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The role of body composition in left ventricular remodeling, reverse remodeling, and clinical outcomes for heart failure with mildly reduced ejection fraction: more knowledge to the "obesity paradox"

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Abstract

Background Although the "obesity paradox" is comprehensively elucidated in heart failure (HF) with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), the role of body composition in left ventricular (LV) remodeling, LV reverse remodeling (LVRR), and clinical outcomes is still unclear for HF with mildly reduced ejection fraction (HFmrEF).

Methods Our study is a single-centre, prospective, and echocardiography-based study. Consecutive HFmrEF patients, defined as HF patients with a left ventricular ejection fraction (LVEF) between 40 and 49%, between January 2016 to December 2021 were included. Echocardiography was re-examined at 3-, 6-, and 12-month follow-up to assess the LVRR dynamically. Body mass index (BMI), fat mass, fat-free mass, percent body fat (PBF), CUN-BAE index, and lean mass index (LMI) were adopted as anthropometric parameters in our study to assess body composition. The primary outcome was LVRR, defined as: (1) a reduction higher than 10% in LV end-diastolic diameter index (LVEDDI), or a LVEDDI < 33 mm/m^2, (2) an absolute increase of LVEF higher than 10 points compared with baseline echocardiogram, or a follow-up LVEF ≥50%. The secondary outcome was a composite of re-hospitalization for HF or cardiovascular death.

Results A total of 240 HFmrEF patients were enrolled in our formal analysis. After 1-year follow-up based on echocardiography, 113 (47.1%) patients developed LVRR. Patients with LVRR had higher fat mass (21.7 kg vs. 19.3 kg, $P = 0.034$) and PBF (28.7% vs. 26.6%, $P = 0.047$) compared with those without. The negative correlation between anthropometric parameters and baseline LVEDDI was significant (all $P < 0.05$). HFmrEF patients with higher BMI, fat mass, PBF, CUN-BAE index, and LMI had more pronounced and persistent increase of LVEF and decline in LV mass

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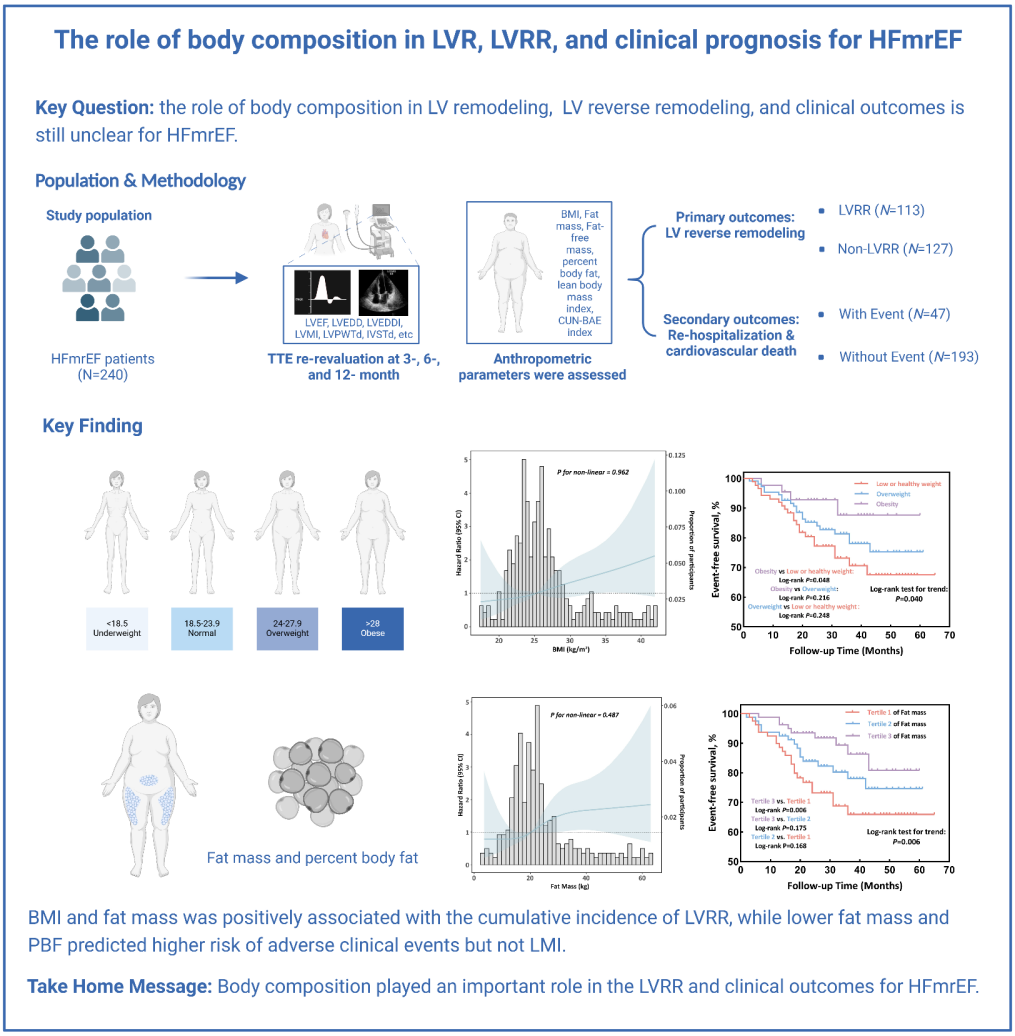
index (LVMI). Univariable Cox regression analysis revealed that higher BMI (HR 1.042, 95% CI 1.002–1.083, $P=0.037$) and fat mass (HR 1.019, 95% CI 1.002–1.036, $P=0.026$) were each significantly associated with higher cumulative incidence of LVRR for HFmrEF patients, while this relationship vanished in the adjusted model. Mediation analysis indicated that the association between BMI and fat mass with LVRR was fully mediated by baseline LV dilation. Furthermore, higher fat mass (aHR 0.957, 95% CI 0.917–0.999, $P=0.049$) and PBF (aHR 0.963, 95% CI 0.924–0.976, $P=0.043$) was independently associated with lower risk of adverse clinical events.

Conclusions Body composition played an important role in the LVRR and clinical outcomes for HFmrEF. For HFmrEF patients, BMI and fat mass was positively associated with the cumulative incidence of LVRR, while higher fat mass and PBF predicted lower risk of adverse clinical events but not LMI.

Graphical abstract



Keywords Body composition, Heart failure with mildly reduced ejection fraction, Left ventricular reverse remodeling

Introduction

Heart failure (HF) is a global public health problem caused significant morbidity, considerable mortality, poor quality of life, and heavy health care expenditure [1, 2].

HF is a heterogenous and multi-faced clinical syndrome characterized by systemic congestion, and impaired cardiac structure and function [3, 4]. The pathophysiological hallmark of HF is myocardial remodeling, especially for left ventricle (LV). Pathological LV remodeling (LVR) is characterized by chamber dilation, ventricular wall thinning, or eccentric hypertrophy [5]. The mechanism of LVR is complex. Multiple factors, including mechanical stress, neurohormonal activation, inflammation and metabolic abnormality, participate in this pathological process [6, 7]. Persistent LVR correlates with poor prognosis of HF. Higher mortality and re-hospitalization rate have been observed in patients with more severe LVR [8–10]. Myocardial reverse remodeling, especially left ventricular reverse remodeling (LVRR), is an important indicator of the cardiac functional recovery and is associated with survival benefits and improved clinical outcomes for HF patients [11]. LVRR was characterized by restoration of LV geometry, normalization of LV systolic/diastolic function, and reversal of alterations of the cellular and extracellular composition [6, 12]. LVRR is an important therapeutic objective for HF treatment.

While obesity is a well-established risk factor for HF, overweight and obesity was associated with better prognosis and substantially improved survival in HF patients, which is termed as "obesity paradox" [13, 14]. It is still unclear whether the "obesity-survival paradox" in HF is a reliable phenomenon or a consequence of statistically methodological limitation such as reverse causation, mediation effect, confounding effect, or suppression effect. Moreover, the underlying mechanism of "obesity paradox" is still ambiguous. Earlier appearance of symptoms and access to medication, better tolerability of guideline-directed medical therapy (GDMT), higher levels of circulating cardioprotective adipokines, greater anti-inflammatory effects of elevated lipoproteins, greater weight reserves against the cardio-metabolic changes and cardiac cachexia may be the potential reasons for "obesity paradox" [13, 15, 16]. Interestingly, "obesity paradox" was also observed in the relationship between obesity and myocardial remodeling in HF with reduced ejection fraction (HFrEF). Previous study had demonstrated that obesity was an independent predictor for LVRR in patients with HFrEF, which may provide an explanation of the "obesity paradox" for HFrEF patients [17, 18]. Moreover, higher body mass index (BMI) was tightly associated with recovered/improved left ventricular ejection fraction (LVEF), and was an effective predictor for HF with improved ejection fraction (HFimpEF) [19].

However, the reasonability and reliability using body mass index (BMI) as an isolated anthropometric parameter to evaluate "obesity paradox" has been doubted [20]. One plausible explanation of "obesity paradox" is the inaccuracy and limitation of the BMI in characterizing the severity of obesity [21]. The absolute amount of body fat and its location, or its ratio to muscle can't be accurately reflected by BMI. The other anthropometric indices, including fat mass, percent body fat (PBF), fat-free mass, and lean mass, can characterize the body composition and obesity more comprehensively. Furthermore, although the "obesity paradox" was well described in HFrEF and HF with preserved ejection fraction (HFpEF), clinical research concerning the "obesity paradox" for HFmrEF patients was limited [22, 23]. To data, the impact of body composition on LVRR and long-term prognosis is unclear in patients with HFmrEF. Thus, we conducted this prospective cohort study to explore the role of body composition in LVR, LVRR, and long-term clinical outcomes for patients with HFmrEF.

Methods

Study design and participants

Our study was a single-centre, prospective, echocardiography-based, observational study, which was approved by the Ethics Committee of Qilu Hospital of Shandong University. The study was performed in accordance with the Declaration of Helsinki. A total of 394 consecutive patients diagnosed as HFmrEF at Qilu Hospital cardiology department and managed by an established CHF management system between January 2016 to December 2021 were enrolled in our study. The study protocol and flowchart were shown in Fig. 1.

The inclusion criteria included: (i) Confirmed HFmrEF at screening period, defined as patients with a LVEF between 40% and 49%; (ii) New York Heart Association (NYHA) functional class II to IV; (iii) available echocardiography at baseline and programmed follow-up; (iv) age≥18 years old, (v) retrievable necessary clinical data. The exclusion criteria included: (i) incomplete essential clinical data, (ii) age < 18 years old, (iii) heart transplantation, cardiac resynchronization therapy, or left ventricular assist device implantation status, (iv) malignant diseases, such as neoplasm, and (v) any condition with life expectancy less than 1 year.

At the terminal of our study, 58 patients with incomplete clinical data, 3 patients with age less than 18 years old, and 93 patients with unfinished programed follow-up were excluded. After exclusion, the remaining 240 HFmrEF were enrolled in our final analysis (Fig. 1).

Echocardiography examination

The echocardiographic data was obtained from echocardiographic reports conducted by 2-dimensional and targeted M-mode echocardiography with Doppler color flow mapping. The Phillip EPIQ7C system (Philips Ultrasound, Bothell, WA, USA), UST-52,105 probe (1.0–5.0 MHz), and Hitachi Aloka Prosound F75 system

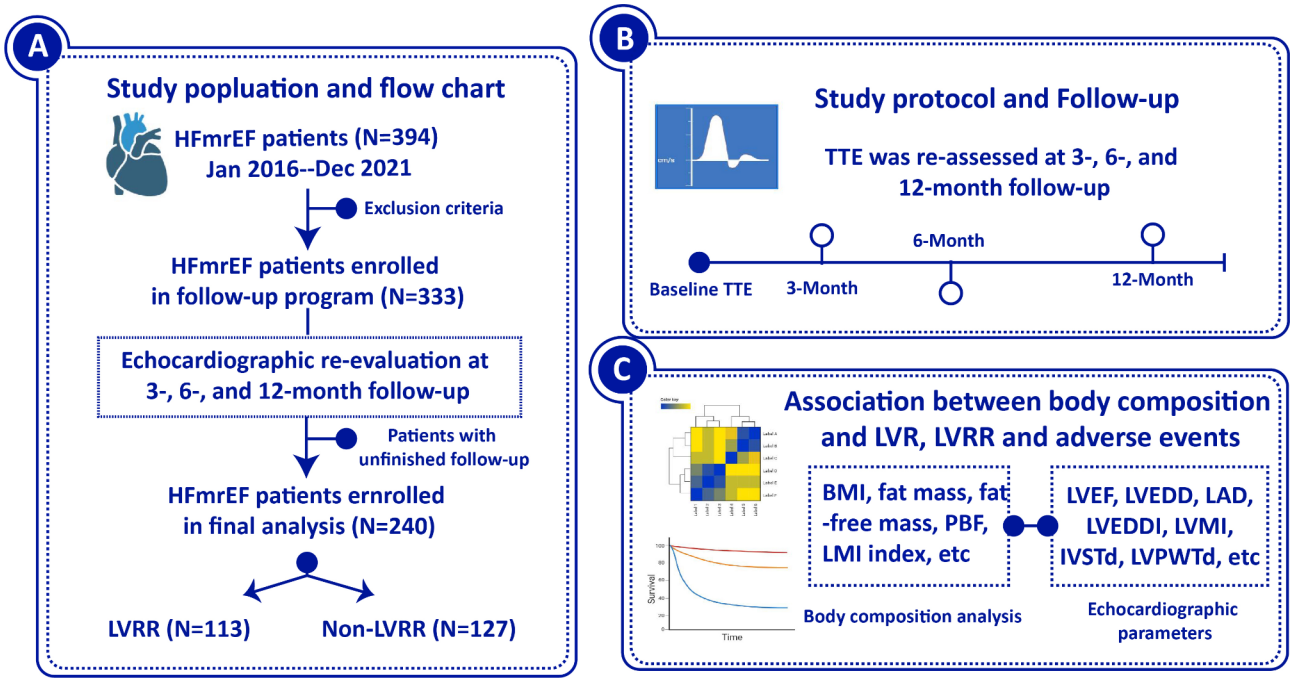


Fig. 1 Study design, protocol, and flow chart

were used for our echocardiographic study. Comprehensive echocardiographic parameters were measured according to the American Society of Echocardiography and European Association of Cardiovascular Imaging recommendation. The LVEF is calculated via biplane modified Simpson's method in the apical four- and two-chamber view. The left ventricular end-diastolic diameter (LVEDD), interventricular septal end-diastolic thickness (IVSTd), and left ventricular posterior wall end-diastolic thickness (LVPWTd) was measured using parasternal long-axis views. The left atrial diameter (LAD) was measured via apical 4-chamber views at the end of systole. The right ventricular end-diastolic diameter (RVEDD) was measured via the minor-axis in the apical four-chamber view at the end of diastole. The echocardiographic index was calculated as the following formula:

Left ventricular end-diastolic diameter index (LVEDDI, mm/m^2) = LVEDD/body surface area (BSA).

Left ventricular mass index (LVMI, g/m^2) = $0.80 \times 1.04 \times [(IVSTd + LVEDD + LVPWTd)^3 - LVEDD^3] + 0.6$ g/ BSA.

Relative wall thickness (RWT) = 2×[LVPWTd/LVEDD].

BSA was calculated via the Du Bois formula. Left ventricular hypertrophy (LVH) was diagnosed when LVMI above the reference upper limits (95 g/m^2 in women and 115 g/m^2 in men). Participants with LVH was further categorized as concentric hypertrophy (RWT ≥ 0.43) and eccentric hypertrophy (RWT < 0.43) according to RWT. The mitral valve function was assessed through a semi-qualitative way based on color doppler flow imaging. All Echocardiography was performed by a panel of experienced sonographers and echocardiographic experts.

Body composition assessment

The body composition parameters enrolled in our study included BMI, fat-free mass, fat mass, PBF, the Clínica Universidad de Navarr—Body Adiposity Estimator (CUN-BAE) index, and lean mass index (LMI). The BMI was calculated by the formula: BMI (kg/m^2) = body weight (kg)/ the square of the height (m^2). According to Working Group on Obesity in China, we defined low weight was defined as low weight/underweight as a BMI less than 18.5 kg/m^2, healthy/normal weight as a BMI of 18.5–23.9 kg/m^2, overweight as a BMI of 24.0–27.9 kg/m^2, and obesity as a BMI ≥ 28.0 kg/m^2 [24, 25].

The estimated fat-free mass was calculated according to the Kuch formula: Fat-free mass (kg) = 5.1×(height $[m]^{1.14}$) ×(weight $[kg]^{0.41}$) for males, and 5.34×(height $[m]^{1.47}$) ×(weight $[kg]^{0.33}$) for females [26]. The Kuch formula, an accurate tool to estimate fat-free mass, was derived from bioelectrical impedance analysis (BIA), and has been applicated in several clinical studies [27, 28]. Fat mass was calculated via the formula: Fat mass (kg) = body weight (kg)– fat-free mass (kg). The PBF was calculated as the ratio of fat mass to total body weight. Furthermore, the CUN-BAE index was also calculated [29, 30]. The CUN-BAE index is a reliable and easy-to-apply tool to estimate PBF, which has been confirmed by large-population studies [31, 32]. The CUN-BAE index was calculated via the formula: CUN-BAE index = -44.988 + (0.503×age)

+ (10.689×sex) + (3.172×BMI)– (0.026×BMI^2) + (0.181×BMI×sex)– (0.020×BMI×age)– (0.005×BMI^2×sex) + (0.00021×BMI^2×age). The value of sex was codified as 0 for males and 1 for females. The LMI was calculated via the formula: LMI (kg/m^2) = (1-BF%) × BMI (kg/m^2) [29, 30]. As for no reference value could be recommended for Chinese population, the patients were categorized into three groups according to the gender-specific tertiles of fat-free mass, fat mass, PFB, CUN-BAE index, or LMI. The method to assess and estimate body composition has been widely applicated in previous studies [33, 34]. High consistency between estimated anthropometric parameters and body composition measured by dual-energy X-ray absorptiometry (DEXA) has been validated in previous studies concerning anthropometric measurements, highlighting the validity of the estimated anthropometric indices adopted in our study [26, 35, 36].

Clinical and laboratory data

Comprehensively essential data were prospectively collected by experienced data inspectors. Clinical variates, including (i) demographic data, (ii) physical examination parameters: admission monitored blood pressure, heart rate, NYHA functional class, (iii) cardiovascular complications, (iv) echocardiographic parameters, (v) laboratory data, including hemoglobin, N-terminal B-type natriuretic peptide (NT-proBNP), serum potassium, serum sodium, and the estimated glomerular filtration rate (eGFR), and (vi) medical therapy, including angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin II receptor blockers (ARB)/ angiotensin receptor/ neprilysin inhibitors (ARNI), beta-blockers, mineralocorticoid-receptor antagonist (MRA), and sodium-glucose cotransporter-2 inhibitor (SGLT2i), were collected for the analysis of our study. The eGFR was calculated via the Chronic Kidney Disease Epidemiology Collaboration creatinine 2021 (CKD-EPI 2021) equation.

Follow-up protocol and study outcomes

The study scheme was illustrated in Fig. 1. The HF patients enrolled in our study was managed by an established CHF management system as previous described [37]. All patients were managed by a panel of experienced specialist HF cardiologists. The optimal guideline-directed medical therapy was well administrated. All participants would receive the echocardiographic transvaluation at 3-, 6-, and 12- month follow-up to dynamically reassess cardiac function and myocardial reverse remodeling. Patients got LVRR at any follow-up timepoint were all categorized as LVRR group in our final analysis. The protocol for follow-up was ratified by the Institutional Review Board of Qilu Hospital.

The primary outcome of our study was LVRR. The standardized definition of LVRR is still non-uniform. In accordance with previous literature [38–40], the composite criteria of LVRR adopted by our study included: (1) a reduction higher than 10% in LVEDDI, or a LVEDDI < 33 mm/m^2, (2) an absolute increase of LVEF higher than 10 points compared with baseline echocardiogram, or a follow-up LVEF ≥50%. The change in LVEDDI was calculated as follows: (LVEDDI of baseline echocardiogram– LVEDDI of follow-up echocardiogram)/LVEDDI of baseline echocardiogram ×100%. The secondary outcome of our study was a composite of re-hospitalization for HF or death from cardiovascular causes.

Statistical analysis

The continuous variables were expressed as medians with interquartile ranges (25th–75th percentiles) or mean ± standard deviations, and were compared via Mann-Whitney U test or t-test. The categorical variables were expressed as frequencies and percentages, and were compared through Chi-square test or Fisher's exact probability tests.

To assess the relationship between body composition and baseline LV remodeling in HFmrEF patients, Pearson's correlation analysis was conducted. Furthermore, the multivariate linear regression analysis was conducted to eliminate the influence of gender and age. To explore the association between body composition and LVRR or clinical outcomes, Kaplan–Meier curve analysis, log-rank (Mantel-Cox) test, and log-rank test for trend were conducted. To further assess the role of body composition in LVRR and clinical prognosis, univariable and multivariable Cox regression analysis was conducted. The hazard ratio (HR) and 95% confidence intervals (CIs) was calculated. Univariable Cox regression was performed for the crude model, and multivariable Cox-proportional hazard analyses was performed for the adjusted model to eliminate potential confounders. These covariates with statistical significance ($P < 0.05$) in the crude model would be further adopted in the multivariable analysis. The restricted cubic spline (RCS), using four knots, was performed to investigate the potential non-linear relationship between anthropometric parameters and LVRR. The mediation analysis was performed using the 'mediation' R package to evaluate the proportional contribution of baseline myocardial remodeling on the association of body composition with LVRR. Statistically significant echocardiographic parameters in the crude Cox regression model, including baseline LVEF and LVEDDI, was selected as mediating variables, while the other variables were adopted as covariates. Mediation analysis using LVRR as mediator was also conducted to explore the potential mediation role of LVRR in the association between body composition and clinical outcomes. A

two-tailed p-value less than 0.05 was regarded as statistically significant.

The data were analyzed via IBM SPSS Statistics version 25, 2017 (IBM, Armonk, New York), R (version 4.1.0) software and GraphPad Prism version 8, 2018 (GraphPad Software, Inc.).

Results

Baseline demographic and clinical characteristics

A total of 240 HFmrEF patients were enrolled in our final analysis. The demographic and clinical characteristics of the study population stratified by LVRR and clinical events were illustrated in Table 1. For overall HFmrEF patients, the median age was 48 years old, and 75% patients was male. The main etiology of HF was ischemic etiology (36.6%). The majority of HFmrEF patients (62.1%) had NYHA functional class III or IV. For comorbidities, hypertension, diabetes mellitus, and atrial fibrillation was coexisted in 30.0%, 17.9%, and 15.0% of the patients, respectively. Furthermore, optimal medical therapy was widely used. The prescription rate of ACEI/ARB/ARNI, beta-blockers, MRA and SGLT2i was 99.2%, 100%, 89.6%, and 39.6%, separately.

During the 1-year follow-up period, 113 (47.1%) HFmrEF patients got LVRR. The anthropometric parameters varied dramatically between patients with LVRR or without. Although not statistically significant, the BMI was higher in patients with LVRR compared with those without. Moreover, higher proportion of overweight and obesity was observed in patients with LVRR. Furthermore, HFmrEF patients with LVRR exhibited higher fat mass and PBF (all $P<0.05$). The levels of the CUN-BAE index and LMI were similar between patients with LVRR or without for HFmrEF. Apart from anthropometric parameters, HF patients with LVRR tended to be younger and had less severe symptoms. Their baseline myocardial remodeling was milder, reflected by higher baseline LVEF and lower LVEDDI. No statistically significant difference was observed in the laboratory tests and medical treatment.

After a median follow-up of 35 months (95% CI 32–38 months), a total of 47 (19.6%) patients suffered cardiovascular death or re-hospitalization for HF. Compared to those without clinical events, the BMI, fat-free mass, fat mass, PBF, and LMI was lower in patients suffered adverse clinical events (all $P<0.05$). Furthermore, patients with adverse clinical events tended to be older, and had lower DBP, heart rate, lower prevalence of coronary artery disease, as well as severer mitral regurgitation.

The demographic, clinical, biochemical, and echocardiographic characteristics also varied significantly across the anthropometric measurements, which had been illustrated in Table S1-6. In general, patients with higher BMI, fat-free mass, or fat mass were younger, and had higher frequency of hypertension. Furthermore, patients in higher tertiles of anthropometric parameters had higher LVEDD and lower LVEDDI.

Correlation between body composition and LV remodeling

We evaluated the correlation between anthropometric parameters and baseline echocardiographic parameters (Fig. 2). As indicated in previous studies, the high consistency between the CUN-BAE index and PBF was also observed in our study. The anthropometric indices positively correlated to LVEDD and LV wall thickness, which was consistent to previous multiple echocardiographic studies. However, the inverse correlation between LVEDDI with BMI (r=-0.49, $P<0.001$), fat-free mass (r=-0.55, $P<0.001$), fat mass (r=-0.50, $P<0.001$), PBF (r=-0.30, $P<0.001$), and LMI (r=-0.52, $P<0.001$) was significant for HFmrEF patients. After adjusted by sex and age, the multivariate linear regression analysis also revealed the tightly negative association between LVEDDI and above anthropometric parameters (Table S7). The anthropometric parameters did not significantly correlate to LVEF and LVMI.

Longitudinal echocardiographic trajectories during follow-up

The dynamic change of echocardiographic parameters of HFmrEF patients stratified by anthropometric parameters tertiles was depicted in Fig. 3. More pronounced and persistent increase of LVEF and decline in LVMI was observed in HFmrEF patients with obesity, highest tertile of fat mass, PBF, CUN-BAE index, and LMI (Fig. 3, all $P<0.05$). For the longitudinal changes of echocardiographic parameters across the tertiles of fat-free mass, no obvious difference was detected.

Impact of body composition on LVRR

The univariable and multivariable Cox-proportional hazard analyses was conducted to explore the impact of body composition on LVRR. The crude Cox regression model showed that higher baseline BMI (HR 1.042, 95% CI 1.002–1.083, $P=0.037$) and fat mass (HR 1.019, 95% CI 1.002–1.036, $P=0.026$) were each significantly associated with higher LVRR rate for HFmrEF (Table 2). Kaplan–Meier curve analysis and the log-rank trend test also illustrated that cumulative incidence of LVRR was significantly higher in HFmrEF patients with obesity or with highest tertile of fat mass (all $P<0.05$, Fig. 4). However, these correlations were attenuated and no longer significant after additional adjustment for potential confounders. No statistical significance was observed in the relationship between other anthropometric parameters and LVRR. No obvious nonlinear relationships between anthropometric parameters and LVRR were detected

Table 1 Baseline demographic and clinical characteristics of the whole study population

Variable	Overall, *N* = 240	Categorized according to LVRR			Categorized according to clinical events		
		LVRR (*N* = 113)	Non-LVRR (*N* = 127)	*P* value	With event (*N* = 47)	Without event (*N* = 193)	*P* value
Age, years	48 (34–57)	45 (33–55)	51 (39–58)	**0.021**	52 (43–63)	47 (33–55)	**0.008**
Male sex, n (%)	180 (75.0)	85 (75.2)	95 (74.8)	0.940	35 (74.5)	145 (75.1)	0.925
Anthropometric parameters							
BMI, kg/m^2	26.0 ± 4.9	26.7 ± 5.8	25.4 ± 3.8	0.052	24.6 ± 3.5	26.2 ± 4.4	**0.021**
BMI strata, n (%)				0.303			0.118
Low weight	3 (1.3)	2 (1.8)	1 (0.8)		1 (2.1)	2 (1.0)	
Healthy weight	84 (35.0)	34 (30.1)	50 (39.3)		21 (44.7)	63 (32.6)	
Overweight	109 (45.4)	52 (46.0)	57 (44.9)		21 (44.7)	88 (45.6)	
Obesity	44 (18.3)	25 (22.1)	19 (15.0)		4 (8.5)	40 (20.8)	
Fat-free mass, kg	54.9 (47.2–59.0)	55.8 (48.3–60.3)	54.4 (46.5–58.5)	0.061	53.0 (45.1–57.1)	55.7 (47.9–59.8)	**0.030**
Fat mass, kg	20.3 (16.3–24.2)	21.7 (16.8–25.7)	19.3 (16.1–23.6)	**0.034**	18.5 (14.6–21.7)	21.2 (16.5–25.2)	**0.004**
PBF, %	27.4 (23.0-33.3)	28.7 (23.7–34.5)	26.6 (22.6–31.0)	**0.047**	25.3 (21.9–32.0)	28.2 (23.6–33.7)	**0.025**
CUN-BAE index, %	28.2 (24.8–34.9)	29.3 (24.9–35.6)	27.9 (24.6–34.3)	0.627	26.9 (23.7–32.0)	28.6 (24.9–35.1)	0.236
LMI, kg/m^2	18.3 (17.1–19.2)	18.4 (17.2–19.4)	18.2 (17.0-18.9)	0.191	18.1 (17.0-18.7)	18.4 (17.3–19.3)	**0.030**
Systolic blood pressure, mmHg	117 (101–131)	118 (108–134)	116 (102–130)	0.187	114 (99–131)	118 (108–131)	0.171
Diastolic blood pressure, mmHg	75 ± 14	76 ± 14	74 ± 14	0.300	71 ± 15	76 ± 14	**0.022**
Heart rate, beats/min	75 (67–85)	77 (69–89)	73 (63–85)	**0.020**	70 (61–81)	75 (68–87)	**0.008**
NYHA functional class, n (%)				**0.005**			0.751
II	91 (37.9)	54 (47.8)	37 (29.2)		20 (42.6)	71 (36.8)	
III	108 (45.0)	39 (34.5)	69 (54.3)		20 (42.6)	88 (45.6)	
IV	41 (17.1)	20 (17.7)	21 (16.5)		7 (14.8)	34 (17.6)	
Hypertension, n (%)	72 (30.0)	40 (35.4)	32 (25.2)	0.085	17 (36.2)	55 (28.5)	0.303
Diabetes mellitus, n (%)	43 (17.9)	25 (22.1)	18 (14.2)	0.109	13 (27.7)	30 (15.5)	0.052
Atrial fibrillation, n (%)	36 (15.0)	12 (10.6)	24 (18.9)	0.073	5 (10.6)	31 (16.1)	0.350
Coronary artery disease, n (%)	103 (42.9)	45 (39.8)	58 (45.7)	0.361	28 (59.6)	75 (38.9)	**0.010**
Prior HFrEF history, n (%)	132 (55.0)	58 (51.3)	74 (53.8)	0.281	23 (48.9)	109 (56.5)	0.351
HF etiology				0.054			0.234
Ischemic etiology	88 (36.6)	36 (31.9)	52 (40.9)		24 (51.1)	64 (33.2)	
Dilated cardiomyopathy	70 (29.2)	31 (27.4)	39 (30.8)		11 (23.4)	59 (30.6)	
Hypertensive cardiomyopathy	4 (1.7)	4 (3.5)	0 (0)		0 (0)	4 (2.1)	
Peripartum cardiomyopathy	16 (6.7)	10 (8.9)	6 (4.7)		1 (2.1)	15 (7.8)	
Arrhythmogenic cardiomyopathy	9 (3.7)	2 (1.8)	7 (5.5)		3 (6.4)	6 (3.1)	
Valvular heart disease	7 (2.9)	5 (4.4)	2 (1.6)		1 (2.1)	6 (3.1)	
Other etiologies	46 (19.2)	25 (22.1)	21 (16.5)		7 (14.9)	39 (20.1)	
Echocardiographic parameters							
LVEF, %	44 (41–46)	45 (42–47)	43 (41–46)	**0.001**	43 (41–46)	44 (42–47)	0.202
LVEDD, mm	58.0 (54.0–60.0)	57.0 (53.0–60.0)	58.0 (55.0–61.0)	**0.034**	57.0 (52.0–60.0)	58.0 (54.0–61.0)	0.383
LVEDDI, mm/m^2	31.3 (28.2–33.7)	30.2 (27.2–32.3)	31.9 (29.6–34.8)	**< 0.001**	32.4 (29.6–34.0)	30.7 (28.0-33.4)	0.079
LVMI, g/m^2	113.4 (95.9-129.4)	112.4 (94.9-126.5)	115.6 (96.7-133.4)	0.154	115.8 (96.3-136.2)	113.3 (95.8-126.8)	0.396
LAD, mm	40.0 (36.0–44.0)	40.0 (36.0–44.0)	40.0 (36.0–45.0)	0.632	40.0 (36.0–44.0)	40.0 (36.0–44.0)	0.857
RVEDD, mm	24.0 (22.0–27.0)	24.0 (22.0–27.0)	24.0 (21.0–26.0)	0.142	24.0 (21.0–25.0)	24.0 (22.0–27.0)	0.196
IVSTd, mm	9.0 (8.0–11.0)	10.0 (8.0–11.0)	9.0 (8.0–11.0)	0.205	10.0 (8.0–11.0)	9.0 (8.0–11.0)	0.491
LVPWTd, mm	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	0.372	9.0 (8.0–10.0)	9.0 (8.0–10.0)	0.262
RWT	0.32 (0.28–0.36)	0.33 (0.29–0.36)	0.31 (0.28–0.35)	**0.044**	0.32 (0.30–0.38)	0.32 (0.28–0.35)	0.069
Mitral regurgitation, n (%)				0.096			**0.006**
No	60 (25.0)	34 (30.1)	26 (20.5)		4 (8.5)	56 (29.0)	
Mild	160 (66.7)	73 (64.6)	87 (68.5)		37 (78.7)	123 (63.7)	
Moderate or more	20 (8.3)	6 (5.3)	14 (11.0)		6 (12.8)	14 (7.3)	
LV geometry, n (%)				0.817			0.074
No hypertrophy	104 (43.3)	51 (45.1)	53 (41.7)		18 (38.3)	86 (44.6)	
Eccentric hypertrophy	122 (50.8)	55 (48.7)	67 (52.8)		23 (48.9)	99 (51.3)	

Table 1 (continued)

Variable	Overall, *N* = 240	Categorized according to LVRR			Categorized according to clinical events		
		LVRR (*N* = 113)	Non-LVRR (*N* = 127)	*P* value	With event (*N* = 47)	Without event (*N* = 193)	*P* value
Concentric hypertrophy	14 (5.8)	7 (6.2)	7 (5.5)		6 (12.8)	8 (4.1)	
Laboratory examination							
NT-proBNP, pg/ml	897.5 (313.5–2098.0)	884.0 (173.0-2649.5)	976.0 (426.4–1921.0)	0.222	1140.0 (292.7–2023.0)	872.0 (325.5-2137.5)	0.780
Hemoglobin, g/L	144.0 (133.0-155.75)	143.0 (130.0-154.0)	145.0 (137.0-156.0)	0.286	142.0 (127.0-150.0)	145.0 (134.0-156.0)	0.120
Creatinine, mmol/L	76.0 (68.0–87.0)	75.0 (67.0–85.0)	76.0 (69.0–88.0)	0.657	77.0 (65.0–88.0)	75.0 (68.0-86.5)	0.832
eGFR, mL/min/1.73m^2	102.4 (88.4-112.1)	102.7 (94.6-113.7)	102.1 (86.7-109.6)	0.145	100.7 (86.0-110.5)	102.6 (91.6-112.9)	0.225
Sodium, mmol/L	141.0 (139.0-142.0)	141.0 (139.0-142.0)	141.0 (139.0-142.0)	0.873	141.0 (139.0-142.0)	141.0 (139.0-142.0)	0.905
Potassium, mmol/L	4.3 (4.0-4.5)	4.3 (4.0-4.6)	4.3 (4.0-4.5)	0.969	4.3 (3.9–4.6)	4.3 (4.0-4.5)	0.645
Complete left bundle branch block, n (%)	15 (6.3)	6 (5.3)	9 (7.1)	0.570	3 (6.4)	12 (6.2)	0.999
Medication, n (%)							
ACEI/ARB/ARNI	238 (99.2)	113 (100)	125 (98.4)	*NS*	46 (97.9)	192 (99.5)	0.354
Beta-blocker	240 (100.0)	113 (100)	127 (100)	*NS*	47 (100)	193 (100)	*NS*
MRA	215 (89.6)	98 (86.7)	117 (92.1)	0.172	42 (89.4)	173 (89.6)	0.956
SGLT2i	95 (39.6)	43 (38.1)	52 (40.9)	0.647	17 (36.2)	78 (40.4)	0.594
Diuretics	82 (34.2)	40 (35.4)	42 (33.1)	0.704	19 (40.4)	63 (32.6)	0.313
Anti-platelet drugs	110 (45.8)	50 (44.2)	60 (47.2)	0.642	30 (63.8)	80 (41.5)	**0.006**
statin	124 (51.7)	58 (51.3)	66 (52.0)	0.921	33 (70.2)	91 (47.2)	**0.005**
Revascularization therapy	87 (36.3)	38 (33.6)	49 (38.6)	0.425	19 (40.4)	68 (35.2)	0.507

ACE-I, angiotensin-converting inhibitor; ARB, angiotensin II receptor blocker; BMI: body mass index, eGFR, the rate of estimated glomerular filtration rate; HF: heart failure, IVSTd: interventricular septal end-diastolic thickness, LAD: left atrial diameter, LMI: Lean mass index, LV: left ventricular, LVEDD: left ventricular end-diastolic diameter, LVEDDI: left ventricular end-diastolic diameter index, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, LVRR: left ventricular reverse remodeling, LVPWTd: left ventricular posterior wall end-diastolic thickness, MRA, mineralocorticoid-receptor antagonist, NT-proBNP: N-terminal B-type natriuretic peptide, NYHA: New York Heart Association, RVEDD: right ventricular end-diastolic diameter, RWT: relative wall thickness, SGLT2i: sodium-glucose cotransporter 2 inhibitor

via RCS plot (Figure S1). The sensitivity analysis using 6-month echocardiography data also revealed that the anthropometric measurements was associated with the cumulative incidence of LVRR at 6-month follow-up in the univariable Cox regression model, while the relationship vanished in the adjusted model (Table 3).

The role of body composition in clinical outcomes

As shown in Fig. 5 , the rate of rehospitalization for HF and cardiovascular death was significantly lower in for HFmrEF patients with obesity, higher fat-free mass, fat mass, PBF, or LMI (all *P* for log-rank test for trend < 0.05). Univariable Cox regression analysis also revealed that higher BMI, fat mass, PBF, fat-free mass, and LMI was associated with higher risk of adverse clinical outcomes for HFmrEF (Table 4). However, only fat mass (aHR 0.957, 95% CI 0.917–0.999, *P* = 0.049) and PBF (aHR 0.963, 95% CI 0.924–0.976, *P* = 0.043) was confirmed as independent factor for prognosis of HFmrEF after adjusted by potential confounders. Apart from LMI (*P* for non-linearity: 0.046), no obvious nonlinear relationship between anthropometric induces and clinical outcomes was detected (Figure S2).

Mediation analysis

Given that the association between body composition and LVRR vanished after adjustment by covariates, we want to explore the underling mechanism. We speculate that the higher LVRR rate in patients with higher BMI or fat mass was attributed to their milder baseline LV dilation, considered the significantly negative relationship between baseline LVEDDI and anthropometric parameters. Thus, we conducted the mediation analysis using baseline LVEF and LVEDDI as mediator variables to explore whether and how baseline LVR affect the relationship between body composition with LVRR. Baseline LVEDDI were found to be the full mediating factor in the relationship between BMI and fat mass with LVRR in HFmrEF (Fig. 6A-B).

For HFmrEF patients, we also wanted to explore whether the "obesity paradox" of clinical prognosis could be explained by the inverse relationship between body composition and LVRR. Thus, further mediation analysis was conducted using LVRR as mediator variate. However, the mediation effect of LVRR was weak in the association between anthropometric parameters and clinical outcomes (Fig. 6C-F).

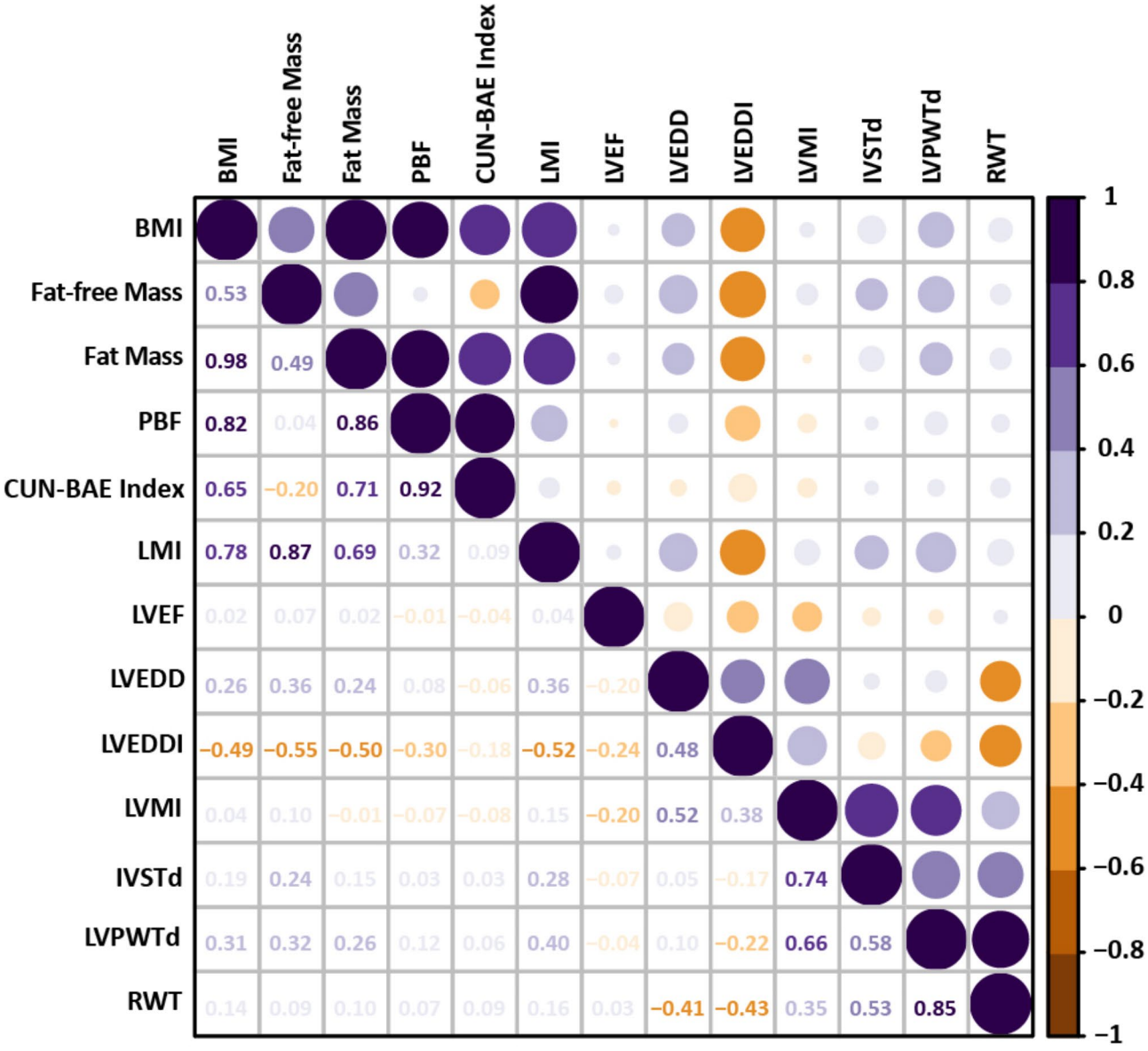


Fig. 2 The correlation between anthropometric parameters and echocardiographic parameters depicted by heat map

Discussion

In the echocardiography-based cohort study concerning the "obesity paradox" in HFmrEF, our main findings included: (i) the anthropometric parameters correlated inversely with baseline LVEDDI; (ii) HFmrEF patients with higher BMI, fat mass, PBF, CUN-BAE index, or LMI, had more significant improvement of LVEF and decline in LVMI over time; (iii) higher BMI and fat mass was associated with higher LVRR rate for HFmrEF patients; (iv) fat mass and PBF were independent predictors for adverse clinical events for HFmrEF; (v) the association of body composition and LVRR was largely mediated by baseline LVEDDI. To our best knowledge, our research was the first prospective cohort study to explore the role of body composition in LVR, LVRR and long-term clinical prognosis for HFmrEF patients, which will offer more insights and knowledge to the "obesity paradox" in HF.

"Obesity paradox" is an enduring topic in the field of CHF. Although obesity is an important contributor to the growing prevalence of HF, obesity was associated with improved survival and better outcomes in individuals with prevalent CHF, which has been revealed in multiple study populations [41]. The phenomenon of "obesity paradox" has been reported in different HF phenotypes [42, 43]. Although the inverse relationship between BMI and clinical prognosis has been comprehensively elucidated in HFrEF and HFpEF, little clinical researches has revealed the "obesity paradox" in HFmrEF until recently [42–44]. Moreover, in previous studies, it is inappropriate

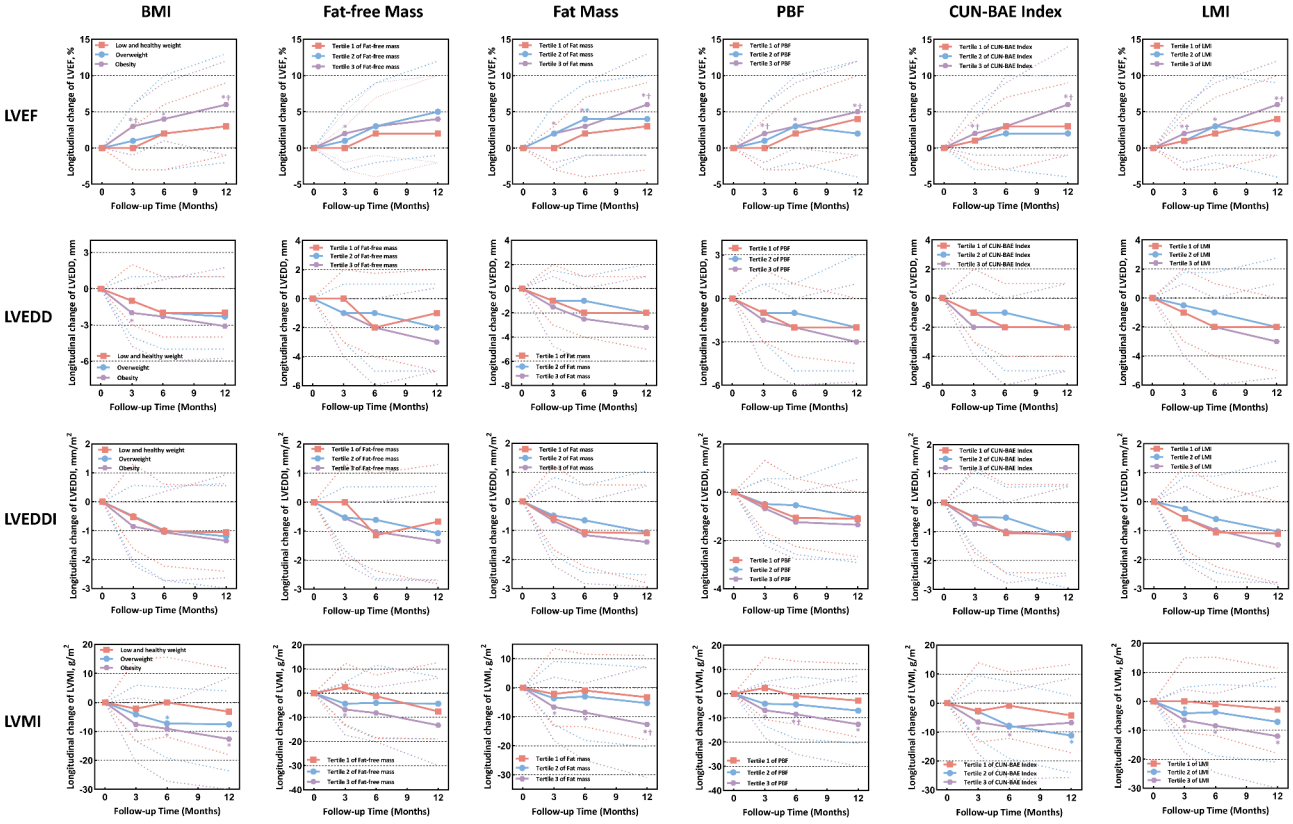


Fig. 3 Longitudinal change of echocardiographic parameters during follow-up period stratified by anthropometric parameter tertiles. The dotted line indicated the 25th-75th percentiles. For P value, * indicated *P* value < 0.05 versus Tertile 1, † indicated P value < 0.05 versus Tertile 2

using BMI as the single anthropometric index to estimate the total adiposity burden. There are numerous defects and limitations for BMI as a surrogate measure of the amount of adipose tissue. BMI can't accurately reflect the absolute amount and actual distribution of body fat [45]. More direct measurement of adiposity and body composition, such as fat mass, fat-free mass, and percent body fat, was more appropriate for interpretation of "obesity paradox". Thus, we conduct the prospective study to comprehensively understand the role of body composition in HFmrEF using multiple anthropometric induces. In consistent to previous studies, we also found that higher BMI was associated with lower rate of adverse clinical events. More significantly, we explore the impact of body composition on LVR and LVRR via a rigorous and longitudinal echocardiographic follow-up scheme, which provide deeper insights to "obesity paradox" in HF.

The impact of body composition on LV structure and function is complex. Excess body weight and increased total blood volume resulted in a rise in cardiac output, stroke volume, and LV end-diastolic pressure. These hemodynamic changes further leaded to enlargement of cardiac chamber and an increase in heart weight and LV wall thickness, thus exacerbated LVR and LV dysfunction [46, 47]. In consistent to previous researches, our study also revealed that the anthropometric indexes, including BMI, fat-free mass, fat mass, and LMI, positively correlated to LVEDD and LV wall thickness for HFmrEF patients. However, a significant inverse relationship between anthropometric indices and LVEDDI was observed in our study. Similar morphologic alteration was also detected in another single-center study. AlRahimi et al. reported the negative correlation between BMI and LV end-diastolic volume index (LVEDVI) for males [48]. Although LVEDD and LV end-diastolic volume (LVEDV) reflected the LV diameter and volume more intuitionistic, LVEDDI and LVEDVI eliminated the bias caused by BSA and body composition to some extent, which could assess the degree of LV dilation more accurately. What is more important, the relationship between body composition and LVR was unclear for HFmrEF patients. Our study revealed that higher body weight and fat mass negatively correlated to baseline LV dilation for HFmrEF. This intriguing finding should be verified in large scale multicenter studies.

LVRR is the pathophysiological hallmark of myocardial recovery and the important therapeutic target for HF. LVRR indicates normalization of LV geometry, significantly increased LV contractility, and improvement of LV function, thus was associated with survival benefits and

Table 2 Association between body composition and LVRR via univariable and multivariable Cox regression analysis

	Unadjusted model		Adjusted model	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**
BMI				
Continuous per 1 unit increase	**1.042 (1.002–1.083)**	**0.037**	1.000 (0.947–1.055)	0.988
Low and healthy weight (*N* = 87)	Reference	--	Reference	--
Overweight (*N* = 109)	1.292 (0.844–1.977)	0.238	1.188 (0.758–1.862)	0.452
Obesity (*N* = 44)	**1.670 (1.001–2.786)**	**0.049**	1.082 (0.577–2.030)	0.807
Fat-free Mass				
Continuous per 1 unit increase	1.022 (0.999–1.045)	0.060	1.001 (0.968–1.034)	0.963
Tertile 1 (< 54.9 kg for males, < 41.7 kg for females, *N* = 79)	Reference	--	Reference	--
Tertile 2 (54.9–58.9 kg for males, 41.7–44.1 kg for females, *N* = 80)	1.160 (0.723–1.861)	0.538	0.945 (0.568–1.572)	0.672
Tertile 3 (> 58.9 kg for males, > 44.1 kg for females, *N* = 81)	1.472 (0.937–2.312)	0.094	0.879 (0.483–1.599)	0.672
Fat Mass				
Continuous per 1 unit increase	**1.019 (1.002–1.036)**	**0.026**	0.999 (0.975–1.023)	0.912
Tertile 1 (< 16.6 kg for males, < 20.1 kg for females, *N* = 79)	Reference	--	Reference	--
Tertile 2 (16.6–22.7 kg for males, 20.1–23.5 kg for females, *N* = 80)	1.360 (0.848–2.180)	0.202	1.275 (0.772–2.104)	0.343
Tertile 3 (> 22.7 kg for males, > 23.5 kg for females, *N* = 81)	**1.598 (1.006–2.538)**	**0.047**	1.336 (0.780–2.288)	0.291
PBF				
Continuous per 1 unit increase	1.021 (0.996–1.046)	0.108	1.000 (0.970–1.031)	0.990
Tertile 1 (< 23.0% for males, < 31.9% for females, *N* = 80)	Reference	--	Reference	--
Tertile 2 (23.0-28.1% for males, 31.9–35.9% for females, *N* = 79)	1.300 (0.818–2.067)	0.267	0.950 (0.580–1.556)	0.837
Tertile 3 (> 28.1% for males, > 35.9% for females, *N* = 81)	1.410 (0.894–2.224)	0.139	1.057 (0.633–1.764)	0.833
CUN-BAE Index				
Continuous per 1 unit increase	1.010 (0.985–1.035)	0.435	0.999 (0.970–1.029)	0.961
Tertile 1 (< 24.9% for males, < 34.9% for females, *N* = 79)	Reference	--	Reference	--
Tertile 2 (24.9–28.3% for males, 34.9–40.1% for females, *N* = 80)	1.147 (0.725–1.815)	0.559	1.185 (0.720–1.951)	0.503
Tertile 3 (> 28.3% for males, > 40.1% for females, *N* = 81)	1.276 (0.813–2.003)	0.289	1.016 (0.574-1.800)	0.955
LMI				
Continuous per 1 unit increase	1.106 (0.987–1.239)	0.082	0.998 (0.853–1.168)	0.981
Tertile 1 (< 18.3 kg/m^2 for males, < 16.3 kg/m^2 for females, *N* = 80)	Reference	--	Reference	--
Tertile 2 (18.3–19.1 kg/m^2 for males, 16.3–16.6 kg/m^2 for females, *N* = 78)	1.200 (0.753–1.913)	0.443	1.017 (0.617–1.675)	0.947
Tertile 3 (> 19.1 kg/m^2 for males, > 16.6 kg/m^2 for females, *N* = 82)	1.376 (0.875–2.165)	0.167	1.157 (0.691–1.937)	0.580

The multivariate Cox regression was adjusted for age, SBP, etiology, NYHA functional class, LVEF, LVEDDI, and NT-proBNP

better prognosis [6]. Better cardiac reverse remodeling of the obese patients may be the underlying mechanism for "obesity paradox" in HF. Previous literatures have pointed out the important role of body composition in LVRR for HF patients. Cescau et al. reported that higher BMI (OR 1.10, 95% CI 1.02–1.19) was associated with higher likelihood of LVRR for HFrEF patients [17]. Another single center prospective study also found that higher BMI (OR 1.151, 95% CI 1.046–1.267) and epicardial adipose tissue volume (OR 1.008, 95% CI 1.000-1.015) was associated with higher rate of LVRR for patients with non-ischemic cardiomyopathy in crude Cox regression model. However, after adjusted by confounders, only the epicardial adipose tissue volume (OR 1.010, 95% CI 1.001–1.019) was validated as the independent predictor for LVRR for [49]. For CHF patients receiving cardiac resynchronization therapy (CRT), BMI was also associated with LVRR and could predict the response to CRT [18]. In the present study, univariable Cox regression analysis indicated that BMI and fat mass was associated with higher cumulative incidence of LVRR for HFmrEF patients via echocardiography dynamic reexaminations. However, this relationship vanished after adjusted by covariates. Our further mediation analysis revealed that higher rate of LVRR in obese patients benefited from their lower baseline LVEDDI and milder LV dilation. The plausible explanation for the "obesity-paradox" may be that patients with higher BMI, fat-free mass, or fat mass had higher frequency of hypertension, and the propensity of arterial hypertension in obese CHF patients made them more likely to tolerate the drug titration of GDMT. Thus, patients with higher BMI exhibited better cardiac reverse remodeling, and had better prognosis than those with lean body mass. For that higher BMI in general was correlated with higher muscle mass, another viewpoint put more emphasis on the adverse impact of sarcopenia on myocardial remodeling in patients with lower weight, thus affect the relationship between BMI and LVRR [49, 50]. Moreover, the lower proinflammatory cytokines, such as tumor necrosis factor alpha, in patients with

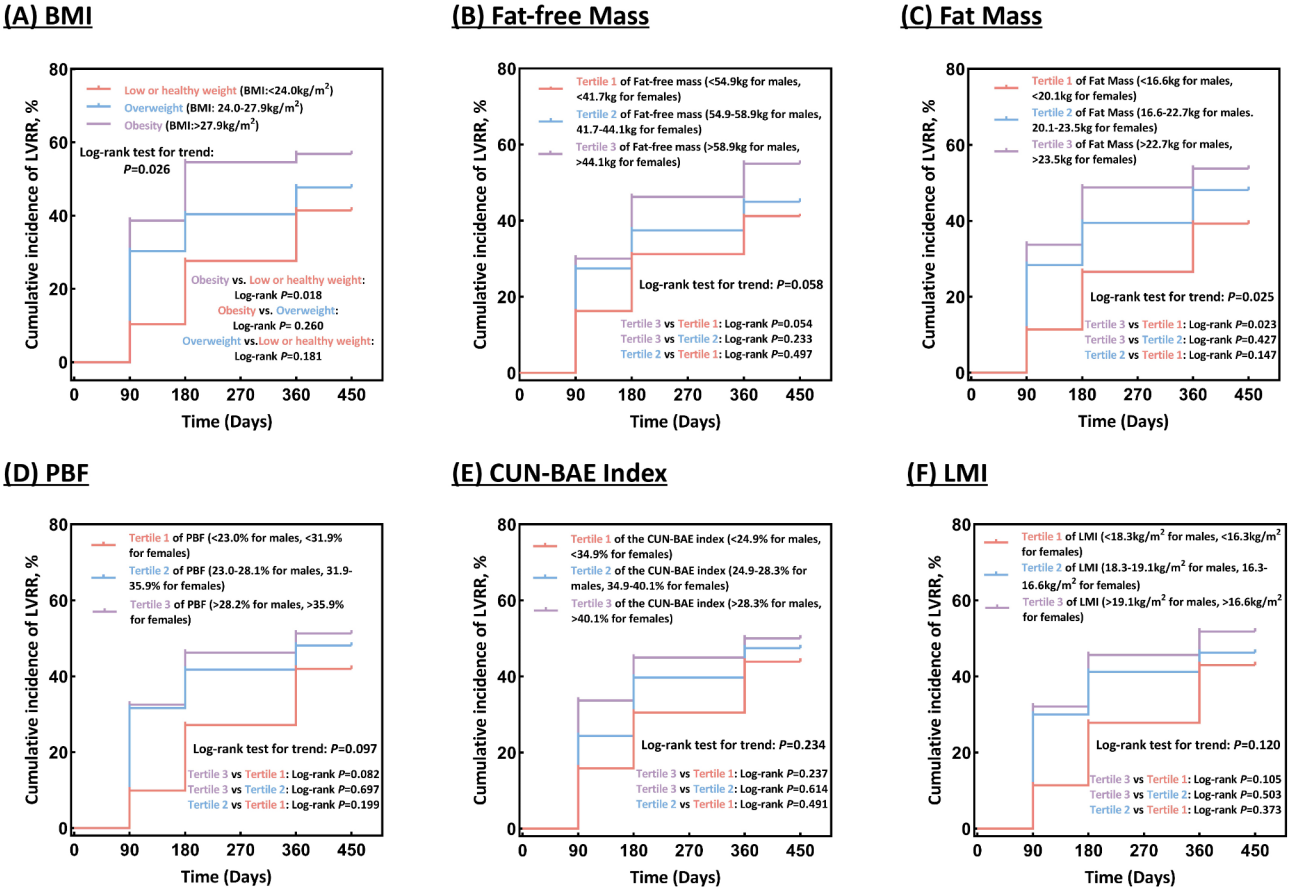


Fig. 4 Association between body composition and LVRR plotted by Kaplan–Meier curves

higher BMI could ameliorate cardiac cachexia, which provided another explanation of "obesity paradox" [18, 51]. The detailed pathophysiological mechanism should be explored in further biological experiments.

Body composition is also tightly associated with the short-term and long-term prognosis for CHF patients. Apart from above mentioned "obesity paradox", higher fat mass, PBF and lean mass was also associated with improved survival for CHF patients, which has been validated in multiple clinical researches. Konishi et al. revealed that increased fat mass (HR 0.954, 95% CI 0.916–0.993) was independently associated with reduced all-cause mortality for HF patients [52]. A retrospective cohort study identified that increased PBF (HR 0.45, 95% CI 0.22–0.93) correlated with lower risk of short-term cardiac events [53]. A post-hoc analysis of the China PEACE 5p-HF Study also reported that higher LMI exerted a cardioprotective effects and was associated with lower 1-year mortality for HF patients [54]. In our study, we also found that patients with higher BMI, fat mass, PBF, and LMI was with lower risk of re-hospitalization or cardiovascular death. The proposed explanations for the association between body composition and clinical prognosis of HF were complex and ambiguous. Firstly, HF is a catabolic state, and patients with higher body fat and muscle mass had better metabolic reserve and benefits to against cardiac cachexia [13]. secondly, the adipokines and myokines secreted by adipose tissue and skeletal muscle, including omentin, myonectin, and brain-derived neurotrophic factor, could exert cardioprotective effect [55, 56]. Thirdly, the low cardiorespiratory fitness and favorable hemodynamic profile may be the other underlying mechanism for "obesity paradox".

There were still some limitations in our study. Firstly, our research was just a single-centre study. Due to the prospective design and rigorous echocardiography transvaluation scheme, the sample size was limited. Furthermore, for the specificity of our study cohort, the conclusion should not be popularized and utilized to general clinical practice. Secondly, the body composition indices in our study were estimated via anthropometric prediction equation but not directly measured by DEXA, bioelectrical impedance analysis, or magnetic resonance imaging. Furthermore, the fat mass was calculated based on the estimated fat-free mass, which could not fully reflect the actual fat mass. Although these anthropometric estimation formulas derived from large population study was highly consistent to direct measurements,

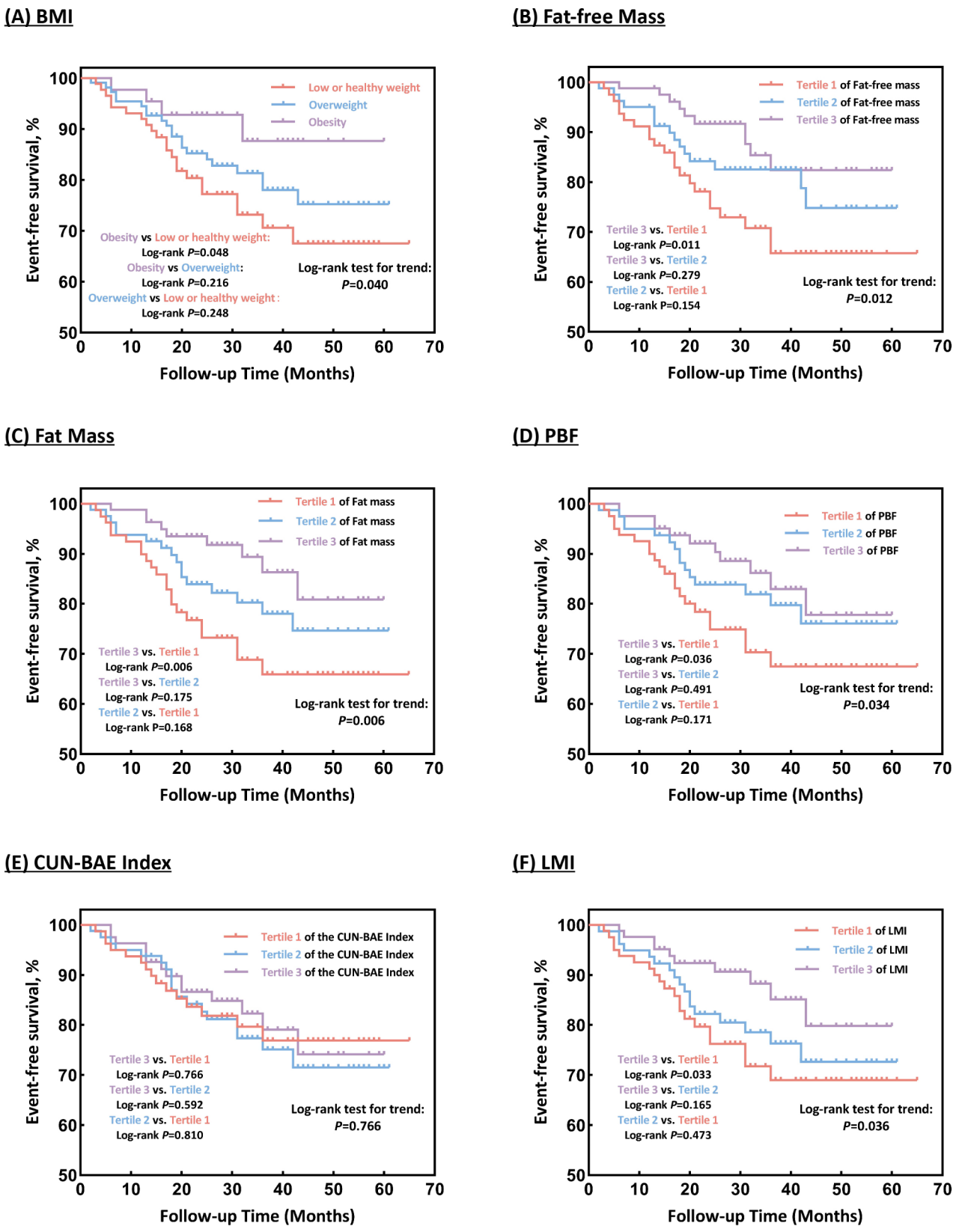


Fig. 5 Association between body composition and adverse clinical events plotted by Kaplan–Meier curves

Table 3 Sensitivity analysis for the association between body composition and LVRR via univariable and multivariable Cox regression analysis using 6-month echocardiography data

	Unadjusted model		Adjusted model	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**
BMI				
Continuous per 1 unit increase	**1.059 (1.018–1.102)**	**0.004**	1.009 (0.956–1.066)	0.738
Low and healthy weight (*N* = 87)	Reference	--	Reference	--
Overweight (*N* = 109)	1.610 (0.978–2.649)	0.061	1.534 (0.909–2.588)	0.109
Obesity (*N* = 44)	**2.271 (1.288–4.004)**	**0.005**	1.364 (0.695–2.673)	0.367
Fat-free Mass				
Continuous per 1 unit increase	**1.031 (1.006–1.057)**	**0.016**	1.000 (0.967–1.033)	0.979
Tertile 1 (< 54.9 kg for males, < 41.7 kg for females, *N* = 79)	Reference	--	Reference	--
Tertile 2 (54.9–58.9 kg for males, 41.7–44.1 kg for females, *N* = 80)	1.207 (0.699–2.082)	0.499	0.898 (0.505–1.597)	0.714
Tertile 3 (> 58.9 kg for males, > 44.1 kg for females, *N* = 81)	**1.774 (1.069–2.945)**	**0.027**	0.901 (0.480–1.693)	0.746
Fat Mass				
Continuous per 1 unit increase	**1.025 (1.007–1.042)**	**0.005**	1.000 (0.976–1.025)	0.975
Tertile 1 (< 16.6 kg for males, < 20.1 kg for females, *N* = 79)	Reference	--	Reference	--
Tertile 2 (16.6–22.7 kg for males, 20.1–23.5 kg for females, *N* = 80)	1.750 (0.988-3.100)	0.055	1.628 (0.899–2.947)	0.108
Tertile 3 (> 22.7 kg for males, > 23.5 kg for females, *N* = 81)	**2.443 (1.420–4.205)**	**0.001**	1.827 (0.984–3.394)	0.056
PBF				
Continuous per 1 unit increase	**1.029 (1.001–1.057)**	**0.041**	1.005 (0.972–1.038)	0.770
Tertile 1 (< 23.0% for males, < 31.9% for females, *N* = 80)	Reference	--	Reference	--
Tertile 2 (23.0-28.1% for males, 31.9–35.9% for females, *N* = 79)	1.225 (0.707–2.124)	0.469	1.240 (0.708–2.172)	0.453
Tertile 3 (> 28.1% for males, > 35.9% for females, *N* = 81)	**1.865 (1.126–3.088)**	**0.015**	1.381 (0.777–2.458)	0.272
CUN-BAE Index				
Continuous per 1 unit increase	1.015 (0.988–1.043)	0.281	1.001 (0.969–1.033)	0.974
Tertile 1 (< 24.9% for males, < 34.9% for females, *N* = 79)	Reference	--	Reference	--
Tertile 2 (24.9–28.3% for males, 34.9–40.1% for females, *N* = 80)	1.493 (0.876–2.543)	0.140	1.502 (0.858–2.628)	0.154
Tertile 3 (> 28.3% for males, > 40.1% for females, *N* = 81)	1.686 (0.999–2.848)	0.051	1.267 (0.675–2.380)	0.461
LMI				
Continuous per 1 unit increase	**1.179 (1.046–1.330)**	**0.007**	1.040 (0.884–1.223)	0.342
Tertile 1 (< 18.3 kg/m^2 for males, < 16.3 kg/m^2 for females, *N* = 80)	Reference	--	Reference	--
Tertile 2 (18.3–19.1 kg/m^2 for males, 16.3–16.6 kg/m^2 for females, *N* = 78)	1.456 (0.837–2.536)	0.184	1.469 (0.833–2.590)	0.183
Tertile 3 (> 19.1 kg/m^2 for males, > 16.6 kg/m^2 for females, *N* = 82)	**2.044 (1.216–3.434)**	**0.007**	1.545 (0.857–2.788)	0.148

The multivariate Cox regression was adjusted for etiology, SBP, heart rate, LVEF, LVEDDI, mitral regurgitation, and NT-proBNP

further investigation based on DEXA or MRA should be conducted to validate our conclusion. Thirdly, the distribution of fat (such as visceral fat, subcutaneous fat, or ectopic fat) could not be assessed in our study. Which type of adipose tissue played a more important role in the "obesity-paradox" was unclear in our study, which limited the interpretation of our results. Fourthly, the criteria of LVRR adopted in our study was mainly depended on LV diameter rather than LV volume. Regional LV remodeling may result in dilated LV diameter but normal volume, which caused the discordance of LVEDDI and LVEDVI to define LVRR. More accurate quantification of LVRR should be assessed by three-dimensional echocardiography or cardiac magnetic resonance.

Conclusions

For Chinese HFmrEF patients, the body composition plays an important role in LVRR and long-term prognosis. Higher BMI and fat mass was associated with higher incidence of LVRR, while this relationship was fully mediated by baseline LVEDDI. It is the fat mass and PBF rather than LMI are the independent predictors for adverse clinical events for HFmrEF patients.

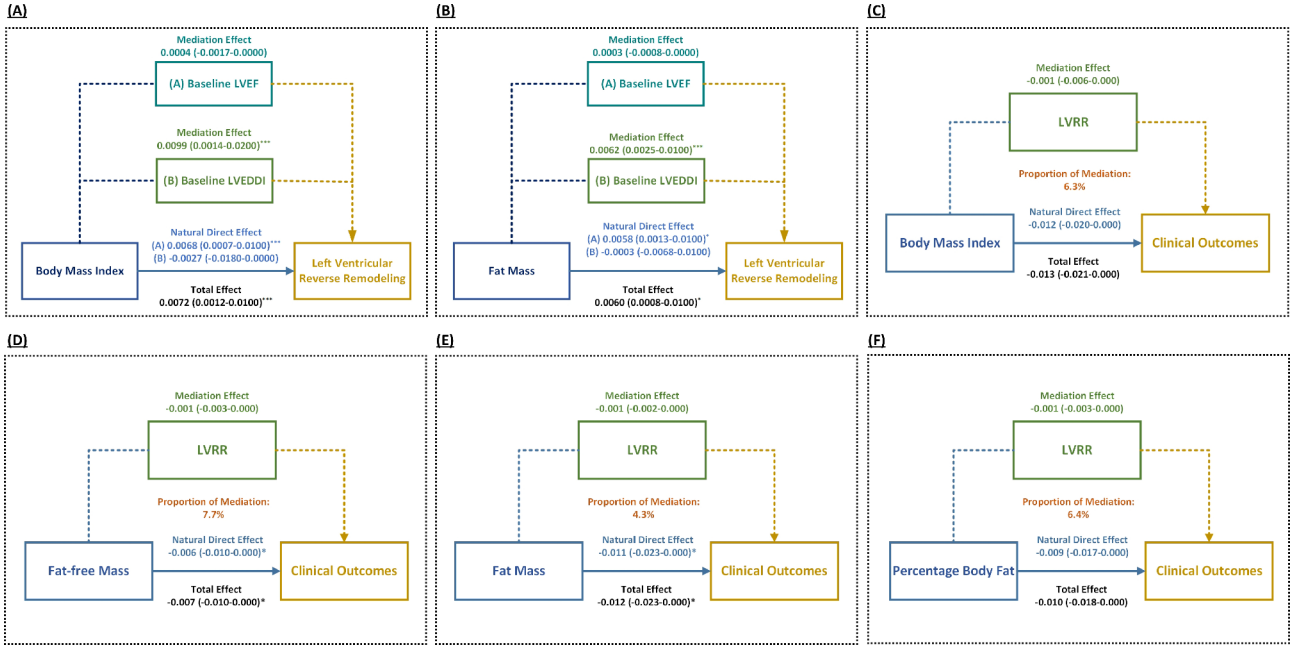


Fig. 6 Mediating effects of baseline LVR on the association between body composition and LVRR (A, B), and mediating effect of LVRR on the association between body composition and clinical prognosis (C-F)

Table 4 Association between body composition and clinical events via univariable and multivariable Cox regression analysis

	Unadjusted model		Adjusted model	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**
BMI				
Continuous per 1 unit increase	**0.903 (0.824–0.989)**	**0.028**	0.920 (0.838–1.010)	0.081
Low and healthy weight (*N* = 87)	Reference	--	Reference	--
Overweight (*N* = 109)	0.703 (0.386–1.279)	0.249	0.708 (0.382–1.310)	0.271
Obesity (*N* = 44)	0.361 (0.124–1.047)	0.061	0.424 (0.143–1.258)	0.122
Fat-free Mass				
Continuous per 1 unit increase	0.968 (0.934–1.003)	0.072	0.984 (0.948–1.022)	0.408
Tertile 1 (< 54.9 kg for males, < 41.7 kg for females, *N* = 79)	Reference	--	Reference	--
Tertile 2 (54.9–58.9 kg for males, 41.7–44.1 kg for females, *N* = 80)	0.621 (0.322–1.196)	0.154	0.867 (0.436–1.727)	0.685
Tertile 3 (> 58.9 kg for males, > 44.1 kg for females, *N* = 81)	**0.399 (0.189–0.843)**	**0.016**	0.546 (0.244–1.222)	0.141
Fat Mass				
Continuous per 1 unit increase	**0.946 (0.906–0.988)**	**0.013**	**0.957 (0.917–0.999)**	**0.049**
Tertile 1 (< 16.6 kg for males, < 20.1 kg for females, *N* = 79)	Reference	--	Reference	--
Tertile 2 (16.6–22.7 kg for males, 20.1–23.5 kg for females, *N* = 80)	0.633 (0.332–1.206)	0.165	0.654 (0.330–1.261)	0.200
Tertile 3 (> 22.7 kg for males, > 23.5 kg for females, *N* = 81)	**0.357 (0.164–0.776)**	**0.009**	**0.383 (0.169–0.871)**	**0.022**
PBF				
Continuous per 1 unit increase	**0.957 (0.917–0.998)**	**0.041**	**0.963 (0.924–0.976)**	**0.043**
Tertile 1 (< 23.0% for males, < 31.9% for females, *N* = 80)	Reference	--	Reference	--
Tertile 2 (23.0-28.1% for males, 31.9–35.9% for females, *N* = 79)	0.626 (0.323–1.216)	0.167	0.656 (0.337–1.277)	0.214
Tertile 3 (> 28.1% for males, > 35.9% for females, *N* = 81)	**0.470 (0.227–0.976)**	**0.043**	**0.441 (0.208–0.937)**	**0.033**
CUN-BAE Index				
Continuous per 1 unit increase	0.980 (0.940–1.022)	0.343	0.964 (0.924–1.007)	0.099
Tertile 1 (< 24.9% for males, < 34.9% for females, *N* = 79)	Reference	--	Reference	--
Tertile 2 (24.9–28.3% for males, 34.9–40.1% for females, *N* = 80)	1.091 (0.549–2.165)	0.804	0.855 (0.416–1.761)	0.672
Tertile 3 (> 28.3% for males, > 40.1% for females, *N* = 81)	0.895 (0.432–1.855)	0.766	0.587 (0.258–1.335)	0.204
LMI				
Continuous per 1 unit increase	0.842 (0.692–1.023)	0.083	0.889 (0.722–1.094)	0.266
Tertile 1 (< 18.3 kg/m^2 for males, < 16.3 kg/m^2 for females, *N* = 80)	Reference	--	Reference	--
Tertile 2 (18.3–19.1 kg/m^2 for males, 16.3–16.6 kg/m^2 for females, *N* = 78)	0.785 (0.411-1.500)	0.464	0.780 (0.405–1.505)	0.459
Tertile 3 (> 19.1 kg/m^2 for males, > 16.6 kg/m^2 for females, *N* = 82)	**0.450 (0.210–0.961)**	**0.039**	0.446 (0.203–1.018)	0.069

The multivariate Cox regression was adjusted for age, DBP, heart rate, diabetes mellitus, and mitral regurgitation

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor/neprilysin inhibitor
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BSA	Body surface area
CUN-BAE	Clínica Universidad de Navarr—Body Adiposity Estimator
DEXA	Dual-energy X-ray absorptiometry
eGFR	Estimated glomerular filtration rate
GDMT	Guideline-directed medical therapy
HF	Heart failure
HFimpEF	HF with improved ejection fraction
HFmrEF	HF with mildly reduced ejection fraction
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
IVSTd	Interventricular septal end-diastolic thickness
LAD	Left atrial diameter
LMI	Lean mass index
LV	Left ventricular
LVEDD	LV end-diastolic diameter
LVEDDI	LV end-diastolic diameter index
LVEF	LV ejection fraction
LVH	LV hypertrophy
LVMI	LV mass index
LVPWTd	LV posterior wall end-diastolic thickness
LVR	LV remodeling
LVRR	LV reverse remodeling
MRA	Mineralocorticoid-receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PBF	Percent body fat
RCS	Restricted cubic spline
RVEDD	Right ventricular end-diastolic diameter
SGLT2i	Sodium-glucose cotransporter-2 inhibitor

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

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Author contributions
Xiaoping Ji and Huixia Lu: Designed and supervised the study and methodology. Kang Fu: Writing the original draft, and conducted formal analysis. Youran Dong, Zhiyuan Wang, Junlin Teng, Congyi Cheng, and Cong Su: contributed the data collection, interpretation of the data, and participated in the literature research.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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