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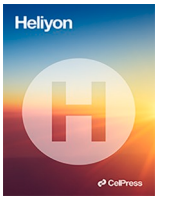

Research article

Body mass index and clinical outcomes in patients with heart failure with preserved ejection fraction mediated by diastolic blood pressure status?

YingQiu Hu [a,*,1], ZhenBang Gu [b,1], MeiLing Xu [c], WenFeng He [d], LiDong Wu [a], ZhiCheng Xu [e,**], LinJuan Guo [e]

[a] *Emergency Department of the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China*
[b] *Medical School of Nanchang University, Nanchang, Jiangxi, China*
[c] *Urology Department of the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China*
[d] *Department of Medical Genetics, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China*
[e] *Department of Cardiology, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, Jiangxi, China*

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ABSTRACT

Background: The "obesity paradox" has been elucidated in patients with heart failure (HF). Current guidelines introduce a target diastolic blood pressure (DBP) < 80 mmHg but >70 mmHg in HF patients. Due to reduced coronary perfusion, low DBP has a deleterious impact on cardiovascular outcomes. This present study aimed to assess the relationship between BMI and adjudicated clinical outcomes in HFpEF patients according to the status of DBP.

Methods: We analyzed the data in 1749 HFpEF patients from the Americas of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) Trial. The population was stratified by DBP (<70 mmHg, and ≥70 mmHg) and BMI strata (normal weight, overweight, and obesity). Cox proportional hazards models and competing-risks regression analysis were performed.

Results: At baseline, the median BMI and DBP were 32.9 kg/m^2 (interquartile range 28.0–38.5 kg/m^2) and 70 mmHg (interquartile range 62–80 mmHg), respectively. In the multivariable analysis, obesity was associated with better survival rates in the total HFpEF population (all-cause death: HR = 0.439, 95% CI 0.256–0.750; and cardiovascular death: HR = 0.378, 95% CI 0.182–0.787). In patients with DBP<70 mmHg, obesity was not significantly associated with reduced risks for

Abbreviations: HF, heart failure; DBP, diastolic blood pressure; BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; eGFR, estimated glomerular filtration rate; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; ISH, International Society Hypertension; NHLBI, National Heart, Lung, and Blood Institute; BNP, type B natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; SBP, systolic blood pressure; MI, myocardial infarction; HR, heart rate; EF, ejection fraction; NYHA, New York Heart Association; PAD, peripheral artery disease; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; CCB, calcium channel blocker; BP, blood pressure; LV, left ventricle; IR, insulin resistance; LVDD, left ventricle diastolic dysfunction.

* Corresponding author.
** Corresponding author.
E-mail addresses: 19979088619@163.com (Y. Hu), 1306680982@qq.com (Z. Gu), 619693059@qq.com (M. Xu), fengfeng_982366@126.com (W. He), 414442021@qq.com (L. Wu), 532141796@qq.com (Z. Xu), 727456372@qq.com (L. Guo).
[1] Co-first authors: YingQiu Hu and ZhenBang Gu.

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all-cause death (HR = 0.531, 95% CI: 0.263–1.704) and cardiovascular death (HR = 0.680, 95% CI: 0.254–1.819). However, multivariate analyses for cardiovascular death (HR = 0.339, 95% CI: 0.117–0.983) and all-cause death (HR = 0.389, 95% CI: 0.156–0.969) were significant in patients with DBP≥70 mmHg. Nevertheless, there were no interactions between DBP and BMI.
Conclusions: The obesity paradox was observed in patients with HFpEF, regardless of DBP strata (<70 mmHg, and ≥70 mmHg).

1. Introduction

Heart failure (HF) continues to be a serious public health problem worldwide, and the number of HF cases worldwide almost doubled from 33.5 million in 1990 to 64.3 million in 2017 [1]. Obesity has now reached the epidemic proportion and adversely impacted cardiovascular health [2,3], especially the deleterious effects on cardiovascular structure and increased HF incidence across the ejection fraction spectrum [4]. Despite the increased prevalence of HF in obese individuals, substantial evidence indicates that obesity may confer a survival benefit in patients with established HF regardless of left ventricular ejection fraction, a phenomenon termed the 'obesity paradox' [2,4–7], while the exact mechanisms remain poorly understood. One possible explanation is that obese individuals always get earlier diagnoses and prompt HF treatments, therefore having a better prognosis [8,9]. In addition, obese patients may have better metabolic profiles, higher cardiorespiratory fitness levels, and increased various anti-inflammatory adipokines [8,9]. Given the heterogeneity of HF, recent efforts have been made to better characterize the BMI effects in specific subgroups, suggesting that the obesity paradox in HF could be modified by etiology and coexisting comorbidities [10–12]. The paradoxical relationship between BMI and mortality might not be evident in ischemic HF patients or HF patients with diabetes mellitus [11,13].

The relationship between diastolic blood pressure (DBP) and myocardial perfusion has been proved, as primary coronary blood flow occurs during diastole [14–16]. A fall in DBP has been shown to reduce coronary perfusion pressure, resulting in ischemia and myocardial damage [15,16]. Although elevated DBP is well established as a risk factor for cardiovascular disease, J-curve association between DBP and outcomes occurred in those specified cardiovascular diseases [16,17]. An analysis of patients with acute myocardial infarction showed that lower DBP<70 mmHg was associated with an increased risk for death [16]. Also, there was an increased risk of morbidity and mortality in patients at high cardiovascular risks with DBP<70 mmHg [17]. The recently published 2020 ISH (International Society Hypertension) guideline recommended a target DBP of<80 mmHg but >70 mmHg in patients with HF [18]. Nevertheless, whether the prognostic benefits of obesity in HF could be affected by the DBP remains unclear.

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous condition, representing approximately 50% of all HF cases. Herein, we hypothesized that the DBP could modify the association between BMI and cardiovascular outcomes in HFpEF patients. Based on the data from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, we aimed to assess the relationship between BMI and adjudicated clinical outcomes in HFpEF patients according to the status of DBP.

2. Materials and methods

2.1. Study design and patients

The TOPCAT trial was conducted with the approval of local institutional review boards. The design and the primary findings of this trial have been previously described in detail [19,20]. Between August 2006 and January 2012, a total of 3445 patients who suffered symptomatic HF with left ventricular ejection fraction of at least 45% were enrolled at 270 sites in the Americas, Russia, and Georgia. Each patient provided written informed permission, and each participating center's institutional review board authorized the protocol. By contacting the Biologic Specimen and Data Repository Information Coordinating Center and submitting an application, the data set was received from the National Heart, Lung, and Blood Institute (NHLBI) (BIOLINCC, https://biolincc.nhlbi.nih.gov) (applied by Dr. Guo LJ, Jiangxi Provincial People's Hospital). Patients aged ≥50 years were included if they had undergone hospitalization for HF during the previous year or had an increased natriuretic peptide level (BNP ≥100 pg/mL or N-terminal pro-BNP ≥360 pg/mL) within the 60 days of screening and controlled blood pressure (defined as a target systolic blood pressure of <140 mmHg or ≤160 mmHg if the patient was taking more than three medications to control hypertension). Patients with a life expectancy of fewer than three years, history of severe hyperkalemia, estimated glomerular filtration rate (eGFR) < 30 mL/min per 1.73 m^2, known infiltrative or hypertrophic cardiomyopathy were excluded in the TOPCAT trial.

2.2. Selected population

As there are racial disparities in patient demographics and event rates between patients from the Americas versus Russia and Georgia [21], our current analysis was limited to the patients from the American cohort (including the US, Canada, Argentina, and Brazil). Body mass index (BMI, calculated as weight in kilograms divided by square height in meters [kg/m2]) is the most widely used classification of obesity and correlates with total fat mass [22]. Based on the World Health Organization classification of BMI, patients were divided into three groups: normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥30 kg/m^2) [23]. Notably, underweight patients (BMI<18.5 kg/m^2) accounted for only a minority of the whole population, and they might have 'cardiac

Table 1
Baseline characteristics distribution among the categories of BMI and DBP.

	Whole cohort (n = 1749)	Group with DBP < 70 mmHg (n = 739)				Group with DBP ≥ 70 mmHg (n = 1010)			
		Normal weight (n = 107)	Overweight (n = 168)	Obesity (n = 464)	P value	Normal weight (n = 101)	Overweight (n = 238)	Obesity (n = 671)	P value
Demographics									
Age, years	72.0 (64.0–79.0)	78.0 (70.0–84.0)	77.5 (72.0–83.0)	71.0 (64.0–78.0)	<0.001	79.0 (71.5–83.5)	75.0 (66.8–81.0)	68.0 (61.0–76.0)	<0.001
Female, n (%)	874 (50.0%)	56 (52.3%)	72 (42.9%)	218 (47.0%)	0.305	58 (57.4%)	110 (46.2%)	360 (53.7%)	0.079
White race, n (%)	1371 (78.4%)	89 (83.2%)	143 (85.1%)	378 (81.5%)	0.555	81 (80.2%)	193 (81.1%)	487 (72.6%)	0.016
Smoker					0.006				0.945
Non-smokers, n (%)	45 (42.06%)	74 (44.05%)	167 (35.99%)	45 (42.06%)		46 (45.54%)	103 (43.28%)	308 (45.97%)	
Current smoker, n (%)	12 (11.21%)	8 (4.76%)	19 (4.09%)	12 (11.21%)		8 (7.92%)	20 (8.40%)	48 (7.16%)	
Previous smoker, n (%)	50 (46.73%)	86 (51.19%)	278 (59.91%)	50 (46.73%)		47 (46.53%)	115 (48.32%)	314 (46.87%)	
Alcohol drinks, per/week					<0.001				0.014
0	1293 (73.9%)	69 (64.5%)	107 (63.7%)	360 (77.6%)		85 (84.16%)	163 (68.49%)	509 (76.20%)	
1–4	321 (18.4%)	24 (22.43%)	40 (23.81%)	81 (17.46%)		14 (13.86%)	50 (21.01%)	112 (16.77%)	
≥5	135 (7.7%)	15 (14.02%)	22 (13.10%)	24 (5.17%)		2 (1.98%)	25 (10.50%)	47 (7.04%)	
Physical and laboratory examination									
SBP, mmHg	129 (118–138)	114.0 (102.0–124.0)	120.0 (110.0–130.0)	120.0 (110.0–132.0)	<0.001	130.0 (120.0–140.0)	131.0 (121.0–140.0)	134.0 (124.0–142.0)	0.005
DBP, mmHg	70 (62–80)	60 (56–64)	60 (58–66)	61 (59–65)	0.040	78.0 (72.0–80.0)	79.5 (72.0–82.0)	80.0 (74.0–84.0)	0.002
HR, bpm	68.0 (61.0–76.0)	65.0 (60.0–74.0)	64.0 (59.3–72.0)	66.5 (60.0–75.0)	0.062	70.0 (62.0–77.5)	68.0 (60.8–76.0)	70.0 (63.0–80.0)	0.001
BMI, kg/m^2	32.9 (28.0–38.5)	22.5 (21.3–23.7)	27.2 (26.2–28.5)	36.5 (33.0–41.8)	<0.001	23.5 (22.5–24.4)	28.1 (26.6–29.0)	36.6 (33.2–41.2)	<0.001
NYHA class, n (%)					<0.001				0.015
I–II	1133 (64.8%)	74 (69.2%)	122 (72.6%)	255 (55.0%)		71 (70.3%)	179 (75.2%)	432 (64.4%)	
III–IV	613 (35.0%)	33 (30.8%)	46 (27.4%)	207 (44.6%)		30 (29.7%)	59 (24.8%)	238 (35.5%)	
EF (%)	58.0 (52.5–64.0)	56.0 (52.0–60.0)	59.0 (50.3–64.8)	59.0 (52.0–63.0)	0.538	57.0 (50.0–65.0)	57.0 (51.0–63.3)	58.0 (54.0–65.0)	0.327
eGFR, mL/min*1.73 m^2	61.2 (49.0–76.5)	62.8 (47.3–73.7)	58.8 (45.6–75.3)	57.1 (46.2–70.5)	0.228	61.4 (52.1–79.2)	61.6 (50.8–76.8)	64.8 (51.2–80.7)	0.141
BNP, pg/ml	253.0 (149.0–440.0)	298.0 (200.0–597.0)	311.0 (159.0–624.0)	245.0 (145.8–389.8)	0.010	365.0 (197.0–504.0)	250.0 (153.0–468.0)	239.0 (138.5–423.0)	0.094
Comorbidities									
Previous HF Hospitalization, n (%)	1032 (59.0%)	57 (53.3%)	83 (49.4%)	290 (62.5%)	0.007	48 (47.5%)	120 (50.6%)	434 (64.7%)	<0.001
Previous MI, n (%)	357 (20.4%)	24 (22.4%)	50 (29.8%)	109 (23.5%)	0.227	13 (12.9%)	39 (16.5%)	122 (18.2%)	0.393
Ischemic heart diseases, n (%)	651 (37.2%)	45 (42.1%)	79 (47.0%)	203 (43.8%)	0.677	26 (25.7%)	84 (35.3%)	214 (31.9%)	0.223
Previous stroke, n (%)	158 (9.0%)	10 (9.4%)	14 (8.3%)	50 (10.8%)	0.645	8 (7.9%)	17 (7.2%)	59 (8.8%)	0.731
PAD, n (%)	203 (11.6%)	12 (11.2%)	18 (10.7%)	76 (16.4%)	0.121	10 (9.9%)	21 (8.9%)	66 (9.8%)	0.904
DM, n (%)	785 (44.9%)	24 (22.4%)	62 (36.9%)	264 (56.9%)	<0.001	16 (15.8%)	75 (31.7%)	344 (51.3%)	<0.001
HTN, n (%)	1575 (90.0%)	86 (80.4%)	148 (88.1%)	416 (89.7%)	0.029	85 (84.2%)	209 (88.2%)	631 (94.0%)	<0.001
Dyslipidemia, n (%)	1244 (71.1%)	67 (62.6%)	125 (74.4%)	362 (78.0%)	0.004	53 (52.5%)	162 (68.4%)	475 (70.8%)	0.001
COPD, n (%)	287 (16.4%)	19 (17.8%)	28 (16.7%)	86 (18.5%)	0.862	15 (14.9%)	28 (11.8%)	111 (16.5%)	0.218
Atrial fibrillation	752 (43.0%)	49 (45.8%)	79 (47.0%)	191 (41.2%)	0.354	43 (42.6%)	110 (46.2%)	280 (41.7%)	0.484
Treatments									
Spironolactone, n (%)	882 (50.4%)	50 (46.7%)	73 (43.5%)	242 (52.2%)	0.129	53 (52.5%)	126 (52.9%)	338 (50.4%)	0.764
Diuretics, n (%)	1557 (89.0%)	93 (86.9%)	146 (86.9%)	430 (92.9%)	0.027	80 (79.2%)	193 (81.1%)	615 (91.7%)	<0.001
Beta blocker, n (%)	1376 (78.7%)	88 (82.2%)	137 (81.6%)	380 (82.1%)	0.986	73 (72.3%)	185 (77.7%)	513 (76.5%)	0.554
Statin, n (%)	1141 (65.2%)	62 (57.9%)	119 (70.8%)	346 (74.7%)	0.002	49 (48.5%)	142 (59.7%)	423 (63.0%)	0.019
ACEI/ARB, n (%)	1382 (79.0%)	71 (66.4%)	121 (72.0%)	377 (81.4%)	0.001	71 (70.3%)	183 (76.9%)	559 (83.3%)	0.002
CCB, n (%)	674 (38.5%)	33 (30.8%)	67 (39.9%)	184 (39.7%)	0.214	33 (32.7%)	77 (32.4%)	280 (41.7%)	0.017
Warfarin, n (%)	587 (33.6%)	38 (35.5%)	63 (37.5%)	146 (31.5%)	0.332	33 (32.7%)	86 (36.1%)	221 (32.9%)	0.652
Aspirin, n (%)	1023 (58.5%)	65 (60.8%)	98 (58.3%)	300 (64.8%)	0.299	46 (45.5%)	133 (55.9%)	381 (56. 8%)	0.105

EF, ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; DM, diabetes mellitus; HTN, hypertension; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; BNP, type B natriuretic peptide; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blocker; CCB, calcium channel blocker.

cachexia' known to be associated with worse prognosis, those classified as underweight (n = 8) were excluded from the following analysis. Furthermore, we classified patients into two categories (baseline DBP < 70 mmHg, and ≥70 mmHg), based on several studies reporting that DBP less than 70 mmHg was associated with increased risks of cardiovascular events [14,17,18,24].

2.3. Clinical outcomes

Patients from the TOPCAT trial were followed for a mean period of 3.3 years. The primary outcome was a composite outcome of

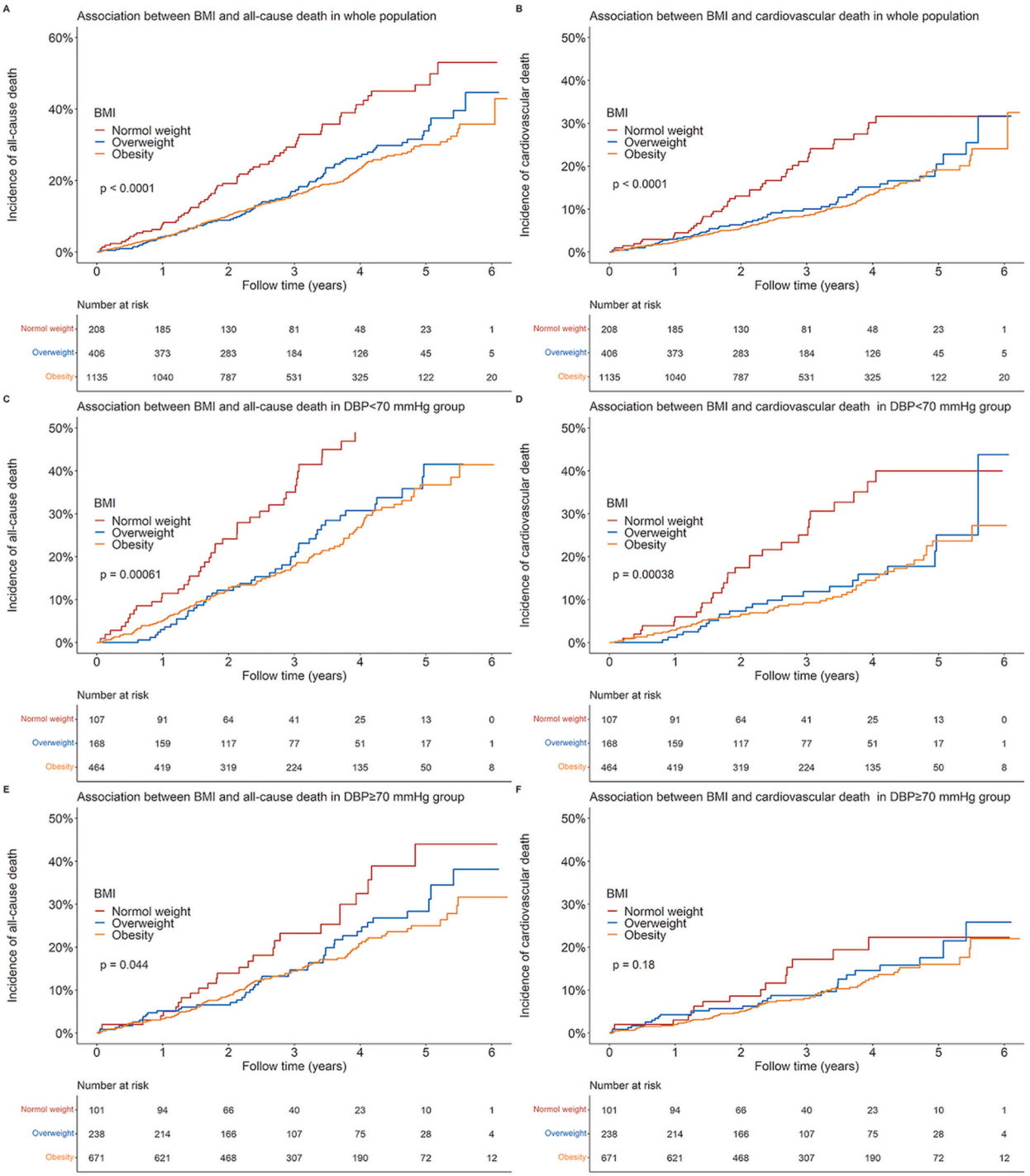

Fig. 1. Clinical outcomes comparisons between DBP category according to BMI category. DBP = diastolic blood pressure; BMI = body mass index.

aborted cardiac arrest and HF hospitalization, as reported previously. The secondary outcomes included HF hospitalization, any hospitalization, cardiovascular death and all-cause death. Results were tracked during the follow-up by interactions with the individuals and inspections of their medical records at the clinic. Each event's adjudication was made separately by the Clinical Endpoints Center.

2.4. Statistical analysis

The demographic and clinical characteristics were presented as counts and percentages for categorical variables or as the means with standard deviations (normal distribution) or medians with interquartile ranges (non-normal distribution) for continuous variables. For the purposes of analysis, we stratified the included population by DBP strata (<70 mmHg, and ≥70 mmHg) and then considered 3 BMI groups: normal weight, overweight and obesity. The intergroup differences were assessed using the Person chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Clinical outcomes were described as events per 100 patient-years, and cumulative rates were illustrated graphically with plots indicating the number of patients at risk for each event. Kaplan-Meier estimates were used to examine the unadjusted cumulative incidence estimates of mortality in patients with different BMI groups stratified by DBP. The crude and multivariable-adjusted hazard ratios with their 95% confidence interval for clinical outcomes were estimated by using Cox regression models and Fine and Gray's competing risk models. Death was the competing risk in models concerning any hospitalization, HF hospitalization and primary composite outcome, and non-cardiovascular death was the competing risk for cardiovascular death. Adjustments were performed for age, gender, HR, SBP, smoker, alcohol, New York Heart Association class, previous HF hospitalization, previous stroke, diabetes mellitus, hypertension, atrial fibrillation, peripheral artery disease, previous MI, eGFR, dyslipidemia, diuretics, statin, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blocker (ARB), type B natriuretic peptide.

It was decided that statistical significance was indicated by a 2-sided P value of <0.05. GraphPad Prism 6.0 and IBM SPSS 26 (IBM, NY, USA) programs with a graphical user interface were used to run the statistical analyses. R version 4.1.1 (survival and cmprsk) was also performed.

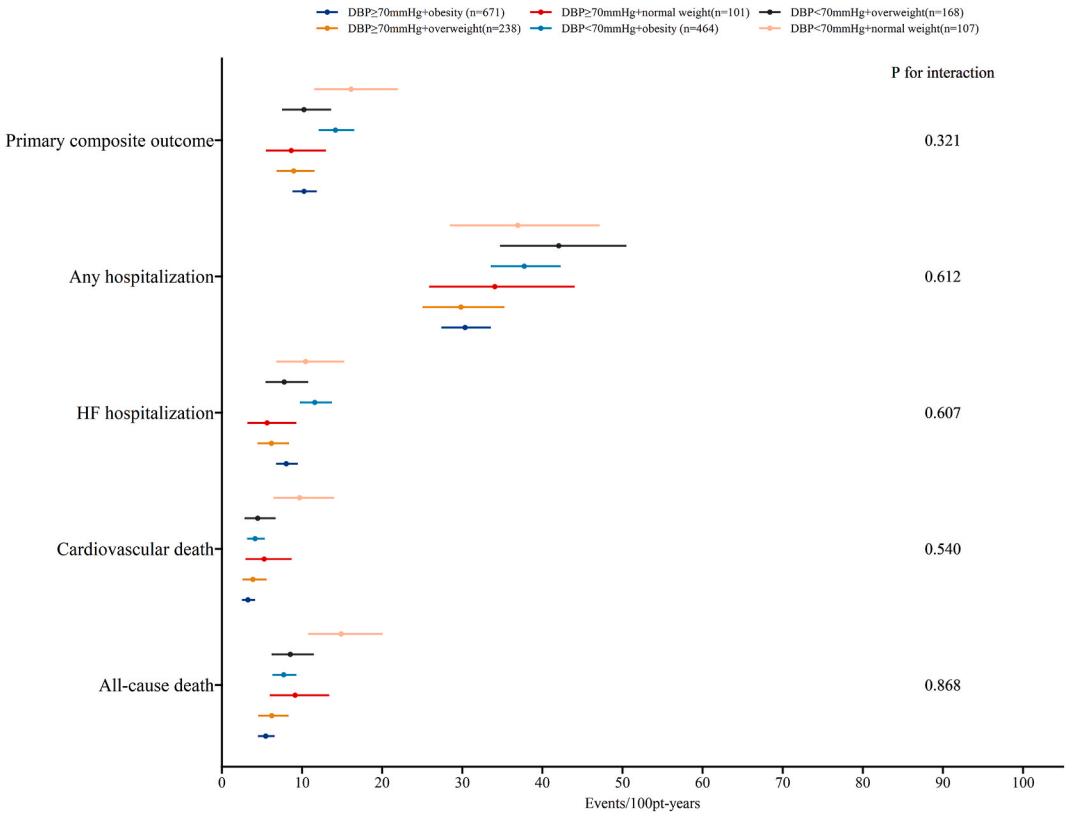

Fig. 2. The incidence of clinical outcomes between DBP category. DBP = diastolic blood pressure; HF = heart failure.

3. Results

3.1. Baseline characteristics

We excluded patients without baseline BMI and BP values (n = 10) and underweight patients (BMI<18.5 kg/m^2, n = 8). The studied population consisted of 1749 (median age, 72 years; 50% female; 78.4% white) participants from the American population. The overall mean follow-up was 3.0 ± 1.5 years. At baseline, the median BMI and DBP were 32.9 kg/m^2 (interquartile range 28.0–38.5 kg/m^2) and 70 mmHg (interquartile range 62–80 mmHg), respectively (Supplementary Fig. 1).

Table 1 presents the demographic and clinical characteristics of the study population grouped by baseline DBP and BMI categories. In DBP < 70 mmHg group, the overweight/obese subjects were younger, and had more proportion of diabetes mellitus, hypertension, and dyslipidemia. Whereas normal weight subjects appeared older, and had less proportion of diuretics, statin, and ACEI/ARB. Furthermore, obese patients had higher blood pressure and lower BNP values, and were enrolled more frequently through the HF hospitalization stratum. The results were similar in the DBP ≥ 70 mmHg group. Despite the level of DBP, the distribution of spironolactone treatment was similar across the BMI stratum.

3.2. BMI and clinical outcomes in patients stratified by DBP status

Compared with those in the higher DBP category (DBP ≥ 70 mmHg), patients with DBP < 70 mmHg were more likely to suffer adverse clinical outcomes across all the BMI groups (Fig. 1). The occurrence of HF hospitalization was similar between DBP < 70 mmHg (10.43 vs. 7.78 vs. 11.59 events per 100 patient-years) and DBP ≥ 70 mmHg group (5.64 vs. 6.18 vs. 8.03 events per 100 patient-years). The occurrences of all-cause death (P < 0.001) and cardiovascular death (P < 0.001) were significantly different according to the BMI and DBP status. For patients with DBP<70 mmHg, the incidence of cardiovascular death was 9.70 (95% CI: 6.44 to 14.01) per 100 patient-years in patients with normal weight, 4.47 (95% CI: 2.83 to 6.70) per 100 patient-years in overweight patients,

Table 2
Cox regression and competing risk regression analysis for outcomes in HFpEF patients according to the DBP levels.

	Total (N = 1749)		DBP < 70 mmHg (N = 739)		DBP ≥ 70 mmHg (N = 1010)	
	Unadjusted HR (95% CI)	Adjusted HR[#] (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[※] (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[☆] (95% CI)
Primary composite outcome						
Normal weight	Reference	Reference	Reference	Reference	Reference	Reference
Overweight	0.809 (0.593, 1.104)	0.793 (0.469, 1.342)	0.665 (0.437, 1.012)	0.610 (0.294, 1.268)	1.066 (0.660, 1.722)	1.180 (0.540, 2.580)
Obesity	1.001 (0.764, 1.312)	1.120 (0.669, 1.873)	0.930 (0.656, 1.320)	0.988 (0.476, 2.050)	1.200 (0.778, 1.852)	1.532 (0.676, 3.472)
Any hospitalization						
Normal weight	Reference	Reference	Reference	Reference	Reference	Reference
Overweight	1.026 (0.830, 1.267)	0.927 (0.659, 1.304)	1.156 (0.854, 1.566)	1.077 (0.632, 1.837)	0.945 (0.705, 1.268)	0.867 (0.536, 1.404)
Obesity	1.000 (0.825, 1.212)	0.967 (0.686, 1.363)	1.085 (0.824, 1.428)	1.055 (0.618, 1.802)	0.956 (0.731, 1.250)	0.897 (0.543, 1.482)
HF hospitalization						
Normal weight	Reference	Reference	Reference	Reference	Reference	Reference
Overweight	0.925 (0.633, 1.352)	1.124 (0.564, 2.240)	0.820 (0.495, 1.361)	0.974 (0.369, 2.570)	1.140 (0.632, 2.054)	1.304 (0.481, 3.536)
Obesity	1.265 (0.908, 1.762)	1.626 (0.817, 3.235)	1.213 (0.791, 1.861)	1.185 (0.430, 3.268)	1.467 (0.861, 2.498)	2.234 (0.808, 6.179)
All-cause death						
Normal weight	Reference	Reference	Reference	Reference	Reference	Reference
Overweight	0.602 (0.440, 0.825)	0.404 (0.231, 0.704)	0.571 (0.375, 0.870)	0.411 (0.181, 0.936)	0.700 (0.433, 1.131)	0.457 (0.205, 1.019)
Obesity	0.527 (0.402, 0.693)	0.439 (0.256, 0.750)	0.505 (0.353, 0.722)	0.531 (0.263, 1.074)	0.610 (0.398, 0.935)	0.389 (0.156, 0.969)
Cardiovascular death						
Normal weight	Reference	Reference	Reference	Reference	Reference	Reference
Overweight	0.561 (0.372, 0.845)	0.320 (0.140, 0.730)	0.471 (0.270, 0.821)	0.168 (0.044, 0.644)	0.739 (0.393, 1.388)	0.496 (0.157, 1.564)
Obesity	0.493 (0.347, 0.701)	0.378 (0.182, 0.787)	0.441 (0.279, 0.699)	0.680 (0.254, 1.819)	0.618 (0.352, 1.086)	0.339 (0.117, 0.983)

Adjusted by age, gender, HR, SBP, smoker, alcohol, NYHA class, previous HF hospitalization, previous stroke, DM, HTN, AF, PAD, previous MI, CCB, dyslipidemia, diuretics, statin, ACIE/ARB, eGFR, BNP.

and 4.14 (95% CI: 3.14 to 5.35) per 100 patient-years in obese patients. Among patients with a DBP of <70 mmHg, the event rate of all-cause death increased as the BMI decreased (14.89 vs. 8.54 vs. 7.71) (Fig. 2). Similar relationships were observed for any hospitalization and the primary composite outcome (Fig. 2).

Results of univariate and multivariate Cox regression analysis and Fine and Gray's competing risk analysis are shown in Table 2. In the whole population, overweight or obesity was not associated with the primary composite outcome, any hospitalization, and HF hospitalization. However, an obesity-associated survival benefit was observed in the whole population of HEpEF patients. Obesity was associated with a reduced risk of all-cause death (HR = 0.439, 95% CI 0.256–0.750) and cardiovascular death (HR = 0.378, 95% CI 0.182–0.787). Similar results for overweight were observed (all-cause death: HR = 0.404, 95% CI 0.231–0.704; and cardiovascular death: HR = 0.320, 95% CI 0.140–0.730). Therefore, the 'obesity paradox' was found in the whole population with HFpEF.

Among the DBP < 70 mmHg group, compared with patients with normal weight, the adjusted HRs (95% CI) for cardiovascular death in overweight and obese weight were 0.168 (0.044–0.644) and 0.680 (0.254–1.819), respectively; and the adjusted HRs (95% CI) for all-cause death in overweight and obese weight were 0.411 (0.181–0.936) and 0.531 (0.263–1.074), respectively. In the DBP ≥ 70 mmHg group, the adjusted HRs (95% CI) for cardiovascular death in overweight and obese weight were 0.496 (0.157–1.564) and 0.339 (0.117–0.983), respectively; and the adjusted HRs (95% CI) for all-cause death in overweight and obese weight were 0.457 (0.205–1.019) and 0.389 (0.156–0.969), respectively. Nevertheless, there were no interactions between DBP and BMI (all $P_{interaction} \geq 0.05$).

4. Discussion

This was the first study to evaluate whether the obesity paradox would be affected by different DBP categories in patients with HFpEF from the TOPCAT trial [25]. The findings of the current analysis demonstrated that higher BMI was associated with better event-free survival in the whole HFpEF patients. The obesity paradox was observed in patients with HFpEF, regardless of DBP strata (<70 mmHg, and ≥70 mmHg).

Low DBP was common in HF patients and was associated with poor prognosis [18,26]. Previous studies demonstrated that the reduction of either systolic blood pressure or DBP could ameliorate overall cardiovascular risk [17,27,28]. Yet, concern has persisted that low DBP is inversely associated with cardiovascular outcomes [17,29,30]. The analyses from the ONTARGET and TRANSCEND trials exhibited that a lower DBP (<70 mmHg) was associated with higher risks of mortality, myocardial infarction, and HF hospitalization [17]. Protogerou et al. found that in subjects with uncontrolled systolic hypertension, DBP < 60 mmHg was harmful, and the optimal DBP level was 70 mmHg [30]. DBP is the determining factor of coronary perfusion pressure as myocardial perfusion occurs almost exclusively during diastole [16]. It is theoretically possible that any further reduction of DBP below the lower limit of coronary autoregulation could increase comorbidities and frailty [31].

The obesity-associated survival benefit in HF populations would be modified by many contributing factors [10–12,32,33]. Gentile et al. enrolled 5155 HF patients found that the prognostic benefit of obesity was maintained only in non-ischemic HF [10]. A study that enrolled 504 HF patients with a median follow-up of 6.1 years revealed that the obesity paradox was only observed in patients with non-ischemic HF [33]. However, another study indicated that patients classified as obese had the most favorable survival trends in both ischemic and non-ischemic HF [12]. As the strong association with DBP and ischemic heart disease, we sought to determine whether BMI had a different impact on survival in HFpEF patients with DBP < 70 mmHg versus DBP > 70 mmHg. Intriguingly, our analysis revealed that the mortality-obesity paradox phenomenon existed in both HFpEF patients with DBP < 70 mmHg and ≥70 mmHg.

In our study, overweight and obese patients were more likely to have hypertension, diabetes, peripheral artery disease, and previous hospitalization of HF, but they were younger. We speculated that overweight/obese patients presented symptoms in a less severe stage of disease and received earlier life-saving therapies [34]. In the American population from the TOPCAT trial, a larger proportion of obese and overweight patients were taking diuretics, statin, and ACEI/ARB. Overweight and obese patients had higher BP, which allowed a more intensive treatment with cardioprotective medications such as ACEI/ARB. Due to limited dilation of coronary resistance vessels when perfusion pressure decreases, low DBP (<70 mmHg) would aggravate cardiovascular prognosis [17,18,30,35]. A study reported that metabolically healthy obese individuals had significantly better fitness status compared to metabolically abnormal normal weights, which conferred beneficial effects on the cardiovascular system, including blood pressure regulation, myocardial oxygen demand, and endothelial function [5].

After accounting for the effects of BMI and blood pressure, a history of preeclampsia remains predisposed to a poorer LV diastolic function and decreased DBP in middle age, leading to an increased likelihood of developing HFpEF later in life, which possibly because of persistent cardiovascular risk as well as persistent endothelial dysfunction impediments [36]. The systemic and cardiac sympathetic activation observed in patients with HFpEF also suggests a similar possibility [37]. Optimizing pulmonary artery diastolic pressure using CardioMEMS improves metabolic co-morbidities in HFpEF [38]. Furthermore, overweight, diabetes mellitus and hypertension are potential contributors to insulin resistance (IR) in patients with HF, while the prevalence of prediabetes is higher in non-diabetic non-overweight normotensive HF patients, and both prediabetes and IR are associated with more severe HF, supporting HF as a major cause of IR [39]. IR is closely associated with type 2 diabetes. Patients with type 2 diabetes and HFpEF co-morbidities have a higher BMI, greater disease burden, and worse prognosis compared to patients without type 2 diabetes [40].

The critical mechanisms of HFpEF and diabetes mellitus are related to endothelial dysfunction. Mone et al. [41] found that empagliflozin modulated the expression of circulating microRNAs involved in the regulation of endothelial function in frail patients with HFpEF and diabetes mellitus. The study by van Ommen et al. [42] reviewed the risk factors and mechanisms that might contribute to the gender-specific progression of left ventricle diastolic dysfunction (LVDD) to HFpEF, suggesting that the risk factors for

hypertension, diabetes and obesity were more important for females. The lifestyle interventions might have greater benefits in reducing females' risk of progression from LVDD to HFpEF [42].

4.1. Strengths and limitations

This was the first study to evaluate whether the obesity paradox would be affected by different DBP categories in patients with HFpEF. The first potential limitations of our study included its retrospective nature and our selected group of HF patients with preserved ejection fraction. Sources of potential bias or imprecision sometimes could not be avoided. The widespread debate over the obesity paradox in HF is perplexed by selection bias in observational studies. Second, data on the dose of diuretics, beta-blockers, and ACEI/ARB were not available. BMI was presented at referral, a single arbitrary point in time, although the extent of adiposity and/or loss of muscle mass might be an evolving process with the progression of the disease. Third, BMI is a surrogate measure of body fat and generally defines overweight/obesity. One potential limitation was related to the use of BMI per se as an obesity index, which was not able to evaluate ectopic fat and distinguish body lean mass from fat mass. We did not have waist circumference measurements or waist-to-hip ratio, which were both indices of abdominal adiposity. Whether the relationship is due to the shortcomings of BMI as a risk factor needs to be further elucidated. Extrapolation of our data to the general population of HF patients must be done with caution.

5. Conclusions

In light of these data from the TOPCAT trial, the obesity paradox was present in HFpEF patients regardless of DBP strata ($<$70 mmHg, and $\geq$70 mmHg).

Ethics approval and consent to participate

The study was approved by the institutional review board at all participating institutions, and all participants provided written informed consent at enrollment.

Author contribution statement

YingQiu Hu, ZhiCheng Xu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

ZhenBang Gu, MeiLing Xu: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

WenFeng He, LiDong Wu, LinJuan Guo: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16515.

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