Predicting Mortality Risks Using Body Mass Index and Weight Loss at Admission in Patients with Heart Failure

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Background: The association of the combination of body mass index (BMI) and weight change at admission with prognoses in patients with heart failure (HF) is unclear. Therefore, we investigated whether BMI and weight changes at admission affect mortality in patients with HF. **Methods:** This retrospective cohort study lasted 99 months, starting in April 2014, and included 4,862 patients with HF from a Japanese real-world database. Cubic and thin-plate smoothing spline analyses were performed to investigate the association of BMI and weight changes with mortality. The percentage weight change was calculated every 6 months. The study outcome was the presence or absence of death. **Results:** The patients' mean age was 81.5±9.6 years, and 1,239 (25.5%) patients died. Cubic spline analysis revealed a negative correlation of BMI with mortality hazard ratio (HR) (BMI of 18.5 kg/m^2 and 25 kg/m^2; HR=1.3 [1.2–1.4] and 0.8 [0.7– 0.9], respectively). Cubic spline analysis of weight change showed that weight loss tended to increase the mortality HR (each 6% decrease in weight change rate was associated with a 1.1 times higher mortality risk (95% CI [1.0–1.2]). Thin-plate smoothing spline analysis showed that the odds ratio (OR) negatively correlated with BMI (1-year mortality: BMI of 18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2; OR at 0% weight change=1.5, 1.0, and 0.7, respectively; 2-year mortality: BMI=18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2; OR at 0% weight change=1.4, 0.9, and 0.7, respectively). **Conclusion:** A low BMI in patients with HF was associated with a higher risk of mortality. Weight loss in patients, regardless of BMI, was associated with a higher OR for mortality.

Key Words: Cachexia, Heart failure, Asian, Prognosis, Obesity paradox

INTRODUCTION

Heart failure (HF) primarily manifests as a symptom associated with aging and is a significant public health concern. Advanced HF is associated with severe muscle wasting known as cardiac cachex-

ia.[1] The prognosis of patients with cardiac cachexia is poor, with mortality reaching 50% by 18 months.[2] A high body mass index (BMI) is a risk factor for HF[3]; hence, obese patients in the general population are advised to lose weight to prevent HF. However, a recent study reported a better life prognosis in patients with a high

BMI compared with normal-weight patients after HF diagnosis.[3] This phenomenon is termed the "obesity paradox," and the role of weight loss in patients with HF has been debated. Most studies conducted to support the obesity paradox in HF have considered only patient weight or BMI at enrollment; however, few studies have examined the impact of changes in BMI over time on prognosis.[11] Moreover, while several studies have investigated the association between weight loss and the prognosis of patients with HF,[4,5] few studies have investigated the association between the combination of BMI, weight change at admission, and patient prognosis.[7,12,13] Therefore, this study investigated the effects of BMI and weight change at admission on mortality in patients with HF.

MATERIALS AND METHODS

Ethics Statements

The Ethics Committee of Hospital, National Center for Geriatrics and Gerontology determined that an ethical review was not required owing to the use of a publicly available database (No. 1639). The requirement for informed consent was waived because the patient data were anonymized. This study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[6]

Study Design and Data Source

This retrospective cohort study used the administrative claims database compiled by the Japan Medical Data Center Inc., which is one of the most frequently used sources of real-world data. In the database, each patient is assigned a unique anonymized identification number, and data associated with visits to medical facilities is chronologically traced using this anonymized personal ID. Thus, information on outcomes, such as death, can be obtained. We received data containing these unique identification numbers; however, patient personal information, including name or address, could not be obtained.

Patient Selection

This study included data from patients hospitalized between April 2014 and June 2022. The participants were defined as those who met the following inclusion criteria: patients (i) assigned the International Classification of Disease-10 code I50 (HF) and with New York Heart Association classification information, (ii) with available BMI information at admission, (iii) with a history of hospitalization 3–12 months before the hospitalization in (i), and (iv) who were ≥ 40 years of age. Data from patients with similar BMIs at admission and 3–12 months prior were excluded because they were unreliable.[7]

Variables

Patient data, including age, sex, BMI, weight change, New York Heart Association classification, comorbidities, and Barthel Index, were collected. The BMI of each patient was calculated by dividing their weight by the square of their height. The percentage weight change was derived from the BMIs at admission and 3–12 months and was calculated every 6 months. The New York Heart Association classification of each patient was determined on a 4-point scale based on subjective symptoms produced by physical exertion.[8] Comorbidities were scored using the Charlson Comorbidity Index.[9] The Barthel Index was used to assess activities related to daily living on a 100-point scale for all 10 items, with higher scores indicating greater independence.[10] The outcomes measured in this study were the presence or absence of (1) death during the observation period, (2) in-hospital death, (3) death within 1 year of admission, and (4) death within 2 years of admission.

Statistical Analyses

We determined quantitative variables using histograms, with parametric variables presented as mean ± standard deviation and non-parametric variables presented as median (interquartile range). The data were analyzed using the Mann–Whitney U test. Categorical data are expressed as frequency (percentage). We modeled nonlinear associations by fitting a four-knot restricted cubic spline for BMI and weight change using a Cox regression model to determine their association with mortality or in-hospital mortality. Four knots were used in the 5th, 25th, 75th, and 95th percentile quartiles of the BMI and weight change distributions. The reference points were 22.0 kg/m^2 for BMI and 0% for weight change.

Moreover, we used thin-plate smoothing splines to generate contour plots of the odds ratios (ORs) of BMI and weight change for mortality within 1 and 2 years after admission. The reference point for the thin-plate smoothing spline analysis was set as the mean. Patients who survived within 1 or 2 years of admission and were censored within the same period were excluded from the analyses. We adjusted for age, sex, Charlson Comorbidity Index, Barthel Index, and New York Heart Association classification in the multivariate analysis. In a sub-analysis, we limited the study population to individuals aged ≥ 65 years and conducted a thin-plate smoothing spline analysis. We also modeled nonlinear associations by fitting a cubic spline with mortality during the observation period and in-hospital death as outcomes to determine the association between weight change and prognosis in patients repeatedly hospitalized for HF.

All statistical analyses were performed using R statistical software (version 4.2.1; The R Project for Statistical Computing, Vi-

enna, Austria). The R packages "rms" and "mgcViz" were used for the cubic spline analysis and to visualize the generalized additive model for the thin-plate smoothing spline analysis, respectively.

RESULTS

Among 5,432 individuals considered eligible for inclusion in this study, we excluded 570 for having the same BMI at admission and 3–12 months previously; thus, the final analysis included 4,862 patients.

The patients' mean age was 81.5 ± 9.6 years, and 2,174 (44.7%) and 2,688 (55.3%) were women and men, respectively (Table 1). Overall, 1,239 (25.5%) patients died during the observation period. Cubic spline analysis of BMI showed that BMI was negatively correlated with the mortality hazard ratio (HR) (BMI of 18.5 kg/m^2, HR = 1.3 [1.2–1.4]; BMI of 25 kg/m^2, HR = 0.8 [0.7–0.9]) (Fig. 1). Cubic spline analysis showed that, with 0% weight change as the reference rate, weight gain had a low mortality HR of approximately 0%–10% (weight change rate of +5%, HR = 1.0 [0.9–1.0]). However, with weight change > 10%, the mortality HR was high, and weight loss tended to increase the mortality HR by approximately -6% (weight change rate of -6%, HR = 1.1 [1.0–1.2]).

Table 1. Patient characteristics (n=4,862)

	Value
Age (y)	81.5 ± 9.6
Sex	
Female	2,174 (44.7)
Male	2,688 (55.3)
BMI (kg/m^2)	22.0 ± 3.5
Weight change rate (%)	-1.2 (-5.6–3.1)
NYHA classification	
Class 1	254 (5.2)
Class 2	1,227 (25.2)
Class 3	1,885 (38.8)
Class 4	1,496 (30.8)
CCI score	4 (3–6)
Barthel Index (%)	
≥ 0 and < 50	1,680 (34.6)
≥ 50 and < 100	1,181 (24.3)
100	1,361 (28.0)
Missing	640 (13.2
Death	1,239 (25.5)
1-year death	166 (3.4)
2-year death	312 (6.4)
Survival time (mo)	28 (7–63)

Values are presented as mean±standard deviation or number (%) or median (interquartile range).
BMI, body mass index; NYHA, New York Heart Association; CCI, Charlson Comorbidity Index.

In the thin-plate smoothing spline analysis, 1,327 patients were censored within 1 year of admission for reasons other than death, while 1,869 patients were censored within 2 years of admission, resulting in a final analysis of 3,535 and 2,993 patients, respectively. Of the patients analyzed, 166 (4.7%) and 312 (10.4%) died within 1 and 2 years, respectively. In the unadjusted model, the OR increased with decreasing BMI regardless of mortality (1-year mortality: BMI of 18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2, OR at 0% weight change of 1.5, 1.0, and 0.7, respectively; 2-year mortality: BMI of 18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2, OR at 0% weight change of 1.4, 0.9, and 0.7, respectively) (Fig. 2). The adjusted models also showed a higher OR with decreasing BMI regardless of mortality (1-year mortality: BMI of 18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2, OR at 0% weight change of 1.2, 1.0, and 0.8, respectively; 2-year mortality: BMI of 18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2, OR at 0% weight change of 1.2, 0.9, and 0.8, respectively) (Fig. 3). For all BMIs, a mild weight gain of approximately 0%–10% resulted in a lower mortality OR, whereas weight loss resulted in a higher mortality OR (Figs. 2, 3). Moreover, 1-year and 2-year mortality analyses of 3,311 and 2,805 individuals aged ≥65 years showed a trend similar to that of the initial analysis, irrespective of the adjustment. In both the 1-year and 2-year mortality analyses, lower BMI and weight loss were associated with higher ORs for mortality (unadjusted model, 1-year mortality: BMI of 18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2, OR at 0% weight change of 1.4, 1.0, and 0.7, respectively; 2-year mortality: BMI of 18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2, OR at 0% weight change of 1.3, 0.9, and 0.7, respectively) (Supplementary Fig. S1). The results obtained in the adjusted model were as follows: 1-year mortality (BMI of 18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2, OR at 0% weight change of 1.2, 1.0, and 0.8, respectively) and 2-year mortality (BMI of 18.5 kg/m^2, 22 kg/m^2, and 25 kg/m^2, OR at 0% weight change of 1.2, 0.9, and 0.8, respectively) (Supplementary Fig. S2).

During the study period, we observed 1,259 hospitalizations for HF. Overall, 316 patients (25.1%) died during the observation period, 99 (7.9%) of whom died in the hospital. Cubic spline analysis of weight change showed that weight gain had a low mortality HR of approximately 0%–7% but a high mortality HR of > 7%. Weight loss tended to have a high mortality HR of approximately -8% when death within the observation period was the outcome (weight change rate of -8%, HR = 1.2 [1.0–1.5]) (Fig. 4). When in-hospital mortality was used as the outcome, a weight gain of approximately 0%–8% was associated with a lower mortality HR; however, a weight gain of > 8% was associated with a higher mortality HR, while a weight loss of approximately 9% tended to increase the mortality HR (weight change rate of -9%, HR = 1.6 [1.0–2.3]) (Fig. 4). We observed the highest HR for the mortality
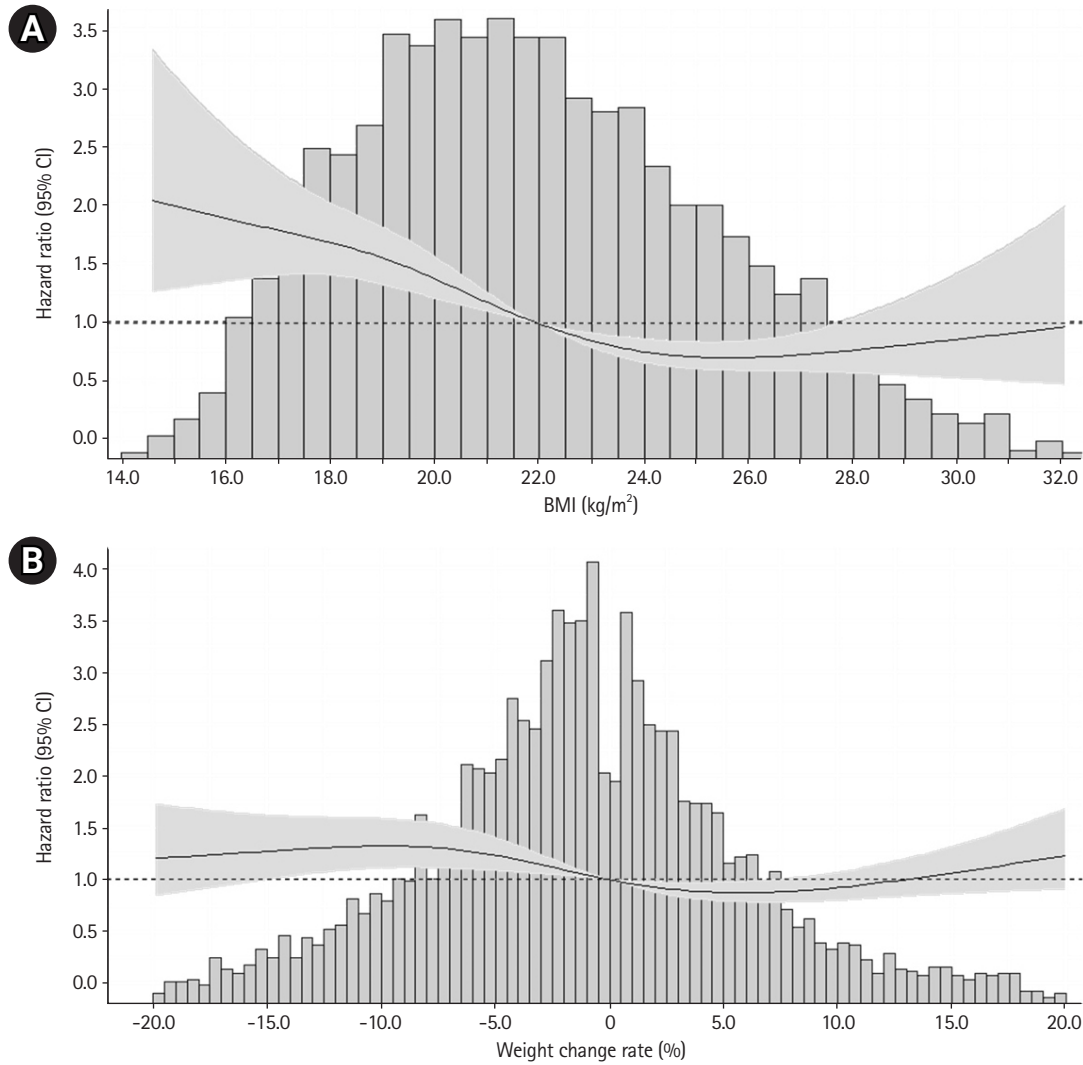
Fig. 1. Restricted cubic splines for mortality. (A, B) The association between BMI/weight change and mortality hazard ratios allowed for nonlinear effects with 95% CIs. The model fitted with four knots restricted the cubic spline to BMI/weight change. The bar graph shows the histogram. BMI, body mass index; CI, confidence interval.
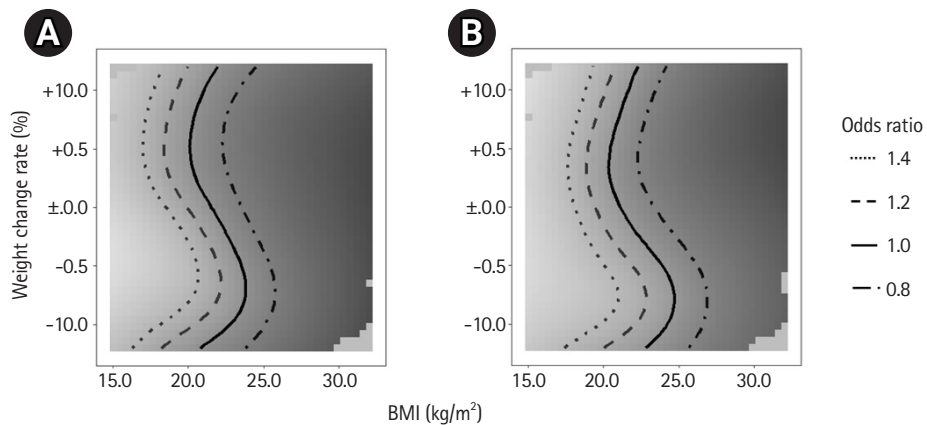

Fig. 2. Body mass index (BMI) and weight change in mortality odds ratio (OR) using a contour map (unadjusted model): (A) 1-year mortality and (B) 2-year mortality. The solid black line indicates an OR of 1.0. The dashed-and-dotted, dashed, and dotted lines indicate ORs of 0.8, 1.2, and 1.4, respectively. There is a higher OR for mortality with a lower BMI and weight gain/loss.
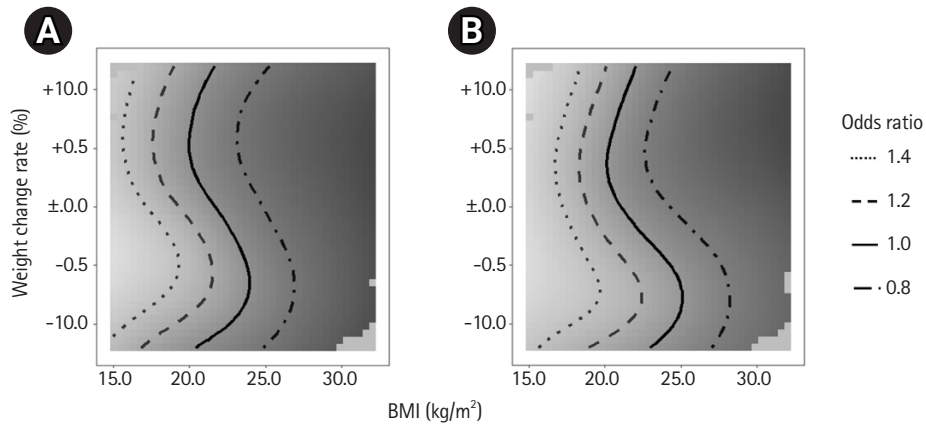
Fig. 3. Body mass index and weight change in mortality odds ratio (OR) using a contour map (adjusted model): (A) 1-year mortality and (B) 2-year mortality. The model was adjusted for age, sex, Charlson Comorbidity Index, Barthel Index, and New York Heart Association classification.
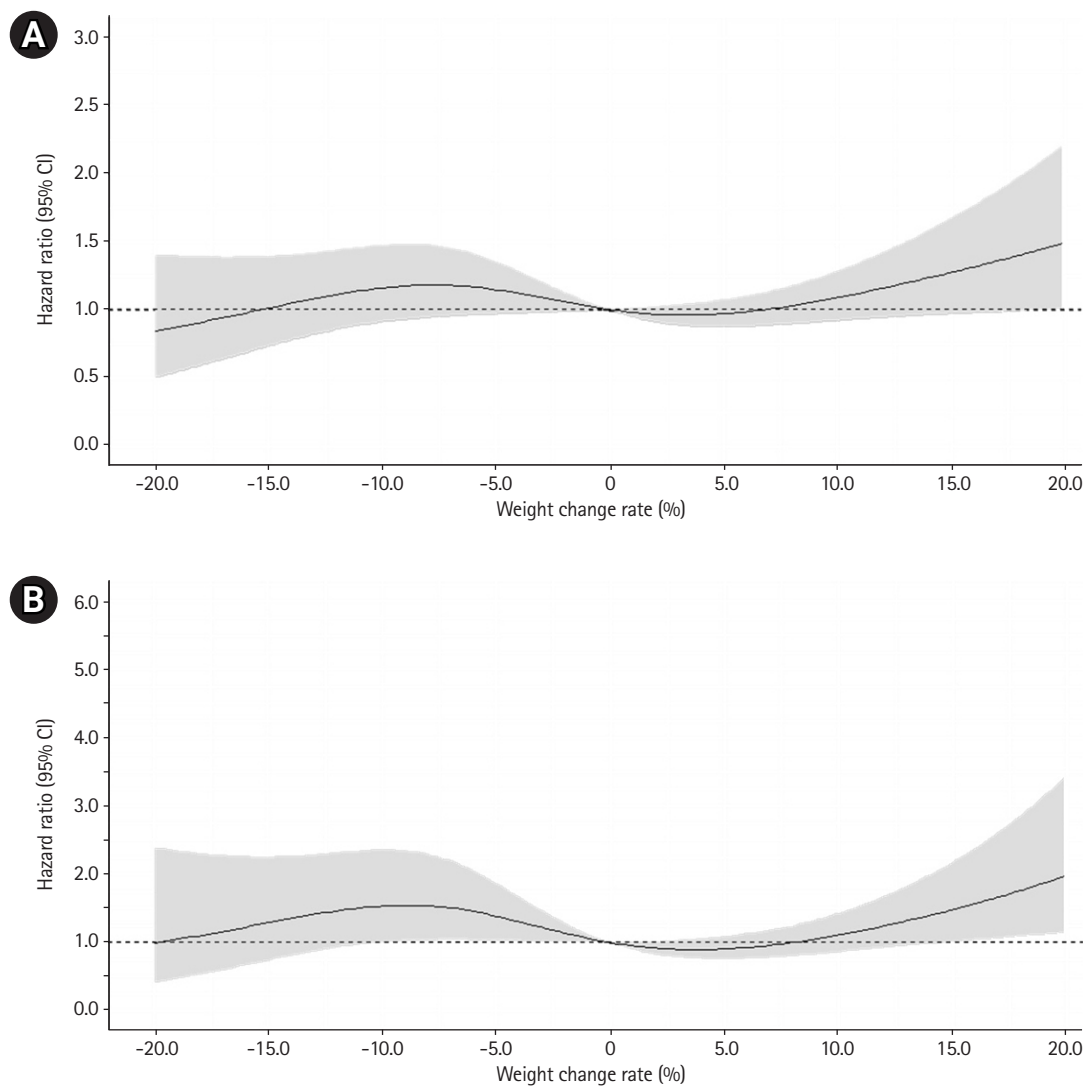

Fig. 4. Restricted cubic spline analysis of patients repeatedly hospitalized for heart failure. The association between weight change and mortality hazard ratios allowed for nonlinear effects with 95% CIs: (a) restricted cubic splines for (A) mortality and (b) in-hospital mortality. CI, confidence interval.

risk predicted by weight loss in patients with repeated hospitalizations for HF (HR = 1.2 and 1.6 for mortality and in-hospital mortality, respectively) compared with those without repeated hospitalization for HF (HR = 1.1).

DISCUSSION

This retrospective cohort study examined BMI and the rate of weight change in relation to mortality in patients with HF using real-world data. The results demonstrated that a low BMI in patients with HF was associated with a higher mortality risk; moreover, weight loss, regardless of BMI, was associated with a higher mortality. Weight loss in patients repeatedly hospitalized for HF was associated with a higher mortality risk. Additionally, the combination of low BMI and weight loss predicted death in patients with HF.

In one meta-analysis, Oreopoulos et al.[11] reported a lower mortality risk in obese or overweight individuals with chronic heart failure (CHF) than those with normal weight and CHF. In contrast, underweight patients had significantly higher mortality rates than those with a normal BMI. Anker et al.[5] also reported that a weight loss of ≥ 6% during follow-up was the strongest predictor of decreased survival. Several studies have examined the associations between BMI and prognosis; weight loss and prognosis; and a combination of BMI, weight loss, and prognosis. Pocock et al.[12] observed a > 150% increase in mortality in patients with CHF who were lean (mean baseline and 6-month BMI < 22.5 kg/m^2) and had weight loss (> 5% weight loss over 6 months) compared with patients who were heavier and had little weight change. Tager et al.[13] reported the best prognosis for patients with CHF and 5% weight gain, although gradual weight loss was associated with increased mortality. Konishi et al.[7] observed higher mortality rates in patients with reduced weight in all baseline BMI subgroups (< 18.5 kg/m^2, 18.5–24.9 kg/m^2, and 25.0 kg/m^2). As previously reported, the survival benefits of obesity in patients with HF may be explained by several mechanisms.[14] For example, a higher BMI may indicate a higher metabolic reserve, allowing patients to withstand the catabolism caused by chronic diseases. Patients with a higher BMI may have greater muscle mass, strength, and cardiopulmonary function than those with a lower BMI. Although the mechanism remains controversial, the results of this study are consistent with those of previous reports, with a high BMI indicating a low mortality risk and vice versa. Additionally, we observed increased mortality risk with weight loss and decreased mortality risk with gradual weight gain, regardless of patient BMI at admission.

To the best of our knowledge, this study is the first to investigate and identify a nonlinear association between the combination of continuous BMI and weight change values and prognosis. The difference between the present study and previous reports is the lack of categorization of BMI and weight loss rates. Previous reports on the association between BMI and weight change combinations and prognosis categorized participants according to BMI and rate of weight change.[7,12,13] Categorization using BMI or weight loss cutoffs could lead to the grouping of patients at different degrees of risk. For example, as observed in the present study, participants with BMIs of 18.5 kg/m^2 and 22 kg/m^2 demonstrated different mortality risks, with a higher risk for a BMI of 18.5 kg/m^2 (Fig. 1). As highlighted in a previous report, this trend may be overlooked when grouped and analyzed. The cutoff values for BMI and weight loss rate varied from study to study, with no uniformity.[7,12,13] In contrast, we observed a nonlinear relationship between BMI and weight change using continuous values without categorization.

Weight loss is associated with a high risk of mortality in patients with repeated hospitalizations for HF. In patients with repeated hospitalization for HF, in-hospital mortality was reportedly higher among those with weight loss or gain > 5.0% compared with those with stable weight (-2.0% to +2.0%; OR = 1.46 and 1.23, respectively).[7] We observed an HR of 1.6 for the association of weight loss with in-hospital mortality in patients admitted with repeated HF. Furthermore, the HR for the association between weight change and death during the observation period in patients with repeated HF hospitalizations was higher than that in patients without repeated HF hospitalizations (1.2 vs. 1.1). Progressive HF leads to cardiac cachexia[15] and a poor prognosis due to weight loss. Therefore, patients with repeated hospitalizations for HF were more likely to have cachexia than those without such repeated hospitalizations; hence, the mortality rate may have increased with weight loss.

This study has several limitations. First, the data did not indicate whether weight loss was intentional. Second, BMI was used as an index of body composition; however, it was not considered with respect to detailed body composition, such as muscle mass, fat storage, and water content. However, BMI may be a good surrogate for lean body mass[16,17] and is a practical index that is easily collected clinically without expensive equipment.

In conclusion, low BMI and weight loss on admission were associated with mortality in patients with HF. Future studies are required to determine whether weight loss, even if intended, is associated with a poor prognosis.

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AUTHOR CONTRIBUTIONS

Conceptualization, YI, KMaeda, KMurotani, AS, JU, AN, TI, NM; Funding acquisition, KMaeda; Methodology, YI, KMaeda, KMurotani; Supervision, KMaeda, NM; Writing–original draft, YI, KMaeda; Writing–review & editing, YI, KMaeda, KMurotani, AS, JU, AN, TI, NM.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4235/agmr.23.0213.

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