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Adiposity and clinical outcomes in East Asian patients with heart failure and preserved ejection fraction

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ABSTRACT

Background: Despite the obesity paradox, visceral adiposity is associated with poor clinical outcomes in patients with heart failure with preserved ejection fraction (HFpEF). However, it remains unclear whether a relationship between visceral fat and clinical outcomes exists in Asian patients with HFpEF, in whom obesity is rare.

Methods: Visceral and subcutaneous adipose tissue (VAT and SAT) volume and area were measured using computed tomography (CT) in 196 HFpEF patients. The primary endpoint was a composite of all-cause mortality or HF hospitalization.

Results: Participants had a normal body mass index (BMI) (22.5 ± 4.4 kg/m^2), and obesity (BMI > 30 kg/m^2) was rare (4.6 %). The primary outcome was observed in 64 patients during a median follow-up of 11.6 months. Lower VAT and SAT volumes were associated with underweight and malnutrition. Composite outcomes increased as body weight, BMI, and height-indexed SAT volume and area decreased. Lower height-indexed VAT volume and area were also associated with the outcomes. The height-indexed SAT area provided independent and incremental prognostic value over age, BMI, blood pressure, and creatinine and albumin levels.

Conclusions: In lean East Asian patients with HFpEF, a lower VAT volume was associated with poorer clinical outcomes. CT-based assessments of adiposity may provide incremental prognostic value over simple anthropometric indices in lean HFpEF patients.

1. Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for more than half of all HF cases [1]. The prevalence of HFpEF relative to HF with reduced ejection fraction (HFrEF) has been increasing at an alarming rate due to the aging population and increasing burden of lifestyle-related comorbidities, such as systemic hypertension, diabetes, chronic kidney disease, and obesity [2]. Obesity is common in patients with HFpEF (60–75 %) [1]. Obesity and increased adiposity are associated with increased volume retention, more severe inflammatory state, worse cardiac hemodynamics, reduced exercise capacity, greater symptom severity, and poor quality of life [3–8] and may be involved in the pathogenesis of HFpEF [1,2,9–11]. Despite the adverse effects of obesity and adiposity, previous studies have shown an "obesity paradox" in which a higher body mass index (BMI) is associated with lower mortality in HFpEF [12,13].

Although BMI is widely used as a measure of general obesity, it does not provide information on the regional fat distribution [14]. Recent studies demonstrated the pathophysiological importance of visceral adiposity in HFpEF [14]. Excess visceral adiposity is associated with worse hemodynamics and a reduced exercise capacity [15,16]. Despite the obesity paradox, increased visceral adiposity is associated with worse clinical outcomes in patients with HFpEF [12,13]. This trend has also been observed among Asian patients with HFpEF, in whom obesity (defined as BMI > 30 kg/m^2) is less prevalent (25.5 %) than that among Western patients [13,17]. Notably, regional variation exists in

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comorbidities across Asia. The prevalence of obesity in HFpEF is substantially lower in East Asian countries (6.5 %) such as Japan and South Korea [17,18], and the patients may rather have underweight or sarcopenia. However, the relationship between visceral fat and clinical outcomes in East Asian patients with HFpEF remains unclear. Therefore, this study aimed to evaluate the relationship between the amount of visceral and subcutaneous adipose tissues (VAT and SAT, respectively) measured using abdominal computed tomography (CT) and prognosis in Japanese patients with HFpEF.

2. Methods

2.1. Study population

This retrospective observational study examined the association between the amount of VAT and SAT and clinical outcomes in Japanese patients with HFpEF. Some participant data from this study were previously published [7,19–23], but not in relation to the prognostic value of adiposity. Patients presenting at Gunma University Hospital in Maebashi, Japan between January 2014 and December 2020 were screened for HFpEF. HFpEF was defined using the typical clinical symptoms of HF (exertional dyspnea, fatigue, or peripheral edema), EF $\geq$ 50 %, and with at least one of the following: directly measured pulmonary capillary wedge pressure $>$ 15 mmHg, B-type natriuretic peptide (BNP) levels $>$ 200 pg/mL, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity (E/e') $>$ 15, left atrial volume index $>$ 34 mL/m^2, or previous HF-related hospitalization [24,25]. We excluded patients with EF $<$ 50 %, a recovered EF (previous EF $<$ 40 %), pulmonary arterial hypertension, significant left-sided valvular heart disease, acute coronary syndrome, congenital heart disease, or cardiomyopathy. Patients with abdominal CT examinations (non-contrast) were identified from this cohort. If patients had multiple abdominal CT scans during the study period, the oldest examination was used as an index evaluation. Clinical demographics, past medical history, current medications, laboratory results, and standard echocardiography were collected from a chart review. This study was approved by our clinical research review board with waiver of consent (HS2021-197) and was performed in accordance with the Declaration of Helsinki.

2.2. Assessment of anthropometrics, nutritional status, and visceral and subcutaneous fat amount

Ideal body weight (in kilograms) was calculated from height (in centimeters): (height − 100) − ([height − 150] /a), where a = 4 for men and 2.5 for women [26]. Excess body weight (kg) was determined as the actual body weight – ideal body weight. Nutritional status was assessed using the Geriatric Nutritional Risk Index (GNRI) [27]. Abdominal CT scans were obtained according to the clinical indications. Waist circumference (WC) was measured based on abdominal CT at the level of the 3rd lumbar vertebra. The waist-to-height ratio (WHtR) was calculated as waist (cm) divided by height (cm) [13].

The VAT and SAT amounts were assessed by volume and area using commercially available semi-automated software (SYNAPSE VINCENT, Fujifilm Inc., Tokyo, Japan) [28]. Unenhanced abdominal CT data were imported into the software as Digital Imaging and Communication in Medicine format. The software automatically identified the total adipose tissue volume enclosed within the whole abdominal cavity (VAT volume) and total adipose tissue volume outside the abdominal cavity between the diaphragm and pubic symphysis levels (SAT volume). The VAT and SAT areas were calculated based on tomographic cross-sectional areas at the level of the 3rd lumbar vertebra and defined as the area containing pixels with an attenuation value of −190 to −30 HU (Fig. 1) [15]. Fat volumes and areas were then indexed to the square of height (in meters) to account for body size [15,28]. All CT measurements were performed in a blinded manner (Y.S.).

2.3. Outcome assessment

All subjects were followed up from the day of abdominal CT assessment. The primary endpoint of this study was the composite of all-cause mortality and hospitalization for HF. Hospitalization for HF was defined as dyspnea and pulmonary edema on chest radiography, requiring intravenous diuretic treatment.

2.4. Statistical analysis

Data were reported as the mean (standard deviation), median (interquartile range, IQR), or number (%) unless otherwise specified. Between-group differences were compared using the chi-square test, unpaired *t*-test, or Mann-Whitney *U* test. Pearson's and Spearman's analyses were used to assess the correlations between the two variables of interest. The unadjusted risk of the composite outcome across the tertiles of the measures of adiposity was assessed using Kaplan–Meier (KM) curve analysis. Univariable and multivariable Cox proportional hazards models were then applied to evaluate hazard ratios and their 95 % confidence intervals. To account for potential confounding factors, two multivariable Cox models were used: 1) clinical model: age, sex, diastolic blood pressure (BP), levels of creatinine and albumin, and indications for CT scan (evaluation for cardiovascular diseases, respiratory diseases, infection or fever or unknown origin, hematologic malignancy,

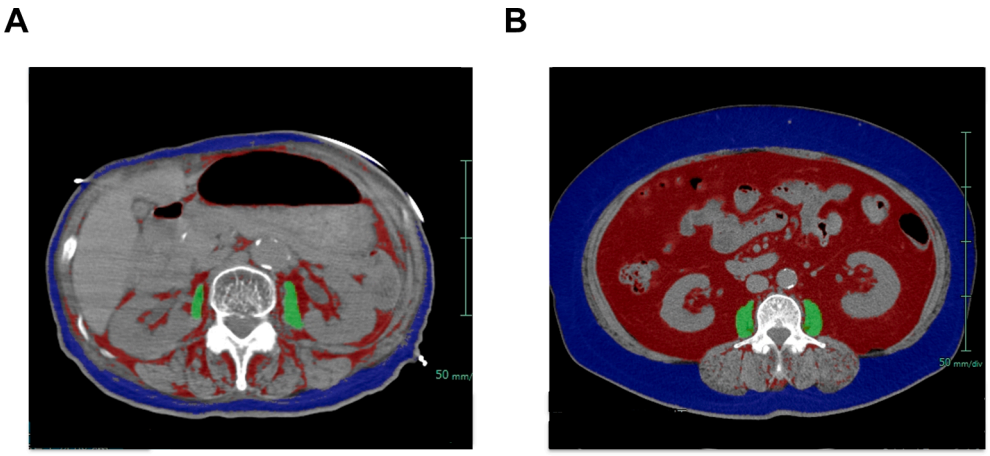

Fig. 1. Abdominal computed tomography images of patients with heart failure with preserved ejection fraction. (A-B) Cross-sectional abdominal computed tomography images for the adiposity analyses from a lean HFpEF patient (BMI of 17.1 kg/m^2) show a much lesser degree of both visceral and subcutaneous amounts of adipose tissue than those from an obese patient (BMI 32.9 kg/m^2). Red and blue areas indicate visceral and subcutaneous adipose tissue, with the green area indicating abdominal skeletal muscle. BMI, body mass index; HFpEF, heart failure with preserved ejection fraction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

solid malignancy, non-neoplastic abdominal diseases, or others); and 2) echocardiographic model: age, sex, ratio of early mitral inflow velocity to annular tissue velocity (E/e' ratio), estimated pulmonary artery systolic pressure (ePASP), and left ventricular global longitudinal strain (GLS). To avoid multicollinearity, we did not include body weight, BMI, or GNRI in the multivariable models. The incremental prognostic value of CT-based adipose measurements was assessed using the likelihood ratio test by comparing models with and without the variables. The test follows a chi-squared distribution, with degrees of freedom equal to the number of added variables. All tests were two-sided, with P values of < 0.05 considered significant. All analyses were performed using SPSS (SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical characteristics

A total of 413 HFpEF patients were identified, of whom 226 underwent abdominal CT imaging. Of the 226 patients, 28 were excluded due to the lack of prognostic data and 2 were not tested in a compensated state, remaining 196 HFpEF patients for the final analysis (**Supplemental Fig. 1**). Patients included in the analysis (n = 196) had higher diastolic BP, lower levels of hemoglobin and albumin, lower renal function, and lower GLS, but other baseline characteristics were similar to patients not referred for CT imaging (n = 187)(**Supplemental Table 1**).

Overall, enrolled patients (n = 197) had a normal BMI (mean 22.5 ± 4.4 kg/m^2); the BMI distribution indicating that prevalence of obesity (BMI > 30 kg/m^2) was rare (4.6 %) (Fig. 2). However, one-third of patients had diabetes. During a median follow-up period of 11.6 months (IQR, 4.2–28.5), 64 patients developed the composite events (36 all-cause deaths and 28 hospitalizations for HF). Comparisons of the clinical characteristics between patients with and without composite events are presented in Table 1. There were no significant differences in age, sex, systolic and diastolic BP, heart rate, prevalence of comorbidities, and indications for CT scan. While HFpEF patients with the events were treated with diuretics more frequently than those without, the use of other medications was similar between the groups. Patients with composite events had lower hemoglobin and albumin levels, higher BNP levels, lower GNRI, higher ePASP, and worse renal function than those without composite events. Other echocardiographic variables were similar between the groups.

Regarding anthropometric measures, body height and ideal body weight were similar between the patients with and without composite events (Table 2). Actual body weight, excess body weight, BMI, WC, and WHtR were significantly lower in HFpEF patients with composite events than in those without composite events. On volumetric (3D) CT measurements, HFpEF patients with composite events had lower absolute VAT and SAT volumes and areas than those without composite events; these differences remained significant after indexing for height.

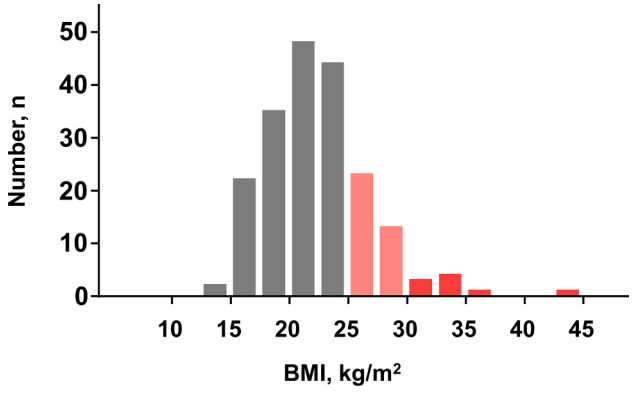

Fig. 2. Distribution of body mass index in the study population. The distribution of BMI among all patients shows that the prevalence of obesity (BMI > 30 kg/m^2) is low (4.6 %). Abbreviations as in Fig. 1.

Table 1
Clinical demographics.

	Event (−) (n = 132)	Event (+) (n = 64)	P value
Age (years)	75 ± 11	75 ± 11	0.56
Female, n (%)	64 (48 %)	27 (42 %)	0.41
Indications for CT scan, n (%)			
Cardiovascular diseases	37 (28 %)	12 (19 %)	
Respiratory diseases	9 (7 %)	3 (5 %)	
Infection/FOU	17 (13 %)	10 (16 %)	
Hematologic malignancy	3 (2 %)	4 (6 %)	0.14
Solid malignancy	45 (34 %)	22 (34 %)	
Non-neoplastic abdominal diseases	5 (4 %)	8 (13 %)	
Others	16 (12 %)	5 (7 %)	
Vital signs			
Systolic BP (mmHg)	129 ± 21	128 ± 23	0.81
Diastolic BP (mmHg)	68 ± 15	64 ± 11	0.05
Heart rate (bpm)	75 ± 17	73 ± 17	0.35
Comorbidities			
Hypertension, n (%)	101 (77 %)	56 (88 %)	0.07
Coronary artery disease, n (%)	33 (25 %)	13 (20 %)	0.47
Atrial fibrillation, n (%)	63 (48 %)	35 (55 %)	0.36
Diabetes mellitus, n (%)	43 (33 %)	20 (31 %)	0.85
Medications			
ACEI or ARB, n (%)	56 (42 %)	32 (50 %)	0.32
Beta-blocker, n (%)	50 (38 %)	25 (39 %)	0.87
Diuretic, n (%)	79 (60 %)	49 (77 %)	0.02
MRA, n (%)	47 (36 %)	15 (23 %)	0.09
Laboratory data			
Hemoglobin (g/dL)	11.6 ± 2.2	10.3 ± 2.0	<0.001
Albumin (g/dL)	3.5 ± 0.6	3.2 ± 0.7	0.002
Creatinine (mg/dL)	1.2 ± 1.1	1.7 ± 1.3	0.007
eGFR (mL/min/1.73 m^2)	56 ± 24	40 ± 20	<0.001
GNRI (points)	95 ± 14	87 ± 13	<0.001
BNP (pg/mL)	168 (86, 283)	316 (241, 490)	<0.001
Echocardiography			
LV ejection fraction (%)	62 ± 6	63 ± 7	0.55
GLS (%)	−15.9 ± 4.2	−16.3 ± 4.2	0.53
LV mass index (g/m^2)	102 ± 27	107 ± 34	0.23
E/e' ratio	16.8 ± 7.3	18.3 ± 10.2	0.28
LA volume index (mL/m^2)	54 ± 36	58 ± 36	0.45
ePASP (mmHg)	30 ± 9	35 ± 13	0.02

Values are mean ± SD, median (interquartile range), or n (%). ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; BNP, B-type natriuretic peptide; BP, blood pressure; E/e', ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity; eGRF, estimated glomerular filtration rate; ePASP, estimated pulmonary artery systolic pressure; FOU, fever of unknown origin; GLS, global longitudinal strain; GNRI, Geriatric Nutritional Risk Index; LA, left atrial; LV, left ventricular; and MRA, mineralocorticoid receptor antagonists.

3.2. Associations between CT-derived adiposity and nutritional status

Excess body weight was highly correlated with increased visceral and subcutaneous adiposity (**Supplemental Fig. 2, Supplemental Table 2**). Moderate correlations were observed between the GNRI and CT-based measurements of VAT and SAT (**Supplemental Fig. 2, Supplemental Table 2**). These data suggest that lower VAT and SAT values were associated with underweight and malnutrition statuses in patients with HFpEF.

3.3. Outcome analysis

KM curve analysis showed that patients in the first (lowest) and second (intermediate) tertiles of actual body weight had poorer outcomes than those in the third (highest) tertile (Fig. 3**A**). There was a dose-dependent increase in the composite outcomes as BMI decreased (Fig. 3**B**). KM curves demonstrated similar trends toward higher rates of

Table 2
Anthropometric findings and measures of visceral and subcutaneous adipose tissue.

	Event (−) (n = 132)	Event (+) (n = 64)	P value
Body height (cm)	156 ± 10	156 ± 9	0.99
Ideal body weight (kg)	55 ± 7	55 ± 17	0.95
Body weight (kg)	57 ± 15	52 ± 11	0.02
Excess body weight (kg)	2.2 ± 11.9	−2.2 ± 9.0	0.01
Body mass index (kg/m^2)	23.1 ± 4.6	21.4 ± 3.6	0.01
Waist circumference (cm)	85.7 ± 13.6	81.1 ± 10.3	0.01
Waist to height ratio	0.55 ± 0.08	0.52 ± 0.07	0.01
VAT and SAT volume			
VAT volume (cm^3)	3107 ± 2077	2317 ± 1670	0.009
Height-indexed VAT volume (cm^3/m^2)	1242 ± 768	938 ± 645	0.007
SAT volume (cm^3)	3512 ± 2514	2228 ± 1517	<0.001
Height-indexed SAT volume (cm^3/m^2)	1425 ± 994	933 ± 670	<0.001
VAT and SAT area			
VAT area (cm^2)	143 ± 96	103 ± 77	0.004
Height-indexed VAT area (cm^2/m^2)	57.1 ± 35.8	41.6 ± 29.8	0.003
SAT area (cm^2)	99.8 ± 71.4	62.2 ± 43.1	<0.001
Height-indexed SAT area (cm^2/m^2)	40.4 ± 28.1	25.8 ± 18.6	<0.001

Values are mean ± SD, or median (interquartile range). SAT, subcutaneous adipose tissue; and VAT, visceral adipose tissue.

composite outcomes as WC and WHtR decreased (Fig. 3**C-D**).

Regarding CT-derived measures of adiposity, patients in the first and second tertiles of height-indexed VAT volume had poorer outcomes than those in the third tertile (Fig. 4**A**). Similar results were obtained for the height-indexed VAT areas (Fig. 4**B**). There was a dose-dependent association between height-indexed SAT volume and outcomes, in which patients with lower SAT volume demonstrated worse outcomes (Fig. 4**C**). A similar dose-dependent relationship was observed between height-indexed SAT area and outcomes (Fig. 4**D**) and in the analyses using absolute values of VAT and SAT areas (**Supplemental Fig. 3**).

In univariate Cox proportional hazard models, patients in the lowest tertiles of actual body weight, BMI, WC, WHtR, absolute and indexed VAT areas, absolute SAT area, absolute and height-indexed VAT volumes, and height-indexed SAT volume demonstrated an increased risk of the composite outcome compared with those in the highest tertiles (Table 3). There was a dose-dependent inverse relationship between GNRI, height-indexed SAT area, and absolute SAT volume and composite outcomes. Sex-specific outcome analyses consistently demonstrated the association between poorer nutritional status, lower visceral and subcutaneous fat, and outcomes in both sexes (**Supplemental Fig. 4**). In multivariate Cox proportional hazards models adjusted for age, sex, diastolic BP, levels of creatinine and albumin, and indications for CT scan (Clinical models), the associations between CT-derived measures of adiposity and outcomes remained significant; however, the association between anthropometric measures and composite outcome did not ($p \geq 0.08$). The association between CT-based 3D and 2D measurements of VAT and SAT and outcomes also remained significant after adjusting for age, sex, E/e' ratio, ePASP, and GLS (echo models).

In the sequential nested models, the addition of creatinine and albumin levels significantly improved the model based on age, BMI, and diastolic BP (Fig. 5). The prognostic value was further improved by adding height-indexed SAT area (likelihood ratio test chi-squared value, 43.0 vs 38.0; $p = 0.03$). However, the addition of height-indexed VAT

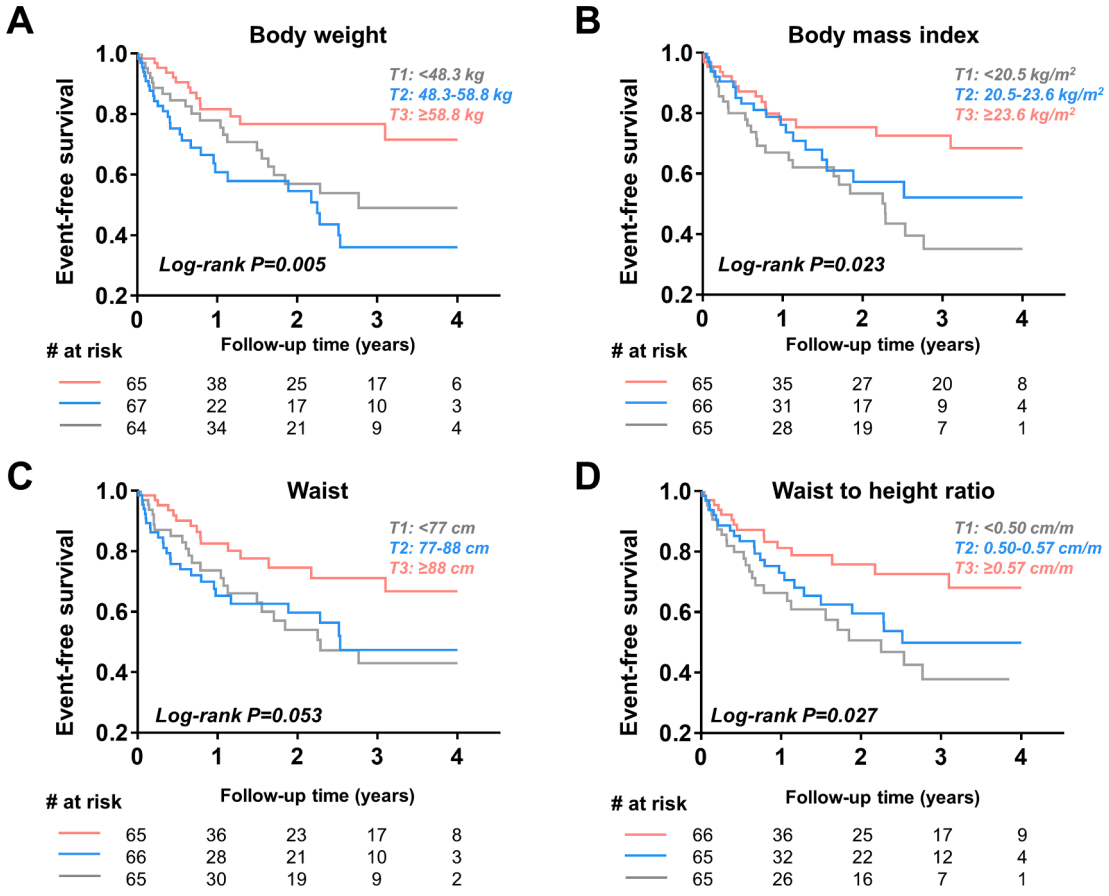

Fig. 3. Kaplan–Meier curve analyses demonstrating the association between body measurements and composite outcomes.(A) Kaplan–Meier curve analyses show that patients in the lowest and intermediate tertiles of actual body weight have poorer outcomes than those in the highest tertile. **(B)** There is a dose-dependent increase in the composite outcomes as BMI decreased. **(C-D)** Similar trends are observed when dividing the participants based on the tertiles of waist circumference or waist-to-height ratio. T, tertile; Abbreviations as in Fig. 1.

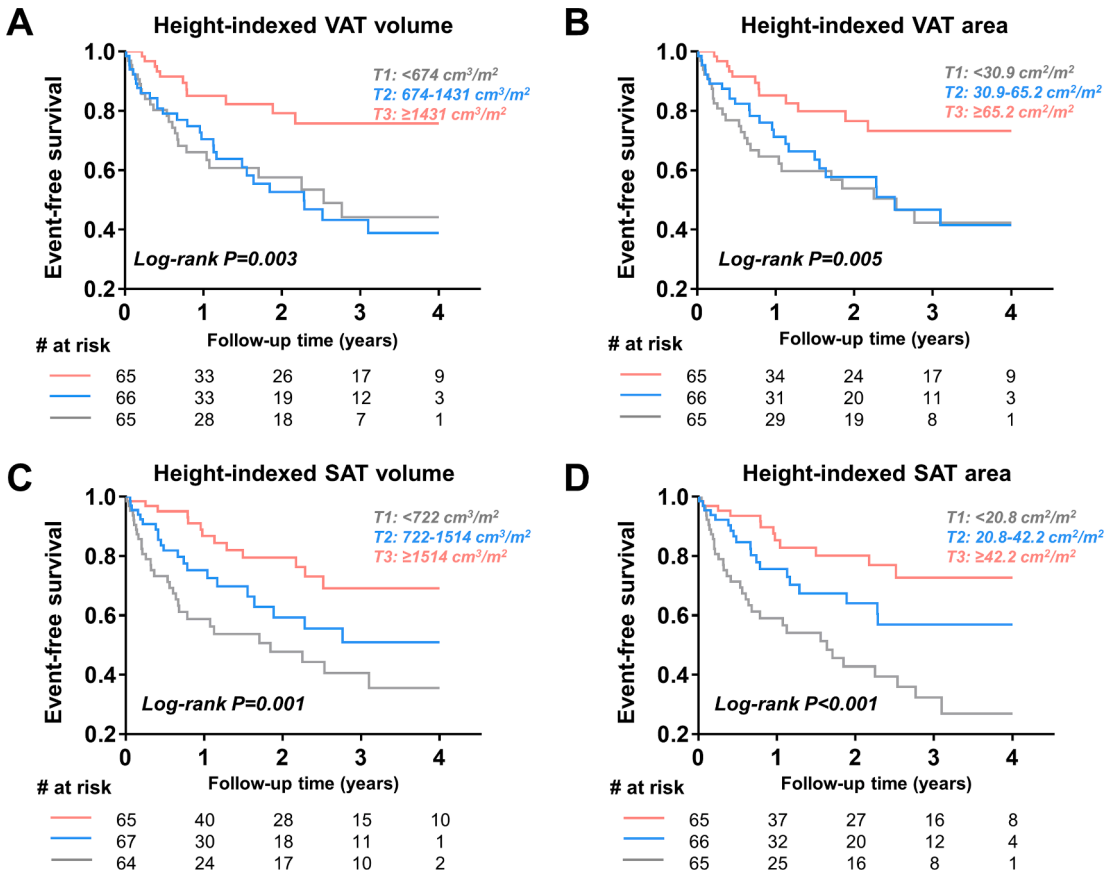

Fig. 4. Kaplan–Meier curve analyses demonstrating the association between CT-based fat measurements and composite outcomes.(A-B) Patients in the lowest and intermediate tertiles of height-indexed VAT volume or area have poorer outcomes than those in the highest tertile. **(C-D)** There are dose-dependent associations between height-indexed SAT volume or area and outcomes, in which patients with lower SAT amounts have worse outcomes. CT, computed tomography; SAT, subcutaneous adipose tissue; and VAT, visceral adipose tissue.

area did not demonstrate an incremental prognostic value over the model based on age, BMI, diastolic BP, and levels of creatinine and albumin (likelihood ratio test chi-squared value, 41.4 vs 38.0; p = 0.07).

In sensitivity analyses evaluating the individual endpoints, height-indexed VAT area and volume and height-indexed SAT area and volume were associated with all-cause mortality (**Supplemental Fig. 5**). While height indexed VAT area and volume were also associated with HF hospitalization, height-indexed SAT area and volume were not (**Supplemental Fig. 6**).

4. Discussion

In this study, we examined the regional fat distribution using abdominal CT in Japanese patients with HFpEF and investigated the association between CT-derived measurements of visceral and subcutaneous adiposity and clinical outcomes. We found that prevalence of obesity was low, lower visceral and subcutaneous adiposity were associated with underweight and malnutrition statuses, and a dose-dependent increase in the composite outcomes as BMI or body weight (an indicator of general adiposity) decreased. We found similar results in the association between the amount of SAT and composite outcomes, in which patients with a lower SAT volume or area had higher rates of adverse events. Additionally, lower WC, WHtR, and VAT volume or area were associated with composite outcomes in patients with HFpEF. Previous studies examining HFpEF patients from wide regions of Asia have demonstrated an association between abdominal obesity and the risk of mortality and morbidity. However, our data suggested that lower visceral fat was associated with an increased risk in East Asian patients with HFpEF, where the prevalence of obesity was low.

4.1. Potential mechanisms of the associations between lower visceral fat and worse clinical outcomes

Consistent with prior reports [17,18], we found a substantially low prevalence of obesity in our cohort. This low prevalence of obesity was also consistent with recent studies performed in Japan and Korea [29,30]. In our study, we confirmed the results of previous studies and observed the obesity paradox between markers of general adiposity (BMI and body weight) and clinical outcomes in HFpEF [13,31]. We further demonstrated similar results in the association between the amount of SAT and outcomes.

Recent studies have shown the pathophysiological importance of regional adipose tissue distribution in patients with HFpEF, especially visceral adiposity [10]. Increased visceral adiposity is associated with adipose tissue dysfunction, in which the upregulation of proinflammatory adipokines (e.g., leptin, tumor necrosis factor-α, interleukin-6, and resistin) and downregulation of anti-inflammatory adipokines (e.g., adiponectin and omentin-1) leads to chronic low-grade systemic inflammation. Previous studies have demonstrated that the amount of visceral fat is larger in patients with HFpEF than in patients without HF, in whom the increased visceral adiposity is associated with hemodynamic derangements, reduced exercise capacity, and poorer quality of life [5,15,16,32,33]. Despite the obesity paradox, visceral adiposity is associated with worse clinical outcomes in patients with HFpEF [12,34]. This association was also reported in Asian populations, in whom a higher WHtR is associated with poorer outcomes (mean BMI 27.1 ± 6.0 kg/m^2) [13]. These data suggest adverse prognostic effects of visceral adiposity even in Asian patients with HFpEF.

To our knowledge, this is the first study to investigate the association

Table 3
Univariable and multivariable Cox proportional hazard models for the association with adverse events.

	Univariable analysis		Clinical model		Echo model	
Variables	**HR (95 % CI)**	**P value**	**HR (95 % CI)**	**P value**	**HR (95 % CI)**	**P value**
Body height						
2 T vs 1 T	1.65 (0.91–3.01)	0.10	2.43 (1.11–5.32)	0.03	1.45 (0.69–3.04)	0.32
3 T vs 1 T	1.13 (0.59–2.15)	0.71	2.25 (0.83–6.16)	0.11	0.83 (0.30–2.31)	0.72
Body weight						
2 T vs 1 T	1.39 (0.80–2.42)	0.25	1.92 (0.92–4.00)	0.08	1.20 (0.65–2.21)	0.56
3 T vs 1 T	0.50 (0.26–0.98)	0.04	0.82 (0.33–2.03)	0.66	0.44 (0.20–0.98)	0.04
Body mass index						
2 T vs 1 T	0.68 (0.38–1.21)	0.19	1.03 (0.54–1.96)	0.92	0.76 (0.42–1.38)	0.37
3 T vs 1 T	0.43 (0.23–0.80)	0.01	0.70 (0.35–1.42)	0.32	0.47 (0.25–0.91)	0.03
GNRI						
2 T vs 1 T	0.44 (0.26–0.79)	0.006	0.66 (0.31–1.38)	0.27	0.53 (0.28–1.01)	0.05
3 T vs 1 T	0.23 (0.16–0.47)	<0.001	0.34 (013–0.92)	0.03	0.33 (0.15–0.72)	0.005
CT findings (2D)						
Waist circumference						
2 T vs 1 T	1.01 (0.58–1.78)	0.96	1.32 (0.67–2.60)	0.42	1.03 (0.57–1.85)	0.93
3 T vs 1 T	0.50 (0.26–0.95)	0.04	0.61 (0.29–1.29)	0.20	0.51 (0.25–1.05)	0.07
Waist to height ratio						
2 T vs 1 T	0.74 (0.42–1.30)	0.30	0.98 (0.52–1.85)	0.94	0.83 (0.46–1.49)	0.83
3 T vs 1 T	0.43 (0.22–0.81)	0.009	0.56 (0.28–1.12)	0.10	0.51 (0.26–1.00)	0.05
VAT area						
2 T vs 1 T	0.99 (0.57–1.71)	0.97	0.96 (0.52–1.78)	0.89	0.99 (0.56–1.77)	0.99
3 T vs 1 T	0.38 (0.19–0.75)	0.005	0.38 (0.18–0.80)	0.01	0.41 (0.20–0.87)	0.02
Height-indexed VAT area						
2 T vs 1 T	0.83 (0.48–1.44)	0.52	0.90 (0.49–1.66)	0.74	0.83 (0.47–1.48)	0.54
3 T vs 1 T	0.35 (0.17–0.68)	0.002	0.33 (0.16–0.70)	0.004	0.39 (0.19–0.79)	0.01
SAT area						
2 T vs 1 T	0.68 (0.39–1.18)	0.17	0.80 (0.44–1.66)	0.74	0.82 (0.46–1.47)	0.50
3 T vs 1 T	0.25 (0.12–0.49)	<0.001	0.27 (0.12–0.59)	<0.001	0.29 (0.14–0.60)	0.001
Height-indexed SAT area						
2 T vs 1 T	0.48 (0.28–0.85)	0.01	0.74 (0.44–1.35)	0.32	0.57 (0.31–1.04)	0.57
3 T vs 1 T	0.25 (0.13–0.49)	<0.001	0.29 (0.14–0.62)	0.001	0.30 (0.15–0.62)	0.001
CT findings (3D)						
VAT volume						
2 T vs 1 T	0.97 (0.56–1.68)	0.92	0.89 (0.48–1.66)	0.72	1.02 (0.58–1.80)	0.95
3 T vs 1 T	0.37 (0.19–0.74)	0.005	0.43 (0.21–0.88)	0.02	0.42 (0.20–0.88)	0.02
Height-indexed VAT volume						
2 T vs 1 T	1.00 (0.58–1.72)	0.99	0.91 (0.50–1.67)	0.76	1.07 (0.61–1.87)	0.82
3 T vs 1 T	0.34 (0.17–0.69)	0.003	0.35 (0.16–0.74)	0.006	0.39 (0.18–0.82)	0.01
SAT volume						
2 T vs 1 T	0.43 (0.24–0.77)	0.005	0.49 (0.25–0.96)	0.04	0.52 (0.28–0.98)	0.04
3 T vs 1 T	0.14 (0.14–0.52)	<0.001	0.33 (0.16–0.67)	0.002	0.32 (0.16–0.65)	0.002
Height-indexed SAT volume						
2 T vs 1 T	0.64 (0.37–1.12)	0.12	0.66 (0.34–1.26)	0.20	0.73 (0.40–1.32)	0.30
3 T vs 1 T	0.31 (0.16–0.60)	<0.001	0.44 (0.22–0.89)	0.02	0.38 (0.18–0.78)	0.009

Clinical models are adjusted for age, sex, diastolic blood pressure, albumin and creatinine levels, and the indications for CT scan. Echo models are adjusted for age, sex, E/e', ePASP, and GLS. CI, confidence interval, HR hazard ratio, T, tertile; and other abbreviations as in Tables 1 and 2.

between visceral obesity, evaluated using CT-based 2D and 3D measurements, and clinical outcomes in East Asian patients with HFpEF. In contrast to the results of the Asian population [13], we demonstrated that increased VAT amounts were associated with better clinical outcomes in lean patients with HFpEF (mean 22.5 ± 4.4 kg/m^2, obesity prevalence 4.9 %). This result was consistent, regardless of the indices used to evaluate visceral adiposity. Potential explanations could be the discrepancy in the absolute amount of visceral fat between East Asian and Western populations. The VAT area was substantially smaller in our population than in the Western population (height-indexed VAT area of 57 ± 37 cm^2/m^2 in men and 47 ± 32 cm^2/m^2 in women in the current study; 93 ± 49 cm^2/m^2 in American men and 70 ± 42 cm^2/m^2 in American women) [15]. These data, along with moderate correlations of VAT measurements with excess body weight and the GNRI, indicated that lower VAT amounts were associated with underweight and malnutrition statuses in East Asian patients with HFpEF. The current data may be in agreement with prior studies showing an association between unintentional weight loss, malnutrition status, and poorer outcomes in lean Japanese patients with HFpEF (mean BMI 22.1–23.1 kg/m^2) [35,36]. Collectively, these data suggest that a lower VAT amount might reflect underweight or malnutrition statuses that are associated with sarcopenia, frailty, and cachexia in lean patients with HFpEF, leading to a worse clinical course [37]. Further studies are required to determine the mechanisms underlying the association between decreased visceral adiposity and outcomes in lean Asian populations.

4.2. Clinical implications

These findings have important therapeutic implications. Obesity is common in patients with HFpEF [3,10,38], and excess adiposity may be a therapeutic target in HFpEF patients with morbid obesity [38,39]. Intentional weight loss via caloric restriction or aerobic training is associated with a reduction in visceral fat and improvements in exercise capacity and quality of life in obese patients with HFpEF (mean BMI 39.3 ± 5.6 kg/m^2) [39]. Conversely, the results of previous studies and our study indicate that improvements in nutritional status may contribute to better clinical outcomes in lean patients with HFpEF [35,36]. To achieve this, nutritional assessments, which include anthropometric measurements (e.g., body weight, body height, BMI, and WC), body composition analyses (dual-energy X-ray absorptiometry, and bioelectrical impedance analysis), biochemical testing (e.g., albumin, prealbumin, and

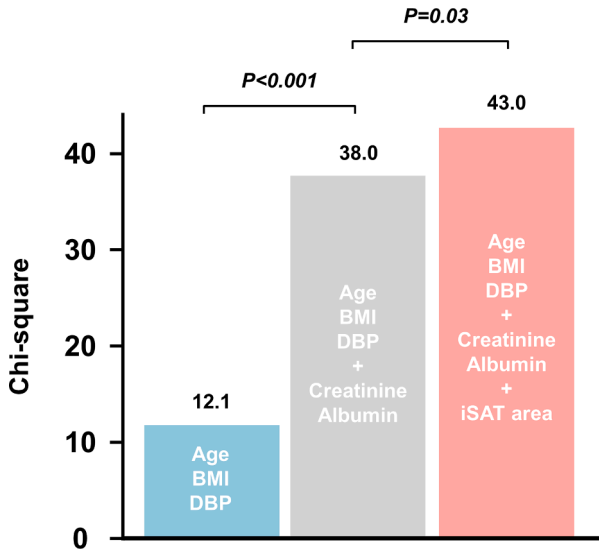

Fig. 5. Incremental prognostic value of height-indexed subcutaneous adipose tissue. The addition of creatinine and albumin levels significantly improves the model based on age, BMI, and DBP. The prognostic value is further improved by adding height-iSAT area. DBP, diastolic blood pressure; iSAT, indexed SAT; Abbreviations as in Figs. 1 and 4.

cholesterol levels), and nutritional screening tools (e.g., GNRI, Mini Nutritional Assessment®, and Controlling Nutritional Status) may be the first step [37,40]. Regional fat distribution can be evaluated by measuring the WC, WHtR, and waist-to-hip ratio. Although these indices are easily and noninvasively obtainable, they do not accurately differentiate regional body composition or directly evaluate the amount of fat. In the present study, CT-derived measurements of adiposity were independently associated with clinical outcomes, but simple anthropometric measures were not. In particular, height-indexed SAT area demonstrated an incremental prognostic value over the model based on age, BMI, diastolic BP, and creatinine and albumin levels, suggesting that CT-based fat assessments may provide additional risk stratification in lean patients with HFpEF.

The EMPEROR-Preserved trial demonstrated that empagliflozin reduces clinical outcomes in patients with HFpEF [41]. It has also been reported that sodium-glucose cotransporter 2 (SGLT2) inhibitors are associated with decreased body weight and visceral fat [42]. The current data did not discourage the use of SGLT2 inhibitors in lean East Asian patients with HFpEF. Our results may indicate the adverse prognostic impacts of underweight status, malnutrition status, or unintentional weight loss over therapy-related weight reduction. Empagliflozin is well tolerated, even in Asian diabetic patients with low BMI [43]. Further studies are warranted to confirm the safety and effectiveness of SGLT2 inhibitors for lean patients with HFpEF.

4.3. Limitations

This was a retrospective study from a tertiary referral center and had inherent flaws related to selection and referral bias. There is also referral bias in that all participants were referred for abdominal CT scan. The sample size and event rate were modest. Due to the retrospective design of the study, there was some variability in the CT scanners. Nutritional status was assessed using GNRI alone. Usage of SGLT2 inhibitors was rare and we could not assess their impact on the relationship between adiposity and clinical outcomes.

5. Conclusions

In lean East Asian patients with HFpEF, lower VAT and SAT amounts were associated with poorer clinical outcomes. When available, CT-based assessment of adiposity may better characterize underweight and malnutrition statuses and provide incremental prognostic value over simple anthropometric indices in lean patients with HFpEF.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclosure

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101162.

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