


Prognostic impact of muscle and fat mass in patients with heart failure

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Abstract

Background Cachexia, characterized by loss of muscle with or without loss of fat mass, is a poor prognostic factor in patients with heart failure (HF). However, there is limited investigation on the prognostic impact of muscle and fat mass separately in HF. We hypothesized that muscle and fat mass have different effects on the prognosis of HF.

Methods This was an observational cohort study of 418 patients (59% were men) admitted with a diagnosis of HF (71 ± 13 years [mean ± standard deviation]), with left ventricular ejection fraction (LVEF) of 39 ± 16%, including 31.3%, 14.8%, and 53.8% of patients with preserved LVEF (LVEF ≥ 50%), mid-range LVEF (40–50%), and reduced (<40%) LVEF, respectively. Dual-energy X-ray absorptiometry was performed with the patients in the stable state after decongestion therapy.

Results The mean body mass index of patients was 22.1 ± 4.6 kg/m², and the mean appendicular skeletal mass (ASM) index was 6.88 ± 1.23 kg/m² in men and 5.59 ± 0.92 in women; 54.1% of the patients showed reduced muscle mass defined by the international cut-off value (7.0 kg/m² for men and 5.4 for women). The mean fat mass was 20.4 ± 7.2% in men and 27.2 ± 8.6% in women. During a median follow-up of 37 months, 92 (22.0%) of 418 patients with HF died (1 and 3 year mortality: 8.4% and 17.3%, respectively). Lower values of both skeletal muscle and fat mass were independently associated with increased risk of mortality adjusted for age, sex, haemoglobin, New York Heart Association functional class, and height squared (hazard ratio with 95% confidence interval of 0.825 [0.747–0.908] per 1 kg increase of ASM, *P* < 0.001, and 0.954 [0.916–0.993] per 1 kg increase of fat mass, *P* = 0.018, respectively).

Conclusions More than half of the patients with HF showed reduced muscle mass. Lower values of both muscle and fat mass were associated with higher mortality in HF.

Keywords Sarcopenia; Cachexia; Frailty; Skeletal muscle; Fat mass; Heart failure

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Introduction

Obesity is a public health problem with an increased risk of all-cause and cardiovascular disease mortality.¹ Weight reduction is recommended for obese or overweight individuals who

would benefit from weight loss.¹ However, among those diagnosed with a chronic disease such as heart failure (HF) or cancer, being overweight is a favourable prognostic factor, which is the so-called obesity paradox.² In a prospective cohort study

including 6142 patients with HF across four continents, a higher body mass index was associated with decreased mortality (9% decrease at 1 year for every 5 kg/m² increase in body mass index).³ Cachexia, which is characterized by loss of muscle with or without loss of fat mass,⁴ is a major possible mechanism underlying the obesity paradox. Anorexia, inflammation, insulin resistance, and increased muscle protein breakdown are frequently associated with cachexia, and the key component of the definition of cachexia was at least 5% loss of body weight during the previous 12 months or less.⁴ In a previous study, weight loss of $\geq 6\%$ was a strong predictor of impaired survival in patients with HF.⁵ However, in most studies, cachexia is defined by total body weight loss; thus, the impact of each body component, namely, muscle and fat mass, on survival in HF is unknown.

Dual-energy X-ray absorptiometry (DXA) is recommended for the measurement of muscle mass,^{6,7} and it also provides data regarding fat mass. Muscle mass plays an important role especially in older frail patients as it helps them maintain physical activity, which in turn improves health-related outcomes,^{8,9} whereas fat mass may also have some clinical benefits.¹⁰ Skeletal muscle as an endocrine organ produces hormones known as myokines, some of which may have beneficial effects on the heart. An exercise-induced myokine ameliorated acute myocardial ischemic injury.¹¹ In another study, skeletal muscle may act as a second pump and contribute to cardiac output through a blood volume shift from the legs to the heart.¹² On the contrary, adipose tissue produces soluble tumour necrosis factor- α receptors and could play a protective role in patients with HF by neutralizing the adverse effects of tumour necrosis factor- α .¹³ Adipose tissue expresses the natriuretic clearance receptor, which suppresses circulating natriuretic peptides, potentially leading to the early detection of HF by making the patients symptomatic.¹⁴ Therefore, we hypothesized that muscle and fat mass have different effects on the prognosis of HF.

Methods

Study population

The study was an observational cohort study of patients with HF. Among 841 consecutive patients who were hospitalized for worsening HF at the Yokohama City University Medical Center between December 2012 and July 2017, 422 patients, regardless of their age and severity, underwent DXA and were retrospectively analysed for this study. The diagnosis of HF was based on the Framingham criteria.¹⁵ Patients with incomplete data (i.e. patient's height, $n = 1$) and those who died during hospitalization ($n = 3$) were excluded. Thus, 418 patients were included in the final analysis. All participants were notified regarding their participation in the study, and signed informed consent was obtained from each patient.

This study was approved by our institutional ethics board and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Clinical and laboratory measurement

Haematology and biochemistry tests were performed at discharge. Underlying diseases (hypertension, diabetes, coronary artery disease, atrial fibrillation, implanted devices, valvular diseases, chronic obstructive pulmonary disease, stroke, and malignancy) were diagnosed at discharge according to the international clinical data standards.¹⁶ The estimated glomerular filtration rate was calculated using the modified formula described in the Modification of Diet in Renal Disease study, which was conducted by the Japanese Society of Nephrology.¹⁷ CONTrolling NUTritional status (CONUT), a screening tool for malnutrition, was calculated according to the original study.¹⁸ Echocardiography was performed with standard parasternal and apical views during hospitalization.

Body composition analysis

We used a DXA scan (Discovery, Hologic Japan Inc., Tokyo, Japan) to measure muscle and fat mass in the whole body. DXA was performed with the patients in the stable state after decongestion therapy and before discharge. The patients' body weights were measured on the same day. In this period, we recommend DXA to all patients admitted for HF as a screening method for osteoporosis because HF is an independent risk factor for osteoporotic fractures.¹⁹ Appendicular skeletal muscle mass (ASM) was defined as the sum of the lean soft tissue masses in the extremities. ASM index (ASMI) and fat mass index were calculated as each mass divided by height squared (kg/m²). The cut-off values determined by the Asian Working Group for Sarcopenia (≤ 7.00 kg/m² for men and ≤ 5.40 kg/m² for women) were adopted.²⁰ The percentage fat mass was calculated as the percentage of fat mass (kg) divided by the total body weight (kg).

Follow-up

After discharge, most patients were followed up in outpatient clinics at least every 3 months. The clinical outcome data were obtained from a review of medical records of the hospital and information sent from the introduced hospital/clinic. Clinical outcomes were evaluated for a median (25th–75th percentile) follow-up of 37.0 (19.0–55.4) months. The study focused on all-cause mortality, and the composite endpoint consisting of all-cause mortality and HF rehospitalization was also tracked. HF rehospitalization was defined as a condition that required

intravenous drug administration with typical HF symptoms and pulmonary oedema or congestion on chest radiography. To verify the diagnosis of HF, three physicians on the event committee reviewed all medical records. If these physicians disagreed on the event classification, they adjudicated differences.

Statistical analysis

Data for continuous variables were expressed as the mean \pm standard deviation with normal distribution, or as median (25th–75th percentile) with a skewed distribution. We analysed the baseline clinical characteristics using Student's *t*-test for continuous variables with normal distribution, Mann–Whitney test for continuous variables with skewed distribution, and χ^2 tests or Fisher's exact test for categorical variables. The correlation between the patients' muscle and fat mass was assessed with the use of the Pearson coefficient. To characterize muscle mass and fat mass in HF, we performed univariate and multivariate linear regression analyses for each mass. To estimate the cumulative incidence of an event, we employed Kaplan–Meier time-to-event curves using the log-rank test according to the quartiles of each body component. Cox-proportional hazards models were used to investigate the association between each body component and clinical outcomes. Multivariate models included the variables with $P < 0.05$ in the univariate analysis and validated in a large-scale cohort²¹ [age, sex, creatinine, haemoglobin, and New York Heart Association (NYHA) functional class]. Patients' height squared was also included to adjust their body size. To evaluate the incremental prognostic value of body composition, we constructed the following two models for each outcome: a baseline model, which incorporated the same variables as those in the multivariate Cox model plus body weight, and the baseline model + ASM and fat mass. We compared the areas under the curve (AUCs) between the two models and calculated the net reclassification improvement and integrated discrimination improvement. The presence of a nonlinear association between each body component and all-cause mortality was evaluated using regression spline models. All statistical tests were two-tailed, and a P value < 0.05 was considered statistically significant. Analyses were carried out using JMP Pro software 12 (SAS Institute Japan Inc., Tokyo, Japan) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study patients

The study cohort consisted of 59.1% male participants, and the mean age was 71 ± 13 years. The median length of stay was 18 days (interquartile range, 14–27). Baseline

characteristics of the study population according to reduced and preserved left ventricular ejection fraction (LVEF) are presented in *Table 1*. The study cohort consisted of 193 (46.2%) patients with preserved LVEF (LVEF $\geq 50\%$: $N = 131$, 31.3%)/mid-range ($40\% \leq$ LVEF $< 50\%$: $N = 62$, 14.8%) LVEF [heart failure with preserved ejection fraction (HFpEF)/heart failure with mid-range ejection fraction (HFmrEF)] and 225 (53.8%) patients with HF with reduced LVEF [LVEF $< 40\%$: heart failure with reduced ejection fraction (HFrEF)]. Patients with HFrEF were younger and more likely to be male, whereas the body mass index was similar between the two groups. The median CONUT score was available in 413 patients, with a median value of 2 (interquartile range, 1–4), and 18.2% was categorized as moderate to severe malnutrition.

Body composition

Patients underwent DXA a median of 6 days (interquartile range, 1–12) before discharge. Body mass index was similar between patients with and without DXA (22.1 ± 4.6 vs. 21.7 ± 4.1 kg/m², $P = 0.18$). At discharge, leg oedema remained in 37 of 397 (9.3%) patients and was not documented in 21 patients. Results from DXA are shown separately by sex in *Table 2*. The mean ASMI in all HF patients was 6.88 ± 1.23 kg/m² in men and 5.59 ± 0.92 in women; 54.1% (61.1% of men and 43.9% of women) of the patients showed reduced muscle mass according to the Asian Working Group for Sarcopenia guidelines. Most of the components were not different between patients with HFrEF and those with HFpEF/HFmrEF. Univariate and multivariate linear regression analysis results for ASM and fat mass as continuous variables are shown in Supporting Information, *Table S1* and *Table 3*, respectively. The association between fat mass and B-type natriuretic peptide (BNP) as well as that between ASM and LVEF is shown in *Figure S1*. The absence of hypertension was associated with lower ASM, whereas the absence of coronary artery disease, lower haemoglobin, and higher BNP was associated with lower fat mass, and lower LVEF was associated with both lower ASM and lower fat mass. Measured skeletal muscle mass was associated with fat mass (*Figure S2*), although the association was not robust ($r = 0.598$ and $P < 0.001$ for men and $r = 0.459$ and $P < 0.001$ for women, respectively).

Outcome

During the median follow-up of 37.0 months, 92 (22.0%) patients died and 192 (45.9%) experienced the composite outcome of all-cause mortality and HF rehospitalization. The 1 and 3 year mortality rates were 8.4% and 17.3%, respectively. *Figure 1* depicts the cumulative risk of death stratified by the

Table 1 Characteristics of patients

	Missing data	All	HFpEF/HFmrEF	HFrEF	P
N		418	193	225	
Age (years)	0	71 (13)	75 (11)	68 (14)	<0.001
Male	0	59.1%	51.8%	65.3%	0.005
Body mass index (kg/m ²)	0	22.1 (4.6)	22.2 (4.1)	22.1 (5.0)	0.679
Readmission	0	27.8%	27.5%	28.0%	0.910
Comorbidity					
Hypertension	0	75.1%	82.4%	68.9%	0.002
Diabetes	0	36.6%	37.3%	36.0%	0.839
Coronary artery disease	0	39.0%	38.9%	39.1%	1.000
Atrial fibrillation	0	35.4%	44.0%	28.0%	<0.001
CLBBB	0	10.0%	4.7%	14.7%	<0.001
ICD	0	1.7%	0.5%	2.7%	0.130
CRT	0	1.2%	1.0%	1.3%	1.000
Severe valvular disease	0	3.3%	5.7%	1.3%	0.026
COPD	0	5.3%	6.7%	4.0%	0.273
Stroke	0	8.6%	8.3%	8.9%	0.863
Malignancy	0	8.9%	10.4%	7.6%	0.388
Status at discharge					
NYHA class	0				0.344
≤2		83.7%	82.9%	84.4%	
3		15.8%	17.1%	14.7%	
4		0.5%	0.0%	0.9%	
Systolic blood pressure (mmHg)	1	110 (17)	114 (17)	107 (17)	<0.001
Heart rate (bpm)	1	72 (13)	72 (12)	73 (13)	0.778
Laboratory findings at discharge					
Haemoglobin (g/dL)	0	12.0 (2.2)	11.3 (2.2)	12.6 (2.0)	<0.001
Creatinine (mg/dL)	0	1.39 (1.04)	1.39 (1.02)	1.40 (1.05)	0.917
Estimated GFR (mL/min/1.73m ²)	0	16 (19)	44 (18)	47 (19)	0.107
Sodium (mEq/L)	0	139 (3)	140 (3)	139 (3)	0.314
Total cholesterol (mg/dL)	1	169 (44)	168 (45)	170 (44)	0.585
Lymphocyte count (/μL)	0	1536 (573)	1451 (553)	1609 (580)	0.005
Albumin (g/dL)	1	3.62 (0.53)	3.52 (0.53)	3.70 (0.51)	<0.001
BNP, median (pg/mL)	0	240 [132–417]	237 [120–402]	247 [142–432]	<0.001
Medication at discharge					
Beta blocker	1	72.7%	59.4%	84.0%	<0.001
ACE inhibitor/ARB	0	81.8%	76.2%	86.7%	0.007
Statin	0	44.3%	40.9%	47.1%	0.236
Oral anticoagulant	0	42.3%	50.8%	35.1%	0.002
Digoxin	0	10.0%	10.9%	9.3%	0.627
Loop diuretics	0	78.7%	71.0%	85.3%	<0.001
Dose (mg) ^a		20 [10–40]	20 [0–40]	20 [20–40]	0.230
MRA	0	59.6%	52.8%	65.3%	0.012
LVEF (%)	0	39 (16)	54 (11)	26 (6)	<0.001

Values are mean (standard deviation) or median [interquartile range].

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CLBBB, complete left bundle branch block; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronised therapy; GFR, glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardio-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineral corticoid receptor antagonist; NYHA, New York Heart Association.

^aFurosemide-equivalent dose.

quartiles of each body component. There was a significant difference in mortality among the quartiles of ASMI, fat mass index, and % fat mass ($P < 0.001$, $P = 0.004$, and $P = 0.006$ by log-rank, respectively). The cumulative risk of the composite outcome is shown in *Figure S3*. The lower quartile of ASMI was associated with an elevated risk of the composite outcome.

Univariate and multivariate Cox proportional hazard analysis findings for mortality are shown in *Tables S2* and *4*, respectively. After adjustment for age, sex, height squared, serum creatinine, haemoglobin, and NYHA class, both ASM and fat mass were independently associated with a reduced

risk of all-cause mortality (adjusted hazard ratio (HR) with 95% confidence interval: 0.825 [0.747–0.908] per 1 kg increase of ASM, $P < 0.001$ and 0.954 [0.916–0.993] per 1 kg increase in fat mass, $P = 0.018$, respectively). The HR was similar when the models additionally included LVEF (0.812 [0.731–0.897] per 1 kg increase in ASM, $P < 0.001$, and 0.954 [0.914–0.992] per 1 kg increase in fat mass, $P = 0.018$, respectively). Analysis by quartiles of each mass is shown in *Table S3*. The impact of the lowest quartile of ASM and fat mass on mortality was preserved even when both of them were included in the same model (the adjusted HR of the lowest quartile of ASM was 1.740 [1.069–2.798],

Table 2 Results from dual-energy X-ray absorptiometry

<Men>	All	HFpEF/HFmrEF	HFrEF	P
N	247	100	147	
Body weight (kg)	62.5 (15.2)	61.9 (14.9)	62.3 (15.4)	0.757
Body mass index (kg/m ²)	22.6 (4.5)	23.1 (4.4)	22.2 (4.6)	0.143
Lean body mass (kg)	46.9 (9.0)	46.9 (8.9)	46.9 (9.0)	1.000
Lean body mass (%)	76.1 (6.8)	75.6 (7.3)	76.4 (6.5)	0.350
Lean mass: arms (kg/m ²)	5.3 (1.2)	5.2 (1.2)	5.3 (1.2)	0.578
Lean mass: legs (kg/m ²)	13.8 (3.2)	13.8 (3.3)	13.8 (3.2)	0.856
Appendicular skeletal mass (kg)	19.1 (4.3)	19.1 (4.4)	19.1 (4.2)	0.986
ASMI (kg/m ²)	6.88 (1.23)	6.99 (1.26)	6.81 (1.20)	0.257
Reduced muscle mass ^a	61.1%	60.0%	61.9%	0.791
Fat mass (kg)	13.4 (7.7)	13.9 (7.7)	13.2 (7.6)	0.470
Fat mass (%)	20.4 (7.2)	21.1 (7.6)	20.0 (6.8)	0.219
Fat mass index (kg/m ²)	4.8 (2.6)	5.1 (2.6)	4.7 (2.6)	0.234
<Women>	All	HFpEF/HFmrEF	HFrEF	P
N	171	93	78	
Body weight (kg)	48.5 (11.6)	47.0 (8.2)	50.2 (14.5)	0.092
Body mass index (kg/m ²)	21.6 (4.6)	21.4 (3.5)	21.8 (5.7)	0.571
Lean body mass (kg)	33.3 (5.5)	32.7 (3.8)	33.9 (6.9)	0.199
Lean body mass (%)	70.0 (8.3)	70.6 (7.9)	69.2 (8.7)	0.264
Lean mass: arms (kg/m ²)	3.4 (0.7)	3.3 (0.5)	3.4 (0.8)	0.650
Lean mass: legs (kg/m ²)	9.2 (1.8)	9.1 (1.3)	9.3 (2.2)	0.664
Appendicular skeletal mass (kg)	12.6 (2.4)	12.5 (1.7)	12.7 (3.0)	0.635
ASMI (kg/m ²)	5.59 (0.92)	5.68 (0.81)	5.49 (1.03)	0.178
Reduced muscle mass ^a	43.9%	37.6%	51.3%	0.089
Fat mass (kg)	13.9 (7.7)	13.0 (5.8)	14.9 (9.3)	0.132
Fat mass (%)	27.2 (8.6)	26.6 (8.2)	27.8(9.0)	0.376
Fat mass index (kg/m ²)	6.1 (3.3)	5.9 (2.5)	6.5 (4.0)	0.269

Values are mean (standard deviation).

ASMI, appendicular skeletal mass index; HFpEF/HFmrEF, heart failure with preserved/mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction.

^aReduced muscle mass was defined by cut-off in the Asia Working Group of Sarcopenia: ASMI < 7.0 kg/m² (men) and <5.4 kg/m² (women).

Table 3 Multivariate linear regression for appendicular skeletal mass and fat mass as dependent variables

	ASM		Fat mass	
	Standardized beta	P	Standardized beta	P
Age (years)	-0.289	<0.001	-0.389	<0.001
Male	0.236	<0.001	-0.292	<0.001
Height squared	0.460	<0.001	0.118	0.101
Hypertension	0.073	0.008	0.055	0.216
Diabetes	0.029	0.309	0.083	0.077
Coronary artery disease	0.024	0.423	0.103	0.033
Atrial fibrillation	0.016	0.596	-0.001	0.983
NYHA class	-0.035	0.210	0.080	0.081
Haemoglobin (g/dL)	0.069	0.057	0.211	<0.001
Creatinine (mg/dL)	0.018	0.518	0.060	0.194
Total cholesterol (mg/dL)	0.022	0.424	0.022	0.635
Lymphocyte	0.010	0.735	0.027	0.565
Albumin (g/dL)	0.027	0.362	0.002	0.975
Log BNP	-0.041	0.160	-0.162	<0.001
LVEF (%)	0.150	<0.001	0.118	0.016
Model adjusted R ²	0.73		0.29	

ASM, appendicular skeletal mass; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

$P = 0.026$, and that of the lowest quartile of fat mass was 1.603 [1.030–2.462], $P = 0.037$, respectively). We additionally adjusted these models with log BNP, which showed a similar trend (adjusted HR: 0.840 [0.760–0.923] per 1 kg increase in ASM, $P < 0.001$, and 0.961 [0.923–1.002] per 1 kg increase in fat mass, $P = 0.057$). The AUCs remained unchanged when ASM and fat mass were added to the baseline model based on the total body weight (AUC: 0.759 for baseline and 0.760 for baseline plus ASM and fat mass, $P = 0.61$; net reclassification index of 0.12, $P = 0.30$, and integrated discrimination improvement of 0.004, $P = 0.17$). The same tendency of low ASM and low fat mass having a negative impact on mortality was observed in the subgroup analysis among patients with HFrEF (adjusted HR: 0.831 [0.710–0.967] per 1 kg increase of ASM, $P = 0.016$, and 0.949 [0.891–1.006] per 1 kg increase of fat mass, $P = 0.082$, respectively) and HFpEF/HFmrEF (adjusted HR: 0.806 [0.697–0.919] per 1 kg increase of ASM, $P < 0.001$, and 0.960 [0.906–1.018] per 1 kg increase of fat mass, $P = 0.16$, respectively).

Figure S4 shows the association between ASMI, fat mass index, and probability of death. Restricted cubic spline modelling with four knots was used. The association between ASMI and mortality was neither linear nor had clear cut-off points for each sex.

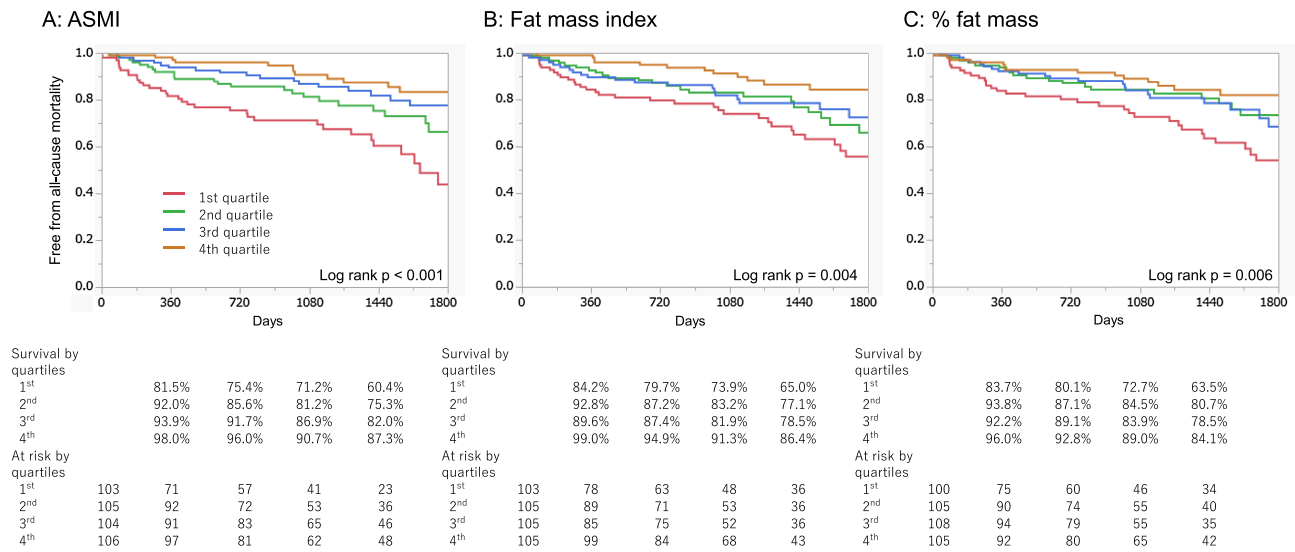


Figure 1 Fikaplan–Meier estimates of the cumulative incidence of all-cause mortality according to quartiles of each body component. Kaplan–Meier curve according to quartiles of ASMI (A), fat mass index (B), and % fat mass (C) for all-cause mortality. ASMI, appendicular skeletal muscle mass index.

Table 4 Cox proportional hazard analysis for mortality

	Unadjusted Cox model			Adjusted Cox model					
	Hazard ratio (95% CI)	P		Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
ASM per 1 kg	0.923 (0.877–0.968)	<0.001		0.825 (0.747–0.908)	<0.001	Not included		0.842 (0.762–0.930)	<0.001
Fat mass per 1 kg	0.921 (0.886–0.954)	<0.001		not included		0.954 (0.916–0.993)	0.018	0.972 (0.932–1.014)	0.18

The multivariate model included age, sex, creatinine, haemoglobin, NYHA class, and height squared. ASM, appendicular skeletal muscle mass; CI, confidence interval.

Discussion

Principal findings

The principal findings in this study are as follows: (i) more than half of the patients hospitalized with HF showed reduced muscle mass, and (ii) lower values of both muscle and fat mass were associated with higher mortality in HF.

Potential mechanisms and comparison with previous studies

Potential mechanisms underlying poor prognosis in HF patients with lower muscle and fat mass have been discussed under the phenomenon called the ‘obesity paradox’. Lavie *et al.* proposed several reasons for the obesity paradox in HF and non-HF settings, which involved protective cytokines, earlier presentation, increased muscle mass and muscular strength, and better cardiorespiratory fitness in obese

patients.² Most of these reasons may also explain poor outcomes in patients with low muscle and fat mass. Coats *et al.* proposed the ‘muscle hypothesis’, which refers to a pathophysiological cycle between left ventricular dysfunction and skeletal and respiratory myopathy.²² Myokines have been proposed as protective cytokines released by the skeletal muscle²³ and may be one of the key players in the muscle hypothesis. However, although many studies have been conducted regarding muscle function and its impact on the patients’ functional capacity and prognosis, information on muscle mass in patients with HF is relatively scarce.^{24–26} Fülster *et al.* reported a lower prevalence of reduced muscle mass (19.5%) than reported in the present study,²⁷ in which such disparity may be due to the clinical (ambulatory vs. hospitalized) and racial differences between their study and the present study. In the present study, lower values of both skeletal muscle and fat mass were associated with high mortality in HF. On the contrary, Melenovsky *et al.* reported that wasting of fat, but not of lean mass, was predictive of adverse outcomes in patients with advanced HF. However, fat mass was assessed by the skin-fold method in this study,²⁸ so that

lean mass measured by Melenovsky *et al.* might not have the same meaning as ASM. They discussed the lipolytic effect of BNP as an underlying mechanism in which high BNP levels in patients with severe HF may reduce their fat mass.²⁹ They also hypothesized that fat loss precedes lean mass depletion, whereas von Haehling *et al.* found that skeletal muscle is lost earlier than fat tissue and the transition from sarcopenia to cachexia was the wasting continuum in HF.³⁰ Although neither of these conflicting concepts is based on longitudinal analysis, patients in the present study were in earlier stages, with BNP levels of approximately 200 pg/mL, in contrast to the BNP levels of approximately 800 pg/mL among patients in the study by Melenovsky *et al.* These reasons may explain why lower values of both skeletal mass and fat mass were associated with higher mortality in our population. Low skeletal muscle mass may act as a marker of malnutrition, which is a poor prognostic factor in HF.^{31,32} Of note, low muscle mass is included in the definition of cachexia⁴ (defined by $<7.25 \text{ kg/m}^2$ in men and $<5.45 \text{ kg/m}^2$ in women) and malnutrition³³ (defined as $<7.0 \text{ kg/m}^2$ in men and $<5.4 \text{ kg/m}^2$ in women). We measured several markers for nutritional status: total cholesterol, lymphocyte count, and serum albumin. However, none of these variables was significantly associated with low ASMI or fat mass index after multivariate adjustment.

Regarding LVEF, the impact of muscle and fat mass on mortality was similar between those with HFrEF and HFpEF/HFmrEF in the present study. Reduced functional capacity in HFpEF has been widely investigated in recent studies,^{34–36} most of which were focused on skeletal muscle function, but not on muscle mass. The prognostic evidence of muscle or fat mass is also scarce in HFpEF. Haykowsky *et al.* reported a relationship between regional adipose distribution and exercise intolerance in HFpEF.³⁵ They concluded that increased intra-abdominal fat was the strongest independent predictor of impaired functional capacity. They also reported that intermuscular fat had a negative impact on exercise intolerance.³⁶ Data from the SICA-HF study^{27,37} provided information regarding functional capacity and muscle mass in HFpEF, although no information regarding prognosis was provided. Most of the studies reporting the shorter survival in patients with cardiac cachexia are based on data from patients with HFrEF^{5,38}; thus, whether the pathophysiology is common between patients with HFpEF and HFrEF remains unclear.

Strengths and limitations

To the best of our knowledge, this is the first study to reveal that both muscle and fat are associated with mortality in patients with HF, incorporating detailed data in ASM by DXA, which is recommended to measure muscle mass. Although fat mass estimated by the skin-fold method is reported to be associated with that by DXA scan,²⁸ the correlation might

be insufficient ($r^2 = 0.56$), and this method does not distinguish skeletal muscle mass out of the whole lean mass. The results of the present study may have some implications in lifestyle modification, possibly supporting the recent guidelines,³⁹ which do not recommend weight loss unless obesity is more advanced (body mass index 35–45 kg/m^2) and it is necessary to manage symptoms. Although it is not very important whether weight loss means muscle loss or fat loss, we may need attention because too much fat may lead to orthopaedic problems or sleep-disordered breathing. There may also be some possibility to support future intervention studies to keep muscle and fat mass. Although exercise interventions may improve muscle mass in older people,⁴⁰ evidence in patients with HF is scarce.

This study has some limitations. Because of the nature of this observational study, the results may be influenced by unknown or unmeasured confounding factor(s). Nearly half of the patients did not undergo DXA. However, we recommended DXA in all patients so that the reason for not undergoing DXA was estimated to be the limited availability of the DXA scanner in most cases. Patient characteristics in HF, especially those regarding body mass, vary significantly between Asian and Western countries; however, the obesity paradox appears to be a common phenomenon regardless of ethnicity.³ Due to a lack of data regarding muscle function (i.e. grip strength and gait speed), we could not determine the presence or absence of sarcopenia as defined in the current guidelines.²⁰ Some patients ($<10\%$) were discharged with residual leg oedema, which can lead to the overestimation of muscle or fat mass to some extent⁴¹; however, the prevalence of residual oedema was lower in the present study than in a previous study.⁴² The length of stay was longer than that in the United Kingdom or United States, although it was within a standard length in Japan,⁴³ which may negatively influence the patients' body composition. The lack of data regarding adipokines or myokines may be a limitation of this study, although it is beyond the scope of this study to investigate the direct mechanism between fat/muscle mass and prognosis. We do not have data on caloric intake, which may be a good marker of nutritional status.

Conclusions

More than half of the patients with HF showed reduced muscle mass. Indices of muscle and fat mass had an impact on predicting mortality in patients with HF.

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Online supplementary material

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

Figure S1. Association between: Log BNP and fat mass, and LVEF and ASM

Figure S2. Correlation between appendicular skeletal mass and fat mass

Figure S3. Kaplan–Meier estimates of the cumulative incidence of the composite of all cause mortality and rehospitalization due to heart failure according to quartiles of each body component

Figure S4. Probability plot for all cause mortality according to each body component

Table S1. Univariate linear regression for ASM and fat mass as dependent variables

Table S2. Univariate Cox proportional hazard analysis for mortality

Table S3. Unadjusted and adjusted Cox proportional hazard model for mortality

Conflict of interests

K.T. has received lecture fees from Daiichi-Sankyo, Mochida, Kyowa-hakko Kirin, Pfizer, Boehringer Ingelheim Japan, and Daiinippon-Sumitomo. His institution has received a research grant from Daiichi-Sankyo, Takeda, Mochida, Kyowa-hakko Kirin, Pfizer, Novartis, Daiinippon-Sumitomo, AstraZeneca, Ono Pharmaceutical, Tsumura, Kaneka, and Oriental Yeast. K.K. has received lecture fees from Astrazeneca, Toa Eiyo Ltd., MSD, Bayer, and Daiichi-Sankyo. His institution has received a research grant from MSD, Daiichi-Sankyo, Ono Pharmaceutical, Pfizer, Bayer, Takeda, Boehringer Ingelheim Japan, Tanabe Mitsubishi, and Astellas Pharma. S.v.H. has been a paid consultant to Vifor Pharma, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Brahms, Chugai Pharma, Roche, and Novartis. S.D.A. has been a paid consultant to or receiving fees for speaking from Bayer, Boehringer Ingelheim, Thermo Fisher Scientific, Novartis, Servier, and Vifor Pharma; his institution has received a research grant from Vifor Pharma and Abbott Vascular. M.K., E.A., Y.M., R.S., S.K., H. N., N.M., N.I., M.K., and T.M. declare that they have no conflicts of interest.

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