)	
CONUT score no. (%)						0.19
Normal	18 (22.2)	10 (20.4)	5 (38.5)	1 (7.1)	2 (40.0)	
Mild	42 (51.9)	30 (61.2)	5 (38.5)	6 (42.9)	1 (20.0)	
Moderate	20 (24.7)	8 (16.3)	3 (23.1)	7 (50.0)	2 (40.0)	
Severe	1 (1.2)	1 (2.0)	0 (0)	0 (0)	0 (0)	
Medication						
Loop diuretics	64 (79.0)	37 (75.5)	9 (69.2)	14 (100)	4 (80)	0.18
Thiazides	6 (7.4)	3 (6.1)	1 (7.7)	2 (14.3)	0 (0)	0.71
Spironolactone	28 (34.6)	16 (32.7)	5 (38.5)	6 (42.9)	1 (20)	0.88
ACEi/ARB	21 (25.9)	14 (28.6)	4 (30.8)	1 (7.1)	2 (40)	0.51
β-Blocker	60 (74.1)	35 (71.4)	9 (69.2)	11 (7.9)	5 (100)	0.23
Ejection fraction (%)	46.8 ± 1.9	47.5 ± 2.6	49.2 ± 5.1	45.7 ± 4.1	37.0 ± 14.7	0.59
HFpEF no. (%)	39 (48.2)	26 (53.1)	8 (61.5)	4 (28.6)	1 (20.0)	0.03
HFrEF no. (%)	42 (51.9)	23 (46.9)	5 (38.5)	10 (71.4)	4 (80.0)	
Systolic blood pressure (mm Hg)	109.2 ± 16.1	111.3 ± 16.7	110.2 ± 18.4	106.3 ± 11.1	94.0 ± 8.0	0.12
Diabetic blood pressure (mm Hg)	59.4 ± 7.9	59.6 ± 7.7	58.3 ± 8.4	59.9 ± 9.8	58.4 ± 4.8	0.94
BUN (mg/dl)	27.4 (19.6–40.5)	25.6 (18.1–37.8)	27.4 (17.4–43.7)	28.1 (22.7–47.4)	27.5 (23.2–33.1)	0.55
Creatinine (mg/dl)	1.31 (1.04–1.86)	1.28 (0.91–1.73)	1.30 (1.12–1.89)	1.73 (1.32–2.11)	1.31 (1.23–2.09)	0.97
BNP (pg/dl)	613.0 (250.5–923.5)	352.5 (198.1–683.3)	630.0 (360.0–1533.0)	956.1 (890.8–1250.0)	613.0 (150.0–2160.0)	0.12
Albumin (mg/dl)	3.6 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	3.5 ± 0.1	3.9 ± 0.2	0.46
Total lymphocyte count (/mm^3)	1436.7 ± 75.5	1449.0 ± 95.6	1714.5 ± 223.7	1153.0 ± 161.4	1387.5 ± 193.0	0.20
Total cholesterol (mg/dl)	161.8 ± 4.1	165.7 ± 4.5	176.5 ± 10.6	140.0 ± 19.8	147.8 ± 12.9	0.03

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CONUT, Controlling Nutritional Status; HFpEF, heart failure with ejection fraction; HFrEF, heart failure with ejection fraction.

groups. There were no significant between-group differences in the time to final hospitalization (follow-up period): 631.2 ± 57.5 days in group D and 676.4 ± 66.0 days in group I ($P = 0.61$). However, there was a significantly higher frequency of hospitalization in group D relative to group I ($P < 0.01$), and this was confirmed by multiple regression analysis ($\beta = -0.25$, $P = 0.03$, 95% CI −0.92 to −0.04). Fig. 1A shows the Kaplan-Meier survival curves for time to cardiac death. Group I had a lower risk of cardiac death than group D ($P < 0.01$), which suggested that increasing BMI from the first to second hospitalization was an important predictor of better event-free survival rate. To better evaluate the effect of BMI, we investigated the role of baseline BMI on survival. In group D, patients with a BMI ≥22 on first discharge had a significantly worse survival rate than patients in group I (Fig. 1B, $P = 0.02$). In those patients with a BMI <22, survival was even worse (Fig. 1C, $P = 0.09$). The Cox proportional hazard model revealed that the risk of subsequent cardiac death in group D was higher than the risk in group I (Fig. 2, hazard ratio (HR), 3.19 [95% CI, 1.25–9.81]; $P < 0.01$). Thus, a larger decrease in BMI between the first and second hospitalization for HF was significantly associated with a higher frequency of subsequent hospitalizations and cardiac death. Finally, we examined whether there is a difference between the patients with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). There was a similar tendency in patients with HFrEF (Fig. 3B, $P = 0.243$), however, the effect of weight loss on rehospitalization was remarkable in patients with HFpEF (Fig. 3A, $P = 0.013$).

4. Discussion

In the present study, we found that patients in whom BMI decreased between the first and second hospitalization for HF had a higher frequency of subsequent hospitalizations and higher cardiovascular mortality. This finding was independent of the initial BMI value. Repeated hospitalization may be both a consequence of, and a contributor to, worse outcome in HF patients.

4.1. Obesity Paradox in HF

Obesity can lead to hypertension, diabetes mellitus, and dyslipidemia, which are all independent risk factors for cardiovascular morbidity and mortality. It has previously been documented that obesity is not only associated with cardiovascular risk, but is also associated with the prevalence and prognosis of HF [3,6–8]. In previous studies, obesity has been shown to have adverse effects on hemodynamics, which impacts cardiac structure and function. Obesity increases central blood flow and cardiac output, leading to left ventricular dilatation and excessive wall stress. Increased venous return increases left ventricular filling pressure, which, in turn, increases pulmonary artery and right ventricular pressures [9–11]. Numerous studies have suggested that, among HF patients, obese patients have a better prognosis than lean patients, a phenomenon known as the "obesity paradox" [12]. Furthermore, underweight HF patients have a worse prognosis [13]. In HF patients, obesity might serve as a metabolic reserve, allowing these patients to better tolerate metabolic stress. However, the mechanisms underlying the obesity paradox remain unclear. Many epidemiological studies have shown that obese patients have higher morbidity due to hypertension, despite the use of anti-hypertensive medication [14–16]. Therefore, it is possible that obese patients have closer medical follow-up than lean patients, and may receive more cardio-protective medications. Alternatively, it has been shown that a high BMI attenuates cardiac sympathetic activity [17], proinflammatory cytokines, and imbalances of catabolic and anabolic pathways [18]. HF patients with a low or normal BMI had a higher mortality than overweight HF patients in a large, randomized controlled trial [19]. Progressive weight loss is often associated with cardiac cachexia in severe heart failure, which results in increased morbidity and mortality [20]. Cardiac cachexia causes a loss of both muscle and fat tissue. In the present study, decreased BMI in patients with HFpEF was more associated with poor outcome, however, it has also been reported that the degree of cachexia was independent of cardiac functional and hemodynamic state [21]. The mechanisms causing

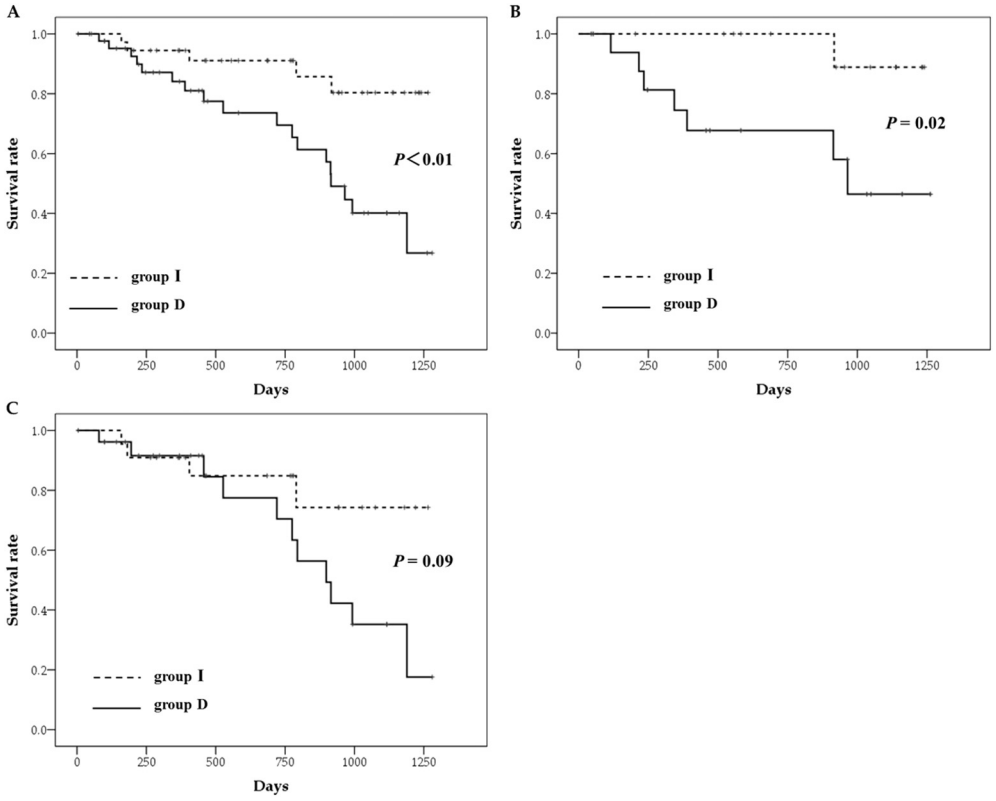

Fig. 1. Kaplan-Meyer survival curves for cardiac death in those patients in whom BMI increased (group I) and those in whom BMI decreased (group D) between the first and second hospitalization. A, Total, B, BMI at first discharge ≧22 kg/cm^2, C, BMI at first discharge <22 kg/cm^2. The dotted line indicates group I and the solid line indicates group D.

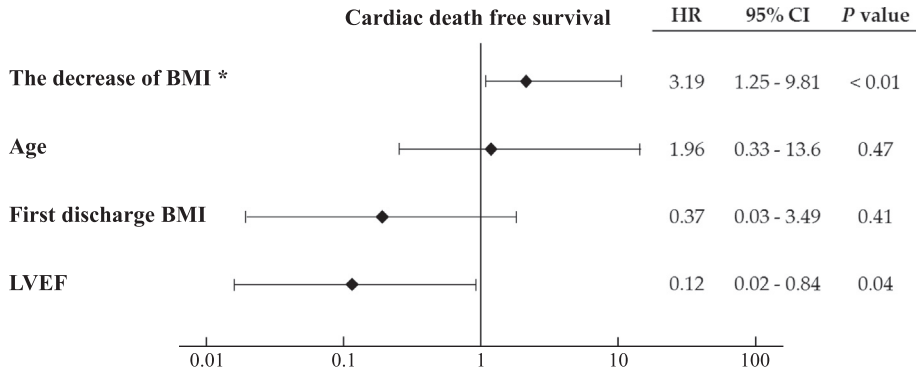

Fig. 2. Forest plot of Cox proportional hazard ratios (HR) with 95% confidence intervals (CIs) for cardiac death; LVEF, left ventricular ejection fraction.

cachexia are unclear, but several etiologies have been suggested. Inflammatory cytokines are known to directly and indirectly contribute to body wasting in HF patients [22,23]. Several studies have shown that tumor necrosis factor (TNF)-α is correlated with the clinical severity of heart failure, which is strongly linked to cachexia in severe HF patients [18,24]. It has been suggested that cytokines including TNF-α are synthesized in reaction to factors such as hypoxemia, oxidative stress, activation of the neurohormonal system [25], hemodynamic overload [26], and endotoxin-like polysaccharides following bacterial translocation due to intestinal edema [27,28]. Because this study did not differentiate unintentional weight loss from cachexia, many study participants might have already had cardiac cachexia.

4.2. Change of BMI in HF

Many studies have reported an association between HF and BMI [1–4,12,13], but few reports have investigated the relationship between BMI changes and HF prognosis. A previous sub-analysis of large-scale clinical trials of HF outpatients found that those patients with a weight loss of about 5% or greater had a higher mortality risk, despite the absence of an association between changes in BMI and subsequent risk of HF hospitalization [5,29–31]. We evaluated changes in BMI at each hospital discharge, after patients had been significantly diuresed. While poor prognosis might reflect worsening HF, we found that a decrease in BMI, rather than low body weight itself, was an important predictive parameter for prognosis, including repeat hospitalizations for HF and mortality. From the data of Table 1, it seems that higher BMI at the first discharge linked more frequent hospitalization (but it was not statistically significant). On the other hand, higher BMI tends to be less risk for CV death in Fig. 2. Apparently, these findings seem contradictory. However, our study showed clearly that the decrease in body weight is actually greater indicator of poor prognosis of HF. Truly, even in patients with higher BMI, it became clear that the prognosis was poor if body weight decreased and the prognosis was good if body weight maintained. The most important thing is not merely the level of BMI but the subsequent weight loss indicates the prognosis. Following BMI after the first hospitalization has the potential to be a simple, non-invasive, and useful guide for predicting poor outcome in HF patients. It is important to pay attention not only to body weight, but also to changes in body weight. In patients with a BMI ≥22 kg/m^2 at the first discharge, decreasing BMI was significantly associated with poor survival. Moreover, survival was also likely to be worse in patients with a BMI <22 kg/m^2, suggesting that lean patients cannot afford to lose weight.

Although the association between decreasing BMI and poor progress was stronger in the patients with HFpEF, the tendency that weight loss ameliorates the prognosis was obvious in the patients with different cardiac functions. Therefore, the patients with both of HFpEF and HFrEF were likely to have poor outcomes due to decreasing BMI. Therefore, an evaluation of BMI changes appears to be more important than measuring BMI at any one time. However, this result does not necessarily guarantee that the converse is also true. It has not been shown whether intentionally increasing BMI can improve prognosis in patients with HF, and further nutritional intervention research will be required to answer this question.

4.3. Limitations

This study had several limitations. First, the number of patients was small and may not represent larger HF populations. Second, this was a single center retrospective observational study and the follow-up period was short. A longer study may provide more accurate prognostic information. Third, we evaluated obesity using BMI, which did not provide information on the precise body composition of adipose tissue and

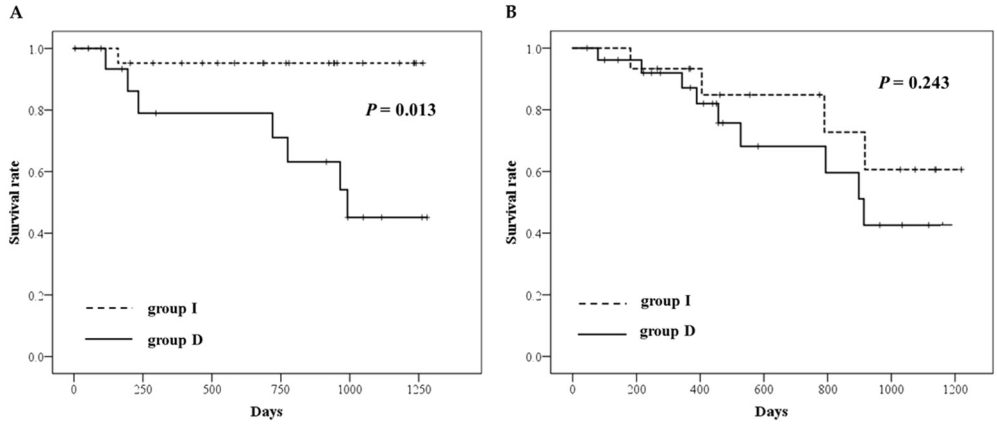

Fig. 3. Kaplan-Meyer survival curves for cardiac death between A, HFpEF and B, HFrEF in those patients in whom BMI increased (group I) and those in whom BMI decreased (group D).

muscle, and we did not evaluate central or visceral obesity. A recent study demonstrated that both higher BMI and higher waist circumference were associated with improved survival in HF [32]. Fourth, weight loss was verified based on weight at the time of discharge from the first hospitalization for HF, and only subjects who were hospitalized for heart failure were targeted in this study. Furthermore, it is an observational study targeting patients who have been hospitalized more than once. Finally, it cannot be guaranteed that the prognosis is better if the patients with HF intentionally increase their body weights. Further intervention studies are considered necessary.

5. Conclusions

The results of the present study suggest that reductions in BMI lead to repeat hospitalizations and poor outcome in HF patients. Changes in BMI might be useful predictors of prognosis in HF patients.

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