Cardiovascular Diabetology

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Association of body composition with left ventricular remodeling and outcomes in diabetic heart failure with reduced ejection fraction: assessment of sarcopenic obesity using cardiac MRI

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Abstract

Background Obesity is common in the heart failure (HF) population and is regarded as an important risk factor for developing HF. Greater skeletal muscle mass has shown to be the underlying protective factor against cardiac failure. Since diabetic mellitus (DM) can impair muscle protein metabolism, leading to skeletal muscle wasting, accompanied by adipose tissue accumulation, sarcopenic obesity (SO) may be a high-risk phenotype with poor outcomes in this specific population, especially in HF with reduced ejection fraction (HFrEF). Thus, the aim of this study was to clarify the clinical profiles, left ventricular (LV) remodeling, and prognostic implications of SO in patients with HFrEF and DM.

Methods A total of 283 patients who underwent cardiac MRI were included. Thoracic skeletal muscle index (SMI) was served as a surrogate of skeletal muscle mass. Patients were stratified according to the median thoracic SMI (42.75 cm^2/m^2) and body mass index (25 kg/m^2). Obesity in conjunction with a SMI lower than the median is referred to as SO. The LV volume and function, as well as the systolic strain, were measured. The clinical characteristics and cardiovascular outcomes (heart failure readmission, cardiovascular mortality and heart transplantation) were recorded.

Results Patients with SO had a greater level of amino-terminal pro-B-type natriuretic peptide and were more likely than nonsarcopenic patients with obesity to present with hypoproteinemia. Among patients with obesity, those with sarcopenia displayed greater LV expansion and more profound LV dysfunction, together with an increase in LV mass. During a median follow-up duration of 35.1 months, a total of 73 (25.8%) subjects reached the composite endpoint, with a worst outcome in the group of patients with SO (log-rank $P=0.04$). Multivariable Cox analysis revealed that patients with SO had an approximately 3-fold greater risk of experiencing adverse outcomes than did those with neither sarcopenia nor obesity (hazard ratio: 3.03, 95% confidence interval: 1.39 to 6.63; $P=0.005$).

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Conclusions SO is a potentially high-risk phenotype with adverse LV remodeling and poor clinical outcomes in diabetic patients with HFrEF that may require more attention.

Keywords Sarcopenic obesity, Diabetes mellitus, Heart failure with reduced ejection fraction, Left ventricular remodeling, Outcome

Introduction

Currently, heart failure (HF), especially HF with reduced ejection fraction (HFrEF), which accounts for approximately 50% of patients in the HF population, remains a major public health problem worldwide, with an unfavorable prognosis and a high prevalence among elderly individuals [1, 2]. At present, obesity has been considered an important clinical profile for HF-related phenotyping. There is an interesting phenomenon termed the "obesity paradox", which describes that patients with a higher body mass index (BMI) have better clinical outcomes than their nonobese counterparts with a similar degree of HF. This phenomenon is more common for HFrEF than for HF with preserved ejection fraction [3]. Although the exact reasons for this phenomenon are not fully understood, there is now evidence to support the role of preserved lean muscle mass that underlies the preventative effect of a higher BMI against skeletal muscle reduction during the progression of HFrEF [4, 5]. However, several studies have shown that obesity may not improve the prognosis of established HFrEF when it coexists with diabetes mellitus (DM), suggesting a unique but detrimental effect of DM on body composition alterations in this population [6–9].

Sarcopenic obesity (SO) is defined as a geriatric syndrome characterized by a concurrent decrease in skeletal muscle mass and function, along with excessive adipose tissue [10]. Data from a population-based study in the United States showed a prevalence of SO of 28.3% in people older than 60 years [11]. Indeed, certain populations, such as patients with HFrEF comorbid with DM, might be at a greater risk of developing SO. In the context of this clinical condition, DM can impair muscle protein metabolism, leading to skeletal muscle wasting and thereafter reduced exercise capacity. Physical inactivity in turn exacerbates insulin resistance and obesity-related skeletal muscle loss and ultimately promotes the occurrence of SO [12]. Therefore, SO may be a high-risk phenotype within the spectrum of HFrEF patients with DM, warranting further investigation. However, to the best of our knowledge, no data are available with comprehensive MRI analysis on this issue. In this study, we aimed to explore clinical profiles and left ventricular (LV) remodeling and examine the prognostic implications of SO in patients with HFrEF and DM.

Methods

Study cohort and data definitions

This retrospective study included patients with HFrEF referred to our hospital between January 2015 and April 2023. The diagnosis of HFrEF was established according to the guidelines from the European Society of Cardiology (2021) [13]. All consecutive patients met the following criteria: (1) had at least one symptom and/or sign of decompensated HF in the previous 3 months; (2) had a reduced (< 40%) LV ejection fraction (LVEF) as assessed by cardiac MRI; and (3) had an elevated amino-terminal pro-B-type natriuretic peptide (NT-proBNP) level. Patients who met at least one of the following criteria were excluded: (1) aged younger than 18 years, (2) had acute coronary syndrome and/or severe arrhythmia in the last 3 months, or (3) had incomplete clinical or MRI information. In this study, we just included patients with Type 2 diabetes. The diagnosis of DM was made when patients fulfilled at least one of the following criteria: (1) self-reported DM, (2) current use of oral glucose-lowering medications, (3) a fasting plasma glucose level higher than 7.0 mmol/L, or (4) a hemoglobin A1c level greater than 6.5% [14]. BMI was calculated as weight divided by height squared. While Asians generally have a greater percentage of body fat than Caucasians of the same age, sex and BMI, this study used a BMI cutoff value of 25 kg/m^2 to define obesity [15, 16]. The flowchart of this study was shown in Fig. 1.

Patients were all in hospital at the time of identification in this study. Baseline data on demographics, clinical characteristics, laboratory measurements and medical treatments were retrieved from hospital records. At our institution, the reference range for albumin assays is 35–47 g/L, and the diagnosis of hypoproteinemia is made when the albumin concentration is less than 35 g/L. Anemia was diagnosed using the World Health Organization criteria: a hemoglobin concentration less than 120 g/L in nonpregnant adult females and less than 130 g/L in adult males [17]. This study was approved by the Biomedical Research Ethics Committees of our hospital and complied with the Declaration of Helsinki. The need for informed consent was waived by the ethics committee. All medical data were protected with full confidentiality and used only for the purpose of the present study.

Cardiac MRI acquisition

Cardiac MRI was performed on a 3-Tesla scanner (MAGNETOM Skyra/Tim Trio; Siemens Healthcare, Erlangen,

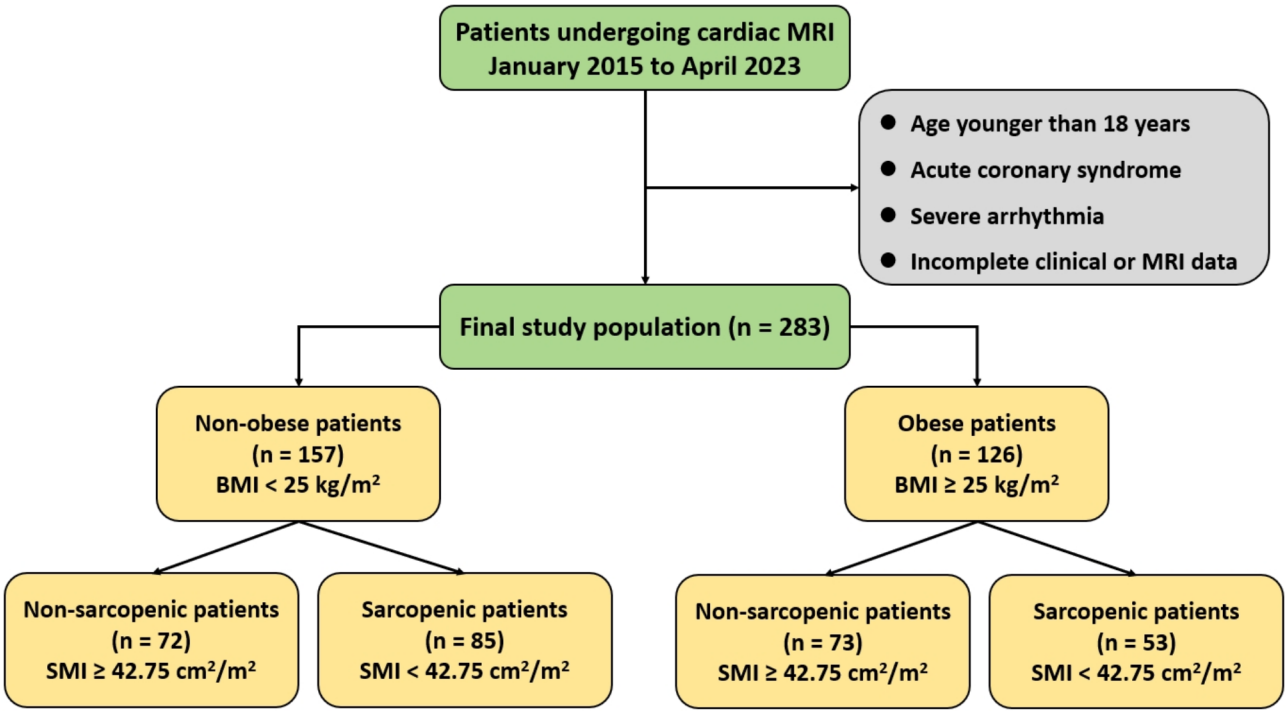

Fig. 1 Study cohort. *MRI* Magnetic resonance imaging, *BMI* Body mass index, *SMI* Skeletal muscle index

Germany) for each patient. As included in the routine scanning protocol, an axial stack of steady-state free precession (SSFP) images covering the entire heart was obtained for localization. The typical acquisition parameters were as follows: temporal resolution = 224.16 ms; echo time (TE) = 1.23 ms; slice thickness = 6.0 mm; flip angle (FA) = 60°; acquisition matrix = 126 × 256 pixels; and field of view (FOV) = 340 × 255 mm^2. For cine imaging, a balanced SSFP sequence was performed with the following parameters: repetition time (TR) = 2.81 ms; TE = 1.22 ms; slice thickness = 8.0 mm; FA = 40°/50°; acquisition matrix = 166 × 208 pixels; and FOV = 340 × 284 mm^2. Twenty-five frames were reconstructed per breath-hold acquisition for the cine images.

Skeletal muscle mass reduction assessment

Several previous studies have addressed the relationship between axial thoracic skeletal muscle size and prognosis in HF patients and have confirmed the feasibility and simplicity of axial thoracic skeletal muscle size measurements for assessing muscle mass reduction [4, 9, 18]. This method of quantifying thoracic skeletal muscle mass could provide important prognostic information related to sarcopenia from routine cardiac MRI images without the need for additional approaches. Thus, in the present study, total bilateral axial thoracic skeletal muscle size standardized by body surface area (BSA) (cm^2/m^2) was used as a surrogate to evaluate the decrease in skeletal muscle mass. In brief, it was an area measurement of multiple muscles taken from a single slice. Thoracic skeletal muscle at the level of the carina, including muscle groups of pectoralis major, pectoralis minor, serratus anterior, periscapular, paraspinal, and trapezius muscles, were manually traced bilaterally to obtain cross-sectional area [9]. The median thoracic skeletal muscle index (SMI) was used as the cutoff value to define the loss of skeletal muscle mass. Patients with SMI lower than 42.75 cm^2/m^2 was regarded as skeletal muscle mass reduction. The status of SO in our study cohort was defined as both having an SMI lower than 42.75 cm^2/m^2 and a BMI higher than 25 kg/m^2.

LV remodeling assessment

All analyses related to LV geometry, volume and myocardial mechanics were completed using commercially available CVI[42] software (Circle Cardiovascular Imaging, Inc., Calgary, Alberta, Canada). For LV geometry and function analyses, endocardial and epicardial borders were traced semiautomatically at the LV end-diastolic and end-systolic phases on the short-axis stacks and manually corrected if needed. The LVEF, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV stroke volume (LVSV) were automatically calculated. LV papillary muscles were included in the LV mass (LVM) measurements but not in the LV volume measurements. LV volumetric measurements and LVM were indexed for BSA. LV hypertrophy (LVH) was defined as an indexed LVM > 115 g/m^2 in men and > 95 g/m^2 in women [19]. For

LV mechanics analyses, a stack of short-axis cine images combined with 4-, 2- and 3-chamber long-axis images were loaded into the feature-tracking module. We delineated the LV endocardial and epicardial borders at the end-diastolic phase (reference phase) of all cine images. The software automatically traced the contours throughout the cardiac cycle. Global myocardial peak strains in longitudinal (GLS), circumferential (GCS) and radial (GRS) components were calculated as the total deformation of the myocardium from its initial length at the end-diastolic phase to its final length at the end-systolic phase and are expressed as a percentage (%).

Clinical outcomes during follow-up

The primary endpoint was the composite of HF readmission, cardiovascular death and heart transplantation, whichever occurred first. Cardiovascular death was defined as death attributable to progressive cardiac decompensation (death preceded by acute worsening or exacerbation of HF), myocardial infarction, sudden death (i.e. unexpected death in patients with a previously stable clinical course). By reviewing electronic medical records or telephone interviews (Dr. G.Z.), we retrospectively collected follow-up data for all subjects until the occurrence of any endpoint or until censoring on March 1, 2024. The duration of follow-up was calculated as the time from cardiac MRI to either the occurrence of any endpoint or the last follow-up date.

Statistical methods

Statistical analyses were performed using SPSS (IBM SPSS, Inc., Armonk, New York, USA) and Prism (GraphPad Software, Inc., San Diego, California, USA) software. Patients were divided into four cohorts according to the SMI and BMI cutoff values: nonsarcopenic/nonobese (SMI > 42.75 cm^2/m^2 and BMI < 25 kg/m^2), sarcopenic/nonobese (SMI < 42.75 cm^2/m^2 and BMI < 25 kg/m^2), nonsarcopenic/obese (SMI > 42.75 cm^2/m^2 and BMI > 25 kg/m^2), and SO (SMI < 42.75 cm^2/m^2 and BMI > 25 kg/m^2). The normality of the data was determined using the Shapiro–Wilk test. Continuous variables are presented as the means and SDs or medians and interquartile ranges (IQRs). Categorical variables are presented as counts and percentages. Between-group differences were examined using Student's t test, the Wilcoxon–Mann–Whitney test, or the chi-square test (Fisher's exact test), as appropriate. Differences in clinical profiles and cardiac MRI findings were tested between (1) nonsarcopenic and sarcopenic individuals in nonobese and obese cohorts and (2) nonobese and obese individuals in nonsarcopenic and sarcopenic cohorts. Adverse event rates among the four groups were compared using Kaplan–Meier survival analysis with the log-rank test. Associations between SO status and prognosis were determined using a multivariable Cox proportional hazards model. SO status was treated as a dummy variable, with nonsarcopenic/nonobese status used as the reference when performing Cox analysis. The clinically critical variables or variables with P values < 0.10 in univariable models were used as adjustment variables in the multivariable Cox model. Differences with a two-tailed P value < 0.05 were considered to indicate statistical significance.

Results

Clinical profiles of the study cohort

This study included a total of 283 patients with a diagnosis of DM comorbid with HFrEF. The mean age of patients were 56.6 ± 11.6 years of age and 71.4% were men. The mean BMI of patients in the overall cohort were 24.7 ± 3.8 kg/m^2. Patients were classified into four cohorts according to the SMI (42.75 cm^2/m^2) and BMI (25 kg/m^2) cutoff values for analysis. Figure 2 showed the differences in axial thoracic skeletal muscle size in individuals among different subgroups. Among the overall study cohort, there was a nonsignificant trend toward a greater incidence of sarcopenia in nonobese patients than in patients with obesity (54.1% vs. 42.1%; $P = 0.06$). On average, patients with obesity were approximately 6.0 years younger at diagnosis and were predominantly male (all $P < 0.05$). In nonobese but not in obese group, individuals with sarcopenia were more likely to have DM duration more than 5 years ($P = 0.049$). Interestingly, among individuals with sarcopenia, those with obesity were less likely to have DM duration more than 5 years in comparison with nonobese individuals (22.6% vs. 48.2%; $P = 0.011$). There were no differences regarding the New York Heart Association (NYHA) functional class, etiology of HF or HF duration between nonsarcopenic and sarcopenic patients in either nonobese or obese cohorts. More detailed clinical characteristics were presented in Table 1.

SO and LV remodeling

Among patients with obesity, compared to those without sarcopenia, patients with sarcopenia showed increased indexed LVEDV [158.0 (114.7, 192.9) mL/m^2 vs. 141.3 (105.2, 165.3) mL/m^2; $P = 0.04$], indexed LVESV [121.7 (88.9, 168.0) mL/m^2 vs. 101.7 (72.8, 129.2) mL/m^2; $P = 0.02$], and a depressed LVEF [21.3 (15.4, 28.0)% vs. 28.0 (20.6, 34.2)%; $P < 0.001$]. Notably, compared to those without SO, patients with SO demonstrated a larger indexed LVM (87.3 ± 19.6 g/m^2 vs. 71.8 ± 13.9 g/m^2; $P < 0.001$), as was also the case in the subgroups of nonobese patients with and without sarcopenia (86.7 ± 19.2 g/m^2 vs. 79.9 ± 16.1 g/m^2; $P = 0.02$). Among the four cohorts, the presence of LVH was most common in patients with SO.

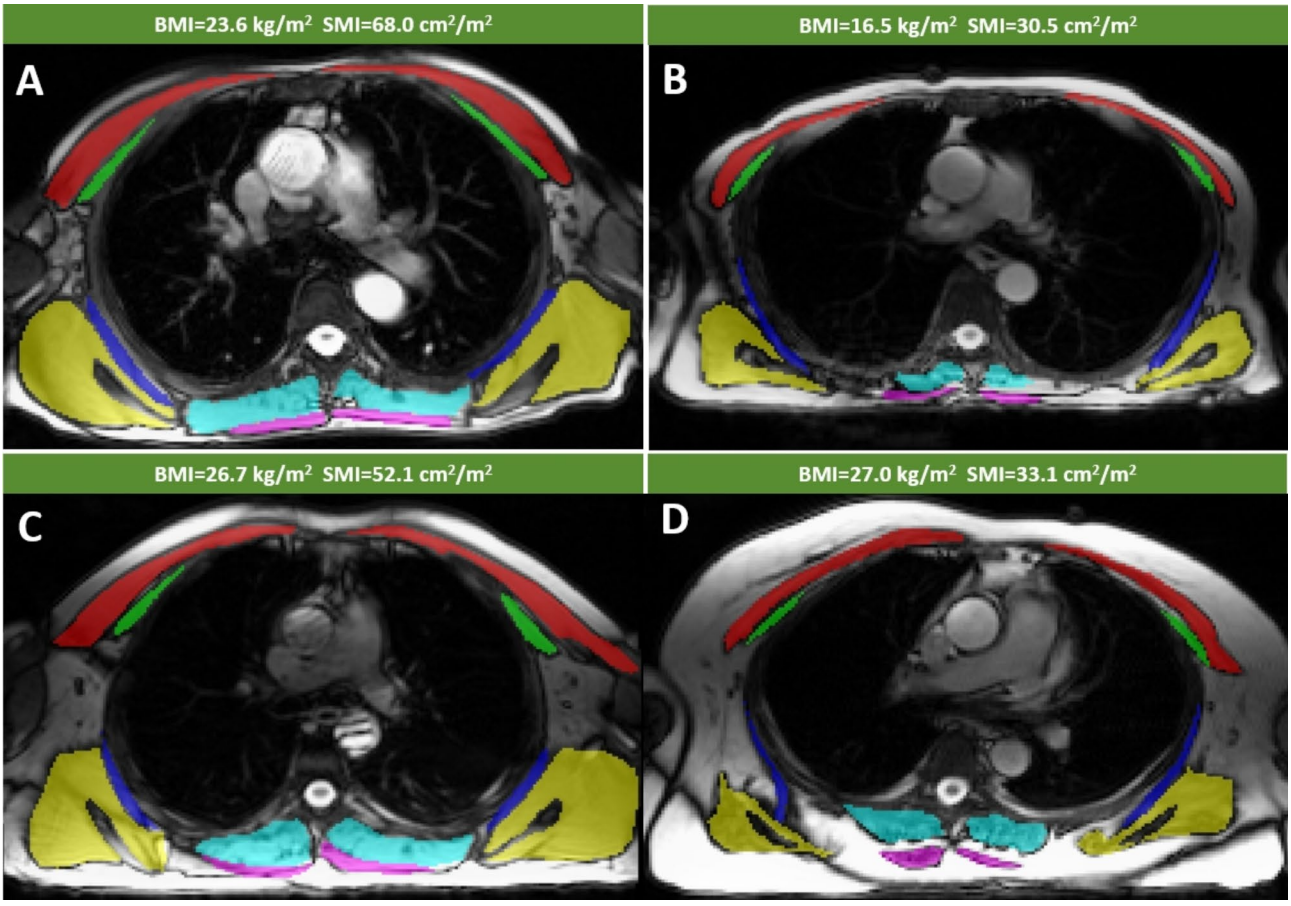

Fig. 2 Examples of four patients referred to cardiac MRI. The area of thoracic skeletal muscle size measured in this study was marked with red (pectoralis major), green (pectoralis minor), blue (serratus anterior), yellow (periscapular), cyan (paraspinal), and purple (trapezius muscles), respectively. *MRI* Magnetic resonance imaging, *BMI* Body mass index, *SMI* Skeletal muscle index

The magnitudes of peak strain in the longitudinal, circumferential, and radial components were comparable between nonobese patients with and without sarcopenia. Nevertheless, in the obese subgroup, more severe decreases in the GLS [-3.9 (-2.6, -5.5)% vs. -5.7 (-4.0, -6.9)%; $P<0.001$], GCS [-6.2 (-4.6, -8.4)% vs. -7.6 (-5.2, -10.0)%; $P=0.005$] and GRS [7.1 (4.6, 10.6)% vs. 8.3 (6.8, 12.2)%; $P=0.02$)] were observed in patients with SO than in those without sarcopenia. In addition, patients with SO displayed a more severe impairment in the magnitudes of GLS [-3.9 (-2.6, -5.5)% vs. -4.6 (-3.3, -6.2)%; $P=0.04$] and GCS [-6.2 (-4.6, -8.4)% vs. -7.1 (-5.0, -10.3)%; $P=0.03$] compared with their counterparts with sarcopenia alone.

SO and clinical outcomes

During a median follow-up duration of 35.1 (IQR, 21.8, 58.7) months after discharge, a total of 73 (25.8%) subjects reached the composite endpoint, among whom 59 patients (20.8%) were rehospitalized due to HF progression, 9 patients (3.2%) died and 5 patients (1.8%) underwent heart transplantation. Kaplan–Meier survival analysis revealed a significantly lower survival rate in the SO subgroup than in the other subgroups (log-rank $P=0.04$) (Fig. 3A). According to the unadjusted Cox proportional hazard analysis, SO status was significantly associated with an increased risk of experiencing the composite endpoint [hazard ratio (HR): 3.81, 95% confidence interval (CI): 1.50 to 6.45; $P<0.001$] when considering nonsarcopenic/nonobese individuals as the reference subgroup. Importantly, the associations between SO status and the risk of experiencing poor outcomes remained significant after multivariable adjustment for age, sex, log NT-proBNP concentrations, hypoproteinemia status, anemia status, DM duration, beta-blocker use status, insulin use status, angiotensin receptor-neprilysin inhibitor use status, sodium–glucose cotransporter-2 inhibitor use status, LVEF and GLS, with an adjusted HR of 3.03 (95% CI: 1.39 to 6.63; $P=0.005$) (Table 2). Additionally, based on the median follow-up duration in each subgroup, we found that the incidence rate of adverse outcomes was 17.1/100 person–years in the SO subgroup, which was the highest among the four subgroups (Fig. 3B).

Table 1 Baseline characteristics of the study cohort

Variables	Non-obese patients			Obese patients		
	Non-sarcopenic ($n=72$)	Sarcopenic ($n=85$)	*P*-value	Non-sarcopenic ($n=73$)	Sarcopenic ($n=53$)	*P*-value
Age, yrs	58.0 ± 11.2	60.4 ± 10.4	0.17	52.5 ± 12.0 [&]	54.3 ± 11.2 *	0.39
Male, n (%)	45 (62.5)	51 (60)	0.32	62 (84.9) [#]	44 (83.0) †	0.77
BMI, kg/m^2	22.4 ± 1.9	21.8 ± 2.1	0.09	28.1 ± 2.8 [&]	27.6 ± 2.4 *	0.29
SBP, mmHg	117.3 ± 19.6	121.3 ± 22.9	0.25	122.1 ± 19.8	123.5 ± 19.7	0.69
DBP, mmHg	77.1 ± 13.0	77.6 ± 14.7	0.79	80.2 ± 15.1	83.4 ± 17.8	0.28
HR, beats/min	87.1 ± 18.0	87.4 ± 17.9	0.92	84.5 ± 16.9	87.7 ± 16.3	0.30
NYHA functional class III–IV, n (%)	60 (83.3)	73 (85.9)	0.66	61 (83.6)	48 (90.6)	0.26
Ischemic cause of HF, n (%)	20 (27.8)	23 (27.1)	0.61	24 (32.9)	19 (35.8)	0.73
HF duration, n (%)						
≤ 1 yr	40 (55.5)	44 (51.7)	0.76	43 (58.9)	27 (50.9)	0.66
> 1 and ≤ 5 yrs	19 (26.4)	27 (31.8)		20 (27.4)	18 (34.0)	
> 5 yrs	13 (18.1)	14 (16.5)		10 (13.7)	8 (15.1)	
DM duration, n (%)						
≤ 1 yr	37 (51.4)	33 (38.8) [#]	0.049	46 (63.0)	31 (58.5) †	0.83
> 1 and ≤ 5 yrs	14 (19.4)	11 (12.9)		11 (15.1)	10 (18.9)	
> 5 yrs	21 (29.2)	41 (48.2) [#]		16 (21.9)	12 (22.6) †	
Major comorbid conditions and laboratory measurements						
CAD, n (%)	30 (41.7)	29 (34.1)	0.33	32 (43.8)	21 (39.6)	0.64
HT, n (%)	27 (37.5)	36 (42.4)	0.54	45 (61.6) [#]	32 (60.4) †	0.89
AF, n (%)	8 (11.0)	11 (20.8)	0.13	19 (26.4) [#]	21 (24.7)	0.81
Hypoproteinemia, n (%)	24 (33.3)	43 (50.6)	0.03	9 (12.3) [#]	26 (49.1)	< 0.001
Albumin, g/L	40.5 ± 5.2	38.7 ± 5.5	0.03	42.7 ± 3.3[&]	40.5 ± 4.6*	0.004
Anemia, n (%)	20 (27.8)	33 (38.8)	0.14	6 (8.2) [#]	11 (20.8) †	0.04
Hemoglobin, g/L	134.8 ± 21.8	129.0 ± 24.9	0.13	149.5 ± 21.4[&]	142.8 ± 24.2*	0.11
NT-proBNP, pg/mL	1889 (1071, 3772)	2456 (1232, 6603)	0.27	1209 (495, 3102)[&]	3835 (1645, 9067)	< 0.001
FBG, mmol/L	7.6 (6.1, 9.6)	7.9 (6.2, 10.6)	0.54	7.3 (6.2, 9.1)	7.3 (6.3, 9.4)	0.85
HbA1c, %	6.9 (6.3, 7.9)	7.4 (6.7, 8.4)	0.04	6.8 (6.3, 8.1)	7.3 (6.6, 8.1)	0.33
TG, mmol/L	1.3 (0.9, 2.0)	1.2 (0.9, 1.9)	0.61	1.9 (1.4, 2.5)[&]	1.5 (1.1, 2.5)*	0.04
TC, mmol/L	4.0 (3.3, 4.6)	4.0 (3.2, 4.7)	0.99	3.9 (3.2, 4.8)	3.9 (3.3, 4.9)	0.44
eGFR, mL/min/1.73m^2	73.4 ± 21.4	70.4 ± 22.6	0.42	79.1 ± 21.9	75.1 ± 26.9	0.37
Cardiovascular medications, n (%)						
β-blocker	58 (80.6)	58 (68.2)	0.08	59 (80.8)	44 (83.0)	0.75
ACEI/ARB	52 (72.2)	57 (67.0)	0.48	51 (69.9)	38 (71.7)	0.82
ARNI	38 (52.8)	39 (45.9)	0.39	41 (56.2)	29 (54.7)	0.87
SGLT-2i	23 (31.9)	32 (37.6)	0.46	32 (43.8)	18 (34.0)	0.26
Loop diuretics	55 (76.4)	67 (78.8)	0.72	54 (74.0)	41 (77.4)	0.66
MRA	57 (79.2)	63 (74.1)	0.46	51 (69.9)	42 (79.2)	0.24
Statins	31 (43.1)	38 (44.7)	0.83	40 (54.8)	29 (54.7)	0.99
Digoxin	12 (16.7)	20 (23.5)	0.29	10 (13.7)	11 (20.8)	0.29
Hypoglycemic medications, n (%)						
Insulin	16 (22.2)	39 (45.9)	0.002	12 (16.4)	23 (43.4)	0.001
Metformin	21 (29.2)	30 (35.3)	0.41	25 (34.2)	15 (28.3)	0.48
α-GI	20 (27.8)	21 (24.7)	0.66	18 (24.7)	15 (28.3)	0.65
Sulfonylureas	15 (20.8)	8 (9.4)	0.04	9 (12.3)	8 (15.1)	0.65

Data are presented as mean ± SD, media (Q1, Q3) or number (percentage)

Student's t test or Wilcoxon–Mann–Whitney test: [&]. P-value < 0.05 vs. patients with non-sarcopenia/non-obesity. *. P-value < 0.05 vs. patients with sarcopenia/non-obesity. Chi-square test (Fisher's exact test): [#]. P-value < 0.05 vs. patients with non-sarcopenia/non-obesity. †. P-value < 0.05 vs. patients with sarcopenia/non-obesity

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association; HF, heart failure; DM, diabetic mellitus; CAD, coronary artery disease; HT, hypertension; AF, atrial fibrillation; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TG, triglycerides; TC, cholesterol; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; MRA, mineralocorticoid receptor antagonist; α-GI, α-Glucosidase inhibitors

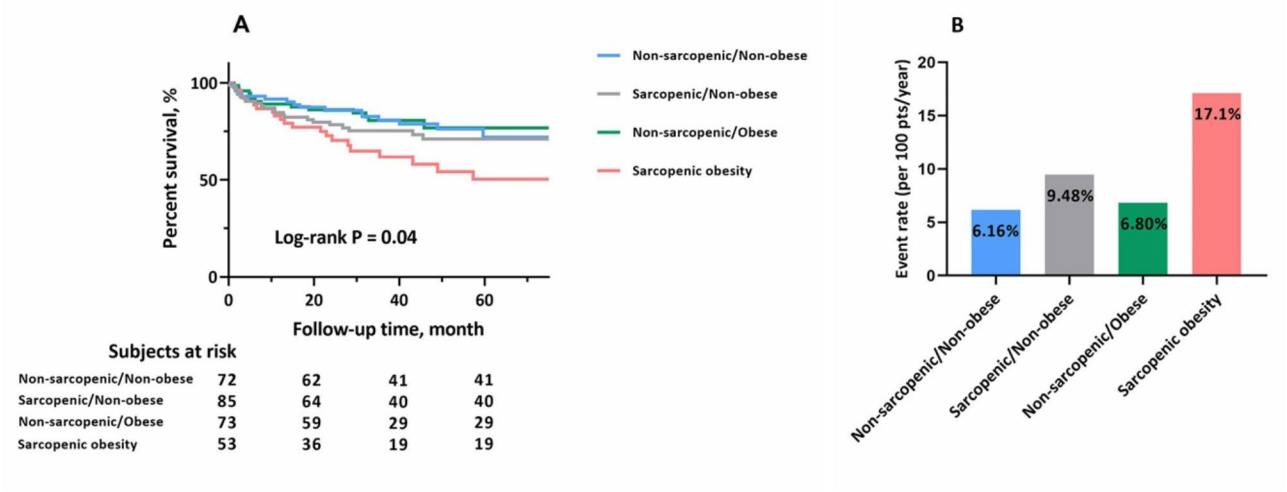

Fig. 3 Survival analysis according to the SO status. Kaplan–Meier survival curves demonstrating the overall survival rates among the four subgroups (**A**). The composite event rate per 100 person-year (**B**). *SO* Sarcopenic obesity

Table 2 Cox proportional hazards analysis to identify the association between SO and clinical outcomes

	HR (95% CI)	*P*-value
Unadjusted model		
Non-sarcopenic/non-obese	1.00 (reference)	
Sarcopenic/non-obese	2.96 (1.28, 5.11)	< 0.001
Non-sarcopenic/obese	1.39 (0.63, 3.05)	0.42
SO	3.81 (1.50, 6.45)	< 0.001
Model 1: adjusted for age, sex, NT-proBNP[§], the presence of hypoproteinemia and anemia, DM duration		
Non-sarcopenic/non-obese	1.00 (reference)	
Sarcopenic/non-obese	2.50 (1.23, 5.09)	0.012
Non-sarcopenic/obese	1.44 (0.64, 3.26)	0.382
SO	3.24 (1.53, 6.87)	0.002
Model 2: adjusted for model 1 combined with the use of β-blocker, insulin, ARNI, and SGLT-2i		
Non-sarcopenic/non-obese	1.00 (reference)	
Sarcopenic/non-obese	2.25 (1.09, 4.66)	0.028
Non-sarcopenic/obese	1.40 (0.62, 3.17)	0.423
SO	3.29 (1.54, 7.08)	0.002
Model 3: adjusted for model 2 combined with LVEF and GLS		
Non-sarcopenic/non-obese	1.00 (reference)	
Sarcopenic/non-obese	1.94 (1.02, 4.08)	0.035
Non-sarcopenic/obese	1.36 (0.59, 3.14)	0.470
SO	3.03 (1.39, 6.63)	0.005

[§]. NT-proBNP is log-transformed before being included in the Cox model

Abbreviations: SO, sarcopenic obesity; HR, hazard ratio; CI, confidence interval; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; DM, diabetic mellitus; ARNI, angiotensin receptor-neprilysin inhibitor; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; LVEF, left ventricular ejection fraction; GLS, global longitudinal peak strain

Discussion

The present study performed a detailed characterization of SO in clinical profiles, LV remodeling, and clinical outcomes in patients with HFrEF concomitant with DM. Our results supported the existence of a distinct SO phenotype with a poor prognosis within the spectrum of this entity. The main findings of this study are summarized as follows: (1) Despite having a similar NYHA functional class, compared to those with obesity but without sarcopenia, patients with SO had a greater level of NT-proBNP but a lower level of albumin. Moreover, patients with SO were more likely to have a more advanced disease progression of DM in comparison with those with sarcopenia alone. (2) Patients with SO displayed greater LV expansion and more profound LV dysfunction, together with an increase in LVM, resulting in eccentric cardiac remodeling. (3) Among HFrEF patients with DM, SO status was associated with a poor disease prognosis, indicated by an approximately 3-fold greater risk of experiencing adverse outcomes than those with neither sarcopenia nor obesity.

Clinical profiles of patients with SO

Obesity is highly prevalent in patients with HFrEF, with approximately 40–50% of patients having either overweight or obesity status [20]. Although obesity has been repeatedly shown to be a major independent risk factor for developing HF, the "obesity paradox" phenomenon seems to exist, as indicated by a better HF prognosis among patients with obesity, making the interaction between obesity and HF, especially HFrEF, more confusing [3, 21–26]. In recent years, the study of body composition changes may have helped to elucidate the survival benefit underlying the protective effect of a greater BMI on disease prognosis for HFrEF patients [4, 5].

DM and obesity often occur concomitantly, and both DM and obesity closely interact with each other. Since DM can reduce muscle protein synthesis, it is necessary to evaluate SO in the context of HFrEF with coexisting

DM. HF patients with obesity display lower levels of natriuretic peptides than nonobese patients, which has been attributed to enhanced degradation of natriuretic peptides in adipose tissue [21]. In our study, only patients with obesity without sarcopenia had expectedly lower median levels of NT-proBNP than their nonsarcopenic/nonobese counterparts. In contrast, we observed remarkably elevated levels of NT-proBNP in patients with SO compared to those in patients with obesity without sarcopenia. The exact reasons for this observation remain unclear. The loss of lean muscle mass together with excess adipose tissue deposition may fail to prevent plasma volume expansion, resulting in increased wall stress and increased natriuretic peptide production. Moreover, we noticed that the serum albumin concentration was lower in patients with sarcopenia than in those without sarcopenia, regardless of BMI, which indicated that patients with sarcopenia were malnourished. However, this finding is partially reasonable for SO patients. In fact, for patients with SO, this abnormality may further suggest a metabolic imbalance in which obesity is involved. Current evidence shows that alterations in hormones, such as adiponectin and leptin, in the context of obesity may play a prominent role in anabolic–catabolic imbalance [27–29]. In clinical practice, the phenotype of SO, but not sarcopenia alone, could be easily ignored, since patients with SO present with a considerably increased BMI, which seems to indicate a relatively robust metabolic substrate. Therefore, recognizing the specific features of SO is necessary for clinicians to identify potential treatment targets.

LV remodeling in patients with SO

Obesity is considered to contribute to an increase in total blood volume in HF patients. The augmentation of blood volume and cardiac output thereby predisposes patients to LV enlargement and eccentric remodeling [30]. However, the alterations involved in LV remodeling in patients with SO are not entirely understood. In our study, elevated LV volumes were observed in patients with SO, accompanied by increased LVM and more prominently impaired LV contractile function across the study cohort. This observation was in keeping with our previous study, which demonstrated that a lower SMI was associated with 'nonfunctional' LV hypertrophy [9]. Moreover, despite the comparable LVH between patients with sarcopenia with and without obesity, we found that the former displayed a more exacerbated decline in LV contractile function. Our study further expanded upon these findings to identify more pernicious types of adverse cardiac remodeling and dysfunction. Perhaps the onset of sarcopenia among diabetic patients with HFrEF implies the progression of HF as well as DM, and obesity promotes this process through the release of proinflammatory adipokines, thereby leading to cardiac inflammation, myocardial ischemia and interstitial collagen deposition [21]. In this sense, regarding diabetic patients with HFrEF, thoracic muscle size assessment along with cardiac structure and function assessment are necessary, which is helpful for identifying patients with SO.

SO status and disease prognosis

The results of our study showed a worse prognosis in patients with SO than in patients with neither sarcopenia nor obesity. This finding was consistent with a previous study by Saito et al., who reported that SO status is a risk factor for adverse outcomes in the general elderly population with HF [31]. More importantly, since sarcopenic/non-obese individuals also had an increased risk compared to non-sarcopenic/non-obese individuals, while individuals with SO presented a more advanced disease progression of DM than individuals with sarcopenia alone, our study further provided evidence that SO phenotype may be more severe than that of sarcopenia alone in diabetic patients with HFrEF. Therefore, it could be just a reflection of SO as a specific phenotype beyond sarcopenia. In fact, SO patients with decreased skeletal muscle mass and increased fat mass have been reported to have impaired cardiorespiratory fitness, contributing to frailty and activity of daily living disability [20]. A sedentary lifestyle further aggravates DM and promotes insulin resistance, which in turn leads to a vicious cycle of skeletal muscle loss and adipose deposition [12]. It has been reported that reduced skeletal muscle mass may contribute to decreased total and central blood flow, which produces lower stroke volume and thereby cardiac output [20]. Furthermore, the paracrine and endocrine effects of adipose tissue on the muscle bed could result in impaired perfusion and inflammatory infiltration [32, 33]. Together, these pathological processes may induce myocardial ischemia and lethal arrhythmia and eventually cause adverse outcomes. Therefore, in patients with HFrEF and DM, skeletal muscle mass assessment should be performed routinely to identify risk and stratify patients with HFrEF and DM by obesity status. Additionally, our study also highlights the additional advantages of using MRI not only in cardiac structure and function but also in skeletal muscle mass assessment.

Study limitations

Our study also has several limitations. First, in the present study, we used a simple alternative index that has been confirmed by the above-mentioned studies to have prognostic value for detecting muscle mass reduction rather than traditionally used appendicular muscle mass [4, 9, 18]. Because this quantification assessment is readily available in subjects undergoing MRI scanning

for cardiac structure and function assessment. Moreover, lower limbs skeletal muscle may be more subject to deconditioning [4]. Second, there are differences in the criteria for obesity between Westerners and Asians due to differences in ethnic background. We classified our patients using the criteria specified for use with Asian. However, regardless of the differences in the classification of obesity, we found that SO was related to adverse outcomes in patients with HFrEF and DM. The generalizability of this disease state to different populations needs to be further verified. Third, several new anthropometric measures, such as the waist-to-height ratio or waist-to-hip ratio, have also been used as biomarkers to reflect changes in body composition [34]. However, these measurements were unavailable in this study due to its retrospective nature. Forth, since this was a retrospective observational study, selecting bias was inevitable. Finally, we didn't record the baseline data regarding other microvascular complications of DM in this study.

Conclusions

In conclusion, in the context of HFrEF with DM, patients with SO displayed profound eccentric remodeling accompanied by a greater deterioration in myocardial contractile function and a greater propensity for adverse outcomes, which suggests that SO may serve as a high-risk cardiac failure phenotype that warrants more attention and aggressive medical treatment.

Abbreviations

HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
BMI	Body mass index
DM	Diabetes mellitus
SO	Sarcopenic obesity
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NT-proBNP	Amino-terminal pro-B-type natriuretic peptide
SSFP	Steady-state free precession
TE	Echo time
FA	Flip angle
FOV	Field of view
BSA	Body surface area
SMI	Skeletal muscle size index
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
LVSV	Left ventricular stroke volume
LVM	Left ventricular mass
LVH	Left ventricular hypertrophy
GLS	Global longitudinal peak strain
GCS	Global circumferential peak strain
GRS	Global radial peak stain
IQR	Interquartile range
HR	Hazard ratio
CI	Confidence interval

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Author contributions

K.S., G.Z. and R.X. interpreted the data and wrote the manuscript. X.M.L. and L.J. analyzed the data and gave advice on data presentation. K.S., Y.G. and L.J. collected the data. Y.G., H.Y.X., Y.L., Y.K.G. and Z.G.Y. participated in the study design. K.S., Y.K.G. and Z.G.Y. revised the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Biomedical Research Ethics Committees of West China Hospital and was complied with the Declaration of Helsinki. Written informed consent was waived because of the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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