ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 5293–5303
Published online 2 October 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13619

ORIGINAL ARTICLE

Impact of weight loss in patients with heart failure with preserved ejection fraction: results from the FLAGSHIP study

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Abstract

Aims Weight loss (WL) is a poor prognostic factor for patients with heart failure (HF) with reduced ejection fraction. However, its prognostic impact on patients with HF with preserved ejection fraction (HFpEF) remains unestablished. The evidence regarding the effects of obesity on the prognosis of WL is also unclear. We aimed to identify the risk factors for WL and examine the association between WL and prognosis of HFpEF in obese and non-obese patients.

Methods and results In this multicentre cohort study, the data of 573 patients hospitalized with HFpEF [median age: 78 years (interquartile range, 71–84 years); 49.2% female] were identified from hospital databases. WL was defined as ≥5% weight reduction within 6 months after discharge. Obesity was defined according to Japanese criteria as body mass index ≥25 kg/m^2. The main study outcomes were all-cause mortality and HF rehospitalization between 6 and 24 months after hospital discharge. Logistic regression analysis and Cox proportional hazards regression analysis were performed to identify independent the risk factors associated with WL and to calculate the hazard ratios (HRs) associated with adverse outcomes. The prevalence of obesity at discharge was 21.1%. At 6 month follow-up, WL occurred in 17.4% and 10.8% of the obese and non-obese patients, respectively. Onset of WL in non-obese patients was associated with prior hospitalization for HF [odds ratio (OR) 2.39, 95% confidence interval (CI) 1.22–4.68, P = 0.011] and high levels of brain natriuretic peptide (OR 2.32, CI 1.17–4.60, P = 0.015). In obese patients, WL was associated with the use of mineralocorticoid receptor antagonists (OR 3.26, CI 1.08–9.76, P = 0.03) and vasopressin receptor antagonists (OR 6.61, CI 2.03–21.2, P = 0.001). During 1021.3 person-years of follow-up, 31 patients died, and upon 1081.0 person-years follow-up, 84 patients required rehospitalization for HF. In proportional hazards analysis, WL was associated with all-cause mortality (HR 5.12, CI 2.08–12.5, $P < 0.001$) and HF rehospitalization (HR 2.63, CI 1.38–5.01, P = 0.003) after adjustment for confounders in non-obese patients, but not in obese patients.

Conclusions Weight loss should be considered as an indicator for monitoring worsening of HF condition in non-obese patients with HFpEF. WL was not associated with adverse events in obese patients with HFpEF, possibly due to appropriate fluid management during follow-up.

Keywords Heart failure with preserved ejection fraction; Weight loss; Cachexia; Obesity; Prognosis; Cohort study

Received: 6 April 2021; Revised: 12 July 2021; Accepted: 4 September 2021
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Introduction

Heart failure (HF) is a chronic progressive disorder that leads to weight loss (WL) due to metabolic imbalance.[1] WL in HF is associated with oedema and elevated B-type natriuretic peptide (BNP) levels[2–4] and is a powerful, poor prognostic factor given that it is suggestive of cardiac cachexia.[5] Cardiac cachexia is a systemic metabolic disturbance[6]; therefore, WL has been interpreted as a simple and sensitive marker of disease progression.[7] However, reports on the prognostic impact of WL have focused mainly on patients with HF with reduced ejection fraction (HFrEF).[2,5,8]

In elderly patients with HF, the proportion of patients with HF with preserved ejection fraction (HFpEF) is higher than that of patients with HFrEF.[9,10] Patients with HFpEF are older, predominantly female, and usually present multiple comorbidities such as chronic obstructive pulmonary disease, anaemia, and hypertension.[9,11–13] While factors derived from the pathogenesis of HF are associated with WL in patients with HFrEF, ageing and comorbidities have also been reported to be associated with WL.[2–4] This means that the underlying mechanisms of WL in patients with HFpEF who are older and have more comorbidities may be different. Although a recent study has described the prognostic impact of WL in patients with HFpEF,[14] risk factors for its development have not been sufficiently examined.

The association between WL and adverse outcomes in individuals with HF and an elevated body mass index (BMI) has been documented previously,[2,3,5,8] regardless of the ejection fraction.[15–17] However, evidence regarding the impact of WL among non-obese patients is limited. It is likely that the clinical significance of WL varies according to the initial BMI. However, this relation remains to be examined in patients with HFpEF.

Therefore, this study aimed to examine the association between WL and outcomes in patients with HFpEF and identify the possible risk factors for this complication.

Methods

Study design and population

This study was based on the 'multicenter prospective cohort study to develop frailty-based prognostic criteria in HF patients (FLAGSHIP)' study.[18] The FLAGSHIP study enrolled ambulatory patients hospitalized due to acute or exacerbated HF and those aged ≥70 years and hospitalized due to acute myocardial infarction (AMI). 'Ambulatory' was defined as the ability to walk 20 m at hospital discharge, with or without the assistance of a walking aid. Exclusion criteria were as follows: severe cognitive impairment defined as a Mini-Mental State Examination score <17 points[19]; severe mental disorder; difficulty answering questionnaires; and assumed short-term mortality (e.g., severe aortic valve stenosis without surgical indication, terminal stage cancer). Patients were followed up for 2 years to assess frailty status and clinical events.

The FLAGSHIP study protocol was organized according to the Guidelines for the Epidemiological Research proposed by the Japanese Ministry of Health, Labour, and Welfare. Additionally, the study protocol was approved by the Ethics Committee of Nagoya University School of Medicine (approval no. 2014-0421). This investigation conforms with the principles outlined in the *Declaration of Helsinki*. Ethical approval was obtained from each participating hospital. All patients provided written informed consent prior to study enrolment.

From the patients enrolled into the FLAGSHIP study, we excluded patients with AMI and selected patients with HFpEF for this study (n =1178). HFpEF was defined as a left ventricular ejection fraction (LVEF) ≥50% at discharge, assessed by transthoracic echocardiography, and calculated using Simpson's method, in accordance with recent guidelines.[20] We excluded patients who were re-hospitalized due to HF or died within 6 months after discharge (regardless of the cause of death) (n = 223) and those with missing body weight data at 6 months after discharge (n = 382). Finally, 573 patients were eligible for analysis (*Figure 1*).

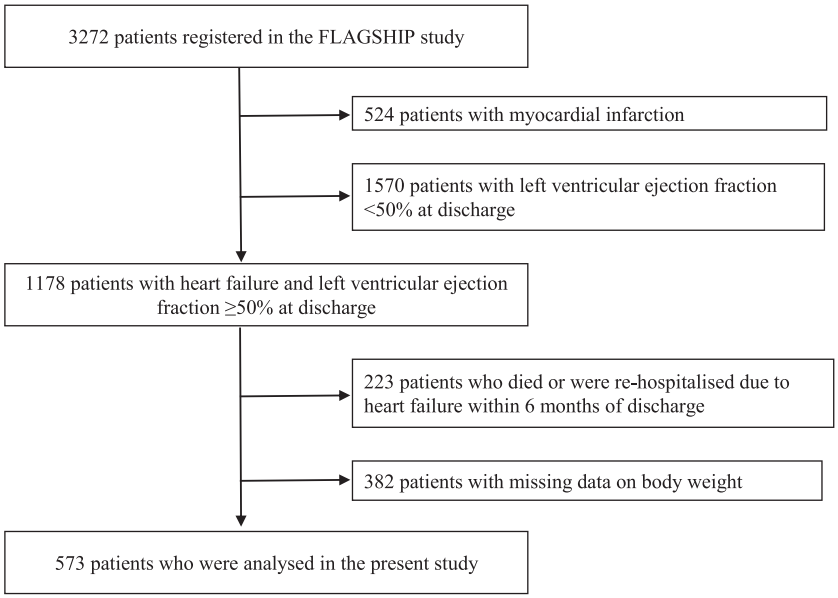
Measurement of body weight and definition of weight loss

Body weight was measured using scales (Digital Health Meter, HD-661, TANITA, Japan) distributed to patients by mail or at routine clinical visits after discharge. Body weight data at discharge and at 6 months after discharge were considered for analysis. WL was defined as a ≥5% weight loss within 6 months from discharge. According to their BMI and based on Japanese criteria,[21] patients were categorized into an obese (BMI ≥ 25 kg/m^2) or non-obese (BMI < 25 kg/m^2) group.

Assessment of post-discharge outcomes

The outcomes of this study were HF rehospitalisations and death due to any cause between 6 and 24 months after hospital discharge. Follow-up data were retrieved from the medical records of the respective hospitals and from a mail survey conducted every 4 months. The diagnosis of HF as a cause of rehospitalization was made by cardiologists at each enrolling institution.

Figure 1 Patient selection flowchart.



Data collection

Patient characteristics, including age, sex, clinical data (HF aetiology, comorbidities, previous admissions due to HF, New York Heart Association class at discharge, and medication use), were collected from medical records. Biochemical data included the levels of BNP, N-terminal-proBNP (NT-proBNP), serum albumin and haemoglobin, and the estimated glomerular filtration rate (eGFR). BNP and NT-proBNP levels ≥200 and ≥900 pg/mL, respectively, were defined as elevated. Anaemia was defined as a haemoglobin level <13 g/dL in men and <12 g/dL in women. Albumin levels <3.4 mg/dL were defined as low. Depression was defined as a score ≥2 in the Geriatric Depression Scale-5 (GDS5).[22] Grip strength (GS) was evaluated using a Jamar dynamometer (Digital Hand Dynamometer, DHD-1, SAEHAN Corporation, South Korea) set at the second handle position at discharge. Two attempts were made with each hand, and the maximum value (in 0.1 kg) of each hand was recorded. Weakness was defined as a GS < 30 kg for men and <17 kg for women. Furthermore, 10 m usual walking speed was performed twice, and the faster result was used as the index of the usual walking speed at discharge. Exercise capacity was assessed using the Performance Measure of Activity in Daily Living-8 (PMADL-8), which is strongly and negatively correlated to the peak VO_2.[23] PMADL-8 is scored from 8 to 32, with higher scores indicating more severe functional limitations than lower scores. Functional limitation was defined as a PMADL-8 score ≥20[24] at discharge and at 6 months after discharge. Appetite was assessed using the Simplified Nutritional Appetite Questionnaire (SNAQ), which includes four items and produces a total score ranging from 4 to 20. Anorexia was defined as a SNAQ score <14[25] at discharge and at 6 months after discharge.

Statistical methods

Continuous variables are reported using medians and interquartile ranges, and categorical variables are reported using counts and percentages. Parameters following a normal distribution were compared using unpaired *t* tests. When data did not follow a normal distribution, the Mann–Whitney test was used for comparison. Categorical variables were analysed using the χ^2 test. Logistic regression analysis was performed to identify independent risk factors associated with WL. Variables with a *P* value <0.1 in univariate analysis were included in multivariable analysis. Kaplan–Meier cumulative survival curves were constructed to evaluate the effect of WL on outcomes and for illustrative purposes and compared using the Mantel–Haenszel log-rank test. A Cox proportional hazards regression analysis was performed to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) associated with adverse outcomes. Additionally, adjustments were made for age and sex in Model 1, and for age, sex, and variables with a *P* value <0.05 in univariate analysis in model 2. A *P* value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA).

Table 1 Baseline characteristics

	Total (n = 573)		Non-obese (n = 452, 78.9%)				Obese (n = 121, 21.1%)			
			WL (n = 49, 10.8%)		non-WL (n = 403, 89.2%)		WL (n = 21, 17.4%)		non-WL (n = 100, 82.6%)	
Age, years	78.0	[71.0–84.0]	81.0	[72.5–86.0]	81.0	[75.0–86.0]	73.0	[68.5–81.5]	75.0	[68.0–81.7]
Female	282	(49.2)	18	(36.7)	205	(50.9)	12	(57.1)	47	(47.0)
BMI, kg/m^2	22.1	[19.6–24.2]	21.6	[19.6–22.9]	21.1	[18.9–22.7]	26.5	[25.7–28.0]	27.1	[25.7–29.0]
Past HF hospitalization	116	(20.0)	18	(36.7)*	74	(18.4)	3	(14.3)	21	(21.0)
Aetiology										
Arrhythmia	150	(26.2)	16	(32.7)	87	(21.5)	8	(36.4)	39	(39.0)
Ischaemic heart disease	142	(24.8)	11	(22.4)	105	(26.1)	3	(14.3)	23	(23.0)
Valve heart disease	131	(22.9)	11	(22.4)	108	(26.7)	2	(9.1)	10	(10.0)
Hypertension	71	(12.4)	6	(19.0)	48	(11.9)	2	(9.1)	15	(15.0)
DCM/HCM	52	(9.1)	1	(2.0)	40	(9.9)	2	(9.1)	9	(9.0)
Pulmonary hypertension	7	(1.2)	0	(0)	6	(1.5)	1	(4.5)	0	(0)
Infiltrative cardiomyopathies	3	(0.5)	0	(0)	3	(0.7)	0	(0)	0	(0)
NYHA Class III–IV	40	(6.0)	4	(8.2)	28	(6.9)	1	(4.8)	7	(7.0)
Comorbidity										
Diabetes mellitus	174	(30.4)	13	(26.5)	111	(27.5)	10	(47.7)	40	(40.0)
COPD	28	(4.9)	1	(2.0)	22	(5.5)	1	(4.8)	4	(4.0)
Af (on admission)	234	(40.9)	18	(36.7)	165	(40.8)	8	(36.4)	43	(43.0)
Cancer	36	(6.2)	1	(2.0)	24	(6.0)	2	(9.5)	9	(9.0)
Medications										
β-blocker	373	(65.1)	27	(55.1)	264	(65.5)	14	(66.7)	68	(68.0)
ACEi/ARB	338	(59.1)	29	(59.2)	221	(55.0)	13	(61.9)	75	(75.0)
MRA	205	(35.8)	21	(42.9)	142	(35.3)	11	(52.4)**	31	(31.0)
Loop diuretic	428	(74.6)	37	(75.5)	305	(75.7)	19	(90.5)**	67	(67.0)
Thiazide diuretic	49	(8.5)	4	(8.2)	38	(9.4)	1	(4.8)	6	(6.0)
Vasopressin receptor antagonist	91	(15.8)	9	(18.4)	63	(15.6)	9	(42.9)**	10	(10.0)
Statin	203	(35.5)	14	(28.6)	136	(33.8)	9	(42.9)	44	(44.0)
Oral inotropic agent	44	(7.7)	3	(6.1)	33	(8.2)	2	(9.5)	6	(6.0)
Anticoagulant	298	(52.1)	24	(49.0)	215	(53.8)	11	(52.4)	48	(48.0)
Aspirin	226	(39.5)	19	(38.8)	164	(40.8)	6	(28.6)	37	(37.0)
Calcium-channel blocker	202	(35.3)	20	(40.8)	122	(30.2)	12	(54.5)	49	(49.0)
PCI during hospitalization	63	(11.0)	4	(8.2)	45	(11.1)	3	(13.6)	15	(15.0)
PM implantation/CRT during hospitalization	39	(6.8)	3	(6.1)	23	(5.7)	0	(0)	13	(13.0)
eGFR, mL/min/1.73 m^2	47.0	[36.0–61.6]	44.2	[31.9–61.5]	48.1	[36.8–62.2]	44.0	[34.9–59.0]	46.0	[35.0–58.3]
Anaemia[a]	350	(61.3)	39	(79.6)*	252	(62.8)	13	(61.9)	46	(46.0)
Low albumin[b]	165	(28.9)	23	(47.9)*	115	(28.5)	6	(28.6)	21	(21.0)
Elevated BNP[c]	277	(48.7)	34	(69.4)*	190	(47.5)	13	(61.9)	40	(40.4)
Depression[d]	200	(34.9)	13	(26.5)	149	(37.0)	7	(33.3)	31	(31.0)
Low GS[e]	228	(39.8)	24	(49)	167	(41.4)	7	(33.3)	30	(30.0)
Walking speed, m/s	0.96	[0.77–1.11]	0.94	[0.80–1.05]	0.94	[0.78–1.11]	1.01	[0.90–1.08]	0.99	[0.75–1.14]

(*Continues*)

Results

Weight loss at 6 months after discharge

Patient characteristics at discharge are shown in *Table 1*. The prevalence of obesity was 21.1%. At 6 months after discharge, WL had occurred in 17.4% and 10.8% of obese and non-obese patients, respectively (P = 0.05). In the non-obese group, patients who experienced WL had a higher prevalence of previous HF exacerbations, anaemia, low albumin levels, and high BNP levels than those who did not present WL. In the obese group, WL was associated with diuretic therapy. In the non-obesity group at 6 months of post-discharge, functional limitations (WL; 59.6%, non-WL; 43.7%), and anorexia (31.9% and 17.6%) in the WL group were significantly more frequent than in the non-WL (*Figure 2*).

A comparison of characteristics between included and excluded patients is shown in the supporting information, *Table S1*. The excluded patients showed no difference in the patient background compared with our study population.

The results of univariate and multivariate analyses to identify risk factors for WL are shown in *Table 2*. After adjusting for age and sex in multivariate analysis, past HF hospitalizations and high BNP levels were significantly associated with WL in the non-obese group. Additionally, mineralocorticoid receptor antagonists and vasopressin receptor antagonists were significantly associated with WL in the obese group.

Weight loss and subsequent outcomes

During 1021.3 person-years of follow-up, 31 patients died (26 non-obese and 5 obese). Regarding readmissions due to HF, during 1081.0 person-years of follow-up, 84 patients (63 non-obese and 21 obese) experienced this complication. Obese patients had a lower risk of death of any cause (HR: 1.40; 95% CI: 0.54–3.61) and readmission due to HF (HR: 0.80; 95% CI: 0.49–1.32) than non-obese patients.

According to the presence or absence of WL in non-obese and obese groups, event-free survival curves are shown in Figure 3. In the non-obese group, WL was a risk factor for all-cause death and readmission due to HF. However, this was not the case in the obese group. This association remained after adjusting for confounders in Cox proportional hazards analysis (*Table 3*).

The HRs of all-cause death and readmission due to HF for variables are shown in *Table* S2. WL could not be evaluated as a risk factor in the obese group because the occurrence of the primary outcome was low in this group (5 and 21 cases for the WL and non-WL groups, respectively).

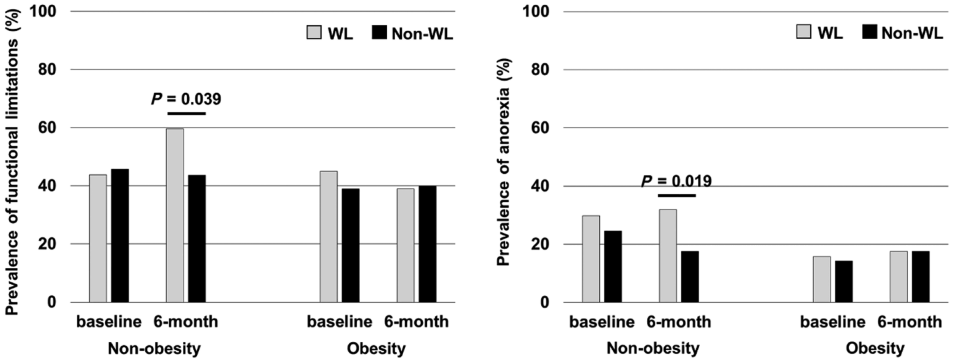
Table 1 (continued)

	Total (n = 573)		Non-obese (n = 452, 78.9%)			Obese (n = 121, 21.1%)		
			WL (n = 49, 10.8%)		non-WL (n = 403, 89.2%)	WL (n = 21, 17.4%)		non-WL (n = 100, 82.6%)
PMADL-8	15	[15–24]	19	[16–23]	20	[15–24]	20	[16–23]	19	[14–25]
Anorexia[f]	120	(22.9)	14	(29.8)	90	(24.5)	3	(15.8)	13	(13.0)
CR after discharge	147	(25.7)	9	(18.8)	111	(27.6)	5	(23.8)	22	(22.0)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; Af, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CR, cardiac rehabilitation; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; GDS5, the Geriatric Depression Scale-5; GS, grip strength; HCM, hypertrophic cardiomyopathy; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; PMADL, performance measure of activity in daily living; SNAQ, Simplified Nutritional Appetite Questionnaire.
Data are presented as median (interquartile range), or n (%).
[a]Haemoglobin levels <13 g/dL in men and <12 g/dL in women.
[b]Albumin levels <3.4 g/dL.
[c]BNP levels ≥200 pg/mL or NT-proBNP ≥ 900 pg/mL.
[d]GDS5 ≥ 2 points.
[e]GS < 30 kg for men and <17 kg for women.
[f]SNAQ <14 points.
*P < 0.05 vs. non-weight loss in non-obese patients.
**P < 0.05 vs. non-weight loss in obese patients.

DOI: 10.1002/ehf2.13619

Figure 2 Functional limitations and anorexia at discharge and after 6 months of hospital discharge. (A) Functional limitations. (B) Anorexia. In non-obesity group (at base line, 6 months): weight loss group; *n* = 49, *n* = 47, non-weight loss group; *n* = 403, *n* = 375. In obesity group (at base line, 6 months): weight loss group; *n* = 21, *n* = 18, non-weight loss group; *n* = 100, *n* = 91



Discussion

This study is the first to report the incidence and prognostic impact of WL exclusively in patients with HFpEF. We found that WL was associated with a poor prognosis in non-obese patients, but not in obese patients. Furthermore, WL was associated with past hospitalizations due to HF and high BNP levels in the former and diuretic therapy in the latter. Therefore, our results reveal that WL in non-obese individuals with HFpEF has a negative prognostic significance.

The reported incidence of WL in patients with HF is approximately 10–15% and increases in New York Heart Association class III and IV patients.[2,3,5,8] Based on our results, its incidence in patients with HFpEF seems to be in line with these figures (10.8% and 17.4% in the non-obese and obese groups, respectively). It is worth noting that most patients included in previous studies presented with HFrEF, were younger (sixth decade of age), and had a higher mean BMI (over 25 kg/m^2) than our patients (whose mean age and BMI were 78 years and 22.1 kg/m^2, respectively). A previous study including lean patients (mean BMI 23 kg/m^2, mean age 73 years) showed a similar incidence of WL (11%).[4] In summary, the incidence of WL in patients with HFpEF and HFrEF seems to be similar.

In the present study, non-obese patients with WL had higher all-cause mortality and re-hospitalization rates than their pairs without WL. The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity study, which included both patients with HFpEF and HFrEF, had already shown that WL impacts prognosis negatively in HF, independently of the LVEF.[2] However, most of the patients in the previous studies were obese and included patients with HFrEF.[2,4] The present study is novel in that it examined the prognostic impact of WL in patients with HFpEF with and without obesity and clarified the negative impact in non-obesity patients.

Progressive WL in HF is often a hallmark of cachexia, which is associated with significantly high morbidity and mortality.[26] Cachexia is driven by various pathophysiological mechanisms, including neuroendocrine abnormalities, inflammatory system activation, increased lipolysis, and muscle wasting.[26,27] This complication affects 10–15% of patients with HF, becomes apparent as disease severity progresses, and is associated with a poor prognosis.[26,27] In our study, WL in the non-obesity group was associated with elevated BNP and a history of HF re-hospitalizations. In general, elevated BNP reflects the severity of HF, and patients with HF deteriorate to cardiac cachexia with repeated readmissions. Furthermore, at 6 months of hospital discharge, a high proportion of patients in the WL group in the non-obesity group presented with functional limitations and anorexia, suggesting that their physical function and nutritional status were deteriorating. Therefore, cardiac cachexia may be associated with the clinical background of WL in the non-obesity group. WL may indicate that the degree of neurohormonal activation has reached a clinically relevant degree; therefore, increasing the mortality risk. The non-obesity group was a population of elderly patients presenting with cachexia with multiple comorbidities. It is reported that an exercise programme for patients with HFpEF with reduced physical function can improve exercise tolerance.[28] Therefore, we speculate that in the non-obesity group, it is necessary to maintain appropriate body weight by monitoring weight loss as a pathological indicator, maintain appropriate nutritional status, and improve physical function through exercise programmes.

Given the small number of obese patients in our study, we could not examine the association between WL and prognosis in this subgroup. Therefore, the results in this group represent preliminary data. While the risk of death associated with WL remained unchanged when obesity was excluded from analysis, re-hospitalizations increased. This may suggest that WL is not associated with an increased risk

Table 2 Logistic regression analysis for variables associated with weight loss at 6 months after discharge

	Non-obese						Obese					
	Univariate			Multivariate*			Univariate			Multivariate*		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.01	(0.98–1.04)	0.44	0.99	(0.96–1.03)	0.78	0.99	(0.95–1.04)	0.86	0.98	(0.93–1.03)	0.51
Female	0.56	(0.30–1.03)	0.06	0.59	(0.31–1.12)	0.11	1.50	(0.58–3.88)	0.40	1.11	(0.38–3.32)	0.84
BMI	1.06	(0.94–1.20)	0.32				1.03	(0.87–1.21)	0.70			
Past HF hospitalization	2.58	(1.37–4.86)	<0.01	2.39	(1.22–4.68)	0.01	0.62	(0.16–2.33)	0.48			
Aetiology												
Arrhythmia	1.75	(0.92–3.33)	0.08	1.75	(0.88–3.47)	0.10	0.96	(0.36–2.53)	0.93			
Ischaemic heart disease	0.82	(0.40–1.66)	0.58				0.55	(0.15–2.04)	0.38			
Valve heart disease	0.78	(0.38–1.59)	0.50				0.94	(0.19–4.67)	0.94			
Hypertension	1.02	(0.41–2.54)	0.95				0.59	(0.12–2.85)	0.51			
DCM/HCM	0.18	(0.02–1.40)	0.10				1.06	(0.21–5.32)	0.94			
Pulmonary hypertension		N/A**						N/A**				
Infiltrative cardiomyopathies		N/A**						N/A**				
NYHA Class III–IV	1.19	(0.39–3.54)	0.75				0.66	(0.07–5.70)	0.70			
Comorbidity												
Diabetes mellitus	0.95	(0.48–1.85)	0.88				1.36	(0.53–3.50)	0.52			
COPD	0.36	(0.04–2.73)	0.32				1.20	(0.12–11.3)	0.87			
Cancer	0.32	(0.04–2.48)	0.28				1.06	(0.21–5.32)	0.94			
Af (on admission)	0.83	(0.45–1.54)	0.56				0.81	(0.31–2.14)	0.67			
Medications												
β-blocker	0.64	(0.35–1.17)	0.15				0.94	(0.34–2.55)	0.90			
ACEi/ARB	1.18	(0.65–2.17)	0.57				0.54	(0.20–1.45)	0.22			
MRA	1.37	(0.73–2.54)	0.30				2.44	(0.97–2.54)	0.06	3.26	(1.08–9.76)	0.03
Loop diuretics	0.26	(0.54–1.17)	0.80				1.17	(0.75–1.81)	0.48			
Thiazide diuretic	0.77	(0.46–1.28)	0.32				0.75	(0.19–2.95)	0.69			
Vasopressin receptor antagonist	1.21	(0.56–2.62)	0.62				6.75	(2.28–19.9)	<0.01	6.61	(2.03–21.2)	<0.01
Statin	0.78	(0.40–1.50)	0.46				0.95	(0.36–2.46)	0.92			
Oral inotropic agent	0.73	(0.21–2.47)	0.61				1.64	(0.30–8.80)	0.55			
Anticoagulant	0.83	(0.46–1.51)	0.56				1.19	(0.46–3.05	0.71			
Aspirin	0.91	(0.50–1.68)	0.78				0.68	(0.24–1.90)	0.46			
Calcium-channel blocker	1.60	(0.87–2.94)	0.12				1.38	(0.53–3.58)	0.49			
PCI during hospitalization	0.74	(0.25–2.16)	0.58				0.64	(0.13–3.08)	0.58			
PM implantation/CRT during hospitalization	1.07	(0.31–3.71)	0.90					N/A**				
eGFR	0.99	(0.97–1.00)	0.24				0.99	(0.97–1.02)	0.85			
Anaemia[a]	2.30	(1.11–4.75)	0.02	1.68	(0.77–3.65)	0.18	1.90	(0.72–5.00)	0.18			
Low albumin[b]	2.30	(1.25–4.22)	<0.01	1.87	(0.96–3.63)	0.06	1.48	(0.51–4.29)	0.46			
Elevated BNP[c]	2.50	(1.32–4.74)	<0.01	2.32	(1.17–4.60)	0.01	2.39	(0.91–6.31)	0.07	2.13	(0.72–6.31)	0.17
Depression[d]	0.61	(0.31–1.19)	1.53				1.11	(0.40–3.02)	0.83			
Low GS[e]	1.35	(0.74–2.45)	0.31				1.16	(0.42–3.18)	0.76			

(*Continues*)

Table 2 (continued)

	Non-obese						Obese					
	Univariate			Multivariate*			Univariate			Multivariate*		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Walking speed	0.96	(0.31–2.95)	0.94				1.35	(0.23–7.96)	0.73			
PMADL-8	0.97	(0.92–1.03)	0.39				0.99	(0.92–1.07)	0.84			
Anorexia[f]	1.30	(0.66–2.54)	0.43				1.12	(0.28–4.40)	0.86			
CR after discharge	0.60	(0.28–1.29)	0.19				1.10	(0.36–3.36)	0.85			

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; Af, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CR, cardiac rehabilitation; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; GDS5, the Geriatric Depression Scale-5; GS, grip strength; HCM, hypertrophic cardiomyopathy; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; PMADL, performance measure of activity in daily living; SNAQ, Simplified Nutritional Appetite Questionnaire.
Data are presented as odds ratio (OR) and 95% confidence interval (95% CI) as assessed by logistic regression analysis.
Data are presented as median (interquartile range), or *n* (%).
[a]Haemoglobin levels <13 g/dL in men and <12 g/dL in women.
[b]Albumin levels <3.4 g/dL.
[c]BNP levels ≥ 200 pg/mL or NT-proBNP ≥ 900 pg/mL.
[d]GDS5 ≥ 2 points.
[e]GS <30 kg for men and <17 kg for women.
[f]SNAQ <14 points.
*Only variables with a P-value <0.1 in univariate analysis were included in multivariate analysis.
**Not applicable.

of re-hospitalizations in obese patients. However, WL in the obesity group was associated with the use of diuretics at discharge in the present study. As patients with HF often present with fluid retention, elimination of oedema by diuretic therapy may be misdiagnosed as WL due to cachexia.[7] In other words, we speculate that the obesity group in this study included patients whose WL was caused by diuretics, and this may have led to an improved prognosis. Hence, WL may be particularly critical among non-obese patients.

Obesity (defined as a BMI ≥ 25 kg/m^2) was not a risk factor for adverse outcomes in the present study. In a previous study including patients with HFpEF, the incidence of the composite outcomes (all-cause death and HF re-hospitalizations) was higher in patients with BMIs <23.5 kg/m^2 and >35 kg/m^2 than in those with a BMI of 26–29 kg/m^2.[16] Although approximately 75% of patients in the obese group had a BMI of 29 kg/m^2 in the present study, the small number of outcomes in this group may have precluded reaching statistical significance. Furthermore, WL in the obesity group was not associated with worsening of symptoms, suggesting WL in obesity group may result from fluid management. In obese patients with HFpEF with diabetes mellitus or metabolic syndrome, hemodynamic monitoring allows for an increase in diuretic dosage, resulting in an improved prognosis.[29] Given that a high proportion of diabetes mellitus and that diuretic prescription was associated with WL in the obesity group in this study, the WL in the obesity group could have reflected the results of proper fluid management. Moreover, it has been suggested that the complication of sarcopenia in obese patients with HFpEF patients may be associated with clinical outcomes.[30] Because about 30% of the obese group in our study included a group with reduced GS, we speculate that the presence of sarcopenic obese cases may have affected the outcome. Future studies should consider the evaluation of different body compartments when assessing BMI.

Limitations

The present study had several limitations. First, only ambulatory patients at the time of discharge and with complete weight data were included in the analysis. Those who died or were readmitted within 6 months of discharge were excluded. Patients who died or early readmitted patients after discharge had a higher HF severity than our study population. Thus, the results of this study cannot be applied to them. Second, confounding factors such as medications, including SGLT2 inhibitors and intentional or unintentional WL, may have varied within 6 months after discharge and thus affected our results. Third, in the FLAGSHIP study, the scales were aligned to the same model, but other measurement conditions were not necessarily controlled, which may have

Figure 3 Kaplan–Meier curves of all-cause death and rehospitalization due to heart failure. (A) Non-obesity group. (B) Obesity group. WL, weight loss

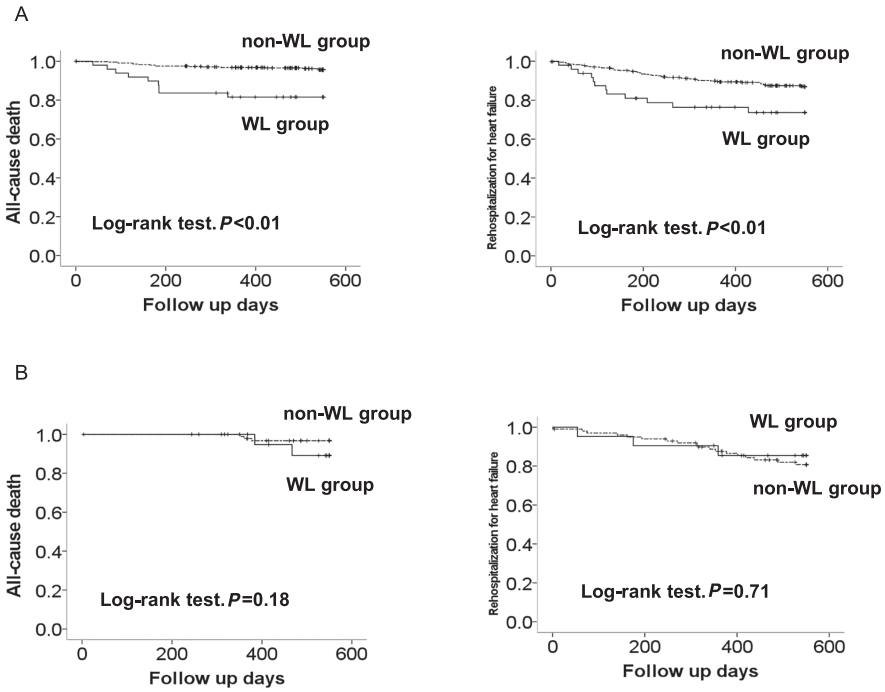


Table 3 Hazard ratios for all-cause death and rehospitalization due to heart failure

	All patients			Non-obese patients		
	Non-WL	WL		Non-WL	WL	
All-cause death						
No. of patients	503	70		403	49	
Person-years of follow-up	957.9	124.0		768.0	84.2	
No. of all-cause death	20	11		17	9	
Incidence rate/1000 person-years	20.9	88.7		22.1	106.9	
HR in the crude model	1	4.30	(2.06–8.99)	1	4.85	(2.15–10.81)
HR in the adjusted model[a]	1	4.07	(1.94–8.54)	1	4.35	(1.89–9.95)
HR in the adjusted model[b,c]	1	3.44	(1.61–7.35)	1	5.12	(2.08–12.5)
Rehospitalization due to heart failure						
No. of patients	503	70		403	49	
Person-years of follow-up	909.4	112.3		730.5	75.0	
No. of re-hospitalizations due to heart failure	69	15		51	12	
Incidence rate/1000 person-years	75.9	133.5		69.8	159.9	
HR in the crude model	1	1.82	(1.03–3.17)	1	2.37	(1.26–4.44)
HR in the adjusted model[a]	1	1.80	(1.02–3.15)	1	2.36	(1.24–4.45)
HR in the adjusted model[d,e]	1	1.90	(1.05–3.43)	1	2.63	(1.38–5.01)

Abbreviations: CI, confidence interval; HR, hazard ratio; WL, weight loss.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, past-heart failure hospitalization, elevated levels of brain natriuretic peptide, low albumin, use of mineralocorticoid receptor antagonists, and use of vasopressin receptor antagonists.
[c]Adjusted for age, sex, past heart failure hospitalisation, arrhythmia as an etiology, low grip strength in non-obese patients.
[d]Adjusted for age, sex, infiltrative cardiomyopathies as an etiology, New York Heart Association class III-IV, use of loop diuretics, use of oral inotropic agent, low albumin, low grip stregth, walking speed in all pateints.
[e]Adjusted for age, sex, infiltrative cardiomyopathies as an etiology, use of oral inotropic agent, low grip strength, walking speed in non-obese patients.

led to the misidentification of weight. Fourth, we may have misclassified patients with HF with recovered EF as patients with HFpEF because the LVEF data were adopted at the time of hospital discharge. Finally, because of the small number of events in the obesity group, we refrained from performing multivariate analysis and adjusting for confounding factors

to investigate the association between WL and outcomes in this subpopulation.

Conclusions

In non-obese patients with HFpEF, WL within 6 months of hospital discharge was an independent risk factor for all-cause mortality and rehospitalization after 6 months post-discharge. Additionally, WL was associated with previous admissions due to HF and elevated BNP or NT-proBNP levels. Thus, WL is an important prognostic indicator after the discharge of patients with HFpEF. Screening and management for this complication after hospitalizations may be necessary to prevent adverse outcomes in patients with HF.

Acknowledgements

We wish to thank the participants of this study for their contribution, without which these analyses would not have been possible. In addition, we would like to thank all FLAGSHIP collaborating investigators.

Conflict of interest

None declared.

Funding

This work was supported by a Grant-in-Aid for Scientific Research (A) from the Japan Society for the Promotion of Science (grant number 16H01862). We did not receive any funding from commercial organizations for the conduction of this study.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Comparison between the study cohort and excluded patients.
Table S2. A Cox proportional hazards regression analysis for all-cause death and rehospitalisation due to heart failure

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