



Canadian Journal of Cardiology ■ (2026) 1–10

Clinical Research

Fat Mass and Cause-Specific Death in Older Patients with Heart Failure

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ABSTRACT

Background: Prior studies in patients with heart failure (HF) have reported inconsistent associations between fat mass and mortality, but they did not account for heterogeneity in causes of death. We evaluated whether higher fat mass relates differently to cardiovascular (CV) and non-CV death in older patients with HF.

Methods: We performed a secondary analysis of the multicentre FRAGILE-HF (Prevalence and prognostic value of physical and social frailty in geriatric patients hospitalized for heart failure) cohort, including patients aged ≥ 65 years hospitalized for decompensated HF. Fat mass was measured by bioelectrical impedance and indexed

RÉSUMÉ

Contexte : Des études antérieures menées chez des patients atteints d'insuffisance cardiaque (IC) ont rapporté des associations incohérentes entre la masse grasseuse et la mortalité, mais elles ne tenaient pas compte de l'hétérogénéité des causes de décès. Nous avons évalué si une masse grasseuse plus élevée était associée différemment à la mortalité cardiovasculaire (CV) et non CV chez les patients âgés atteints d'IC.

Méthodologie : Nous avons réalisé une analyse secondaire de la cohorte multicentrique FRAGILE-HF (prévalence et valeur pronostique de la fragilité physique et sociale chez les patients gériatriques

Keywords: heart failure; fat mass; cause-specific death; older adults

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See page 8 for disclosure information.

Received for publication October 24, 2025. Accepted December 15, 2025.

Heart failure (HF) affects approximately 64 million people worldwide, and populations are rapidly aging.^{1,2} Age-related changes, together with HF-specific pathophysiology, foster catabolic and inflammatory states that promote sarcopenia,³ frailty,⁴ and cardiac cachexia.⁵ Accordingly, assessment of body composition is important for identifying these conditions, which may involve progressive loss of both fat mass and skeletal muscle.³⁻⁵

For body composition assessment, quantifying fat mass is particularly relevant in HF. Adipose tissue contributes metabolic reserve during acute decompensation and periods of reduced

as fat mass index (FMI, kg/m²). Patients were stratified by sex-specific tertiles (low-FMI, middle-FMI, high-FMI). Outcomes were all-cause death, CV death, and non-CV death within 2 years. Kaplan–Meier curves with log-rank tests and Cox models assessed associations with mortality.

Results: In total, 1332 patients were enrolled, and 900 were analyzed (median age, 81 years [interquartile range, 74–86]; 57.6% men). During the follow-up period, 171 deaths occurred, including 95 CV deaths and 76 non-CV deaths. Using low-FMI as the reference category, all-cause death was significantly lower in those with high-FMI (hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.40–0.89; $P = 0.011$). For cause-specific death, CV death was significantly lower in high-FMI (HR 0.33, 95% CI 0.18–0.60; $P < 0.001$), although non-CV death did not differ in middle-FMI (HR 0.81, 95% CI 0.47–1.40; $P = 0.444$) or high-FMI (HR 0.89, 95% CI 0.52–1.54; $P = 0.685$).

Conclusions: Higher FMI is linked to a lower risk of CV death but not non-CV death, indicating that its prognostic value depends on cause of death.

intake, and it exerts endocrine and immunomodulatory effects that interact with the inflammatory and catabolic milieu common in HF.⁶ Specifically, stored triglycerides in adipose tissue can be mobilized when caloric intake is reduced or metabolic demands increase, limiting the need to catabolize skeletal and cardiac muscle; and adipose-derived adipokines and cytokines can modulate neurohormonal activation and systemic inflammation, both of which are closely linked to HF progression and cardiovascular (CV) events.⁶ Assessing fat mass, rather than relying on body mass index that is confounded by edema and cannot separate fat from fat-free compartments, captures the adipose component itself and helps distinguish nutritional loss from fluid-driven weight change.⁷ In addition, measuring fat mass helps identify discordant phenotypes that body mass index often misses, including hidden thinness and sarcopenic obesity, and it complements muscle and functional measures in risk stratification.⁸

Recent systematic reviews report that the association between fat mass and prognosis in HF has not been consistent.⁹ Most studies that used fat mass as an exposure relied on all-cause mortality as the endpoint and did not distinguish causes of death.^{10–16} In older HF populations, non-CV deaths have become increasingly frequent,¹⁷ and separating CV from non-CV deaths may be a key to understanding these inconsistent findings. Consistent with this context, in our prior study using the FRAGILE-HF (Prevalence and prognostic value of physical and social frailty in geriatric patients hospitalized for heart failure) cohort,¹⁸ an increasing number of frailty domains was associated with more non-CV deaths, whereas CV deaths were not clearly related, indicating differences in the distribution of fatal pathways in older patients. Taken together, these observations suggest that clarifying the association between fat mass and survival may require analyses that separate CV from non-CV deaths.

hospitalisés pour insuffisance cardiaque), comprenant des patients âgés de 65 ans ou plus hospitalisés pour une IC décompensée. La masse grasseuse a été évaluée par impédancemétrie bioélectrique et indexée sous forme d'indice de masse grasseuse (IMG, kg/m²). Les patients ont été stratifiés par tertiles spécifiques au sexe (IMG faible, IMG moyen, IMG élevé). Les critères d'évaluation étaient la mortalité toutes causes confondues, la mortalité CV et la mortalité nonCV sur une période de deux ans. Les courbes de Kaplan-Meier avec tests logarithmique par rangs et les modèles de Cox ont permis d'évaluer les associations avec la mortalité.

Résultats : Au total, 1 332 patients ont été recrutés et 900 ont été évalués (âge médian, 81 ans [intervalle interquartile 74-86]; 57,6 % d'hommes). Au cours du suivi, 171 décès sont survenus, dont 95 décès CV et 76 décès nonCV. En utilisant la classe à faible IMG comme catégorie de référence, la mortalité toutes causes confondues était significativement plus faible dans le groupe à IMG élevé (rapport de risque [RR] 0,60, intervalle de confiance [IC] à 95 % 0,40-0,89; $p = 0,011$). En ce qui concerne les décès selon une cause spécifique, la mortalité CV était significativement plus faible dans le groupe à IMG élevé (RR 0,33, IC à 95 % 0,18-0,60; $p < 0,001$), bien que la mortalité nonCV ne diffèrait pas dans le groupe à IMG moyen (RR 0,81, IC à 95 % 0,47-1,40; $p = 0,444$) ou à IMG élevé (RR 0,89, IC à 95 % 0,52-1,54; $p = 0,685$).

Conclusions : Un IMG élevé est associé à un risque plus faible de décès CV, mais pas de décès nonCV, ce qui indique que sa valeur pronostique dépend de la cause du décès.

The aim of this study was to examine the association between fat mass and mortality in older patients with HF, separating CV from non-CV deaths. Such cause-specific resolution may help refine clinical decision-making by aligning strategies that protect CV outcomes with targeted approaches to mitigate non-CV risks.

Materials and Methods

Study design

This study was a secondary analysis of the FRAGILE-HF cohort, which was a prospective, multicentre, observational cohort across 15 hospitals in Japan.¹⁹ Consecutive patients were screened during September 2016 to March 2018, and follow-up was performed after discharge. The study conformed to the Declaration of Helsinki and received approval from the ethics committees of all participating institutions.

Under Japan's Ethical Guidelines for Medical and Health Research Involving Human Subjects, the protocol qualified for an opt-out approach (no written consent required for this observational design without invasive procedures). Study information (objectives, eligibility, and participating centres) was publicly posted on the University Hospital Medical Information Network (UMIN-CTR, UMIN000023929) before enrollment. Participants retained the right to withdraw at any time.

Patient population

We evaluated all consecutive patients aged ≥ 65 years who were admitted for decompensated HF and were ambulatory at discharge. HF decompensation was diagnosed according to the Framingham criteria. We excluded the following individuals: those with prior heart transplantation or left ventricular assist

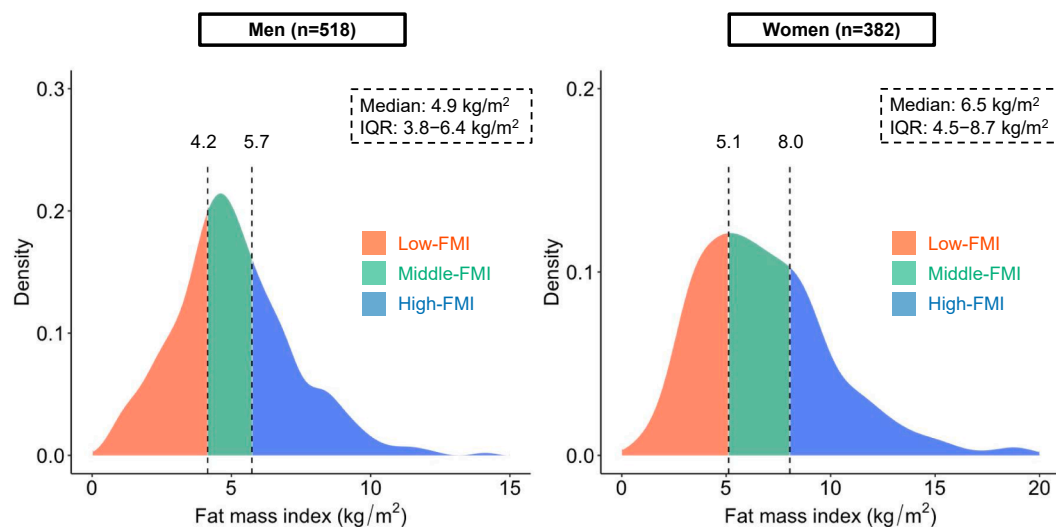


Figure 1. Distribution of fat mass index (FMI) stratified by sex. IQR, interquartile range.

device implantation; those on chronic peritoneal dialysis or hemodialysis; those with acute myocarditis; and those with low natriuretic peptide levels at admission (B-type natriuretic peptide < 100 pg/mL or N-terminal pro-B-type natriuretic peptide < 300 pg/mL). Patients with missing data on fat mass also were excluded from the analysis.

Data collection and definitions

Baseline data recorded on the medical record form included demographic characteristics, comorbidities, medication at discharge, echocardiographic parameters, laboratory data, the Meta-analysis Global Group in Chronic HF (MAGGIC) risk score,^{20,21} and physical function. The MAGGIC risk score was developed to predict all-cause mortality in patients with chronic and acute HF using 13 clinical variables (age, sex, body mass index, systolic blood pressure, left ventricular ejection fraction, New York Heart Association class, creatinine, current smoking, diabetes, chronic obstructive pulmonary disease, time since diagnosis of HF, and use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blocker and beta-blockers).²⁰ The score ranges from 0 to 56 points, with higher scores indicating a higher risk of death. Handgrip strength was measured using a dynamometer.²² Participants were seated with the elbow flexed at 90° and were tested alternately with both hands. The absolute value from 2 trials with each hand was recorded in kilograms. The Short Physical Performance Battery, which consists of 3 components (standing balance, usual gait speed, and repeated chair stands), was administered using established procedures. The score range was 0–12, with 0–4 points assigned to each component (0 = worst; 12 = best).²² Usual gait speed was measured over a marked 4-m course at the participant's usual pace.²³ The 6-minute walk distance was measured according to the American Thoracic Society guidelines.²⁴ Patients were instructed to walk as far as possible in 6 minutes, using assistive devices if needed.

In this analysis, fat mass was indexed using the fat mass index (FMI), defined as fat mass (kg) divided by height squared (m²).^{25,26} Fat mass was measured by bioelectrical impedance

analysis using a commercially available multi-segment body composition analyzer (BC-622; Tanita, Tokyo, Japan). Tanita multi-segment bioelectrical impedance analyzers use prediction equations that have been developed and validated in Japanese adults²⁷ and have been widely applied in previous FRAGILE-HF analyses, in which bioimpedance-derived indices of fat and muscle mass were associated with physical function and prognosis.²⁸ For downstream analyses, FMI was stratified by sex into tertiles, and patients were assigned to low-FMI, middle-FMI, or high-FMI groups (Fig. 1).

The outcomes were all-cause death, CV death, and non-CV death. After discharge, patients were followed at outpatient clinics or other medical facilities at intervals of roughly 3 months, according to clinical need. For individuals not seen in a clinic, survival status and circumstances of death were ascertained by telephone contact and review of medical records across facilities. According to the previous study,^{18,29} site investigators initially assigned each death during follow-up to 1 of the following 8 prespecified causes: (1) HF death; (2) acute coronary syndrome; (3) sudden cardiac death; (4) stroke; (5) renal failure; (6) other CV causes; (7) non-CV/non-renal causes; and (8) unknown. For the present analysis, we then collapsed these groupings into 2 categories—CV death (causes 1–6) and non-CV death (causes 7 and 8). Two board-certified cardiologists, independent of the original FRAGILE-HF team, adjudicated the cause of death; any disagreement was resolved by a third cardiologist.

Statistical analysis

Continuous variables are presented as medians with interquartile range (IQR), and categorical variables are presented as counts and percentages. For baseline comparisons, 1-way analysis of variance or the Kruskal–Wallis test was used for continuous measures, as appropriate to distributional assumptions, and χ^2 tests were applied to categorical measures.

We first examined time-to-event outcomes for all-cause death, CV death, and non-CV death using Kaplan–Meier curves with log-rank tests to compare groups. We then estimated the hazard ratio (HR) with 95% confidence interval (CI)

Table 1. Patient characteristics

Characteristic	Missing value (%)	Overall (n = 900)	Low-FMI (n = 301)	Middle-FMI (n = 299)	High-FMI (n = 300)	P
FMI, kg/m ²	0 (0.0)	5.3 [3.9–7.3]	3.4 [2.6–3.9]	5.4 [4.8–6.2]	8.4 [6.9–9.8]	< 0.001
Age, y	0 (0.0)	81 [74–86]	82 [75–86]	81 [74–86]	79 [72–85]	0.001
Male sex	0 (0.0)	518 (57.6)	173 (57.5)	172 (57.5)	173 (57.7)	0.999
Body mass index, kg/m ²	0 (0.0)	21.0 [18.8–23.5]	18.0 [16.7–19.4]	20.8 [19.8–21.9]	24.6 [23.2–27.0]	< 0.001
NYHA class III or IV	0 (0.0)	113 (12.6)	43 (14.3)	35 (11.7)	35 (11.7)	0.541
Systolic blood pressure, mm Hg	0 (0.0)	113 [104–125]	112 [102–125]	113 [103–124]	113 [104–126]	0.447
Diastolic blood pressure, mm Hg	0 (0.0)	62 [56–69]	60 [53–67]	61 [56–68]	64 [58–70]	< 0.001
Heart rate, bpm	0 (0.0)	69 [60–79]	69 [60–79]	68 [60–79]	70 [60–79]	0.927
Left ventricular ejection fraction, %	9 (1.0)	45.0 [33.0–60.0]	45.0 [33.0–59.0]	45.0 [33.0–58.5]	45.0 [32.0–60.0]	0.897
Heart failure phenotypes	9 (1.0)	—	—	—	—	0.943
HF _r EF	—	363 (40.3)	120 (39.9)	123 (41.1)	120 (40.0)	—
HF _{mr} EF	—	172 (19.1)	55 (18.3)	59 (19.7)	58 (19.3)	—
HF _p EF	—	356 (39.6)	121 (40.2)	113 (37.8)	122 (40.7)	—
MAGGIC risk score	15 (1.7)	26 [22–29]	27 [24–30]	25 [22–28]	25 [20–28]	< 0.001
Smoker	4 (0.4)	—	—	—	—	0.166
Never	—	423 (47.0)	142 (47.2)	138 (46.2)	143 (47.7)	—
Past	—	370 (41.1)	111 (36.9)	133 (44.5)	126 (42.0)	—
Current	—	103 (11.4)	44 (14.6)	28 (9.4)	31 (10.3)	—
Skeletal muscle index, kg/m ²	0 (0.0)	7.0 [6.3–8.0]	6.6 [6.0–7.8]	6.9 [6.2–7.9]	7.5 [6.8–8.5]	< 0.001
Comorbidity						
History of heart failure	2 (0.2)	417 (46.3)	141 (46.8)	130 (43.5)	146 (48.7)	0.434
Atrial fibrillation	0 (0.0)	403 (44.8)	120 (39.9)	133 (44.5)	150 (50.0)	0.044
Coronary artery disease	0 (0.0)	306 (34.0)	91 (30.2)	96 (32.1)	119 (39.7)	0.036
Diabetes	0 (0.0)	309 (34.3)	81 (26.9)	91 (30.4)	137 (45.7)	< 0.001
Hypertension	0 (0.0)	650 (72.2)	195 (64.8)	219 (73.2)	236 (78.7)	0.001
Laboratory data						
B-type natriuretic peptide, pg/mL	118 (13.1)	289.0 [149.0–498.0]	332.0 [162.0–548.0]	282.5 [153.0–451.0]	256.0 [124.0–490.0]	0.012
Albumin, g/dL	26 (2.9)	3.5 [3.2–3.7]	3.4 [3.1–3.6]	3.5 [3.2–3.7]	3.6 [3.2–3.8]	< 0.001
C-reactive protein, mg/dL	19 (2.1)	0.3 [0.1–0.8]	0.2 [0.1–0.7]	0.3 [0.1–0.8]	0.3 [0.1–0.8]	0.065
Hemoglobin, g/dL	2 (0.2)	11.7 [10.4–13.3]	11.4 [10.3–12.8]	11.8 [10.3–13.3]	12.1 [10.7–13.8]	< 0.001
Creatinine, mg/dL	2 (0.2)	1.1 [0.9–1.5]	1.1 [0.9–1.4]	1.1 [0.9–1.4]	1.2 [0.9–1.6]	0.008
eGFR, mL/min per 1.73 m ²	2 (0.2)	55.7 [38.3–71.5]	56.3 [40.4–73.9]	57.1 [40.5–72.4]	51.6 [34.2–67.1]	0.038
Blood urea nitrogen, mg/dL	2 (0.2)	25.0 [19.0–34.0]	25.8 [19.8–34.2]	24.0 [18.9–33.9]	25.0 [19.0–34.0]	0.631
Medications						
Beta-blocker	0 (0.0)	664 (73.8)	207 (68.8)	223 (74.6)	234 (78.0)	0.034
ACE inhibitor or ARB	0 (0.0)	625 (69.4)	195 (64.8)	208 (69.6)	222 (74.0)	0.049
MRA	0 (0.0)	438 (48.7)	143 (47.5)	163 (54.5)	132 (44.0)	0.032
Physical function						
Handgrip strength, kg	9 (1.0)	19.9 [14.6–25.5]	18.3 [13.0–24.0]	20.4 [14.6–25.7]	20.4 [15.1–26.6]	0.002
SPPB, point	16 (1.8)	9 [7–11]	9 [6–11]	9 [7–11]	9 [7–11]	0.218
Usual gait speed, m/s	10 (1.1)	0.8 [0.6–1.0]	0.8 [0.5–1.0]	0.8 [0.6–1.0]	0.8 [0.6–1.0]	0.062
Six-minute walk distance, m	54 (6.0)	256 [170–352]	255 [160–345]	269 [181–360]	240 [160–356]	0.359

Values are median [interquartile range] or n (%), unless otherwise indicated.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; bpm, beats per minute; eGFR, estimated glomerular filtration rate; FMI, fat mass index; HF_{mr}EF, heart failure with mildly reduced ejection fraction; HF_pEF, heart failure with preserved ejection fraction; HF_rEF, heart failure with reduced ejection fraction; MAGGIC, meta-analysis global group in chronic heart failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SPPB, short physical performance battery.

using Cox proportional hazards models for each of the 3 endpoints. Next, we assessed the potential nonlinear relationships between FMI and each cause-specific outcome, using restricted cubic splines. Candidate specifications with 3, 4, and 5 knots were compared; the 3-knot model yielded the lowest Akaike information criterion and was retained. In addition, to account for competing events in the cause-specific endpoints, we fitted Fine–Gray subdistribution hazard models for CV death and non-CV death, treating the alternate cause of death as the

competing-risk, and plotted cumulative incidence functions accordingly. For adjustment, both the Cox and Fine–Gray models included log-transformed B-type natriuretic peptide at discharge and the MAGGIC risk score a priori. The MAGGIC risk score has been validated in Japanese HF cohorts, so we used it together with log-transformed B-type natriuretic peptide as our core covariate set.²¹

Finally, as a sensitivity analysis to evaluate the independence of muscle strength, muscle mass, exercise tolerance, and fat

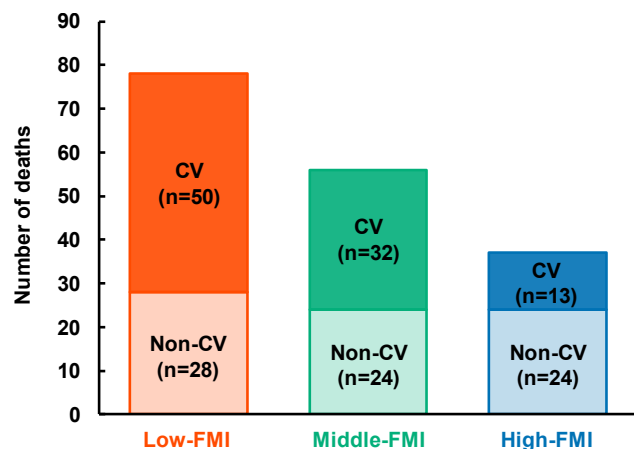


Figure 2. Number of deaths for each cause-specific death stratified by fat mass index (FMI). CV, cardiovascular.

mass, we conducted a Cox proportional hazards model adding handgrip strength, skeletal muscle index, and 6-minute walk distance to the baseline model comprising the MAGGIC risk score and log-transformed B-type natriuretic peptide.

Missing covariate data were addressed using multiple imputation by chained equations, generating 20 imputed datasets; model estimates were then combined using Rubin's rules.³⁰ All statistical testing was 2-sided, with a significance threshold of $P < 0.05$. Analyses were conducted in R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) using RStudio.

Results

Patient characteristics

Among 1332 enrolled patients, 432 were excluded for missing FMI, leaving 900 for analysis. The distribution of FMI and baseline characteristics of patients stratified into 3

groups are shown in [Figure 1](#) and [Table 1](#). The median age was 81 years, and 57.6% were men. The median FMI for men was 4.9 kg/m^2 (3.8-6.4), and the median FMI for women was 6.5 kg/m^2 (4.5-8.7). Across tertiles, body mass index increased stepwise from the low-FMI group to the high-FMI group, and age tended to be lower in the higher FMI groups. In contrast, the 3 groups had broadly comparable clinical profiles, with no material differences in the distribution of HF phenotype and New York Heart Association class.

Association between fat mass index and cause-specific mortality

Over the follow-up period, 171 deaths occurred in total, comprising 95 CV deaths and 76 non-CV deaths. The causes of death stratified by the FMI are shown in [Figure 2](#). By FMI tertiles, the number of CV deaths was 13 in the high-FMI group, 32 in the middle-FMI group, and 50 in the low-FMI group; the number of non-CV deaths were 24, 24, and 28 in these groups, respectively, yielding total numbers of deaths of 37, 56, and 78 across the high-FMI, middle-FMI, and low-FMI groups.

All-cause mortality decreased as FMI increased ([Fig. 3](#)). Using low-FMI as the reference in adjusted Cox models ([Table 2](#)), middle-FMI did not differ (HR 0.73, 95% CI 0.51-1.04; $P = 0.084$), whereas high-FMI was significantly lower (HR 0.60, 95% CI 0.40-0.89; $P = 0.011$). For CV death, middle-FMI was not significant (HR 0.66, 95% CI 0.42-1.04; $P = 0.074$), whereas high-FMI was significantly lower (HR 0.33, 95% CI 0.18-0.60; $P < 0.001$). For non-CV death, neither middle-FMI (HR 0.81, 95% CI 0.47-1.40; $P = 0.444$) nor high-FMI (HR 0.89, 95% CI 0.52-1.54; $P = 0.685$) differed from the reference. Restricted cubic spline modelling showed a significant association between lower FMI and all-cause death and CV death ($P < 0.001$; [Fig. 4](#)).

In Fine-Gray competing-risk analyses ([Table 3](#)), the pattern for CV death was concordant. Middle-FMI was not

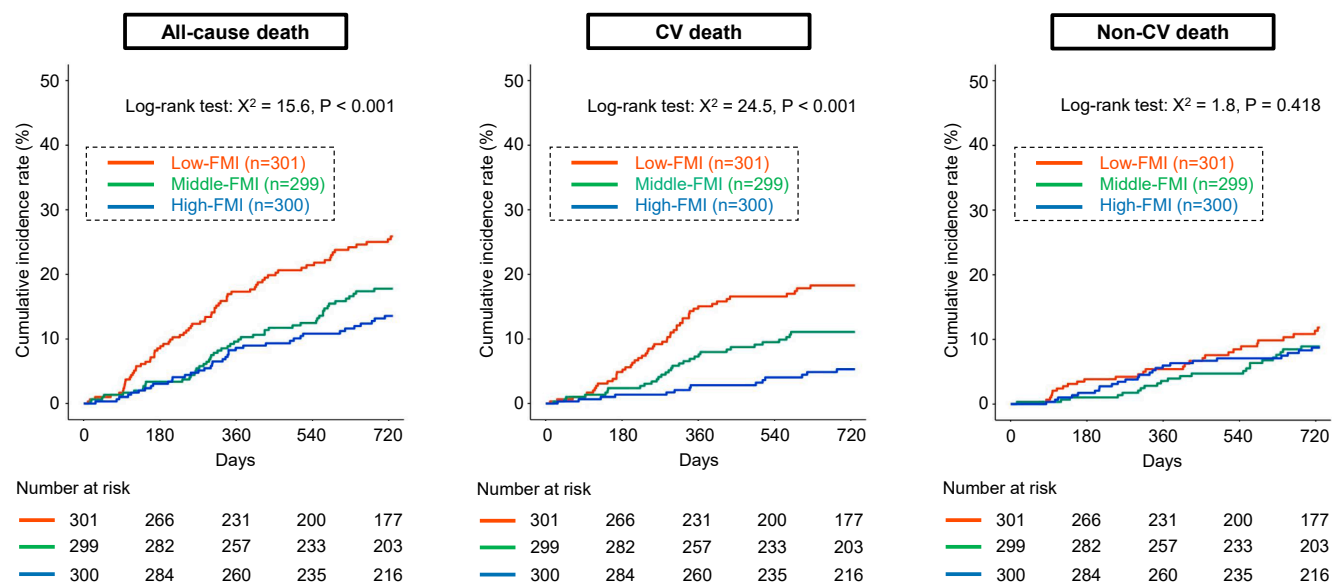


Figure 3. Cumulative incidence curves for cause-specific death categories. CV, cardiovascular; FMI, fat mass index.

Table 2. Unadjusted and adjusted Cox regression analyses for cause-specific death categories

Category	Unadjusted model			Adjusted model*		
	Hazard ratio	95% CI	<i>P</i>	Hazard ratio	95% CI	<i>P</i>
All-cause death						
Low-FMI	1.00	Reference	—	1.00	Reference	—
Middle-FMI	0.63	0.44–0.91	0.013	0.73	0.51–1.04	0.084
High-FMI	0.48	0.32–0.71	<0.001	0.60	0.40–0.89	0.011
CV death						
Low-FMI	1.00	Reference	—	1.00	Reference	—
Middle-FMI	0.57	0.36–0.89	0.013	0.66	0.42–1.04	0.074
High-FMI	0.25	0.14–0.46	<0.001	0.33	0.18–0.60	<0.001
Non-CV death						
Low-FMI	1.00	Reference	—	1.00	Reference	—
Middle-FMI	0.71	0.42–1.24	0.235	0.81	0.47–1.40	0.444
High-FMI	0.74	0.43–1.27	0.272	0.89	0.52–1.54	0.685

CI, confidence interval; CV, cardiovascular; FMI, fat mass index.

* Adjusted for meta-analysis global group in chronic heart failure risk score and log-transformed B-type natriuretic peptide.

significant (HR 0.68, 95% CI 0.43–1.06; $P = 0.090$), whereas high-FMI was significantly lower (HR 0.33, 95% CI 0.18–0.60; $P < 0.001$). For non-CV death, middle-FMI (HR 0.86, 95% CI 0.49–1.48; $P = 0.579$) and high-FMI (HR 0.98, 95% CI 0.56–1.72; $P = 0.957$) showed no association.

Finally, in sensitivity analyses, the relationship between fat mass and cause-specific mortality remained consistent even when handgrip strength, skeletal muscle index, and 6-minute

walk distance were added to the Cox proportional hazards model (Table 4).

Discussion

Principal findings

This study is the first to evaluate the association between fat mass and mortality using cause-specific death in older

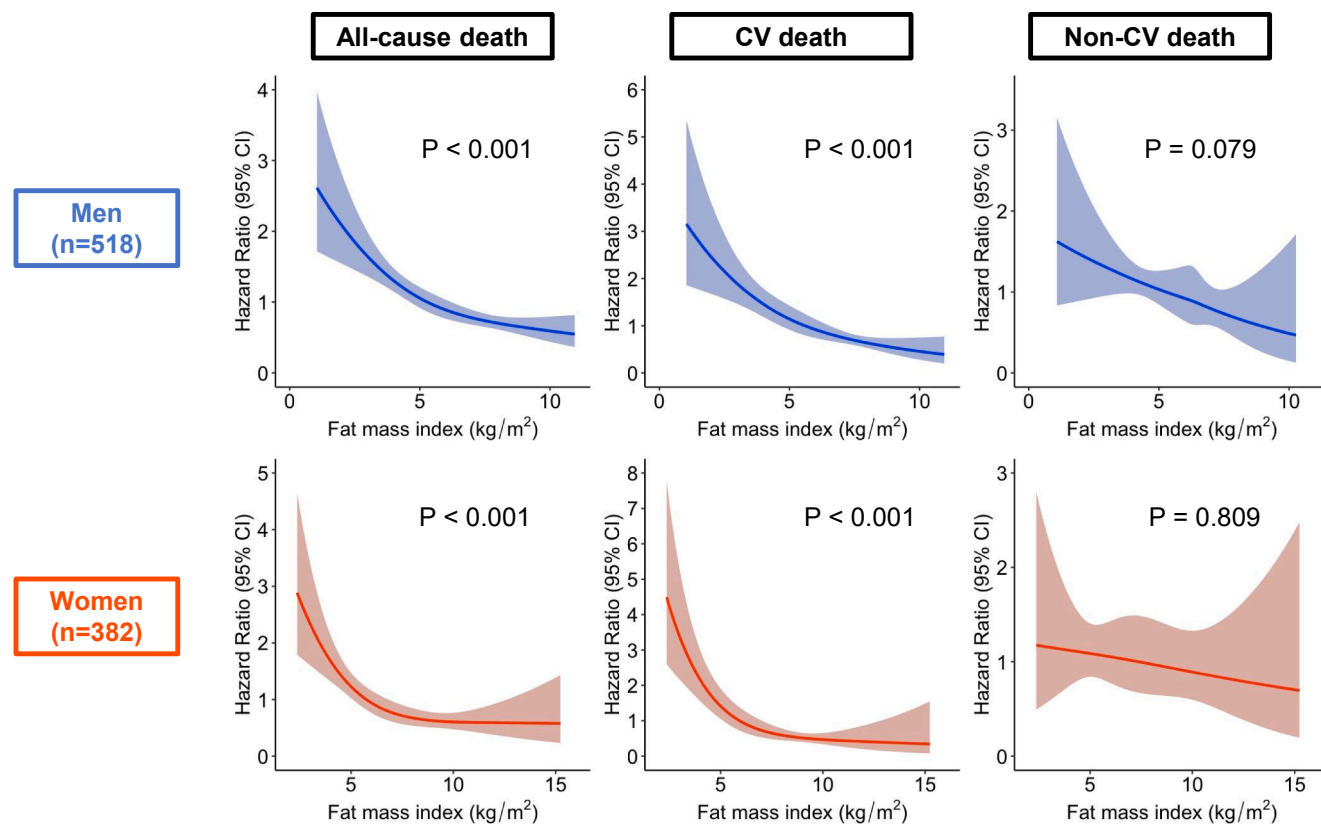


Figure 4. Nonlinear associations between fat mass index and cause-specific death categories. CI, confidence interval; CV, cardiovascular.

Table 3. Unadjusted and adjusted Fine–Gray competing-risk models showing the association of the fat mass index (FMI) with cause-specific death categories

Category	Unadjusted model			Adjusted model*		
	Hazard ratio	95% CI	<i>P</i>	Hazard ratio	95% CI	<i>P</i>
CV death						
Low-FMI	1.00	Reference	—	1.00	Reference	—
Middle-FMI	0.58	0.37–0.91	0.018	0.68	0.43–1.06	0.090
High-FMI	0.26	0.14–0.47	< 0.001	0.33	0.18–0.60	< 0.001
Non-CV death						
Low-FMI	1.00	Reference	—	1.00	Reference	—
Middle-FMI	0.76	0.44–1.32	0.330	0.86	0.49–1.48	0.579
High-FMI	0.82	0.48–1.41	0.467	0.98	0.56–1.72	0.957

CI, confidence interval; CV, cardiovascular; FMI, fat mass index.

*Adjusted for meta-analysis global group in chronic heart failure risk score and log-transformed B-type natriuretic peptide.

patients with HF. The main findings were as follows: (i) higher fat mass was associated with a lower risk of CV death after multivariable adjustment in both Cox and Fine–Gray analyses, and (ii) fat mass showed no significant association with non-CV death, indicating that any association with all-cause death is chiefly driven by CV death.

Comparison with prior evidence of FMI

In this cohort of older patients with HF, higher fat mass was associated with a lower risk of CV death after multivariable adjustment. This finding is consistent with prior studies¹⁶ that used cardiac event (HF death and HF readmission) as the endpoint and likewise observed lower risk among patients with greater adiposity measures.

In our cohort, the sex-specific median FMI values were 4.9 (3.8–6.4) kg/m² in men and 6.5 (4.5–8.7) kg/m² in women, indicating a lower overall FMI distribution than that in several prior reports. For example, a US outpatient HF cohort¹² (mean age 56.2 ± 15.2 years) reported a median FMI of 8.2 kg/m², and a Chinese acute HF cohort (median age 67 years [57–76]) reported median FMI values of 6.6 (5.1–8.1) kg/m² in men and 9.4 (7.6–11.3) kg/m² in women.¹³ The most plausible driver of these differences is age, as our cohort was substantially older (median age 81 years [74–86]), and older Asian populations tend to be leaner.³¹ Taken together, these distributions imply that in a relatively lean Asian cohort with few patients at the extreme high end of FMI, the emergence of a harm signal from

adiposity is less likely, whereas neutral or protective associations concentrated within low-to-moderate FMI ranges are more likely to surface. Therefore, cross-cohort differences in FMI distribution likely contribute to divergent results across studies and should be considered when interpreting the prognostic relevance of fat mass.

Mechanisms of FMI and CV death

Beyond their consistency with prior epidemiologic data, our findings are biologically plausible. Preserved fat stores provide metabolic reserve during decompensation and reduced intake, dampening catabolic stress that contributes to pump failure.^{6,32} Clinically, patients with a very low fat mass rapidly deplete energy stores during illness, a hallmark of cardiac cachexia that is consistently linked to excess mortality in HF.³² Adipose tissue also releases endocrine and immunomodulatory signals that temper neurohormonal and inflammatory activation, key pathways in lethal CV events in HF.^{6,33} These effects may be especially relevant during acute hemodynamic or inflammatory stress, when the ability to mobilize substrate and avoid rapid loss of lean tissue could influence short-term survival.^{6,33} Together, these mechanisms may explain the inverse association between FMI and CV death observed in our study, and the lack of a similar association with non-CV death.

Considerations regarding non-CV death

FMI was not significantly associated with non-CV death. A likely explanation is the combination of mechanistic

Table 4. Cox regression analysis for cause-specific mortality adjusted for muscle mass, muscle strength, and exercise tolerance

Category	Base model + skeletal muscle index			Base model + handgrip strength			Base model + 6-minute walk distance		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
All-cause death									
Low-FMI	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—
Middle-FMI	0.74	0.51–1.06	0.100	0.75	0.52–1.08	0.124	0.75	0.52–1.08	0.120
High-FMI	0.60	0.40–0.89	0.011	0.61	0.41–0.92	0.017	0.58	0.39–0.86	0.007
CV death									
Low-FMI	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—
Middle-FMI	0.67	0.42–1.05	0.079	0.69	0.44–1.09	0.074	0.67	0.43–1.05	0.082
High-FMI	0.31	0.17–0.57	< 0.001	0.32	0.17–0.60	< 0.001	0.30	0.16–0.55	< 0.001
Non-CV death									
Low-FMI	1.00	Reference	—	1.00	Reference	—	1.00	Reference	—
Middle-FMI	0.84	0.48–1.46	0.532	0.86	0.49–1.49	0.588	0.86	0.49–1.50	0.593
High-FMI	0.92	0.53–1.59	0.765	0.98	0.57–1.70	0.956	0.92	0.53–1.59	0.773

CI, confidence interval; CV, cardiovascular; FMI, fat mass index; HR, hazard ratio. The base model was adjusted with the meta-analysis global group in chronic heart failure risk score and log-transformed B-type natriuretic peptide.

asymmetry and the composite nature of this endpoint. In older HF populations, non-CV deaths are largely due to infections, respiratory disease, and malignancy—biological pathways that differ from those in which adiposity may act protectively for CV events.³⁴ In infection, adipose reserves can support short-term metabolic demands,³⁵ yet obesity-related immune skewing and chronic low-grade inflammation may impair host defense.⁶ In respiratory disease, greater fat mass can worsen pulmonary mechanics, ventilation distribution,³⁶ and sleep-disordered breathing, even as nutritional reserves may help preserve general condition.³⁷ In cancer, tumour biology and treatment-related vulnerabilities can tilt the balance toward harm at higher adiposity.³⁸ Because these heterogeneous causes are pooled, positive and negative effects of fat mass likely coexist and offset one another, producing a small averaged association. These features may help explain why no apparent association with non-CV death was observed.

Integrating fat mass, muscle, and fitness

Our results also should be interpreted in light of contemporary concepts linking adiposity, muscle, and fitness in CV disease. Recent work has emphasized that obesity in patients with HF cannot be reduced to excess body weight alone; rather, cardiorespiratory fitness, muscular strength, and physical performance substantially shape risk and may explain much of the so-called obesity paradox.³⁹ In our cohort, patients with higher FMI generally showed more preserved skeletal muscle mass and handgrip strength, and only modest differences in walking performance, compared with those with lower FMI, suggesting that greater overall body reserves rather than isolated adiposity may contribute to the lower risk of CV death observed in the high-FMI tertile. At the same time, although we assessed muscle mass, strength, and physical performance, we did not evaluate broader aspects of lifestyle and overall health status, such as habitual physical activity, and unmeasured differences in these domains may also have contributed to the observed associations.⁴⁰

Clinical value of this study

The clinical value of this study lies, first, in refining marker selection and sharpening CV death risk stratification. Rather than relying solely on body mass index, which is confounded by edema,⁷ incorporating FMI alongside existing risk assessments at discharge can help identify older HF patients with low FMI who are at higher risk of CV death and tailor follow-up intensity and remote monitoring accordingly. Second, these findings highlight the relevance of routine nutritional assessment and, when low FMI is identified, prudent energy and protein optimization within usual care.^{41,42} Overall, viewing FMI through a cause-specific lens can complement existing tools and inform balanced, individualized care pathways for older patients with HF.

Limitations

Our study has several limitations. First, the number of events within each cause-of-death category was modest, which constrains statistical power and the precision of effect estimates. Second, FMI was derived from bioelectrical impedance; although measurements were obtained after

clinical stabilization to approximate euvolemia, residual edema may have influenced the estimates. Third, we did not assess other obesity-related indices, such as waist circumference or waist-to-height ratio, and were therefore unable to compare these measures with FMI. Fourth, the cohort comprised older Asian adults only, which may limit the generalizability of findings to other ethnic groups or to younger patients with HF. Larger, prospectively standardized, multiethnic studies are needed to confirm these findings.

Conclusion

In older patients with HF, higher fat mass was associated with a lower risk of CV death, whereas no association was observed with non-CV death. These results suggest that separating CV and non-CV deaths may be key to interpreting the prognostic relevance of fat mass.

Acknowledgements

The authors gratefully acknowledge all patients who kindly participated in this study.

Data Statement

Data described in the article, codebook, and analytic code will be made available upon request, pending application and approval.

Ethics Statement

The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating hospital.

Patient Consent

The authors confirm that patient consent is not applicable to this article. As this was an observational study that did not entail invasive procedures or interventions, written informed consent was not required under the Ethical Guidelines for Medical and Health Research Involving Human Subjects, per the Japanese Ministry of Health, Labor, and Welfare.

Funding Sources

This study was partially supported by Novartis Pharma Research Grants, a Japan Heart Foundation Research Grant, EN Otsuka Pharmaceutical Co. Ltd., and the Japan Society for the Promotion of Science (JSPS) KAKENHI (grant numbers 21H03309 and 19K11424). The sponsors had no role in the study design, methods, patient recruitment, data collection, analysis, or article preparation.

Disclosures

K.K. reports receiving funding outside the submitted work from Eiken Chemical Co., Ltd. and SoftBank Corp. Y.M. reports receiving honoraria from Otsuka Pharmaceutical Co., EN Otsuka Pharmaceutical Co., Ltd., Novartis Pharma K.K., Bayer Inc., and AstraZeneca, and a collaborative research grant from Pfizer Japan Inc., Otsuka Pharmaceutical Co., EN Otsuka Pharmaceutical Co., Ltd., Nippon Boehringer

Ingelheim Co., Ltd., Roche Diagnostics International, Ltd., and Roche Diagnostics K.K. N.K. reports being affiliated with a department funded by Paramount bed; receiving honoraria from Bristol Myers Squibb, Otsuka Pharma, Novartis, Boehringer Ingelheim, and Eli Lilly; and receiving research grants from AstraZeneca, Bristol Myers Squibb, AMI Inc., and EchoNous. T.K. reports being affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi. All the other authors have no conflicts of interest to disclose.

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