Research Article

Trajectories of Waist-to-Hip Ratio and Adverse Outcomes in Heart Failure with Mid-Range Ejection Fraction

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Keywords

Waist-to-hip ratio · Heart failure with mid-range ejection fraction · Trajectory · Prognosis

Abstract

Background: Waist-to-hip ratio (WHR) is a strong predictor of mortality in patients with heart failure (HF). However, common WHR trajectories are not well established in HF with mid-range ejection fraction (HFmrEF) persons, and their relationship to clinical outcomes remains uncertain. **Method:** We prospectively enrolled 1,396 participants with HFmrEF (left ventricular ejection fraction 40–49%) from April 2013 through April 2017. The waist and hip circumferences of the subjects were measured at regular intervals, and the WHR was calculated as waist circumference divided by hip circumference. Latent mixture modeling was performed to identify WHR trajectories. We then used Cox proportional-hazard models to examine the association between WHR trajectory patterns and incident HF, incident cardiovascular disease (CVD), and all-cause mortality. **Results:** We identified four distinct WHR trajectory patterns: lean-moderate increase (9.2%), medium-stable/increase (32.7%), heavy-stable/increase (48.0%), and heavy-moderate decrease (10.1%). After multivariable adjustment, the heavy-stable/increase and heavy-moderate decrease patterns were associated with an increased all-cause mortality risk (heavy-stable/increase: adjusted hazard ratio [HR] 3.18, 95% confidence interval [CI] 2.75–4.62; heavy-moderate decrease: adjusted HR 2.32, 95% CI 1.71–3.04), incident CVD risk (heavy-stable/increase: adjusted HR 4.03, 95% CI 2.39–4.91; heavy-moderate decrease:

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adjusted HR 3.05, 95% CI 2.34–4.09), and incident HF risk (heavy-stable/increase: adjusted HR 2.72, 95% CI 2.05–3.28; heavy-moderate decrease: adjusted HR 2.39, 95% CI 1.80–3.03) with reference to the lean-moderate increase pattern. **Conclusion:** Among patients with HFmrEF, the trajectories of WHR gain are associated with poor outcomes. These findings highlight the importance of abdominal fat accumulation management during the progression of HFmrEF.

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Introduction

Heart failure (HF) with mid-range ejection fraction (HFmrEF) is a transitional status between HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF) [1, 2]. Patients with HFpEF have a poor prognosis similar to those with HFrEF [3, 4]. Identifying and screening modifiable risk factors for development of HFmrEF are critical to design effective prevention programs, as recommended by the guidelines [5].

Obesity is a known risk factor for the progression of HF [6]; however, a large body of evidence from epidemiologic studies has shown an obesity paradox, i.e., a higher body mass index (BMI) predicts a lower risk of death in patients with HF [7–9]. The precise pathophysiological mechanisms regarding this paradox remain uncertain. The BMI is the most common index to define obesity, whereas abdominal fat accumulation is not well described [10, 11]. Moreover, subjects with a high BMI may be misclassified as having HF because of dyspnea [12]. Particularly, abdominal fat has been confirmed as a risk predictor of HF, and is known to predict mortality in individuals with coronary artery disease or even in the general population [13, 14]. The commonly used measurement of abdominal fat is the waist-to-hip ratio (WHR) [13, 15, 16]. Of note, prior studies were based on a single WHR measure, failing to account for the potential effect of change in WHR values over time [13, 17, 18]. Furthermore, whether patterns of WHR change over time can predict clinical outcome has not been studied in populations with HFmrEF.

In this study, we assessed the association between WHR trajectory patterns and subsequent outcomes in patients with established HFmrEF.

Subjects and Methods

Study Population

Consecutive patients with a newly diagnosed HF were prospectively enrolled from April 2013 to April 2017 in the Second Hospital of Anhui Medical University and the First Affiliated Hospital of Chengdu Medical College. Initially eligible patients included those aged ≥ 18 years who complied with the HF criteria (signs and symptoms), with a left ventricular ejection fraction $\geq 40\%$, and a B-type natriuretic peptide (BNP) level > 35 pg/mL [1]. Patients who had chronic renal failure, hemodialysis, absence of waist circumference and hip circumference measures, systemic inflammatory disease, peripheral artery disease, a BMI < 18.5 kg/m², or an unknown follow-up status were excluded. Briefly, the remaining 1,396 patients who had an ascertained vital status were finally included (Fig. 1A).

Data Collection

The detailed medical histories and relevant baseline clinical assessments (including baseline demographics and laboratory results) of each patient were recorded. All monthly assessments of waist and hip circumference were performed thrice by trained medical technologists in accordance with a standardized protocol described elsewhere [13, 19], and the

Fig. 1. A Flowchart showing the enrollment protocol. **B** Timeline of exposure and follow-up assessment. HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF, left ventricular ejection fraction; WHR, waist-to-hip ratio.

average result was recorded. Waist circumference divided by hip circumference defined the WHR [13, 20]. A high WHR was ≥ 0.90 for men and ≥ 0.85 for women [13, 19, 20]. We evaluated the body composition parameters yearly, using an automated body composition scan (Karada Scan HBF-701; Omron, Tokyo, Japan).

Immediately after the measurement of waist and hip circumference, images were acquired from stable patients using echocardiography (Vivid 9; GE Healthcare, Waukesha,

WI, USA). All images and measurements were performed by two experienced cardiac sonographers with no knowledge of the study data. The left ventricular ejection fraction, left ventricular diameter at the end of diastole, and left ventricular diameter at the end of systole were measured according to the current guideline [1, 21, 22].

HF patients were categorized into HFpEF (EF $\geq 50\%$) and HFrEF (EF $< 40\%$) [1]. Patients with an EF of 40–49% were considered HFmrEF [1]. Weight and WHR were evaluated after hemodynamic optimization in hypervolemic patients to avoid the potential confounding effects of edema [23, 24]. The differentiation between abdominal fat accumulation and HF-related ascites (or visceral congestion) was made based on clinical assessment (comprehensive physical examination), serum BNP measurement, and abdominal ultrasound [25]. During each monthly follow-up visit, a physical examination was performed to evaluate the hemodynamic state. If visceral congestion and/or ascites were suspicious, a BNP measurement and abdominal ultrasound were performed.

Outcomes

The participants were regularly followed up by phone calls, mobile social media software, or clinical visits (≥ 4 times a year) from April 2017 until April 2019 (Fig. 1B). The primary outcomes were a composite of incident HF, incident cardiovascular disease (CVD), and all-cause mortality. Incident HF was hospitalization for congestive HF and was defined as having been admitted with symptomatic congestive HF and actively being on intravenous drug administration for HF according to objective signs of worsening HF [26]. An incident HF diagnosis was carried out by a specialist and was based on clinical assessment, chest X-ray, and echocardiography [26]. Incident CVD was defined as the composite of coronary revascularization, unstable angina pectoris, and nonfatal myocardial infarction [27]. During the 2-year follow-up, all subjects were administered the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ), which are two widely used disease-specific quality-of-life measures for patients with HF [28, 29]. Higher MLHFQ scores and lower KCCQ scores reflect worse quality of life, and the questions involve HF-related symptoms and signs [28, 29].

Statistical Analysis

Clinical data were summarized as percentages for categorical variables and as the mean $\pm$ standard deviation (SD) for continuous variables. The sample size was calculated based on previous studies [27, 30] and 80% power. Comparisons between all variables from multiple groups were assessed by the χ^2 test, Kruskal-Wallis test, or one-way ANOVA. To identify WHR trajectories, we analyzed the WHR records for the same participants. On the basis of the WHR records, a latent mixture modeling (PROC TRAJ) was built for identifying subgroups, which assessed by Bayesian information criterion for model fit [31, 32]. The average posterior probability of each pattern of WHR was 0.91, 0.97, 0.85, and 0.87, reflecting a good fit of trajectory assignment.

The study population was stratified into four distinct WHR trajectory patterns: lean-moderate increase (0.78–0.84), medium-stable/increase (0.86–0.88), heavy-stable/increase (0.90–0.98), and heavy-moderate decrease (1.02–0.87). Cumulative event rates were reported using Kaplan-Meier estimates. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular events were assessed using Cox proportional-hazard models. Several sensitivity analyses were performed. The level of significance was set at $p < 0.05$. SPSS (version 22.0; IBM Corp., Armonk, NY, USA) and STATA (version 12.0; Stata Corp., College Station, TX, USA) were used for statistical analyses.

Fig. 2. Trajectories of WHR. The solid lines are estimated values, and the dotted lines show 95% confidence intervals. WHR, waist-to-hip ratio.

Fig. 3. A–F Quality of life in patients with heart failure with mid-range ejection fraction according to waist-to-hip ratio trajectories. MLHFQ, Minnesota Living with Heart Failure Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire. $\Delta p < 0.05$ compared with the lean-moderate increase group; $\# p < 0.05$ compared with the medium-stable/increase group; $* p < 0.05$ compared with the heavy-stable/increase group.

Results

Baseline Characteristics

The four distinct WHR trajectory patterns are depicted in Figure 2. During the period of 2013–2017, 9.2% ($n = 129$) of the individuals were categorized as having the lean-moderate increase pattern, 32.7% ($n = 456$) the medium-stable/increase pattern, 48.0% ($n = 670$) the heavy-stable/increase pattern, and 10.1% ($n = 141$) the heavy-moderate decrease pattern. Table 1 displays the baseline characteristics of the 1,396 subjects. Compared with the other

Table 1. Patient characteristics in April 2017

Parameter	Lean-moderate increase (n = 129)	Medium-stable/ increase (n = 456)	Heavy-stable/ increase (n = 670)	Heavy-moderate decrease (n = 141)	p value
Age, years	42.5±11.15	44.7±11.52	46.9±11.60	44.3±11.37	<0.001
Men, n (%)	24 (18.6)	240 (52.6)	549 (81.9)	72 (51.1)	<0.001
College/university, n (%)	14 (10.9)	39 (8.6)	34 (5.1)	10 (7.1)	0.037
Never-smokers, n (%)	91 (70.5)	324 (71.1)	478 (71.3)	103 (73.0)	0.967
Alcohol intake, n (%)	41 (31.8)	169 (37.1)	310 (46.3)	48 (34.0)	<0.001
Physical activity ≥3 times/week, n (%)	38 (29.5)	123 (27.0)	201 (30.0)	44 (31.2)	0.666
NYHA class, n (%)					
I	42 (32.6)	141 (30.9)	201 (30.0)	44 (31.2)	0.936
II	72 (55.8)	253 (55.5)	369 (55.1)	78 (55.3)	0.997
III	15 (11.6)	62 (13.6)	100 (14.9)	19 (13.5)	0.761
BMI, kg/m ²	22.2±3.02	24.3±3.16	26.0±3.50	24.7±3.68	<0.001
WHR (April 2013)	0.78±0.06	0.86±0.07	0.90±0.03	1.02±0.04	<0.001
WHR (April 2017)	0.84±0.03	0.88±0.05	0.95±0.06	0.86±0.06	<0.001
Heart rate, bpm	71.2±10.12	73.6±9.59	74.3±10.09	73.1±9.82	<0.001
SBP, mm Hg	116.8±18.74	124.3±16.23	129.2±19.75	122.1±15.64	<0.001
DBP, mm Hg	73.4±10.82	81.5±11.70	85.9±12.52	78.7±9.63	<0.001
Comorbidity, n (%)					
Hypertension	14 (10.9)	98 (21.5)	248 (37.0)	34 (24.1)	<0.001
Diabetes mellitus	6 (4.7)	46 (10.1)	120 (17.9)	16 (11.3)	<0.001
Hyperlipidemia	25 (19.4)	100 (21.9)	154 (23.0)	29 (20.6)	0.787
COPD	21 (16.3)	87 (19.1)	140 (20.9)	25 (17.7)	0.571
Prior PCI	18 (14.0)	75 (16.4)	120 (17.9)	23 (16.3)	0.724
Atrial fibrillation	19 (14.7)	77 (16.9)	123 (18.4)	22 (15.6)	0.692
Acute heart failure (≥3 times/year)	4 (3.1)	19 (4.2)	44 (6.6)	9 (6.4)	0.195
Infectious disease	11 (8.5)	43 (9.4)	74 (11.0)	15 (10.6)	0.745
Peripheral edema present	61 (47.3)	251 (55.0)	429 (64.0)	87 (61.7)	0.001
Rales present	47 (36.4)	178 (39.0)	282 (42.1)	58 (41.1)	0.569
Elevated JVP	32 (24.8)	124 (27.2)	175 (26.1)	40 (28.4)	0.896
Laboratory*					
Fasting glucose, mmol/L	8.1±2.1	8.2±1.4	8.4±0.8	8.2±1.9	0.663
TC, mmol/L	4.75±1.32	5.01±1.28	6.24±1.22	5.10±1.30	<0.001
TG, mmol/L	1.33±0.47	1.71±0.51	1.92±0.48	1.75±0.52	<0.001
HDL-C, mmol/L	1.66±0.48	1.67±0.42	1.63±0.38	1.65±0.45	0.922
LDL-C, mmol/L	2.31±0.96	2.45±0.90	3.54±0.93	1.92±0.78	<0.001
BNP, pg/mL	195.4±105.62	219.2±147.35	227.6±164.43	198.8±116.74	0.013
eGFR, mL/min/1.73m ²	87.2±9.81	86.8±9.12	75.4±9.37	86.3±9.45	0.032
Fat mass, %*	29.9±7.5	30.5±7.4	32.3±7.3	31.7±7.6	<0.001
SCF, %*	20.8±7.9	25.3±7.6	26.4±7.5	25.9±7.6	0.003
VF*	8.6±5.1	9.1±4.9	9.9±5.3	9.5±5.4	0.015
FFM, %*	24.8±4.9	24.7±5.1	25.2±5.5	24.9±4.7	0.370
LVEF, %*	46±3.5	44±2.7	43±2.5	45±4.1	0.350
Change in LVEF (increase/decrease ≥10%), n (%)	17 (13.2)	69 (15.1)	128 (19.1)	25 (17.7)	0.205
LVDd, mm*	51.3±8.5	53.4±7.8	55.7±8.6	53.9±7.5	0.211
LVDs, mm*	42.5±6.1	44.8±5.9	45.7±6.2	44.5±6.4	0.683
Medication, n (%)					
ACE-I/ARB	88 (68.2)	337 (73.9)	504 (75.2)	100 (70.9)	0.333
Spironolactone	38 (29.5)	141 (30.9)	227 (33.9)	45 (31.9)	0.649
Beta-blocker	82 (63.6)	323 (70.8)	489 (73.0)	95 (67.4)	0.179
Diuretics	125 (96.9)	446 (97.8)	657 (98.1)	138 (97.9)	0.874
Statin	72 (55.8)	264 (57.9)	408 (60.9)	83 (58.9)	0.629
Change in medication, n (%)					
Antihypertensive	11 (8.5)	83 (18.2)	222 (33.1)	29 (20.6)	<0.001
Hypoglycemic	4 (3.1)	37 (8.1)	94 (14.0)	13 (9.2)	<0.001
Lipid-lowering drugs	14 (10.9)	50 (11.0)	82 (12.2)	19 (13.5)	0.821

Footnote to Table 1

Values are mean $\pm$ SD or n (%). A p value of <0.05 was considered statistically significant. NYHA, New York Heart Association; BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; JVP, jugular venous pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; SCF, subcutaneous fat; VF, visceral fat; FFM, fat-free mass; LVEF, left ventricular ejection fraction; LVDd, left ventricular diameter diastolic; LVDs, left ventricular diameter systolic; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker. * Average levels based on 5 measurements (in 2013, 2014, 2015, 2016, and 2017).

Fig. 4. Kaplan-Meier analysis of all-cause mortality (**A**), incident CVD (**B**), and incident HF (**C**) in patients with HFmrEF according to WHR trajectories. CVD, cardiovascular disease; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; WHR, waist-to-hip ratio.

Table 2. Association of WHR trajectories with outcomes

	Events	Event rate (per 1,000 person-years)	Demographics ^a HR (95% CI)	Demographics + WHR ^b HR (95% CI)
All-cause mortality				
Lean-moderate increase (<i>n</i> = 129)	13 (10.1)	11.2	1.00 (reference)	1.00 (reference)
Medium-stable/increase (<i>n</i> = 456)	77 (16.9)	20.3	1.09 (0.83–1.22)	1.02 (0.75–1.38)
Heavy-stable/increase (<i>n</i> = 670)	154 (23.0)	29.8	2.18 (0.75–3.62)	1.42 (0.68–1.76)
Heavy-moderate decrease (<i>n</i> = 141)	27 (19.1)	23.7	2.32 (0.71–3.04)	1.48 (0.91–1.89)
Coronary-related events				
Lean-moderate increase (<i>n</i> = 129)	10 (7.8)	8.4	1.00 (reference)	1.00 (reference)
Medium-stable/increase (<i>n</i> = 456)	50 (11.0)	12.3	1.21 (0.66–1.78)	1.49 (0.93–2.19)
Heavy-stable/increase (<i>n</i> = 670)	113 (16.9)	20.3	1.24 (0.95–1.61)	1.35 (0.87–1.95)
Heavy-moderate decrease (<i>n</i> = 141)	21 (14.9)	17.5	2.35 (1.57–3.46)	2.22 (1.34–3.23)
HF-related events				
Lean-moderate increase (<i>n</i> = 129)	17 (13.2)	15.2	1.00 (reference)	1.00 (reference)
Medium-stable/increase (<i>n</i> = 456)	109 (23.9)	31.4	1.13 (0.80–1.52)	1.67 (0.42–2.08)
Heavy-stable/increase (<i>n</i> = 670)	202 (30.1)	43.2	1.47 (0.73–2.38)	1.79 (1.23–2.72)
Heavy-moderate decrease (<i>n</i> = 141)	24 (17.0)	20.5	1.91 (0.65–3.27)	1.53 (1.04–2.26)

WHR, waist-to-hip ratio; HF, heart failure; HR, hazard ratio; CI, confidence interval. ^a Age and sex. ^b April 2017 WHR.

three WHR trajectory patterns, individuals with the heavy-stable/increase pattern were more likely (1) to be men, older, and alcohol drinkers; (2) to have a higher BMI, heart rate, systolic and diastolic blood pressure, total cholesterol, triglycerides, low-density lipoprotein-cholesterol, and BNP level; and (3) to have a higher prevalence of hypertension and diabetes mellitus. Moreover, they were less likely to have higher education and had a lower estimated glomerular filtration rate.

Quality of Life

All participants' quality of life values as assessed by the MLHFQ and KCCQ at the end of the 2-year follow-up are shown in Figure 3. Compared with the other three WHR trajectory patterns, the individuals with the heavy-stable/increase pattern had the highest score on the MLHFQ and the lowest score on the KCCQ.

Outcomes during Follow-Up

For the follow-up period from April 2017 through April 2019, the detailed clinical outcomes of interest are shown in Table 2. The individuals with the heavy-stable/increase pattern had the highest risk of incident HF, incident CVD, and all-cause mortality. The survival curves of cumulative all-cause mortality, incident CVD, and incident HF for the four WHR trajectory groups are shown in Figure 4. As time went on, the WHR trajectory patterns were associated with all-cause mortality (log-rank test $p = 0.003$; Fig. 4A), incident CVD (log-rank test $p = 0.002$; Fig. 4B), and incident HF (log-rank test $p < 0.001$; Fig. 4C).

Cox Proportional-Hazard Analysis

Table 2 shows the unadjusted cumulative incidence of all-cause mortality, incident CVD, and incident HF over time. After adjustment for potential confounders, the results of the multivariable analysis of all-cause mortality, incident CVD, and incident HF are shown in Figure 5. With reference to the lean-moderate increase pattern, the heavy-stable/increase pattern and the heavy-moderate decrease pattern were associated with an increased all-

Fig. 5. Forest plot showing the results of multivariate Cox proportional-hazard analysis of all-cause mortality (**A**), incident CVD (**B**), and incident HF (**C**) in patients with HFmrEF according to WHR trajectories after adjustment for other confounders (hazard ratio = 1 set at the reference of the lean-moderate increase group). Multivariate = demographics + WHR (April 2018 WHR) + cardiovascular risk factors (alcohol intake, body mass index, heart rate, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, low-density lipoprotein cholesterol, B-type natriuretic peptide, estimated glomerular filtration rate) + history of chronic medical conditions (hypertension, diabetes mellitus). CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HR, hazard ratio; WHR, waist-to-hip ratio.

cause mortality risk (heavy-stable/increase pattern: adjusted HR 3.18, 95% CI 2.75–4.62; heavy-moderate decrease pattern: adjusted HR 2.32, 95% CI 1.71–3.04; Fig. 5A), incident CVD risk (heavy-stable/increase pattern: adjusted HR 4.03, 95% CI 2.39–4.91; heavy-moderate decrease pattern: adjusted HR 3.05, 95% CI 2.34–4.09; Fig. 5B), and incident HF risk (heavy-stable/increase pattern: adjusted HR 2.72, 95% CI 2.05–3.28; heavy-moderate decrease pattern: adjusted HR 2.39, 95% CI 1.80–3.03; Fig. 5C). Table 3 shows the sensitivity analyses after excluding some individuals. Whenever we excluded some subjects, in the following, the results revealed no obvious differences between these data and those described in Figure 5.

Discussion

This is the first study to demonstrate an association between higher WHR trajectory patterns (reflecting abdominal fat) and worse outcomes in patients with HFmrEF. Specifically, it provides a critical support for more expanded use of the WHR for abdominal obesity management in the setting of HFmrEF.

Table 3. Sensitivity analysis of hazard ratios and 95% confidence intervals for outcomes according to the WHR trajectories

	Hazard ratio (95% confidence interval)			
	lean-moderate increase	medium-stable/increase	heavy-stable/increase	heavy-moderate decrease
All-cause mortality				
Model 1	1.00 (reference)	1.31 (1.07–1.58)	1.52 (1.13–1.89)	1.65 (1.30–2.11)
Model 2	1.00 (reference)	1.21 (1.10–1.54)	1.08 (1.03–1.22)	1.81 (1.32–2.47)
Model 3	1.00 (reference)	1.39 (1.07–1.95)	1.62 (1.30–2.71)	1.66 (1.22–2.89)
Model 4	1.00 (reference)	1.28 (1.06–1.56)	1.54 (1.13–2.64)	2.08 (1.43–3.22)
Coronary-related events				
Model 1	1.00 (reference)	1.56 (1.15–2.23)	1.29 (1.07–2.32)	1.55 (1.26–2.78)
Model 2	1.00 (reference)	1.38 (1.11–1.88)	1.63 (1.06–2.11)	1.80 (1.40–2.39)
Model 3	1.00 (reference)	1.33 (1.18–1.79)	1.75 (1.30–3.47)	1.83 (1.27–2.86)
Model 4	1.00 (reference)	1.90 (1.52–2.51)	3.71 (2.75–4.89)	3.93 (2.85–5.33)
HF-related events				
Model 1	1.00 (reference)	2.18 (1.67–2.83)	3.16 (1.69–4.03)	4.20 (3.71–4.95)
Model 2	1.00 (reference)	1.29 (1.18–2.30)	1.52 (1.30–1.92)	1.67 (1.27–1.99)
Model 3	1.00 (reference)	1.25 (1.09–1.66)	1.52 (1.22–1.93)	1.97 (1.43–2.85)
Model 4	1.00 (reference)	3.12 (1.95–6.50)	8.10 (5.32–10.20)	9.17 (4.88–14.33)

Model 1: we excluded the participants who had infectious disease, acute heart failure (≥ 3 times/year); adjusted confounders are multivariate, which are the same as in Figure 5. Model 2: we excluded the participants who had diabetes mellitus at baseline or in the follow-up period; adjusted confounders are multivariate, which are the same as in Figure 5. Model 3: we excluded the participants who had a change in left ventricular ejection fraction (increase/decrease $\geq 10\%$) between 2013 and 2017; adjusted confounders are multivariate, which are the same as in Figure 5. Model 4: we excluded the participants who had a change in medications (antihypertensive, hypoglycemic, and lipid-lowering drugs) between 2013 and 2017; adjusted confounders are multivariate, which are the same as in Figure 5. WHR, waist-to-hip ratio; HF, heart failure.

These findings provide unique insight into the role of WHR changes in patients with HFmrEF. A large number of studies have described that the prevalence of abdominal obesity defined by WHR measurement is increasing with age up to 60 years and is then followed by a decline [33, 34]. By integrating the WHR into the modeling approach, we found unique WHR trajectory patterns in these patients with HFmrEF. In particular, we found that subjects who maintained a “heavy” trajectory had the highest mortality, whereas those who remained on a “lean” trajectory had the lowest risk of death. Previous studies have demonstrated that a higher WHR trajectory pattern was one of the predictors of all-cause mortality [13, 19]. In a prospective cohort from Scotland, a higher WHR predicted a higher all-cause mortality risk in female patients with HF [13]; however, the authors did not adopt a trajectory modeling approach to minimize reverse causation. Two large prospective cohort studies using the BMI trajectory approach reported that individuals who gained weight in middle age or maintained a heavy body weight throughout life were at higher risk of mortality [35]; yet the authors did not focus on the association between abdominal fat assessed by the WHR and mortality among patients with HFmrEF. Furthermore, compared with those who maintained a “lean” trajectory, our results suggest that participants with a “heavy” trajectory throughout the HFmrEF settings had a substantially increased cardiovascular risk.

In addition, Tsujimoto and Kajio [24] recently added to the accumulating evidence that abdominal obesity measured via waist circumference significantly heightened cardiovascular mortality among subjects with HFpEF. In addition, a novel finding of our study is that a quality-of-life assessment of our subjects with HFmrEF revealed that a “heavy” trajectory was

significantly associated with a worse quality of life based on MLHFQ and KCCQ scores. Indeed, the impact of quality of life on HFmrEF has been shown to be strong in a retrospective analysis of clinical settings in China [36]; however, the authors did not account for the association between abdominal obesity assessed via the WHR and the psychosomatic state, which might reflect the efficacy of therapy.

Despite the well-recognized effect of abdominal obesity on the development of HF, there remains considerable uncertainty regarding the role of the WHR trajectory in cardiovascular events, due to the complex interaction of various cardiovascular risk factors. Several possible explanations have been proposed. First, patients with HFmrEF frequently suffer from multiple comorbidities, including hypertension, diabetes, obesity, coronary artery disease, and metabolic syndrome [13, 19, 37]. On account of these coexisting conditions, clinical trials have emphasized that an increase in WHR was a major contributor to a systemic proinflammatory state, which is involved in myocardial fibrosis, hypertrophy, and pathological remodeling, ultimately promoting left ventricular dysfunction [13, 38]. As is known, abdominal obesity is strongly related to systemic inflammation, which is recognized to be associated with HF worsening [39, 40]. Inflammation might have been responsible for the worse clinical outcome in participants with a “heavy” trajectory. Second, previous studies have shown that weight gain in middle life has also been related to several cardiometabolic abnormalities, such as insulin resistance, atherogenic dyslipidemia, hyperleptinemia, and low adiponectin levels [24, 35]. Interestingly, even lean middle-aged individuals who had gained weight later had a higher risk of mortality. Results from prior BMI trajectory-based studies showed that HF in individuals with higher BMI levels was associated with a lower mortality risk, which is distinct from our results [35]. Tsujimoto and Kajio [24] revealed that HFpEF patients with higher waist circumference levels had higher mortality rates. These conflicting results may be due to the fact that the WHR is a better abdominal obesity measure than the BMI, possibly being able to evaluate abdominal fat more accurately. Third, obesity is often accompanied by psychosocial disorders, such as depression or anxiety, resulting in poor outcomes, especially in patients with HFmrEF [41, 42]. Previous studies have evaluated the association of weight loss with well-being outcomes in adults with HF [41, 42]. Findings from epidemiologic studies indicate that abdominal obesity shares complex biologic, etiologic, and genetic substrates with psychosocial states of stress [42, 43]. The psychosocial state characterized by chronic hypercortisolism induces abdominal fat accumulation, depressive symptoms, and severely reduced quality of life [43].

Strengths and Limitations

The advantage of this study is that we repeated WHR measurements and evaluated the quality of life among all patients over a period of time. Significantly, the WHR measurement is fast, reliable, noninvasive, and cheap, making it a valuable measurement for clinical practice and lifestyle modification worldwide.

Our study, though, has several limitations. First, this is an observational study based on only two centers; a subgroup analysis considering men and women separately would be worth performing. Second, the WHR was measured by different medical staff members, even though they received standardized training. Third, the present study was conducted on a specific cohort of patients with HF but not on the general population. Hence, our results may not be applicable to other populations or geographic areas. Fourth, it is difficult to differentiate between fat and fluid, and the latter is significant in patients with HFmrEF. Fifth, normal values for the WHR might differ by ethnicity, and the follow-up period for the WHR trajectory was relatively short. Thus, longer follow-ups will be needed for other populations.

Conclusions

Among patients with HFmrEF, trajectories of WHR gain are significantly associated with poor outcomes. Recognition of the WHR trajectory patterns may lead to an early identification of high-risk patients with HFmrEF and optimization of strategies for long-term weight management. These findings highlight the importance of abdominal fat accumulation management across the progression of HFmrEF.

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Statement of Ethics

The study was approved by the Institutional Review Board of the Second Hospital of Anhui Medical University and the First Affiliated Hospital of Chengdu Medical College and was conducted in accordance with the guidelines laid down in the Declaration of Helsinki. All patients provided informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.W. and F.G. conceived and designed the experiments; all authors performed the experiments; J.W. and B.X. analyzed the data; J.W., B.X., and X.W. contributed reagents/materials/analysis tools; P.W. and X.L. drafted and revised the paper. All authors read and approved the final manuscript.

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