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Mediation effect analysis of lipoprotein levels on BMI and cardiovascular outcomes in patients with heart failure

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Abstract

Background Among heart failure patients with obesity, the prognosis is better than those with normal weight, a phenomenon known as the obesity paradox. However, it is unclear whether lipoprotein levels play a mediating role in the machine of the obesity paradox.

Methods The study included 1663 heart failure patients hospitalized from January, 2019 through August, 2022. Kaplan-Meier survival analysis and Log-rank tests were performed for three endpoints in order to determine cumulative event-free survival. We investigated the correlation between Body Max Index (BMI) and outcomes by multifactorial Cox models. Mediation analysis was applied to study the presence and magnitude of mediation effects of triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein A1 and apolipoprotein B, with the association between BMI and endpoints.

Results In MACCEs, the median follow-up period was 679 days. In Cox model, compared with the underweight group, a high BMI level was significantly associated with lower all-cause mortality (HR=0.47, 95%CI 0.31~0.69, $p<0.001$, obese vs underweight), cardiovascular mortality (HR=0.46, 95%CI 0.30~0.73, $p<0.001$, obese vs underweight) and the incidence of MACCEs (HR=0.68, 95%CI 0.53~0.88, $p=0.003$, obese vs underweight). Mediation analysis revealed that TG was the strongest mediator between BMI and endpoints, with proportions of mediated effects of 6.6% (95%CI 2.2%~18.0%, $p=0.0258$, in all-cause death),7.0% (95%CI 2.3%~18.9%, $p=0.0301$, in cardiovascular death) and 10.2% (95%CI 3.3%~27.4%, $p=0.0185$, in MACCEs).

Conclusions There is an "obesity paradox" in patients with heart failure, and lipoprotein levels especially triglyceride mediate the association between BMI and cardiovascular outcomes.

Keywords Heart failure, Obesity, Lipoprotein, Mediating effect

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Introduction

Heart failure (HF) is a prevalent and intricate clinical syndrome that impacts a global population exceeding 40 million individuals, thereby leading to substantial rates of morbidity, mortality, and financial burdens [1]. The incidence of heart failure in the United States is projected to escalate by 46% between 2012 and 2030, leading to the number of people suffering from heart failure will exceed 8 million by 2030 [2]. Obesity has emerged as a burgeoning concern within the realm of public health. It has been widely acknowledged as an independent risk factor for cardiovascular ailments, exhibiting a conspicuous correlation with conditions such as coronary heart disease(CHD),heart failure, and atrial fibrillation(AF) [3]. Metabolic abnormalities, notably obesity, hyperglycemia, and hyperlipidemia, are causally linked with the progression of type 2 diabetes, atherosclerosis, and cardiovascular disease culminating in HF [4]. Numerous studies have consistently demonstrated a counterintuitive association between obesity and HF, which overweight and obese individuals exhibit improved prognoses and reduced risk of complications compared to those with normal or low weight, a phenomenon referred as the "obesity paradox." [5, 6] This paradoxical relationship has also been observed within the Chinese population of HF patients [7, 8]. Lipoproteins are essential for the transportation of dietary fats, such as triglycerides, cholesterol, and fatty acids within the bloodstream [9]. In the context of chronic heart failure, the presence of bacterial endotoxins can aggravate the condition by stimulating immune activation. Interestingly, obese individuals with HF exhibit elevated levels of lipoproteins, which can potentially bind to inflammatory endotoxins and function as a neutralizing agent. This interaction may serve to regulate immune function and safeguard the body [10]. Consequently, this mechanism could potentially explain the phenomenon known as the obesity paradox. However, the confirmation of the mediating role of lipoprotein levels in the association between obese patients with HF and improved clinical outcomes remains unsubstantiated in real-world studies. Hence, a retrospective cohort study was undertaken to examine the mediating influence of lipoprotein levels on the relationship between BMI and cardiovascular outcomes in patients with heart failure.

Materials and methods

Study population

There were 1663 patients with HF who were hospitalized in the Department of Cardiovascular Medicine of Nanjing Drum Tower Hospital from January, 2019 to August, 2022 in this retrospective cohort study (Fig. 1). They were categorized according to the quartiles of BMI into the underweight group(BMI< 22.39kg/m^2), normal group(22.39kg/m^2≤BMI<24.70kg/m^2), overweight group(24.70kg/m^2≤BMI< 27.58kg/m^2), and obese group(BMI≥27.58kg/m^2). According to the *2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure*, the diagnostic criteria for HF were based on the definitions established in the guidelines [11]. The inclusion criteria for this study were (1) meeting the clinical

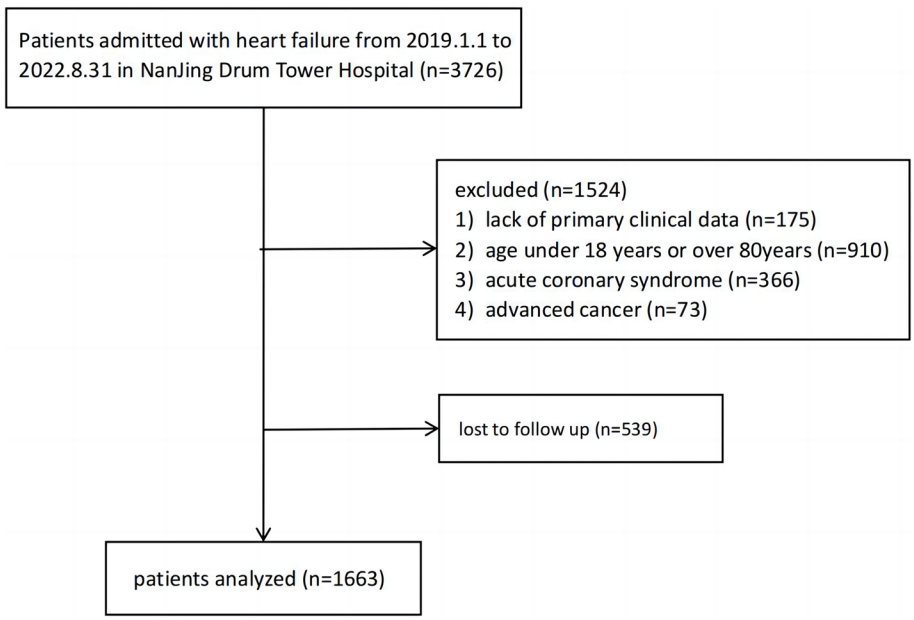

Fig.1 Flow diagram of patient selection

diagnostic criteria for chronic heart failure (2) between 18-80 years (3) complete clinical data is available. Exclusion criteria were (1) history of combined malignant tumors (2) congenital heart disease (3) after heart and other major organ transplantation (4) acute coronary syndrome (5) patients with missing data and lost to follow up.

Data collection

The electronic hospitalization system was used by trained physicians to collect basic patient information, personal past history, utilization of drugs, laboratory test results and cardiac ultrasound data. Basic patient information included age, gender, BMI, NYHA, HR, SBP and DBP. Past history included history of smoking, alcohol consumption, hypertension, DM, CHD, AF and hyperlipidemia. Utilization of drugs included diuretics, digoxin, ACEI/ARB/ARIN, SGLT2i, beta-blockers, antiplatelet agents, statins, calcium channel blockers and aldosterone antagonists. Laboratory test results included AST, ALT, LD,TB,TP,ALB/GLB,Glu,Cr,UA,CRP,eGFR,TG,TC,HDL-C,LDL-C,Apo-A1,Apo-B,Ca,P,K,Na,Cl,WBC,GRA,RBC,HGB,PLT,BNP,and HbA1c.Echocardiographic data included LVEF, IVSTd, LVPWTd, LVDd and LAD.

Clinical follow-up and setting of primary endpoint events

All patients in the study were followed up by a specialized clinician by telephone or in an outpatient clinic. The primary endpoint events for follow-up included (1) all-cause death: defined as cardiovascular and noncardiovascular deaths (2) cardiovascular death: stroke and myocardial infarction considered fatal, congestive heart failure, malignant arrhythmias, and other structural and functional heart conditions (3) major adverse cardiac and cerebral events(MACCEs): nonfatal myocardial infarction, stroke, heart failure exacerbation, and cardiac transplant.

Statistical analysis

SPSS 25.0, R 4.2.2 and SAS 9.4 software were used for data analysis. Categorical data were expressed as n (%), and comparisons between groups were made using the chi-square test. Normal-distributed quantitative data were expressed as mean±standard deviation, and comparisons between groups were made using the t-test or the ANOVA analysis; skewed-distribution quantitative data were expressed as M (P25, P75), and comparisons between groups were made using the rank sum test. Kaplan-Meier survival curves and log-rank tests were used to analyze cumulative event-free survival for the three endpoints. Multifactorial Cox models were constructed by adjusting for age, sex, LVEF, eGFR, CPR, hypertension, and DM to analyze the correlation between BMI and the event rates of the three endpoints and hazard ratios (HR)and 95% confidence intervals(95%CI) were calculated separately.

An analysis of the dose-response relationship between all-cause death, cardiovascular death and MACCEs was performed using restricted cubic spline method when BMI was used as a continuous variable and the optimal cutoff value of BMI was taken according to the Akaike Information criterion. Mediation effect analysis [12] was used to construct mediation models by adjusting for age, sex, LVEF, eGFR, CPR, hypertension and DM with the continuous variable BMI as the independent variable, TG, TC, HDL-C, LDL-C, Apo-A1, and Apo-B as the mediator variables, and all-cause death, cardiovascular death and MACCEs as the dependent variables, respectively. All statistical analyses considered a two-tailed $P<0.05$ to determine statistically significant differences.

Our findings were additionally subjected to several sensitivity analyses to assess their robustness. First, to rule out possible effects of high BNP levels and high glucose levels, we performed subgroup analyses based on median BNP and glucose. Second, lipid markers such as triglycerides may affect liver function, so we performed additional sensitivity analyses based on median ALT and AST. Third, we divided patients into two separate categories according to whether they had comorbid hyperlipidemia and whether they were on lipid-lowering therapy (with or without statins) to perform sensitivity analyses. Finally, risk factors with $p < 0.05$ and considered clinically significant in the univariate analysis between the group of MACCEs and UN-MACCEs included HR, DBP, NYHA Class, AF, LAD, LDH, TP, ALB/GLB, UA, Cr, Ca, Cl, GRA, RBC, HGB, PLT, HbA1c,and the use of ACEI/ARB/ARIN, SGLT2i, Beta -blocker, MRA, diuretic and digoxin were included in the sensitivity analyses by Cox regression models in order to avoid overstratification in the main analysis.

Results

General clinical characteristics of the patient and follow-up outcomes

There were 1663 patients enrolled in this study, 538 of whom had MACCEs events and 1125 did not. Patients were on average 63 years old, of which 550 were female, accounting for 33.1%. Table 1 illustrates the baseline clinical characteristics of the two groups. The median follow-up time was 679 days in the MACCEs. The analysis of the differences in TG, TC, HDL-C, LDL-C, Apo-A1, and Apo-B among different BMI groups is shown in Fig. 2. All-cause death occurred in 231(13.9%) patients, which included 183(11.0%) patients with cardiovascular death, and MACCEs cumulatively occurred in 538(32.4%) patients. For different BMI levels, Additional file 1Figure S1 shows the variability of all-cause death, cardiovascular

Table 1 Basic clinical characteristics of patients with different MACCEs outcomes

Characteristic	Total ($n = 1663$)	UN-MACCEs ($n = 1125$)	MACCEs ($n = 538$)	*P* Value
Age (years)	66 (56,72)	64 (54,71)	69 (61,74)	<0.001**
Female, n (%)	550 (33.07)	360 (32.00)	190 (35.32)	0.179
BMI (kg/m^2)	24.70 (22.40,27.57)	24.91 (22.66,27.89)	24.22 (21.65,26.87)	<0.001**
BMI (kg/m^2)				<0.001**
<22.39	415 (24.95)	244 (21.69)	171 (31.78)	
22.39~24.69	414 (24.89)	290 (25.78)	124 (23.05)	
24.70~27.57	418 (25.14)	282 (25.07)	136 (25.28)	
≥27.58	416 (25.02)	309 (27.47)	107 (19.89)	
Heart Rate (bmp)	77 (68,89)	78 (68,90)	77 (68,88)	0.365
SBP (mmHg)	129 (114,146)	130 (116,146)	128 (112,145)	0.075
DBP (mmHg)	77 (68,89)	78 (69,90)	75 (66,86)	<0.001**
NYHA Class, n (%)				<0.001**
I	123 (7.4)	99 (8.80)	24 (4.46)	
II	669 (40.23)	506 (44.98)	163 (30.30)	
III	710 (42.69)	442 (39.29)	268 (49.81)	
IV	161 (9.68)	78 (6.93)	83 (15.43)	
Medical history, n (%)				
Hypertension	972 (58.45)	655 (58.22)	317 (58.92)	0.786
CHD	613 (36.86)	399 (35.47)	214 (39.78)	0.088
DM	525 (31.57)	316 (28.09)	209 (38.85)	<0.001**
Hyperlipidemia	244 (14.67)	185 (16.44)	59 (10.97)	0.003*
AF	612 (36.8)	391 (34.76)	221 (41.08)	0.012*
Smoke, n (%)	491 (29.52)	345 (30.67)	146 (27.14)	0.140
Alcohol, n (%)	283 (17.02)	196 (17.42)	87 (16.17)	0.525
IVSTd (cm)	0.90 (0.80,1.02)	0.90 (0.80,1.00)	0.90 (0.80,1.04)	0.731
LVPWTd (cm)	0.90 (0.80,1.00)	0.90 (0.80,1.00)	0.90 (0.80,1.00)	0.667
LVDd(cm)	5.89 (5.35,6.53)	5.89 (5.35,6.50)	5.89 (5.37,6.65)	0.236
LAD(cm)	4.66 (4.30,5.10)	4.66 (4.25,5.00)	4.72 (4.40,5.33)	<0.001**
LVEF (%)	41 (32,51)	41 (33,52)	41 (31,50)	0.007*
BNP (pg/mg)	347 (151,734)	300 (127,659)	475 (213,949)	<0.001**
ALT (U/L)	20.1 (13.8,31.3)	20.7 (14.5,31.6)	18.5 (12.8,29.4)	0.002*
AST (U/L)	21.3 (17.0,28.4)	21.3 (17.1,28.0)	21.2 (16.5,29.2)	0.869
LDH (U/L)	215 (184,258)	213 (181,254)	219 (187,271)	<0.001**
TBIL (μmol/L)	13.6 (9.4,19.3)	13.5 (9.5,18.9)	14.1 (9.2,19.6)	0.834
Total Protein (g/L)	64.4 (60.6,68.8)	64.7 (61.1,69.1)	63.4 (59.6,67.8)	<0.001**
ALB/GLB	1.56 (1.37 ,1.74)	1.57 (1.40,1.75)	1.50 (1.29,1.68)	<0.001**
Glucose (mmol/L)	4.95 (4.48,5.86)	4.92 (4.49,5.72)	5.05 (4.45,6.13)	0.084
Cr (μmol/L)	76 (63,95)	73 (62,89)	83 (67,113)	<0.001**
UA (μmol/L)	422 (335,523)	407 (328,498)	446 (350,566)	<0.001**
TG (mg/dL)	1.10 (0.81,1.57)	1.15 (0.85,1.66)	1.02 (0.74,1.38)	<0.001**
TC (mg/dL)	3.79 (3.18,4.54)	3.90 (3.29,4.68)	3.54 (2.95,4.29)	<0.001**
HDL-C (mg/dL)	1.00 (0.81,1.23)	1.00 (0.83,1.24)	0.98 (0.78,1.23)	0.102
LDL-C (mg/dL)	2.12 (1.61,2.76)	2.21 (1.69,2.85)	1.93 (1.47,2.59)	<0.001**
Apo-A1 (g/L)	0.92 (0.80,1.07)	0.93 (0.82,1.08)	0.87 (0.75,1.02)	<0.001**
Apo-B (g/L)	0.67 (0.53,0.83)	0.69 (0.55,0.86)	0.62 (0.49,0.78)	<0.001**
Ca (mmol/L)	2.31 (2.23,2.41)	2.32 (2.24,2.42)	2.29 (2.19,2.39)	<0.001**
P (mmol/L)	1.10 (0.99,1.22)	1.10 (0.99,1.22)	1.10 (0.98,1.22)	0.981
K (mmol/L)	3.93 (3.70,4.20)	3.93 (3.70,4.17)	3.96 (3.69,4.25)	0.129
Na (mmol/L)	141.3 (139.7,142.8)	141.3 (139.8,142.8)	141.2 (139.5,142.8)	0.241

Table 1 (continued)

Characteristic	Total ($n = 1663$)	UN-MACCEs ($n = 1125$)	MACCEs ($n = 538$)	*P* Value
Cl (mmol/L)	105.0 (102.9,106.9)	105.1 (103.2,106.9)	104.7 (102.0,107.1)	0.037*
CRP (mg/L)	3.90 (2.70,6.65)	3.90 (2.60,6.50)	4.10 (2.82,7.77)	0.009*
eGFR (ml/min/1.73m^2)	88.7 (69.1,108.0)	92.8 (75.8,110.4)	78.8 (53.9,98.5)	<0.001**
WBC (10^9/L)	6.1 (5.0,7.3)	6.1 (5.1,7.3)	6.0 (4.8,7.4)	0.083
GRA (%)	63.2 (57.5,69.4)	62.4 (56.5,68.0)	65.4 (58.9,72.1)	<0.001**
RBC (10^12/L)	4.40 (3.95,4.81)	4.45 (4.07,4.89)	4.21 (3.73,4.65)	<0.001**
HGB (g/L)	134 (120.,147)	136 (123,149)	129 (112,142)	<0.001**
PLT (10^9/L)	177 (141,216)	179 (145,219)	169 (130,210)	<0.001**
HbA1c(%)	6.0 (5.6,6.7)	6.0 (5.6,6.6)	6.1 (5.7,7.0)	<0.001**
Drug therapy, n(%)				
ACEI/ARB/ARNI	1169 (70.29)	834 (74.13)	335 (62.27)	<0.001**
Beta-blocker	1301 (78.23)	888 (78.93)	413 (76.77)	0.316
MRA	1071 (64.4)	726 (64.53)	345 (64.13)	0.871
SGLT2i	328 (19.72)	248 (22.04)	80 (14.87)	<0.001**
Diuretic	1071 (64.4)	669 (59.47)	402 (74.72)	<0.001**
Digoxin	197 (11.85)	112 (9.96)	85 (15.80)	<0.001**
Antiplatelet agent	674 (40.53)	457 (40.62)	217 (40.33)	0.911
Statins	1005 (60.43)	676 (60.09)	329 (61.15)	0.678
CCB	256 (15.39)	167 (14.84)	89 (16.54)	0.369

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *NYHA* new york heart association, *CHD* coronary heart disease, *DM* diabetes mellitus, *AF* atrial fibrillation, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor inhibitor, *ARNI* angiotensin receptor neprilysin inhibitor, *MRA* mineralocorticoidreceptor, *SGLT2i* Sodium-glucose cotransporter 2 inhibitor, *CCB* calcium channel blocker. *BNP* B-type natriuretic peptide, *ALT* aspartate transaminase, *AST* alanine aminotransferase, *LDH* lactate dehydrogenase, *TBIL* total bilirubin, *ALB* albumin, *GLB* globulin, *Cr* creatinine, *UA* uric acid, *TG* triglyceride, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *CRP* C-creative protein, *eGFR* estimated glomerular filtration rate, *IVSTD* interventricular septal thickness at diastole, *LVPWTd* left ventricular posterior wall end-diastolic thickness, *LVDd* left ventricular end-diastolic diameter, *LAD* left atrial diameter, *LVEF* left ventricular ejection fraction, *WBC* white blood cell, *GRA* granulocyte, *RBC* red blood cell, *HGB* hemoglobin, *PLT* platelet count, *HbA1c* hemoglobin A1c

* $P<0.05$ ** $P<0.001$

death and MACCEs, all of which were statistically significant ($p<0.001$).

Predictive power of BMI for primary endpoint events

According to Kaplan-Meier survival curves, it demonstrated that the four groups of HF patients with different BMI levels had significantly difference in the three primary endpoints ($p<0.001$, log-rank test) and survival increased clearly with increasing BMI levels (Fig. 3). After adjusting for confounders in model 3, it was found that high BMI levels were associated with lower all-cause mortality (HR=0.47, 95%CI 0.31~0.69, $p<0.001$, obese vs underweight), cardiovascular mortality (HR=0.46, 95%CI 0.30~0.73, $p<0.001$, obese vs underweight) and the incidence of MACCEs (HR=0.68, 95%CI 0.53~0.88, $p=0.003$, obese vs underweight) (Table 2). In addition, the MACCEs was used as the endpoint event in a Cox model constructed in four groups with different BMI levels as a rank variable. The results showed that the risk of MACCEs in patients gradually decreased with increasing BMI levels (HR=0.892,95%CI 0.822~0.968, $p=0.006$) (Fig. 4). Based on restricted cubic spline analysis, we tested whether BMI had a linear relationship with endpoint events, and the results showed that their relationship was nonlinear($p<0.001$). The RCS curves (Fig. 5) showed that the risk of all-cause death(A), cardiovascular death(B)and MACCEs(C)in patients was gradually decreased with the increase of BMI.

Sensitivity analysis

First, when grouped according to median BNP and median glucose for analysis (Additional file 1 Table S2), their results were similar to the results of the multifactorial adjusted Cox model. Second, the results grouped by median ALT and AST (Additional file 1 Table S3) showed that in the range of ALT >20.1 U/L, the difference in all-cause deaths and MACCEs outcomes was not significant in the obesity group compared with underweight group, and the other results were similar to those reported. Third, the results of the analyses of whether patients had comorbid hyperlipidemia and whether they were on lipid-lowering therapy (with or without statins) were consistent with those reported (Additional file 1 Table S4), except that among patients with comorbid

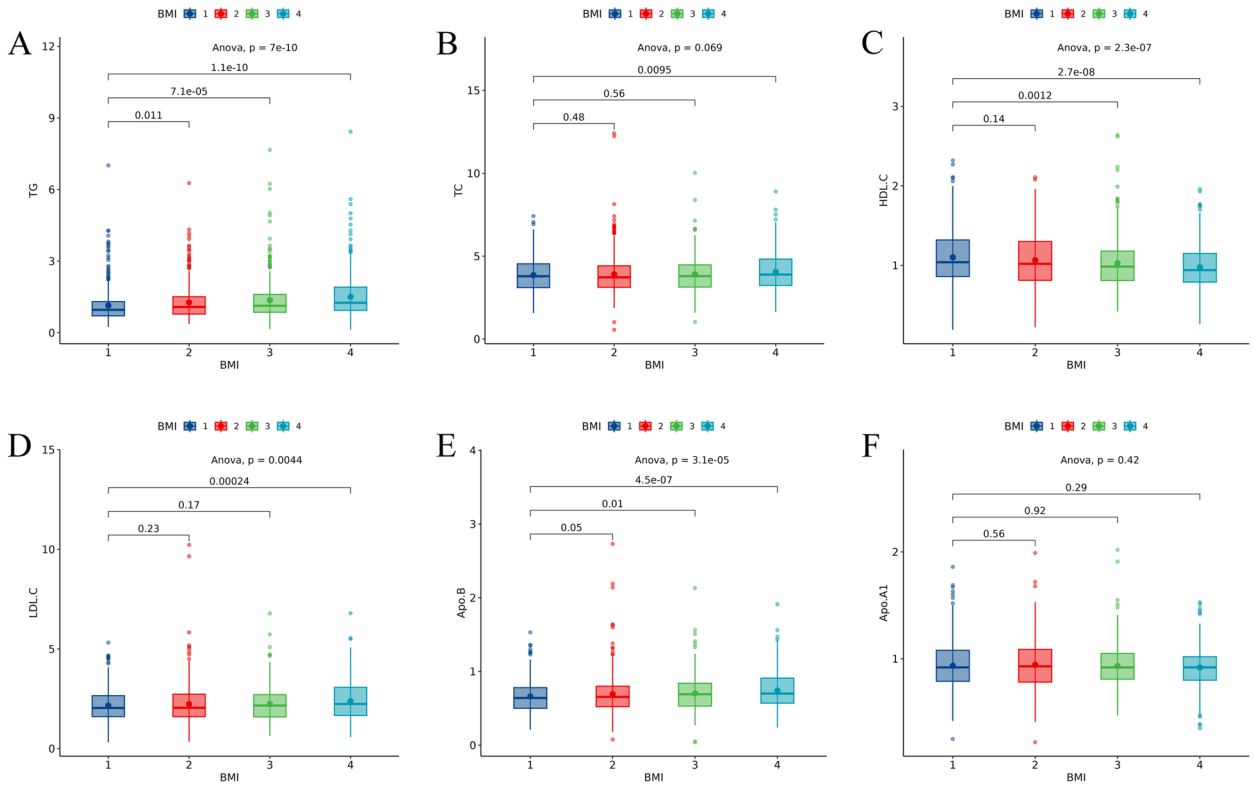

Fig. 2 Differences of each lipid indicators in different BMI groups. BMI1: underweight group, BMI2: normal group, BMI3: overweight group, BMI4: obese group

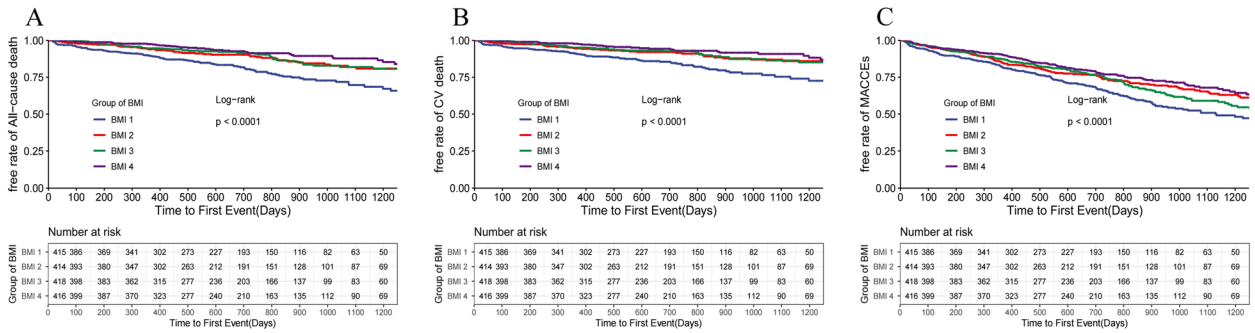

Fig. 3 Kaplan-Meier survival curves for all-cause death (**A**), cardiovascular death (**B**), and MACCEs (**C**) in four groups of patients with BMI levels. BMI1: underweight group, BMI2: normal group, BMI3: overweight group, BMI4: obese group

hyperlipidemia, the difference between the overweight and obese groups compared with the low-body group was not significant. Finally, the results in the stratified analyses of covariates using Cox regression were consistent with reported (Additional file 1 Table S5).

Analysis of mediating effects of lipoprotein levels

The results of the mediation analyses after adjusting for confounding factors showed that TG was the mediator with the strongest association between BMI and cardiovascular outcomes, with the proportion of mediated effects of TG in model 3 after adjustment for confounders being 6.6% (95%CI 2.2%~18.0%, p=0.0258, in all-cause deaths),7.0% (95%CI 2.3%~18.9%, p=0.0301, in cardiovascular deaths) and 10.2% (95%CI 2.3%~27.4%, p=0.0185, in MACCEs), respectively. In model 1, TC and Apo-B also showed strong mediating effects, with TC mediating 3.4% (95%CI 1.1%~21.1%, p=0.0398) and

Table2 The results of cox models in three endpoints under different BMI level

Outcomes	Group	Events(n,%)	Model 1[a]		Model 2[b]		Model 3[c]	
			HR(95%CI)	*p* Value	HR(95%CI)	*p* Value	HR(95%CI)	*p* Value
All-cause death	Underweight	91(21.9)	Reference		Reference		Reference	
	Normal	53(12.8)	0.56 (0.40, 0.78)	<0.001	0.58 (0.41,0.81)	0.001	0.55 (0.39,0.77)	<0.001
	Overweight	49(11.7)	0.50 (0.36,0.71)	<0.001	0.53 (0.38,0.76)	<0.001	0.51 (0.35,0.72)	<0.001
	Obese	38(9.1)	0.38 (0.26,0.55)	<0.001	0.48 (0.33,0.71)	<0.001	0.47 (0.31,0.69)	<0.001
CV death	Underweight	73(17.6)	Reference		Reference		Reference	
	Normal	41(9.9)	0.54 (0.37,0.79)	0.002	0.55 (0.38,0.81)	0.002	0.53 (0.36,0.78)	0.001
	Overweight	39(9.3)	0.50 (0.34,0.74)	<0.001	0.53 (0.36,0.78)	0.001	0.51 (0.34,0.76)	<0.001
	Obese	30(7.2)	0.37 (0.24,0.57)	<0.001	0.46 (0.30,0.71)	<0.001	0.46 (0.30,0.73)	<0.001
MACCEs	Underweight	171(41.2)	Reference		Reference		Reference	
	Normal	124(30.0)	0.70 (0.55,0.88)	0.002	0.72 (0.57,0.90)	0.005	0.69 (0.55,0.87)	0.002
	Overweight	136(32.5)	0.75 (0.60,0.94)	0.012	0.79 (0.63,0.99)	0.039	0.75 (0.60,0.95)	0.015
	Obese	107(25.7)	0.57 (0.45,0.73)	<0.001	0.71 (0.56,0.91)	0.007	0.68 (0.53,0.88)	0.003

[a] Model 1 unadjusted

[b] Model 2 adjusted for age, sex

[c] Model 3 adjusted for age, sex, LVEF, hypertension, DM, eGFR, CRP

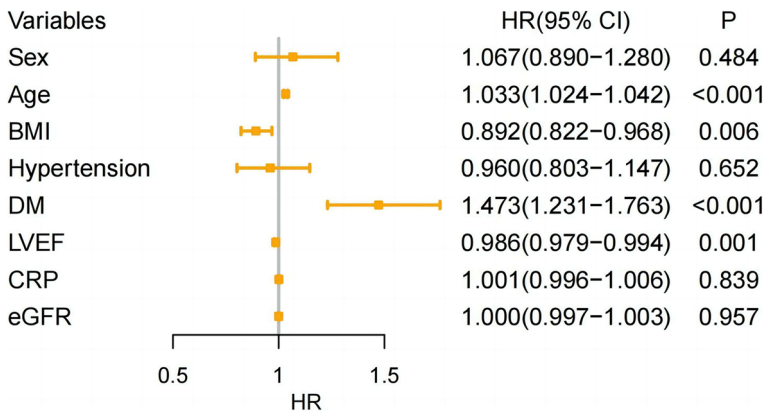

Fig. 4 Multifactorial Cox regression modeling with MACCEs outcome as endpoint event

6.3% (95%CI 2.4%~15.4%, p=0115) in all-cause death and MACCEs, and apo-B only showed a strong mediating effect in MACCEs (mediation ratio 10.6%, 95%CI 4.7%~22.0%, p=0.0018). Notably, after adjusting for confounders in Models 2 and 3, Apo-B still showed a strong mediating effect in MACCEs (Model 2: 5.7%, 95%CI 1.6%~18.6%, p=0.0447; Model 3:6.1%, 95%CI 1.7%~19.6%, p=0.0470) (Table 3).

In addition, according to the Akaike information criterion, we took BMI=24kg/m^2 as the cutoff value and divided it into two groups(Additional file 1 Table S1): BMI≤24kg/m^2 and BMI>24kg/m^2, to explore the mediating effect of TG and other indicators in the range of BMI ≤ 24kg/m^2 (n=692,41.6%). Other factors were not found to be significantly different from the results, except for TC, which showed a strong mediating effect

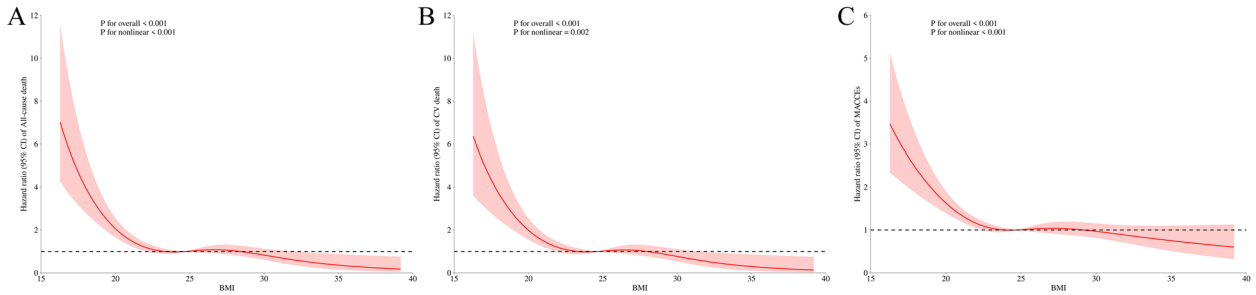

Fig. 5 Restricted cubic spline showing the relationship between BMI as a continuous variable and the risk ratios for all-cause mortality (**A**), cardiovascular death (**B**), and MACCEs (**C**)

Table 3 Results of mediation effects analysis in the total population

variables	Model 1[a]		Model 2[b]		Model 3[c]	
	Percentage of mediation effect	P value	Percentage of mediation effect	P value	Percentage of mediation effect	P value
All-cause death						
TG	9.1 (3.6,21.1)	0.0076*	6.2 (1.9,18.4)	0.0375*	6.6 (2.2,18.0)	0.0258*
TC	3.4 (1.1,10.3)	0.0398*	1.8 (0.3,10.1)	0.1443	-	-
HDL-C	-	-	-	-	-	-
LDL-C	2.8 (0.6,12.9)	0.1030	1.1 (0.1,17.4)	0.2486	-	-
Apo-AI	-	-	2.7 (0.2,28.7)	0.2282	2.3 (0.2,18.9)	0.1881
Apo-B	1.5 (0.0,45.1)	0.3077	-	-	1.1 (0.0,31.8)	0.2979
CV death						
TG	9.1 (3.4,22.1)	0.0123*	6.7 (2.1,19.6)	0.0364*	7.0 (2.3,19.6)	0.0301*
TC	2.9 (0.7,10.9)	0.0737	1.6 (0.2,10.7)	0.1650	-	-
HDL-C	-	-	-	-	-	-
LDL-C	1.6 (0.1,22.3)	0.2396	-	-	-	-
Apo-AI	-	-	3.8 (0.5,24.2)	0.1693	3.5 (0.6,19.0)	0.1395
Apo-B	-	-	-	-	-	-
MACCEs						
TG	14 (6.1,29.0)	0.0026*	10.2 (3.0,29.5)	0.0288*	10.2 (3.3,27.4)	0.0185*
TC	6.3 (2.4,15.4)	0.0115*	2.4 (0.2,25.5)	0.2245	1.9 (0.1,33.8)	0.2724
HDL-C	-	-	-	-	-	-
LDL-C	8.4 (3.7,18.2)	0.0031*	4.4 (1.0,17.3)	0.0810	3.8 (0.7,18.8)	0.1223
Apo-AI	-	-	-	-	-	-
Apo-B	10.6 (4.7,22.0)	0.0018*	5.7 (1.6,18.6)	0.0447*	6.1 (1.7,19.6)	0.0470*

* $p<0.05$

[a] Model 1 unadjusted

[b] Model 2 adjusted for age, sex

[c] Model 3 adjusted for age, sex, LVEF, hypertension, DM , eGFR, CRP

in MACCEs in model 1 (mediation ratio of 4.8%, 95%CI 1.4%~15.1%, p=0.0407). However, it has to be mentioned that the mediating proportions of TG in model 3 were 3.6% (95%CI 1.0%~12.2%, p=0.0599, in all-cause mortality), 3.8% (95%CI 0.9%~15.5%, p=0.0922, in cardiovascular death) and 4.4% (95%CI 1.2%~14.5%, p=0.0535, in MACCEs),and although the differences were not significant(p>0.05), the range of p-value below 0.1, which still demonstrated strong mediation, and this is consistent with the results for the total population. In addition, LDL-C and Apo-B also showed strong mediating effects in MACCEs(p<0.1) (Table 4).

Discussion

We are the first retrospective cohort study to use mediation effect analysis to explore possible mechanisms of the obesity paradox in HF. First, we found that high BMI level was associated with lower rate of endpoint events and this result validates the obesity paradox. Second, there are a mediating role for lipid levels especially triglycerides in all-cause death, cardiovascular death and

Table 4 Results of mediation effects analysis in the range of BMI≤24kg/m^2

variables	Model 1[a]		Model 2[b]		Model 3[c]	
	Percentage of mediation effect	P value	Percentage of mediation effect	P value	Percentage of mediation effect	P value
All-cause death						
TG	3.9 (0.7,0.84)	0.1201	2.9 (0.3,23.5)	0.1889	3.6 (1.0,12.2)	0.0599*
TC	3.4 (0.7,14.5)	0.0922*	2.9 (0.5,15.4)	0.1250	2.3 (0.3,14.2)	0.1473
HDL-C	-	-	-	-	-	-
LDL-C	1.1 (0.0,39.0)	0.3120	-	-	1.1 (0.0,21.4)	0.2672
Apo-AI	1.4 (0.0,81.2)	0.3647	3.1 (0.2,34.4)	0.2367	1.1 (0.0,68.7)	0.3521
Apo-B	-	-	-	-	-	-
CV death						
TG	3.5 (0.4,25.0)	0.1794	3.3 (0.3,27.1)	0.1995	3.8 (0.9,15.5)	0.0922*
TC	2.9 (0.4,17.1)	0.1471	2.9 (0.4,18.3)	0.1559	2.6 (0.3,18.1)	0.1645
HDL-C	-	-	-	-	-	-
LDL-C	-	-	-	-	1.1 (0.0,35.4)	0.3061
Apo-AI	1.4 (0.0,95.0)	0.3929	3.9 (0.3,36.1)	0.2230	3.1 (0.2,29.5)	0.2142
Apo-B	-	-	-	-	-	-
MACCEs						
TG	5.0 (1.1,20.2)	0.0867*	3.7 (0.5,23.2)	0.1556	4.4 (1.2,14.5)	0.0535*
TC	4.8 (1.4,15.1)	0.0407*	4.4 (1.2,15.1)	0.0527*	4.4 (1.1,16.3)	0.0650*
HDL-C	-	-	-	-	-	-
LDL-C	4.0 (1.0,14.6)	0.0598*	3.3 (0.7,14.7)	0.0931*	4.4 (1.1,16.1)	0.0621*
Apo-AI	-	-	1.9 (0.1,22.9)	0.2311	-	-
Apo-B	4.3 (1.0,17.2)	0.0804*	3.1 (0.4,19.0)	0.1480	4.8 (1.2,16.9)	0.0609*

* p<0.1

[a] Model 1 unadjusted

[b] Model 2 adjusted for age, sex

[c] Model 3 adjusted for age, sex, LVEF hypertension, DM eGFR, CRP

MACCEs, which mediate the causal relationship between BMI and outcomes.

Heart failure, as a multifaceted clinical syndrome, is caused by structural or functional abnormalities in the heart that result in diminished cardiac output and/or heightened intracardiac pressure [11, 13]. Despite notable progress in medical therapy and revascularization approaches, HF remains an escalating worldwide epidemic. The global prevalence of HF has surged from 33.5 million in 1990 to 64.3 million in 2017 [14]. The annual incidence of HF in Europe and North America is estimated to range from 2 to 3 per 1000 individuals, with a notable increase in occurrence among older age groups [15]. In China, presently, it is estimated that approximately 330 million individuals are affected by cardiovascular diseases, including 8.9 million individuals with HF [16]. Obesity is characterized by BMI exceeding 30kg/m^2 and the excessive accumulation of adipose tissue(AT) in various regions of the body [17]. Data from the *U.S. Health and Nutrition Examination Survey* reveals that the prevalence of obesity among American adults has already reached a rate of 42.4 percent [18]. A majority of adults is afflicted with overweight or obesity in China [19]. Additionally, obesity is recognized as a significant risk factor for various ailments including cardiovascular disease, diabetes, hypertension and fatty liver, which it has emerged as a pressing health concern [20–22]. Obesity is a contributing factor to the onset of HF due to its detrimental impact on the functioning of the left ventricle [23]. The presence of obesity can induce modifications in the structure and function of the cardiac muscle, resulting in compromised myocardial performance, cardiac hypertrophy, and ultimately HF [24]. Furthermore, obesity holds significant relevance as a risk factor for HF, irrespective of whether it presents as heart failure with preserved ejection fraction (HEpEF) or heart failure with reduced ejection fraction (HErEF) [25].

However, within individuals with HF, patients with a higher BMI do not exhibit a worse prognosis, and even their prognosis may be more favorable compared to those with a normal or low BMI. This paradox is known as the obesity paradox. The initial discovery of this phenomenon was made by Horwich et al [26] in a study. Their findings indicated that HF patients with higher BMI levels exhibited higher survival rates. Numerous studies conducted in recent years [27–30] have consistently demonstrated that obesity confers a favorable outcome in HF patients, which it may potentially offer a certain degree of protection. Moreover, obesity exhibited a reduction in mortality rates among patients regardless of both HFrEF and HFpEF [31]. In this study, we included LVEF as confounders in models, including Cox regression models and mediation models, and obtained the same results. Furthermore, multivariate Cox models were constructed in HFrEF+HFmrEF and HFpEF groups to explore the association between BMI level and outcome events and the obesity paradox was found in both groups (Additional file 1 **Table S7**). The phenomenon of the obesity paradox has been observed in Chinese populations with HF [8]. For instance, a study conducted by Hao Sufang et al [7] revealed that BMI can independently predict mortality in HF patients, with low BMI being associated with higher mortality rates. We similarly obtained comparable results in Chinese HF patients, meaning that the findings are consistent with those in Europe and the United States. Several studies have employed alternative approaches to evaluate obesity among individuals with HF, such as fat content and body surface area (BSA). These studies have examined obesity using other metrics outside BMI, and they have also produced outcomes that the obesity paradox.

There must be some mechanism underlying this strange phenomenon. Lipoproteins, which consist of lipids and proteins, play a crucial role in the transportation of triglycerides and cholesterol within the bloodstream [32], as well as it is frequently utilized to evaluate the risk of patients [33]. For example, since HDL particles carry molecules other than Apo1 (superoxide dismutase, sphingosine-1-phosphate), this makes HDL more potent than HDL-C in terms of antioxidant, anti-inflammatory, and anti-apoptotic functions. Hence, HDL may provide better prognostic information [34, 35]. The endotoxin-lipoprotein hypothesis, proposed in a study conducted by Niebauer et al offers a potential explanation for the obesity paradox [10]. Immune activation in inflammatory diseases is facilitated by bacterial lipopolysaccharide, which can cause these diseases to progress in a harmful direction [36]. Bacterial endotoxin is a potent trigger for the discharge of inflammatory cytokines by circulating immune cells, which the source of immune activation of chronic heart failure may be attributed to bacterial endotoxin, thereby exacerbating the condition of chronic heart failure [37]. However, elevated levels of cholesterol may confer benefits in the context of chronic heart failure. This is due to the capacity of circulating lipoproteins and triglyceride lipoproteins to bind and detoxify bacterial endotoxins, thereby those play a role in modulating immune function and safeguarding the body against bacterial endotoxins. In addition, aerobic exercise, smoking cessation, balanced diet and other healthy activities can increase the level of HDL-C, and these healthy activities may also bring certain benefits to patients [38]. Our study found that both TC and apo-B showed strong mediating effects before adjusting for confounders. In contrast, this mediating effect of TC became insignificant in Models 2 and 3 and possibly related to the smaller sample size.

There appears to be an obesity paradox regardless of whether patients are taking statins or not (Additional file 1 **Table S4**). This poses a challenge that the interpretation of lipid levels may be influenced by the sample size and by other possible mechanisms, which need to be further studied in the future. In obese individuals, the presence of circulating lipoproteins with higher cholesterol levels may effectively counteract inflammatory endotoxins and impede the inflammatory response, ultimately mitigating cardiac inflammation and offering cardiovascular protection [5, 10, 39]. Similarly, in the mediation model we constructed, it can be found that TG is an influential factor that exerts the strongest mediating effect. It was also found that the mediating effect of TG was more pronounced in patients with HFrEF+HFmrEF and without MI (Additional file 1 **Table S6**), which provided more detailed patient grouping information (such as different types of HF and comorbidities) for further understanding the mechanism of the obesity paradox. In conclusion, the protective mechanism of high lipoprotein levels in obese patients may be an explanation for the obesity paradox.

As such, it is imperative that we concentrate on the obesity paradox in HF and the potential mechanisms behind it. This study provides a foundation for further research aimed at deciphering the mechanism underlying the obesity paradox. In the meantime, our research will contribute to a better understanding of obese patients with HF and offer a solid scientific basis for improving their long-term prognosis.

Limitations

The limitations of this study are as follows. First, the retrospective study itself suffered from recall bias of patients, which may have led to inappropriate grouping. Second, only the BMI at admission was calculated without focusing on the changes during follow-up. Third, we only used the BMI to assess the obesity status and did not measure their metabolic status, waist-to-hip ratio. Fourth, single-center findings do not apply well to all HF patients. Therefore, it is necessary to conduct further large prospective cohort studies to confirm our findings.

Conclusion

In conclusion, this research provides evidence supporting the obesity paradox, highlighting the protective nature of obesity for HF. Additionally, the mediating role of lipoprotein levels, especially TG, elucidates a potential mechanism for the protective effect of obesity on HF.

Abbreviations

HF	Heart failure
CHF	Chronic heart failure
BMI	Body mass index
MACCEs	Major adverse cardiac and cerebral events
TG	Triglyceride
TC	Total cholesterol
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
Apo-A1	Apolipoprotein A1
Apo-B	Apolipoprotein B
CHD	Coronary heart disease
AF	Atrial fibrillation
NYHA	New york heart association
HR	Heart rate
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor inhibitor
ARIN	Angiotensin receptor neprilysin inhibitor
SGLT2i	sodlum-glucose cotransporter 2 inhibitor
ALB	Albumin
GLB	Globulin
UA	Uric acid
Cr	Creatinine
CRP	C-creative protein
eGFR	Estimated glomerular filtration rate
WBC	White blood cell
GRA	Granulocyte
RBC	Red blood cell
HGB	Hemoglobin
PLT	Platelet count
BNP	B-type natriuretic peptide
HbA1c	Hemoglobin A1c
LVEF	Left ventricular ejection fraction
IVSTd	Interventricular septal thickness at diastole
LVPWTd	Left ventricular posterior wall end-diastolic thickness
LVDd	Left ventricular end-diastolic diameter
LAD	Left atrial diameter
LDH	Lactate dehydrogenase
TBIL	Total bilirubin
MRA	Mineralocorticoidreceptor
CCB	Calcium channel blocker
AT	Adipose tissue
HEpEF	Heart failure with preserved ejection fraction
HErEF	Heart failure with reduced ejection fraction
BSA	Body surface area
LPS	Lipopolysaccharide

Supplementary Information

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Additional file1 (PDF 299 KB)

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Author contributions

YW: Writing-original draft, Methodology. XLL and BCW: Data curation. XT, LC, HYC and ZYZ: Investigation. XB, BX and RG: Writing-review & editing, Supervision. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials
The information and data of the study population were extracted from the hospital information system. The datasets are not publicly available because the privacy of the participants should be protected. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The need for informed consent was waived by Nanjing Drum Tower Hospital ethical committee because of the retrospective nature of the study.This was a retrospective study in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Nanjing Drum Tower Hospital(2023-428-01).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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