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Association of weight change and in-hospital mortality in patients with repeated hospitalization for heart failure

Masaaki Konishi[1]*, Hidehiro Kaneko[2]*, Hidetaka Itoh[3], Satoshi Matsuoka[4], Akira Okada[5], Kentaro Kamiya[6], Tadafumi Sugimoto[7], Katsuhito Fujiu[2], Nobuaki Michihata[8], Taisuke Jo[8], Norifumi Takeda[3], Hiroyuki Morita[3], Kouichi Tamura[1], Hideo Yasunaga[9] & Issei Komuro[3]

[1]*Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan;* [2]*Department of Cardiovascular Medicine and Department of Advanced Cardiology, The University of Tokyo, Tokyo, Japan;* [3]*Department of Cardiovascular Medicine, The University of Tokyo, Tokyo, Japan;* [4]*Department of Cardiovascular Medicine, New Tokyo Hospital, Matsudo, Japan;* [5]*Department of Prevention of Diabetes and Lifestyle-Related Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;* [6]*Department of Rehabilitation, School of Allied Health Sciences, Kitasato University, Sagamihara, Japan;* [7]*Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu, Japan;* [8]*Department of Health Services Research, The University of Tokyo, Tokyo, Japan;* [9]*Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan*

Abstract

Background Although weight loss in heart failure (HF) is a detrimental condition known as cachexia, weight gain caused by fluid retention should also be considered harmful. However, studies with sufficient number of patients examining the impact of weight change and its interval on in-hospital mortality in HF have not been conducted thus far. We sought to elucidate the association of weight change with in-hospital mortality in patients with HF.

Methods This retrospective observational study used data from the Diagnosis Procedure Combination database, a nationwide inpatient health claims database in Japan. In total, 48 234 patients repeatedly hospitalized for HF (median 82 [74–87] years; 46.4% men) between 2010 and 2018 were included. Weight change was derived from body weight at the first and second admissions.

Results The median weight change and interval between two hospitalizations were −3.1 [−8.3 to −1.8] % and 172 [67–420] days, with 66.9% of overall cohort experiencing any weight loss. As a result of multivariable-adjusted logistic regression analysis, weight loss <−5.0% and weight gain >+5.0% were associated with increased in-hospital mortality (adjusted odds ratio [OR] [95% confidence interval]: 1.46 [1.31–1.62], $P < 0.001$ and 1.23 [1.08–1.40], $P = 0.002$, respectively) whereas mild weight loss and gain of 2.0–5.0% were not (OR [95% confidence interval]: 0.96 [0.84–1.10], $P = 0.57$ and 1.07 [0.92–1.25], $P = 0.37$, respectively), in comparison with patients with a stable weight (fluctuating no more than −2.0% to +2.0%) used as a reference. Restrictive cubic spline models adjusted for multiple background factors illustrated that higher mortality in patients with weight loss was observed across all subgroups of the baseline body mass index (<18.5, 18.5–24.9 and ≥25.0 kg/m^2). In patients with short (<90 days) and middle (<180 days) intervals between the two hospitalizations, both weight loss and weight gain were associated with high mortality, whereas the association between weight gain and high mortality was attenuated in those with longer intervals.

Conclusions Both weight loss and weight gain in patients with repeated hospitalization for HF were associated with high in-hospital mortality, especially weight loss and short/middle-term weight gain. Such patients should be treated with caution in a setting of repeated hospitalization for HF.

Keywords body weight; heart failure; mortality

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**Correspondence to: Masaaki Konishi, Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. Email: m_koni@yokohama-cu.ac.jp;*
Hidehiro Kaneko, Department of Cardiovascular Medicine, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: kanekohidehiro@gmail.com

Introduction

Recent advances in pharmacological and non-pharmacological treatments have reduced the mortality rate of patients requiring acute cardiovascular care.[1] However, a considerable number of patients who survived acute cardiovascular illness are thought to progress to symptomatic heart failure (HF) over the course of many years. Consequently, patients with HF are frequently encountered in daily clinical practice, along with an ageing society.[2] HF is a chronic clinical syndrome that cannot be completely cured, and many patients suffer from disease-related weight loss.[3]

Disease-related weight loss sometimes accompanies inflammatory cytokine activation, hyperadrenergic state, increased metabolic requirements and physical inactivity.[4,5] However, although it is evident that weight loss is closely linked to mortality in cancer,[6] the assessment of weight loss in HF is rather challenging.[7] This is because HF is essentially a disease in which the fluid status changes, and it is difficult to determine whether weight change indicates a change in fluid volume or a change in skeletal muscle or fat.[8] Although weight loss in patients with chronic HF without oedema is associated with increased mortality,[9] acute weight gain is also a predictor of re-hospitalization as a consequence of fluid retention.[10] However, studies with sufficient number of patients examining the impact of weight change and its interval on in-hospital mortality in HF have not been conducted thus far. Such an examination would be useful for risk stratification and would provide a rationale for intervention studies targeting weight gain or weight loss.

Therefore, this study was designed to fill the existing knowledge gap. We hypothesized that weight loss or gain in patients with HF is associated with in-hospital mortality. Using the Diagnosis Procedure Combination (DPC) database, a nationwide inpatient database in Japan, we retrospectively examined weight change with the interval between two hospitalizations for HF and in-hospital mortality during the second hospitalization.

Methods

Study design and data source

This retrospective cohort study used data from the DPC database. The data collected include administrative claims and clinical data of ~8 million hospitalized patients per year from >1200 participating hospitals, including all 82 academic hospitals.[11,12] These hospitals are distributed across all 47 prefectures in Japan. The DPC database represents ~50% of all acute inpatients and covers >90% of all tertiary-care emergency hospitals in Japan. Academic hospitals are required to participate in this database, whereas participation of community hospitals is voluntary. The database collates the main diagnoses and comorbidities present at admission using the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes. Information on treatment, including medication use and procedures, was also available. An anonymized unique identification number was created for each patient in each hospital. The researchers received data that include unique identification numbers but do not include each patient's personal information including name and address. The researchers can link a patient's multiple admissions with each other using his/her unique identification number.

This study was approved by the Institutional Review Board of the University of Tokyo (Approval Number 3501-(3)). The investigation conformed to the principles outlined in the *Declaration of Helsinki*. The need to obtain informed consent was waived owing to the anonymous nature of the data used.

Patient selection

We screened the records of patients aged ≥20 years with New York Heart Association class ≥II, admitted and discharged between January 2010 and March 2018 with the main discharge diagnosis of HF defined by ICD-10 codes I50.0 (congestive HF), I50.1 (left HF) and I50.9 (HF) from our DPC database. Among them, those with HF hospitalization twice or more times during the study period were included. Both the first and second admissions have to be due to HF. The exclusion criteria were as follows: (i) undergoing major procedures under general anaesthesia,[13] (ii) missing body mass index (BMI), (iii) a BMI < 12.5 kg/m^2 or BMI > 60 kg/m^2, (iv) patients with exactly the same body weight in the first hospitalization as the second one, (v) missing history of smoking and (vi) length of hospital stay ≤2 days during the first or second hospitalization. A length of hospital stay ≤2 days was excluded due to uncertainty in the diagnosis of HF.[11,14,15] The second hospitalization record was used in the analysis, except for height and body weight data, which were derived data collected during the first hospitalization. Weight change was derived from body weight at the first and second admissions. Patients with the same body weight in the first as the second hospitalization were excluded due to the high likelihood of unreliable body weight data in either the first or second hospitalization. The main outcome measured in this study was in-hospital mortality during the second hospitalization.

Statistical procedures

Continuous and categorical data were presented as medians with interquartile ranges and numbers with percentages. We used restricted cubic spline (RCS) functions to identify the association between weight change as a continuous parameter and in-hospital mortality. The dose–response association between weight change and in-hospital mortality was adjusted according to the patient background (BMI in the first hospitalization; age; sex; hypertension; diabetes mellitus; chronic renal failure; chronic liver disease; chronic respiratory disease; cancer; anaemia; coronary artery disease; stroke; dementia; neurological disorder; cigarette smoking; New York Heart Association class; medication use within 2 days after admission, such as intravenous inotropic agent, intravenous nitrate, intravenous furosemide, intravenous carperitide, oral beta-blocker, oral angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker and oral mineralocorticoid receptor antagonist; procedures within 2 days after admission, such as respiratory support, haemodialysis, intra-aortic balloon pumping and extra-corporeal membrane oxygenation; and the interval between two hospitalizations) while also adjusting for within-hospital clustering using a generalized estimating equation. The splines were restricted to linear below the first knot point and above the last knot point. In this study, we used five knots, excepting the sub-analysis of BMI 18.5–24.9 kg/m^2 and BMI ≥ 25.0 kg/m^2 with four knots, for the nonlinear effects of continuous assessment. Tests for overall and nonlinear associations between weight change and in-hospital mortality were performed using the χ^2 test. The association of weight change category with in-hospital mortality was evaluated using multivariable logistic regression analysis with adjustment for the same covariates as in the RCS analysis. Odds ratios (ORs) and 95% confidence interval for in-hospital mortality were calculated for each category of weight change with respect to the reference value calculated for the reference group with the lowest mortality in the analysis by deciles and the category with a stable weight (≥−2.0% and < +2.0%) in the analysis by pre-specified five subcategories of weight change (<−5.0%, ≥−5.0% and <−2.0%, ≥−2.0% and <+2.0%, ≥+2.0% and <+5.0%, and ≥+5.0%). The cut-offs in the pre-specified subcategories were derived from those used for patients with cancer cachexia.[16] For subgroup analyses, we divided the study population into two or more groups by baseline BMI category (<18.5, 18.5–24.9 and ≥25.0 kg/m^2), interval between two hospitalizations (<90 or ≥90 days, and <180 or ≥180 days), sex and age (<80 or ≥80 years). A subgroup with an interval of ≥180 and <360 days between two hospitalizations was also analysed. Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using SPSS Version 25 software (SPSS Inc., Chicago, IL, USA) and STATA Version 17 (StataCorp LLC, College Station, TX, USA).

Results

We screened 344 636 records of patients aged ≥20 years with a New York Heart Association class ≥II. Among them, 69 926 patients experienced hospitalization for HF twice or more times, and the final number of patients analysed in this study was 48 234 (*Figure 1*). The baseline clinical characteristics of the study population are summarized in *Table 1*. The median age of the patients was 82 [74–87] years, and 22 379 patients

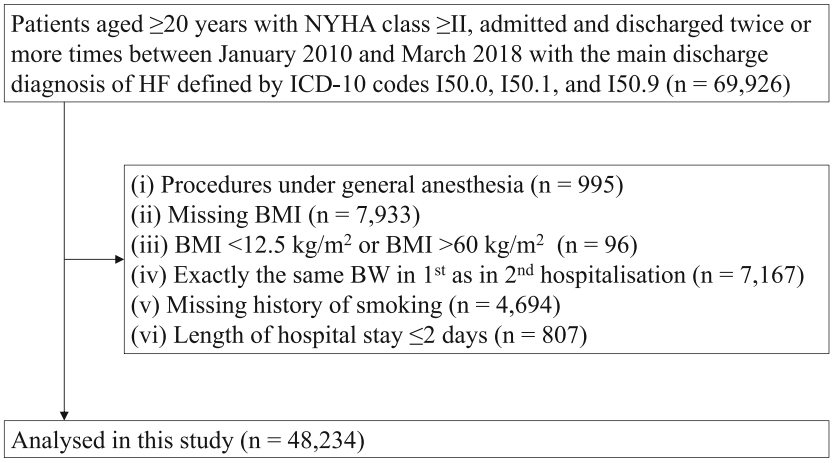

Figure 1 Study flow chart. BMI, body mass index; BW, body weight; HF, heart failure; ICD-10, International Classification of Diseases and Related Health Problems 10th Revision; NYHA, New York Heart Association

Table 1 Patient characteristics

Variable	*n* = 48 234
Age (years)	82 (74–87)
Men, *n* (%)	22 379 (46.4%)
BMI at the 1st hospitalization (kg/m^2)	22.3 (19.9–25.1)
BMI at the 2nd hospitalization (kg/m^2)	21.7 (19.2–24.4)
Hypertension, *n* (%)	36 727 (76.1%)
Diabetes mellitus, *n* (%)	18 049 (37.4%)
Chronic renal failure, *n* (%)	10 289 (21.3%)
Chronic liver disease, *n* (%)	2228 (4.6%)
Chronic respiratory disease, *n* (%)	6703 (13.9%)
Anaemia, *n* (%)	3685 (7.6%)
Cancer, *n* (%)	3296 (6.8%)
Coronary artery disease, *n* (%)	9381 (19.4%)
Stroke, *n* (%)	799 (1.7%)
Dementia, *n* (%)	2714 (5.6%)
Neurological disorder, *n* (%)	1115 (2.3%)
Smoking, *n* (%)	15 963 (33.1%)
New York Heart Association	
Class II, *n* (%)	13 860 (28.7%)
Class III, *n* (%)	19 877 (41.2%)
Class IV, *n* (%)	14 497 (30.1%)
Medication within 2 days after admission	
Intravenous inotropic agent, *n* (%)	7905 (16.4%)
Intravenous nitrate, *n* (%)	7322 (15.2%)
Intravenous furosemide, *n* (%)	30 006 (62.2%)
Intravenous carperitide, *n* (%)	17 702 (36.7%)
Oral beta-blocker, *n* (%)	16 965 (35.2%)
Oral ACE inhibitor/ARB, *n* (%)	15 095 (31.3%)
Oral MRA, *n* (%)	13 165 (27.3%)
Procedures within 2 days after admission	
ECMO, *n* (%)	11 (0.0%)
IABP, *n* (%)	59 (0.1%)
Intubation, *n* (%)	431 (0.9%)
Haemodialysis, *n* (%)	640 (1.3%)

Note: Data are expressed as median (interquartile range) or number (percentage). Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; ECMO, extra-corporeal membrane oxygenation; IABP, intra-aortic balloon pumping; MRA, mineralocorticoid receptor antagonist.

(46.4%) were men. The median weight change and interval between two hospitalizations were −3.1 [−8.3 to −1.8] % and 172 [67–420] days, with 66.9% of overall cohort experiencing any weight loss.

Association between weight change and in-hospital mortality

Figure 2 shows the adjusted dose–response association between weight change and in-hospital mortality in the RCS analysis with five knots. RCS illustrated that in-hospital mortality decreased with increased weight change until weight change of −3.0% and increased with weight change after weight change exceeded −3.0%. Thus, the RCS curve showed a relationship between weight change and in-hospital mortality with the bottom of splines around −3.0%. The tests for overall and nonlinear associations were significant (both $P < 0.001$).

The multivariable logistic regression analysis by deciles of weight change indicated that compared with patients in decile 5 as a reference, patients in deciles 1–4 and 10 had higher in-hospital mortality (*Figure 3*). *Table 2* shows the results of the multivariable logistic regression analysis by the five pre-specified subcategories of weight change. Compared with patients with stable weight (−2.0% to +2.0%) as a reference, patients with weight loss >5.0% (multivariable-adjusted OR 1.46, 95% confidence interval 1.31–1.62) and weight gain ≥5.0% (OR 1.23, 95% confidence interval 1.08–1.40) had higher in-hospital mortality. The patients with mild weight loss and gain of 2.0–5.0% had a similar in-hospital mortality to those with stable weight (OR [95% confidence interval]:

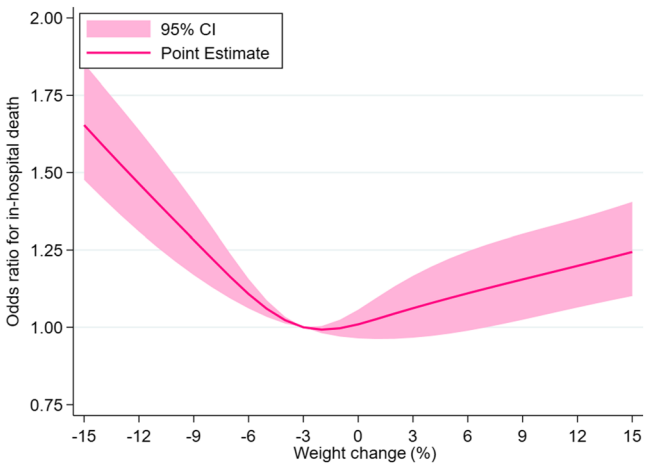

Figure 2 Adjusted dose–response association between weight change and in-hospital mortality in an analysis using restricted cubic splines with five knots. The *y* axis represents the odds ratio for in-hospital mortality between individuals with any weight change. Estimates are shown with 95% confidence intervals (CIs).

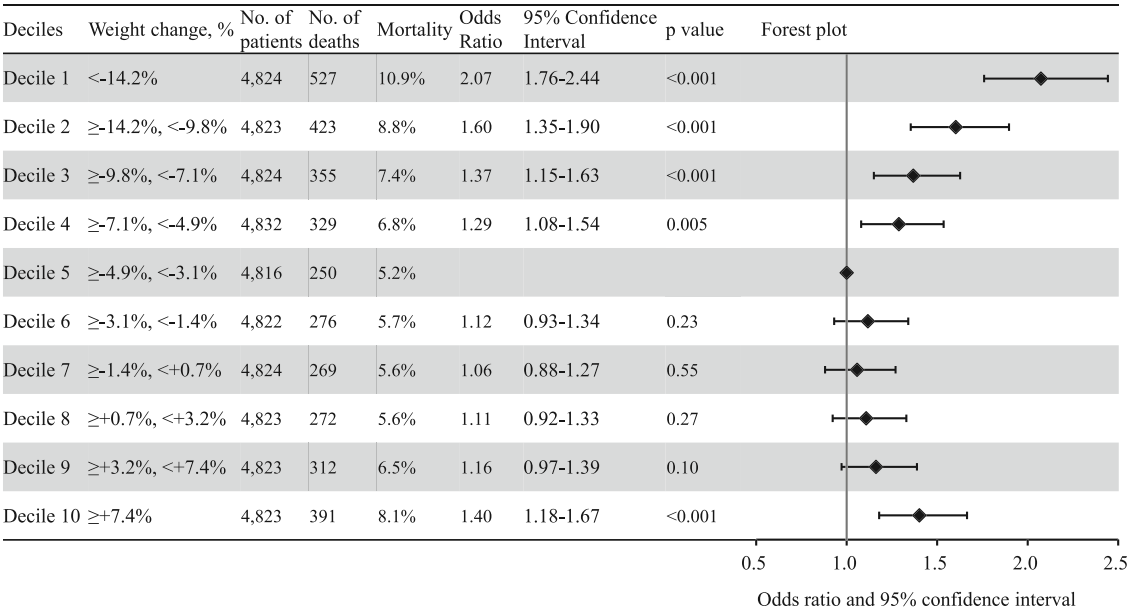

Figure 3 In-hospital mortality according to deciles of weight change. The model was adjusted for body mass index in the first hospitalization; age; sex; hypertension; diabetes mellitus; chronic renal failure; chronic liver disease; chronic respiratory disease; cancer; anaemia; coronary artery disease; stroke; dementia; neurological disorder; cigarette smoking; New York Heart Association class; medication use within 2 days after admission, such as intravenous inotropic agent, intravenous nitrate, intravenous furosemide, intravenous carperitide, oral beta-blocker, oral angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker and oral mineralocorticoid receptor antagonist; procedures within 2 days after admission, such as respiratory support, haemodialysis, intra-aortic balloon pumping and extra-corporeal membrane oxygenation; and the interval between two hospitalizations.

0.96 [0.84–1.10], P = 0.57 and 1.07 [0.92–1.25], P = 0.37, respectively).

Subgroup analysis

Figure 4 illustrates the adjusted dose–response association between weight change and in-hospital mortality in each subgroup. Higher mortality in patients with weight loss was observed across all subgroups of the baseline BMI (<18.5, 18.5–24.9 and ≥25.0 kg/m^2; *Figure 4A*). The results from the subgroups by age and sex illustrated consistent associations with those in the main analysis (*Figure 4B,C*). In patients with short (<90 days) and middle (<180 days) intervals between the two hospitalizations, both weight loss and weight gain were associated with high mortality, whereas the association between weight gain and high mortality was attenuated in those with longer intervals (*Figure 4D,E*). In logistic regression models, a short-term weight gain of 2.0–5.0% and ≥5.0% within 90 days was associated with significantly increased mortality (multivariable-adjusted OR 1.29, 95% confidence interval 1.00–1.65, P = 0.046 and OR 1.49, 95% confidence interval 1.20–1.86, $P < 0.001$, respectively), whereas weight gain of 2.0–5.0% and ≥5.0% over a longer (≥90 days) period did not show statistical significance (multivariable-adjusted OR 0.96, 95% confidence interval 0.79–1.18, P = 0.71 and OR 1.11, 95% confidence interval 0.94–1.30, P = 0.23, respectively; *Table 3*). Similarly, a middle-term weight gain ≥5.0% within 180 days was associated with significantly increased mortality (multivariable-adjusted OR 1.40, 95% confidence interval 1.18–1.67, $P < 0.001$), whereas weight gain over a longer (≥180 days) period did not show statistical significance (*Table 3*). Weight loss <−5.0% in 180–360 days was associated with increased in-hospital mortality, whereas weight gain was not associated with in-hospital mortality (*Table 3*). As a sensitivity analysis, we investigated an adjusted dose–response association between weight change and in-hospital mortality including patients with a hospital stay ≤2 days, which showed a similar finding to that in the main result (*Figure 5*).

Discussion

The principal findings of the present study were as follows: (i) Weight loss was observed in 66.9% of patients with repeated hospitalization for HF, (ii) both weight loss and weight gain were associated with high in-hospital mortality and (iii) the association of short- and middle-term weight gain with in-hospital mortality was prominent compared with that of long-term weight gain.

Table 2 Patient characteristics and in-hospital mortality according to commonly used cut-offs of weight change

Weight change	<−5.0%	≥−5.0% and <−2.0%	≥−2.0% and <+2.0%	≥+2.0% and <+5.0%	≥+5.0%
No. of patients	19 062	8083	9309	4602	7178
Age (years)	82 (75–88)	81 (73–87)	80 (73–87)	81 (73–87)	81 (73–87)
Men, *n* (%)	9100 (47.7%)	3659 (45.3%)	4075 (43.8%)	2067 (44.9%)	3478 (48.5%)
BMI at the 1st hospitalization (kg/m^2)	23.0 (20.6–25.8)	22.5 (20.1–25.3)	22.3 (19.9–25.0)	21.8 (19.5–24.4)	20.7 (18.5–23.4)
BMI at the 2nd hospitalization (kg/m^2)	20.4 (18.2–23.0)	21.9 (19.5–24.5)	22.4 (20.0–25.1)	22.7 (20.2–25.3)	23.2 (20.7–26.2)
Hypertension, *n* (%)	14 372 (75.4%)	6304 (78.0%)	7060 (75.8%)	3520 (76.5%)	5471 (76.2%)
Diabetes mellitus, *n* (%)	7025 (36.9%)	3049 (37.7%)	3449 (37.1%)	1730 (37.6%)	2796 (39.0%)
Chronic renal failure, *n* (%)	4082 (21.4%)	1684 (20.8%)	1965 (21.1%)	980 (21.3%)	1578 (22.0%)
Chronic liver disease, *n* (%)	890 (4.7%)	350 (4.3%)	421 (4.5%)	223 (4.8%)	344 (4.8%)
Chronic respiratory disease, *n* (%)	2745 (14.4%)	1123 (13.9%)	1236 (13.3%)	617 (13.4%)	982 (13.7%)
Anaemia, *n* (%)	1574 (8.3%)	585 (7.2%)	626 (6.7%)	306 (6.6%)	594 (8.3%)
Cancer, *n* (%)	1369 (7.2%)	517 (6.4%)	610 (6.6%)	305 (6.6%)	495 (6.9%)
Coronary artery disease, *n* (%)	3656 (19.2%)	1644 (20.3%)	1857 (19.9%)	900 (19.6%)	1324 (18.4%)
Stroke, *n* (%)	333 (1.7%)	130 (1.6%)	143 (1.5%)	76 (1.7%)	117 (1.6%)
Dementia, *n* (%)	1196 (6.3%)	364 (4.5%)	468 (5.0%)	231 (5.0%)	455 (6.3%)
Neurological disorder, *n* (%)	507 (2.7%)	171 (2.1%)	191 (2.1%)	93 (2.0%)	153 (2.1%)
Smoking, *n* (%)	6011 (31.5%)	2716 (33.6%)	3287 (35.3%)	1569 (34.1%)	2380 (33.2%)
New York Heart Association					
Class II, *n* (%)	5387 (28.3%)	2468 (30.5%)	2764 (29.7%)	1272 (27.6%)	1969 (27.4%)
Class III, *n* (%)	7652 (40.1%)	3233 (40.0%)	3900 (41.9%)	2070 (45.0%)	3022 (42.1%)
Class IV, *n* (%)	6023 (31.6%)	2382 (29.5%)	2645 (28.4%)	1260 (27.4%)	2187 (30.5%)
Medication within 2 days after admission					
Intravenous inotropic agent, *n* (%)	3327 (17.5%)	1293 (16.0%)	1474 (15.8%)	678 (14.7%)	1133 (15.8%)
Intravenous nitrate, *n* (%)	2799 (14.7%)	1332 (16.5%)	1447 (15.5%)	668 (14.5%)	1076 (15.0%)
Intravenous furosemide, *n* (%)	11 735 (61.6%)	4944 (61.2%)	5783 (62.1%)	2866 (62.3%)	4678 (65.2%)
Intravenous carperitide, *n* (%)	6657 (34.9%)	3051 (37.7%)	3463 (37.2%)	1718 (37.3%)	2813 (39.2%)
Oral beta-blocker, *n* (%)	6572 (34.5%)	2883 (35.7%)	3294 (35.4%)	1669 (36.3%)	2547 (35.5%)
Oral ACE inhibitor/ARB, *n* (%)	5577 (29.3%)	2563 (31.7%)	2990 (32.1%)	1571 (34.1%)	2394 (33.4%)
Oral MRA, *n* (%)	5463 (28.7%)	2077 (25.7%)	2395 (25.7%)	1252 (27.2%)	1978 (27.6%)
Procedures within 2 days after admission					
ECMO, *n* (%)	5 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	5 (0.1%)
IABP, *n* (%)	29 (0.2%)	7 (0.1%)	9 (0.1%)	5 (0.1%)	9 (0.1%)
Intubation, *n* (%)	164 (0.9%)	89 (1.1%)	84 (0.9%)	26 (0.6%)	68 (0.9%)
Haemodialysis, *n* (%)	279 (1.5%)	126 (1.6%)	140 (1.5%)	41 (0.9%)	54 (0.8%)
Length of hospital stay (days)	18 [12–29]	17 [11–26]	17 [11–26]	17 [11–26]	18 [12–29]
Outcome					
Mortality, *n* (%)	1618 (8.5%)	436 (5.4%)	523 (5.6%)	278 (6.0%)	549 (7.6%)
Unadjusted odds ratio [95% CI]	1.56 [1.41–1.73]	0.96 [0.84–1.09]	REF	1.11 [0.93–1.25]	1.39 [1.23–1.57]
P value	<0.001	0.52		0.31	<0.001
Adjusted odds ratio [95% CI][a]	1.46 [1.31–1.62]	0.96 [0.84–1.10]	REF	1.07 [0.92–1.25]	1.23 [1.08–1.40]
P value	<0.001	0.57		0.37	0.002

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, confidence interval; ECMO, extra-corporeal membrane oxygenation; IABP, intra-aortic balloon pumping; MRA, mineralocorticoid receptor antagonist; REF, reference.

[a]Adjusted for body mass index in the first hospitalization; age; sex; hypertension; diabetes mellitus; chronic renal failure; chronic liver disease; chronic respiratory disease; cancer; anaemia; coronary artery disease; stroke; dementia; neurological disorder; cigarette smoking; New York Heart Association class; medication use within 2 days after admission, such as intravenous inotropic agent, intravenous nitrate, intravenous furosemide, intravenous carperitide, oral beta-blocker, oral angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker and oral mineralocorticoid receptor antagonist; procedures within 2 days after admission, such as respiratory support, haemodialysis, intra-aortic balloon pumping and extra-corporeal membrane oxygenation; and the interval between two hospitalizations.

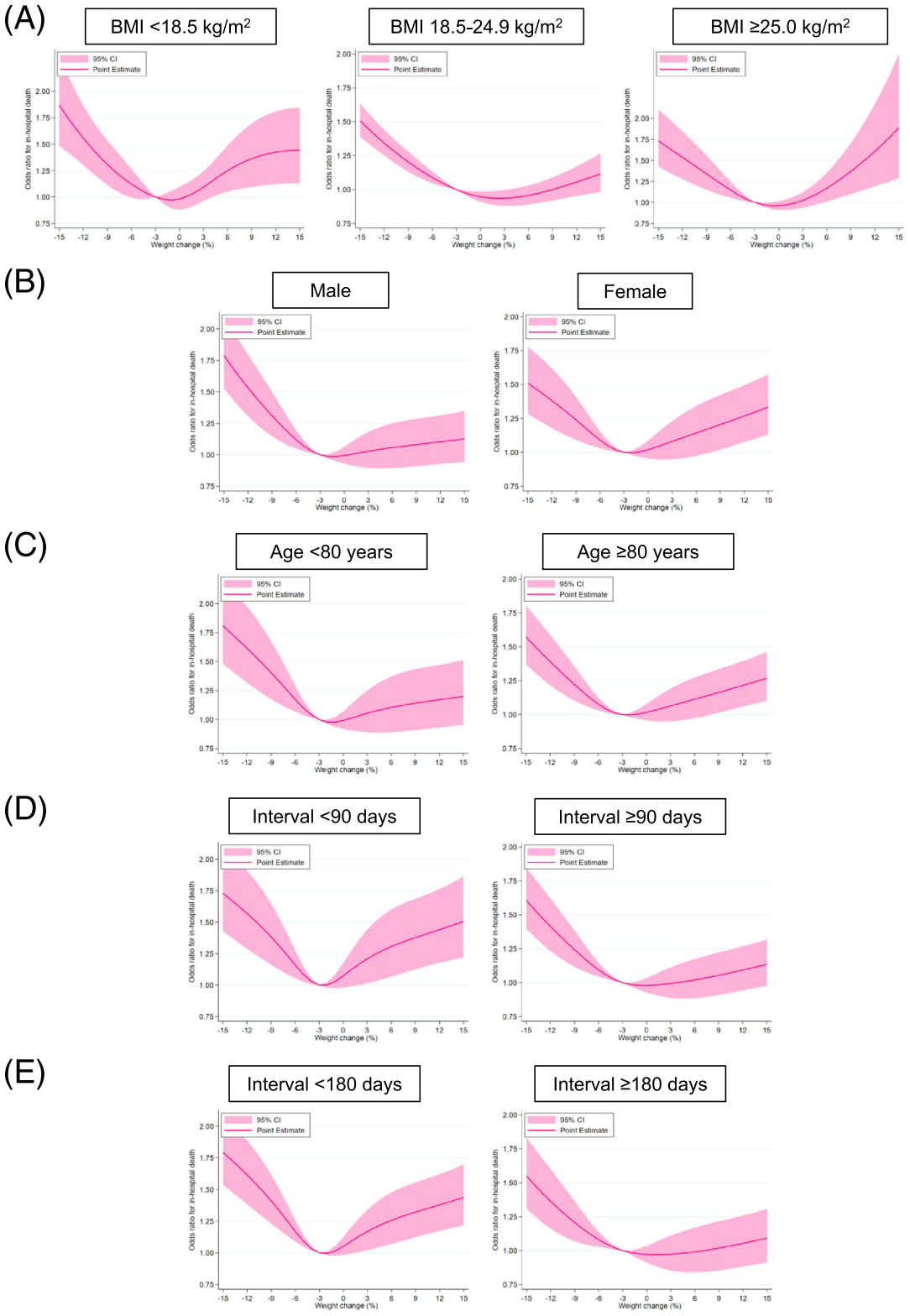

Figure 4 Adjusted dose–response association between weight change and in-hospital mortality in analyses using restricted cubic splines in each subgroup. (A) Patients with body mass index (BMI) <18.5, 18.5–24.9 and ≥25.0 kg/m^2. (B) Male and female patients. (C) Patients aged <80 and ≥80 years. (D) Patients with interval between two hospitalizations <90 and ≥90 days. (E) Patients with interval between two hospitalizations <180 and ≥180 days. The *y* axis represents the odds ratio for in-hospital mortality between individuals with any weight change. Estimates are shown with 95% confidence intervals (CIs).

Table 3 Odds ratios of in-hospital mortality in subgroup analyses by the interval between the two hospitalizations

Weight change	<−5.0%	≥−5.0% and <−2.0%	≥−2.0% and <+2.0%	≥+2.0% and <+5.0%	≥+5.0%
Interval <90 days					
No. of patients	5643	3149	3514	1528	1902
Mortality, *n* (%)	483 (8.6%)	180 (5.7%)	202 (5.7%)	112 (7.3%)	186 (9.8%)
Unadjusted odds ratio [95% CI]	1.53 [1.29–1.82]	0.99 [0.81–1.22]	REF	1.30 [1.02–1.65]	1.78 [1.44–2.19]
P value	<0.001	0.96		0.033	<0.001
Adjusted odds ratio [95% CI][a]	1.48 [1.24–1.77]	1.04 [0.84–1.29]	REF	1.29 [1.00–1.65]	1.49 [1.20–1.86]
P value	<0.001	0.74		0.046	<0.001
Interval ≥90 days					
No. of patients	13 419	4934	5795	3074	5276
Mortality, *n* (%)	1135 (8.5%)	256 (5.2%)	321 (5.5%)	166 (5.4%)	363 (6.9%)
Unadjusted odds ratio [95% CI]	1.58 [1.39–1.79]	0.93 [0.79–1.10]	REF	0.97 [0.80–1.18]	1.26 [1.08–1.47]
P value	<0.001	0.42		0.78	0.003
Adjusted odds ratio [95% CI][a]	1.44 [1.26–1.64]	0.92 [0.77–1.09]	REF	0.96 [0.79–1.18]	1.11 [0.94–1.30]
P value	<0.001	0.32		0.71	0.23
Interval <180 days					
No. of patients	9102	4601	5325	2393	3205
Mortality, *n* (%)	816 (9.0%)	256 (5.6%)	315 (5.9%)	157 (6.6%)	304 (9.5%)
Unadjusted odds ratio [95% CI]	1.57 [1.37–1.79]	0.94 [0.79–1.11]	REF	1.12 [0.92–1.36]	1.67 [1.41–1.96]
P value	<0.001	0.45		0.27	<0.001
Adjusted odds ratio [95% CI][a]	1.50 [1.30–1.72]	0.95 [0.80–1.14]	REF	1.12 [0.91–1.37]	1.40 [1.18–1.67]
P value	<0.001	0.58		0.29	<0.001
Interval ≥180 days					
No. of patients	9960	3482	3984	2209	3973
Mortality, *n* (%)	802 (8.1%)	180 (5.2%)	208 (5.2%)	121 (5.5%)	245 (6.2%)
Unadjusted odds ratio [95% CI]	1.59 [1.36–1.86]	0.99 [0.81–1.21]	REF	1.05 [0.84–1.32]	1.19 [0.99–1.44]
P value	<0.001	0.92		0.67	0.07
Adjusted odds ratio [95% CI][a]	1.42 [1.20–1.67]	0.97 [0.79–1.20]	REF	1.02 [0.80–1.29]	1.06 [0.87–1.29]
P value	<0.001	0.79		0.89	0.59
Interval ≥180 and <360 days					
No. of patients	3733	1486	1742	947	1545
Mortality, *n* (%)	326 (8.7%)	68 (4.6%)	103 (5.9%)	45 (4.8%)	109 (7.1%)
Unadjusted odds ratio [95% CI]	1.52 [1.21–1.91]	0.76 [0.56–1.04]	REF	0.79 [0.55–1.14]	1.21 [0.91–1.60]
P value	<0.001	0.092		0.21	0.18
Adjusted odds ratio [95% CI][a]	1.30 [1.02–1.65]	0.69 [0.50–0.96]	REF	0.74 [0.51–1.07]	0.97 [0.72–1.30]
P value	0.033	0.028		0.107	0.82

Abbreviations: CI, confidence interval; REF, reference.

[a]Adjusted for body mass index in the first hospitalization; age; sex; hypertension; diabetes mellitus; chronic renal failure; chronic liver disease; chronic respiratory disease; cancer; anaemia; coronary artery disease; stroke; dementia; neurological disorder; cigarette smoking; New York Heart Association class; medication use within 2 days after admission, such as intravenous inotropic agent, intravenous nitrate, intravenous furosemide, intravenous carperitide, oral beta-blocker, oral angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker and oral mineralocorticoid receptor antagonist; procedures within 2 days after admission, such as respiratory support, haemodialysis, intra-aortic balloon pumping and extra-corporeal membrane oxygenation; and the interval between two hospitalizations.

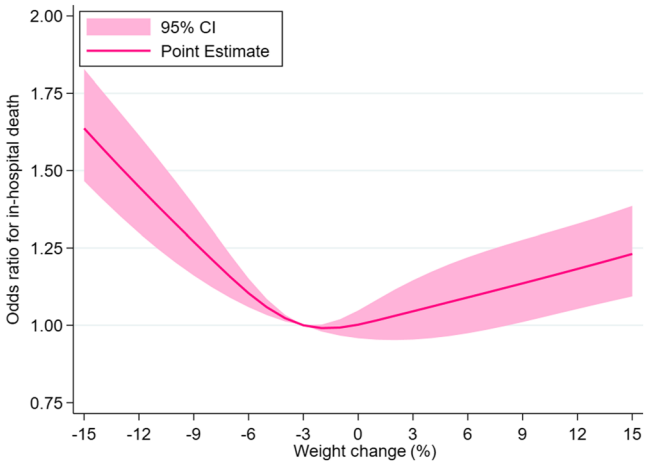

Figure 5 Adjusted dose–response association between weight change and in-hospital mortality in a sensitivity analysis including patients with a hospital stay ≤2 days. The *y* axis represents the odds ratio for in-hospital mortality between individuals with any weight change. Estimates are shown with 95% confidence intervals (CIs).

The most novel finding was that both weight loss and gain were associated with high in-hospital mortality in patients with HF. To date, there have been no reports on the weight gain or loss and in-hospital mortality associated with HF. This finding needs to be divided into two parts; the first is weight loss and in-hospital mortality. Weight loss in HF is often described as cardiac cachexia, which may be associated with the severity of cardiac dysfunction.[17] In our study, the association between weight loss and high mortality remained significant even after adjustment for the New York Heart Association class and mechanical support, both of which are measures of cardiac dysfunction. Although severely diseased cardiac function assessed by more precise examinations (e.g., right heart catheterization or cardiopulmonary exercise test) may be associated with poor outcomes, weight loss was reported as a poor prognostic factor independent of such measures.[18] Aside from the severity of cardiac dysfunction, weight loss may reflect a poor general condition,[19] low nutritional status, and poor resistance to infection[20] and bleeding,[21] which might have contributed to high in-hospital mortality. The detailed association between weight loss and infection or bleeding remains unknown because the studies,[9,18,22,23] including the present study, lacked adjustment for markers of bleeding/infection or cause of death. The association of weight loss with poor outcome was in line with several previous reports[9,18,22,23] and was observed across all subgroups of baseline BMI in our study. Although Niedziela et al. reported that weight loss was associated with increased mortality only in non-obese patients without diabetes,[18,24] we could not compare their study to ours as the baseline characteristics, including ethnicity and setting, differed. Given weight loss as a poor prognostic factor irrespective of the baseline BMI,[6] attention should be paid to weight loss, even in obese patients. Other than baseline BMI, subgroup analyses by sex and age showed similar results, indicating the robustness of the association between weight loss and higher in-hospital mortality observed in the present study.

The association of short- and middle-term weight gain with mortality was prominent in the RCS analysis results, whereas that of long-term weight gain was attenuated. A previous report showed that short-term weight gain after hospitalization for worsening HF was predictive of repeated hospitalization events.[10] One of the proposed mechanisms underlying the association between weight gain and increased mortality may be fluid retention during the short-term period. In addition to fluid retention, it has been suggested that obesity may worsen the prognosis in relation to biventricular remodelling, right ventricular dysfunction, low exercise capacity, abnormal relaxation of pulmonary vasculature, myocardial load due to increased plasma volume, arterial hypertension and atherosclerosis.[25,26]

Weight loss was observed in >60% of patients with repeated hospitalization for HF in our study. This figure seems higher than that in previous reports that included patients with both de novo HF and a history of HF.[27] Patients with a history of worsening HF have been reported as a high-risk population in previous studies, including ours,[15,28,29] and 'frequent flyers' should be treated with caution.[30]

The present study has some limitations. Due to the nature of the administrative claim database, some potentially important data are lacking. These include laboratory testing, measured skeletal muscle/fat mass, weight change during hospitalization, the cause of death, and ejection fraction measured by echocardiography or cardiac magnetic resonance, although a negative prognostic impact of weight loss was observed in previous studies, irrespective of whether

the ejection fraction was preserved or reduced.[9,18,23] Lack of these data would hinder a detailed analysis defining cachexia and focusing on the mechanisms between weight change and mortality. The prevalence of some comorbidities and the prescription rate of HF-related drugs were lower than expected due to the nature of the administrative claim database of the inpatient setting. The interval of weight assessment was not controlled, although the association between weight loss $<-5.0\%$ over an interval of 180–360 days, a commonly used interval to determine weight loss,[5,16] and mortality was consistent with the main result. There may be a selection bias in the analysis as the investigation could not include the patients who did not reach the hospital alive after the discharge from the first hospitalization. Thus, the results cannot be generalized to the patients who did not experience the second hospitalization. Uncertainty in the diagnosis of HF may be another limitation of this nationwide database, although the diagnosis of HF in our database was highly specific (specificity, 97.5%).[31] It may be difficult to generalize our results to obese Caucasian patients due to the differences in patient characteristics across ethnicities, although low BMI appears to be harmful irrespective of ethnicity.[32]

Conclusions

Both weight loss and weight gain in patients with repeated hospitalization for HF were associated with high in-hospital mortality, especially weight loss and short/middle-term weight gain. These results indicate that patients readmitted to the hospital for HF with weight loss or acute weight gain should be treated cautiously.

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Conflicts of interest

Dr. Kaneko and Dr. Fujiu received research funding and scholarship funds from Medtronic Japan Co., Ltd, Biotronik Japan, SIMPLEX QUANTUM Co., Ltd, Boston Scientific Japan Co., Ltd, and Fukuda Denshi, Central Tokyo Co., Ltd. Dr. Kamiya received research funding and scholarship funds from Eiken Chemical Co., Ltd., and SoftBank Corp. The other authors have nothing to declare.

Ethical guidelines statement

The authors certify that they comply with the 'Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle'.[33] This study was approved by the Institutional Review Board of the University of Tokyo and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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