Pragmatic and Observational Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Obesity Paradox in Heart Failure with Mildly Reduced Ejection Fraction

Marielen Reinhardt[1,*], Tobias Schupp[1,*], Mohammad Abumayyaleh[1], Felix Lau[1,2], Alexander Schmitt[1], Noah Abel[1], Muharrem Akin[2], Jonas Rusnak[3], Ibrahim Akin[1], Michael Behnes[1]

[1]Department of Cardiology, Angiology, Haemostaseology and Medical Intensive Care, University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [2]Department of Cardiology, Angiology, Hannover Medical School, Hannover, Germany; [3]Department of Cardiology, Angiology and Pneumology, University Hospital Heidelberg, Heidelberg, Germany

*These authors contributed equally to this work

Correspondence: Tobias Schupp, First Department of Medicine, University Medical Center Mannheim (UMM), Theodor-Kutzer-Ufer 1-3, Mannheim, 68167, Germany, Tel +49 621-383-2204, Email tobias.schupp@umm.de

Objective: The study investigates the prognostic impact of body mass index (BMI) in patients hospitalized with heart failure with mildly reduced ejection fraction (HFmrEF).

Background: Limited data regarding the prognostic impact of BMI in patients with HFmrEF is available.

Methods: Consecutive patients with HFmrEF (ie, left ventricular ejection fraction 41–49% and signs and/or symptoms of HF) were retrospectively included at one institution from 2016 to 2022. Risk stratification was performed according to WHO-defined BMI groups. The primary endpoint was all-cause mortality at 30 months (median follow-up). Kaplan-Meier, uni- and multivariable Cox proportional regression analyses were applied for statistics.

Results: 1832 consecutive patients with HFmrEF were included with a median BMI of 26.7 kg/m^2 (IQR 24.0–30.8 kg/m^2). Patients with lowest BMI (ie, 18.5–24.9 kg/m^2) were associated with highest risk of all-cause mortality at 30 months compared to patients with higher BMI values (40.0% vs 29.0% vs 21.4% vs 20.9%; log rank p = 0.001; HR = 0.721; 95% CI 0.656–0.793; p = 0.001). Even after multivariable adjustment, higher BMI values were associated with improved survival at 30 months (HR = 0.963; 95% CI 0.943–0.985; p = 0.001). In contrast, the risk of HF- related rehospitalization at 30 months was not affected by BMI (log rank p = 0.064).

Conclusion: In patients hospitalized with HFmrEF, lower BMI was associated with increased risk of all-cause mortality at 30 months, suggesting an obesity paradox in HFmrEF.

Keywords: heart failure with mildly reduced ejection fraction, HFmrEF, body mass index, BMI, obesity, mortality

Introduction

The incidence of chronic heart failure (HF) has reached a stable level due to improved treatment of primary causes and evidence-based therapies such as the use of invasive cardiac devices and HF-related pharmacotherapies. However the overall prevalence of HF is increasing as a result of the ageing of the general population.[1–3] HF affects over 64 million individuals worldwide and is associated with a 5-year mortality rate of 50–75%.[1,4] Traditionally, HF has been categorized into two groups based on the left ventricular ejection fraction (LVEF): HF with reduced LVEF (ie, HFrEF) and preserved LVEF (ie, HFpEF). In 2016 and 2021, the ESC HF guidelines have been revised and HF with mildly reduced ejection fraction (ie, HFmrEF), characterized by a LVEF of 41–49%[5] was introduced as third and independent category of HF. This category remains largely unexplored, as patients with HFmrEF have been excluded from most heart failure registries and randomized controlled trials (RCT).[6–8] Since HFmrEF accounts for 10–25% of all HF patients,[9] it is crucial to conduct focused research to understand its underlying characteristics, pathophysiology, treatment, and the prognostic value of comorbidities within this subgroup.[10]

Obesity has become a worldwide burden reaching pandemic dimensions. According to the World Health Organization (WHO), the prevalence of obesity has nearly tripled in the last four decades and is expected to rise further.[11] Obesity is

Received: 12 October 2023
Accepted: 10 January 2024
Published: 5 March 2024

associated with various comorbidities such as type 2 diabetes mellitus, hyperlipidemia, sleep disorders, and hypertension, leading to the development of cardiovascular diseases.[12–14] Although obesity was shown to be an independent risk factor for cardiovascular mortality and morbidity, several studies reported that a higher body mass index (BMI) is linked to a better prognosis for various chronic diseases, a phenomenon known as the "obesity paradox".[15–17] Specifically, overweight and obese patients with chronic heart failure have been found to have a lower risk of death compared to those with normal BMI.[18] In fact, a U-shaped association was found between the BMI and mortality in patients with chronic HF[19,20] and the paradox was observed in patients with HF with preserved ejection fraction (HFpEF) as well as HF with reduced ejection fraction (HFrEF).[21–23] While the rates of overweight and obese patients is commonly high in HFpEF, it seems that the obese phenotype is also typically found in patients with HFmrEF, whereas 38% to 76% of patients with HFmrEF were obese in contemporary studies.[8,24]

The study investigates the prognostic impact of BMI in consecutive patients hospitalized with HFmrEF, aiming to determine whether there is an obesity paradox in patients with HFmrEF.

Methods

Study Patients, Design and Data Collection

For the present study, all consecutive patients hospitalized with HFmrEF at one University Medical Centre were included from January 2016 to December 2022. Using the electronic hospital information system, all relevant clinical data related to the index event were documented, such as baseline characteristics, vital signs on admission, prior medical history, prior medical treatment, length of index hospital and intensive care unit (ICU) stay, laboratory values, data derived from all non-invasive or invasive cardiac diagnostics and device therapies, such as echocardiographic data, coronary angiography and data being derived from prior or newly implanted cardiac devices. The University Medical Centre covers a general emergency department for emergency admission of traumatic, surgical, neurological and cardiovascular conditions. Interdisciplinary consultation is an inbuilt feature of this 24/7 service and connects to a stroke unit, four ICUs with extracorporeal life support and a chest pain unit to alleviate rapid triage of patients. The cardiologic department itself includes a 24-h catheterization laboratory, an electrophysiologic laboratory, a hybrid operating room and telemetry units. Furthermore, the medical centre is a certified HF unit.

The present study derived from the "Heart Failure With Mildly Reduced Ejection Fraction Registry" (HARMER), representing a retrospective single-centre all-comers registry including consecutive patients with HFmrEF hospitalized at the University Medical Centre Mannheim (UMM), Germany (clinicaltrials.gov identifier: NCT05603390). The registry was carried out according to the principles of the declaration of Helsinki and was approved by the medical ethics committee II of the Medical Faculty Mannheim, University of Heidelberg, Germany (ethical approval code: 2022–818). No written informed consent was necessary for the present study.

Inclusion and Exclusion Criteria

All consecutive patients with ≥18 years of age hospitalized with HFmrEF at one institution were included. All included patients underwent at least one standardized transthoracic echocardiography at the cardiologic department at index hospitalization, where the diagnosis of HFmrEF was assessed. The diagnosis of HFmrEF was determined retrospectively according to the "2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF".[25] Accordingly, all patients with LVEF 41–49% and symptoms and/or signs of HF were included. The presence of elevated amino-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels and other evidence of structural heart disease were considered to make the diagnosis more likely but were not mandatory for diagnosis of HFmrEF. The presence of right ventricular dysfunction was defined as a tricuspid annular plane systolic excursion (TAPSE) <18 mm. Standardized transthoracic echocardiography was performed by cardiologists during routine clinical care in accordance with current European guidelines.[26,27] Finally, all echocardiographic examinations and reports were re-assessed post-hoc by two independent cardiologists blinded to the final data analysis. In cases of ambiguous findings or documentation, echocardiographic source data was re-assessed in individual cases based on the available Digital Imaging and Communications in Medicine (DICOM) files.

For the present study, patients with <18 years of age were excluded. Patients with no evidence on weight and/or hight were excluded. Related to the low proportion of patients with BMI <18.5 kg/m^2, these patients were excluded from the present study. No further exclusion criteria were applied for the present study.

Risk Stratification

For the present study, patients were divided into four BMI categories in agreement with the CDC and WHO guidelines as follows: Normal weight was defined as BMI from 18.5 to <25.0 kg/m^2. Overweight was defined as BMI from 25.0 to <30.0 kg/m^2. Obesity class I was defined as BMI from 30.0 to <35.0 kg/m^2. BMI ≥35.0 kg/m^2 included patients with obesity classes II and III. Documentation of height and body weight was derived from documented medical records within the electronic hospital information system. Patients with BMI < 18.5 kg/m^2 (n = 35) were excluded.

Study Endpoints

The primary endpoint was long-term all-cause mortality. Long-term was defined as the median time of clinical follow-up in months. Secondary endpoints comprised in-hospital all-cause mortality (defined as all-cause mortality during the index hospitalization) and all-cause mortality at 12 months of follow-up. Further secondary endpoints included rehospitalization for worsening HF, cardiac rehospitalization, acute myocardial infarction (AMI), stroke, coronary revascularization, and major adverse cardiac and cerebrovascular events (MACCE) at long term follow-up. All-cause mortality was documented using the electronic hospital information system and by directly contacting state resident registration offices ("Bureau of Mortality Statistics"). Identification of patients was verified by place of name, surname, date of birth, and registered living address. HF-related hospitalization was defined as a rehospitalization due to worsening HF requiring intravenous diuretic therapy. HF-related rehospitalization comprised patients with hospitalization due to worsening HF as the primary cause or as a result of another cause but associated with worsening HF at the time of admission, or as a result of another cause but complicated by worsening HF during its cause. Cardiac rehospitalization was defined as rehospitalization due to a primary cardiac condition, including worsening HF, AMI, coronary revascularization and symptomatic atrial or ventricular arrhythmias. MACCE was defined as the composite of all-cause mortality, coronary re-vascularization, non-fatal AMI and non-fatal stroke.

Statistical Methods

Quantitative-data is presented as mean ± standard error of mean (SEM), median and interquartile range (IQR), and ranges depending on the distribution of the data. They were compared using the Student's *t*-test for normally distributed data or the Mann–Whitney *U*-test for non-parametric data. Deviations from a Gaussian distribution were tested by the Kolmogorov–Smirnov test. Qualitative data is presented as absolute and relative frequencies and were compared using the chi-square test or the Fisher's exact test, as appropriate.

Kaplan–Meier analyses were performed stratified by BMI and univariable hazard ratios (HRs) were given together with 95% confidence intervals (Cis). The prognostic impact of BMI was then investigated within multivariable Cox regression models using the "forward selection" option.

Results of all statistical tests were considered significant for p ≤ 0.05. SPSS (Version 28, IBM, Armonk, New York) was used for statistics.

Results

Study Population

A total of 2228 patients with HFmrEF were hospitalized at our institution from 2016 to 2022. 1.97% (n = 44) with incomplete follow-up data, 14.2% (n = 317) with missing data on weight and/or height and 1.57% (n = 35) with BMI <18.5 kg/m^2 were excluded (Figure 1; Flow Chart). The final study comprised 1832 patients hospitalized with HFmrEF with a median BMI of 26.7 kg/m^2 (mean 27.7 kg/m^2; IQR 24.0–30.8 kg/m^2).

When stratified by different BMI categories, patients with BMI 18.5 - <25 kg/m^2 were older (median age 78 vs 77 vs 72 vs 68 years; p = 0.001), presented with higher rates of peripheral artery disease (14.9% vs 11.1% vs 8.5% vs 8.5%; p = 0.008) and malignancies (19.9% vs 13.5% vs 12.1% vs 11.4%; p = 0.001) (Table 1). In contrast, patients with the highest

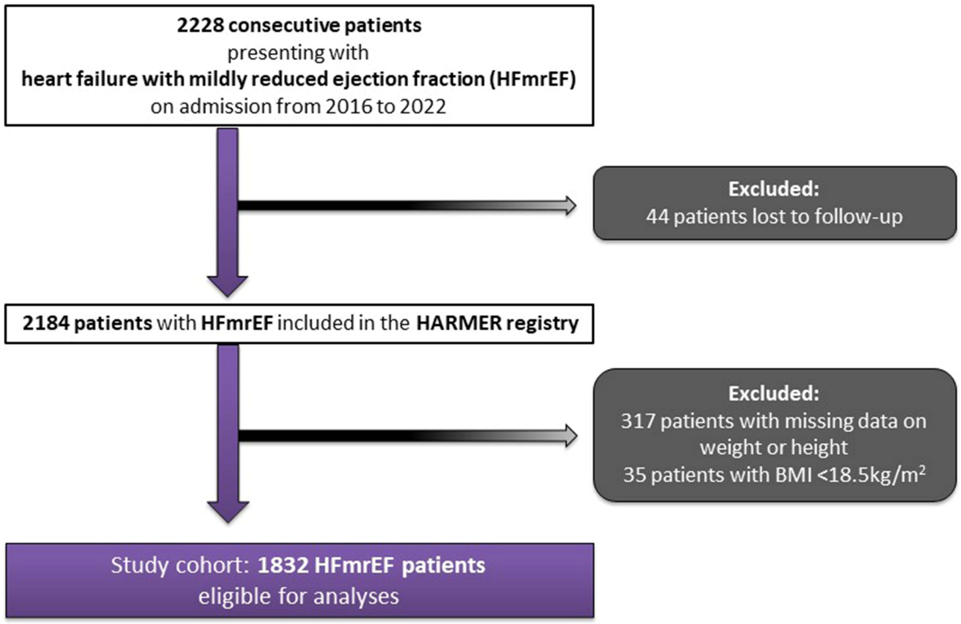

Figure 1 Flow chart of the study population.

BMI (ie, BMI $\geq$ 35 kg/m^2) presented with higher rates of cardiovascular risk factors, such as arterial hypertension (87.1% vs 82.5% vs 77.4% vs 72.2%; p = 0.001) and diabetes mellitus (55.2% vs 47.7% vs 35.9% vs 24.4%; p = 0.001). The highest rate of pre-existent coronary artery disease (CAD) was shown in patients with BMI 30 - <35 kg/m^2 (47.9%; p =

Table 1 Baseline Characteristics

	BMI 18.5 - <25 kg/m^2 (n=562)	BMI 25 - <30 kg/m^2 (n=704)	BMI 30 - <35 kg/m^2 (n=365)	BMI ≥35 kg/m^2 (n=201)	p value
Age, median (IQR)	78 (69–85)	77 (66–83)	72 (60–81)	68 (57–77)	**0.001**
Male sex, n (%)	335 (59.6)	483 (68.6)	251 (68.8)	113 (56.2)	**0.001**
Body mass index, kg/m^2, median (IQR)	22.9 (21.6–23.8)	26.7 (25.5–28.0)	31.4 (30.5–32.9)	36.9 (35.4–39.8)	**0.001**
SBP, mmHg, median (IQR)	141 (123–160)	142 (125–163)	144 (140–170)	140 (123–160)	0.155
DBP, mmHg, median (IQR)	79 (68–89)	79 (70–90)	80 (70–90)	78 (67–93)	0.470
Heart rate, bpm, median (IQR)	80 (68–97)	80 (68–94)	80 (67–95)	84 (71–64)	0.177
Medical history, n (%)					
Coronary artery disease	223 (39.7)	288 (40.9)	175 (47.9)	71 (35.3)	**0.016**
Prior myocardial infarction	134 (23.8)	168 (23.9)	97 (26.6)	41 (20.4)	0.428
Prior PCI	147 (26.2)	201 (28.6)	125 (34.2)	55 (27.4)	0.060
Prior CABG	46 (8.2)	80 (11.4)	44 (12.1)	14 (7.0)	0.064
Prior valvular surgery	25 (4.4)	33 (4.7)	18 (4.9)	6 (3.0)	0.730
Congestive heart failure	197 (35.1)	225 (32.0)	122 (33.4)	76 (37.8)	0.403
Decompensated heart failure < 12 months	58 (10.3)	63 (8.9)	40 (11.0)	30 (14.9)	0.106
Prior ICD	14 (2.5)	7 (1.0)	9 (2.5)	7 (3.5)	0.075
Prior sICD	3 (0.5)	0 (0.0)	2 (0.5)	1 (0.5)	0.288
Prior CRT-D	5 (0.5)	11 (1.6)	9 (2.5)	4 (2.0)	0.287
Prior Pacemaker	51 (9.1)	75 (10.7)	34 (9.3)	8 (4.0)	**0.039**
Chronic kidney disease	185 (32.9)	202 (28.8)	109 (29.9)	63 (31.3)	0.428
Peripheral artery disease	84 (14.9)	78 (11.1)	31 (8.5)	17 (8.5)	**0.008**
Stroke	93 (16.5)	112 (15.9)	47 (12.9)	23 (11.4)	0.187
Liver cirrhosis	12 (2.1)	19 (2.7)	7 (1.9)	4 (2.0)	0.827
Malignancy	112 (19.9)	95 (13.5)	44 (12.1)	23 (11.4)	**0.001**
COPD	67 (11.9)	86 (12.2)	36 (9.9)	27 (13.4)	0.581

(*Continued*)

Table 1 (Continued).

	BMI 18.5 - <25 kg/m^2 (n=562)	BMI 25 - <30 kg/m^2 (n=704)	BMI 30 - <35 kg/m^2 (n=365)	BMI ≥35 kg/m^2 (n=201)	p value
Cardiovascular risk factors, n (%)					
Arterial hypertension	406 (72.2)	545 (77.4)	301 (82.5)	175 (87.1)	**0.001**
Diabetes mellitus	137 (24.4)	253 (35.9)	174 (47.7)	111 (55.2)	**0.001**
Hyperlipidemia	147 (26.2)	218 (31.0)	137 (37.5)	65 (32.3)	**0.003**
Smoking					
Current	99 (17.6)	123 (17.5)	72 (19.7)	40 (19.9)	0.720
Former	90 (16.0)	126 (17.9)	74 (20.3)	32 (15.9)	0.360
Family history	46 (8.2)	64 (9.1)	41 (11.2)	24 (11.9)	0.271
Comorbidities at index hospitalization, n (%)					
Acute coronary syndrome					
Unstable angina	12 (2.1)	39 (5.5)	23 (6.3)	12 (6.0)	**0.007**
STEMI	43 (7.7)	67 (9.5)	34 (9.3)	14 (7.0)	0.511
NSTEMI	64 (11.4)	92 (13.1)	51 (14.0)	23 (11.4)	0.624
Acute decompensated heart failure	133 (23.7)	133 (18.9)	73 (20.0)	59 (29.4)	**0.007**
Cardiogenic shock	13 (2.3)	22 (3.1)	8 (2.2)	2 (1.0)	0.353
Atrial fibrillation	235 (41.8)	297 (42.2)	143 (39.3)	71 (35.3)	0.297
Cardiopulmonary resuscitation	13 (2.3)	18 (2.6)	9 (2.5)	2 (1.0)	0.619
Out-of-hospital	6 (1.1)	8 (1.1)	4 (1.1)	0 (0.0)	0.521
In-hospital	7 (1.2)	10 (1.4)	5 (1.4)	2 (1.0)	0.969
Stroke	87 (15.5)	95 (13.5)	40 (11.0)	20 (10.0)	0.109
Medication at index admission, n (%)					
ACE-inhibitor	179 (31.9)	238 (33.8)	141 (38.6)	87 (43.3)	**0.012**
ARB	104 (18.5)	161 (22.9)	106 (29.0)	51 (25.4)	**0.002**
Beta-blocker	311 (55.)	400 (56.8)	216 (59.2)	109 (54.2)	0.610
Aldosterone antagonist	47 (8.4)	60 (8.5)	42 (11.5)	23 (11.4)	0.237
ARNI	3 (0.5)	11 (1.6)	2 (0.5)	2 (1.0)	0.230
SGLT2-inhibitor	4 (0.7)	18 (2.6)	8 (2.2)	12 (6.0)	**0.001**
Loop diuretics	200 (35.6)	244 (34.7)	148 (40.5)	93 (46.3)	**0.010**
Statin	235 (41.8)	332 (47.2)	183 (50.1)	83 (41.3)	**0.037**
ASA	180 (32.0)	265 (37.6)	117 (32.1)	68 (33.8)	0.133
P2Y12-inhibitor	58 (10.3)	69 (9.8)	39 (10.7)	17 (8.5)	0.845
DOAC	130 (23.1)	182 (25.9)	86 (23.6)	46 (22.9)	0.645
Vitamin K antagonist	46 (8.2)	51 (7.2)	38 (10.4)	11 (5.5)	0.157

Notes: Level of significance p≤0.05. Bold type indicates statistical significance.
Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ASA, acetylsalicylic acid; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; DBP, diastolic blood pressure; DOAC, directly acting oral anticoagulant; IQR, interquartile range; (N)STEMI, non-ST-segment elevation myocardial infarction; SBP, systolic blood pressure; SGLT2, sodium glucose linked transporter 2; (s-)ICD, (subcutaneous) implantable cardioverter defibrillator.

0.016). In contrast, the rates of pre-existent congestive HF (35.1% vs 32.0% vs 33.4% vs 37.8%; p = 0.403) and the proportion of patients with HF-related hospitalization within the last 12 months (10.3% vs 8.9% vs 11.0% vs 14.9%; p = 0.106) did not significantly differ across the BMI groups. With regard to comorbidities at index hospitalization, patients with BMI ≥ 35 kg/m^2 had higher rates of acute decompensated heart failure (29.4%; p = 0.007). The rates of ST-segment AMI (STEMI) (7.7% vs 9.5% vs 9.3% vs 7.0; p = 0.511) and non-ST-segment AMI (NSTEMI) (11.4% vs 13.1% vs 14.0% vs 11.4%; p = 0.624) did not differ significantly across the BMI groups.

As outlined in Table 2, the most common aetiology of HF across all groups was ischemic cardiomyopathy (BMI 18.5 – <25 kg/m^2, 53.2%; BMI 25 - <30 kg/m^2, 60.8%; BMI 30 - <35 kg/m^2, 64.9%; BMI ≥ 35 kg/m^2, 54.7%; p = 0.002). Compared to patients with BMI 18.5 - <25 kg/m^2, patients with BMI ≥ 35 kg/m^2 showed higher values of interventricular septal end diastole (IVSd) (12 vs 11 mm; p = 0.001), left ventricular end-diastolic diameter (LVEDD) (52 vs 47 mm; p = 0.001) and TAPSE (21 vs 20 mm; p = 0.001). On the contrary, the rates of valvular heart diseases, including moderate-to-severe aortic valve regurgitation (6.9% vs 2.5%; p = 0.001), moderate-to-severe mitral

Table 2 Heart-Failure Related and Procedural Data

	BMI 18.5 - <25 kg/m^2 (n=562)	BMI 25 - <30 kg/m^2 (n=704)	BMI 30 - <35 kg/m^2 (n=365)	BMI ≥35 kg/m^2 (n=201)	p value
Heart failure etiology, n (%)					
Ischemic cardiomyopathy	299 (53.2)	428 (60.8)	237 (64.9)	110 (54.7)	**0.002**
Non-ischemic cardiomyopathy	37 (6.6)	48 (6.8)	19 (5.2)	17 (8.5)	
Hypertensive cardiomyopathy	41 (7.3)	60 (8.5)	30 (8.2)	24 (11.9)	
Congenital heart disease	3 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	
Valvular heart disease	42 (7.5)	23 (3.3)	7 (1.9)	5 (2.5)	
Tachycardia-associated	31 (5.5)	41 (5.8)	18 (4.9)	11 (5.5)	
Tachymyopathy	12 (2.3)	12 (1.7)	4 (1.1)	5 (2.5)	
Pacemaker-induced cardiomyopathy	8 (1.4)	4 (0.6)	3 (0.8)	1 (0.5)	
Unknown	101 (18.0)	100 (14.2)	51 (14.0)	32 (15.9)	
NYHA functional class, n (%)					
I/ II	402 (71.6)	532 (75.6)	266 (72.9)	131 (65.2)	0.099
III	108 (19.2)	114 (16.2)	74 (20.3)	48 (23.9)	
IV	52 (9.3)	58 (8.2)	25 (6.8)	22 (10.9)	
Echocardiographic data					
LVEF, %, median (IQR)	45 (45–47)	45 (45–47)	45 (45–47)	45 (45–47)	0.541
IVSd, mm, median (IQR)	11 (10–13)	12 (11–13)	12 (11–13)	12 (11–14)	**0.001**
LVEDD, mm, median (IQR)	47 (42–52)	49 (45–54)	50 (45–54)	52 (47–56)	**0.001**
TAPSE, mm, median (IQR)	20 (17–22)	20 (17–23)	20 (18–24)	21 (19–24)	**0.001**
LA diameter, mm, median (IQR)	41 (36–47)	41 (37–47)	43 (39–48)	41 (39–48)	**0.037**
LA area, cm^2, median (IQR)	21 (16–25)	22 (18–26)	21 (18–26)	23 (18–27)	0.232
E/A, median (IQR)	0.8 (0.6–1.3)	0.8 (0.6–1.1)	0.9 (0.7–1.2)	0.8 (0.6–1.2)	0.271
E/E`, median (IQR)	9.3 (6.0–14.0)	9.0 (6.0–13.5)	10.0 (7.0–13.0)	9.0 (7.0–13.0)	0.836
Diastolic dysfunction, n (%)	404 (71.9)	508 (72.2)	260 (71.2)	147 (73.1)	0.970
Moderate-severe aortic stenosis, n (%)	68 (12.1)	66 (9.4)	32 (8.8)	13 (6.5)	0.090
Moderate-severe aortic regurgitation, n (%)	39 (6.9)	24 (3.4)	6 (1.6)	5 (2.5)	**0.001**
Moderate-severe mitral regurgitation, n (%)	94 (16.7)	95 (13.5)	26 (7.1)	12 (6.0)	**0.001**
Moderate-severe tricuspid regurgitation, n (%)	128 (22.8)	96 (13.6)	45 (12.3)	16 (8.0)	**0.001**
VCI, median (IQR)	20 (15–25)	19 (15–24)	19 (16–25)	21 (16–27)	0.668
Aortic root, mm, median (IQR)	32 (29–35)	33 (30–37)	33 (30–37)	33 (29–36)	**0.003**
Coronary angiography, n (%)	188 (33.5)	322 (45.7)	172 (47.1)	93 (46.3)	**0.001**
No evidence of coronary artery disease	45 (23.9)	51 (15.8)	30 (17.4)	20 (21.5)	0.271
1-vessel disease	30 (16.0)	62 (19.3)	33 (19.2)	21 (22.6)	
2-vessel disease	38 (20.2)	72 (22.4)	33 (19.2)	24 (25.8)	
3-vessel disease	75 (39.9)	137 (42.5)	76 (44.2)	28 (30.1)	
CABG	8 (4.3)	32 (9.9)	19 (11.0)	7 (7.5)	0.080
Chronic total occlusion	21 (11.2)	41 (12.7)	22 (12.8)	10 (10.8)	0.917
PCI, n (%)	99 (52.7)	180 (55.9)	98 (57.0)	41 (44.1)	0.180
Sent to CABG, n (%)	12 (6.4)	21 (6.5)	5 (2.9)	5 (5.4)	0.372
Baseline laboratory values, median (IQR)					
Potassium, mmol/L	3.9 (3.6–4.2)	3.9 (3.6–4.2)	3.9 (3.6–4.2)	3.9 (3.6–4.2)	0.557
Sodium, mmol/L	139 (137–141)	139 (137–141)	139 (137–141)	139 (138–141)	0.163
Creatinine, mg/dL	1.04 (0.85–1.48)	1.07 (0.84–1.42)	1.11 (0.89–1.41)	1.05 (0.90–1.46)	0.449
eGFR, mL/min/1.73 m^2	63 (44–87)	67 (48–85)	66 (45–88)	65 (44–86)	0.503
Hemoglobin, g/dL	11.7 (10.1–13.5)	12.6 (10.6–14.0)	12.8 (10.9–14.3)	13.2 (11.3–14.4)	**0.001**
WBC count, x 10^9/L	8.03 (6.23–10.00)	8.06 (6.40–10.11)	8.38 (6.60–9.85)	8.56 (7.21–10.50)	0.079
Platelet count, x 10^9/L	226 (180–295)	224 (174–274)	224 (186–283)	234 (188–290)	0.444
HbA1c, %	5.7 (5.4–6.4)	5.9 (5.5–6.6)	6.1 (5.6–7.0)	6.3 (5.6–7.5)	**0.001**
LDL- cholesterol, mg/dL	93 (72–121)	99 (75–129)	101 (74–128)	100 (76–122)	0.148
HDL- cholesterol, mg/dL	43 (35–55)	43 (35–52)	40 (34–49)	39 (32–50)	**0.004**
C-reactive protein, mg/L	14 (3–45)	12 (3–42)	11 (3–38)	12 (4.4–44)	0.392
NT-pro BNP, pg/mL	3874 (1457–8415)	2587 (1005–8384)	1991 (711–4126)	1602 (433–3059)	**0.001**
NT-pro BNP (eGFR corrected), pg/mL	2026 (827–4615)	1759 (673–3998)	1210 (506–2406)	953 (432–1824)	**0.001**
Cardiac troponin I, µg/L	0.03 (0.02–0.19)	0.03 (0.02–0.17)	0.03 (0.02–0.19)	0.02 (0.02–0.20)	0.702

(*Continued*)

Table 2 (Continued).

	BMI 18.5 - <25 kg/m^2 (n=562)	BMI 25 - <30 kg/m^2 (n=704)	BMI 30 - <35 kg/m^2 (n=365)	BMI ≥35 kg/m^2 (n=201)	p value
Medication at discharge, n (%)					
ACE-inhibitor	257 (47.9)	336 (49.1)	191 (52.9)	101 (52.1)	0.443
ARB	108 (20.1)	174 (25.4)	102 (28.3)	56 (28.9)	**0.016**
Beta-blocker	398 (74.3)	536 (78.2)	287 (79.5)	156 (80.4)	0.155
Aldosterone antagonist	70 (13.1)	91 (13.3)	57 (15.8)	37 (19.1)	0.140
ARNI	3 (0.6)	15 (2.2)	3 (0.8)	3 (1.5)	0.074
SGLT2-inhibitor	10 (1.9)	26 (3.8)	20 (5.5)	23 (11.9)	**0.001**
Loop diuretics	251 (46.8)	315 (46.0)	175 (48.5)	112 (57.7)	**0.032**
Statin	340 (63.4)	496 (72.4)	264 (73.1)	124 (63.9)	**0.001**
Digitalis	24 (4.5)	32 (4.7)	23 (6.4)	4 (2.1)	0.148
Amiodarone	11 (2.1)	15 (2.2)	12 (3.3)	5 (2.6)	0.630
ASA	260 (48.5)	371 (54.2)	185 (51.2)	95 (49.0)	0.227
P2Y12-inhibitor	158 (29.5)	233 (34.0)	129 (35.7)	60 (30.9)	0.183
DOAC	174 (32.5)	232 (33.9)	112 (31.0)	66 (34.0)	0.796
Vitamin k antagonist	36 (6.7)	41 (6.0)	30 (8.3)	10 (5.2)	0.422

Note: Level of significance p≤0.05. Bold type indicates statistical significance.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; DOAC, directly acting oral anticoagulant; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; IVSd, Interventricular septal end diastole; LA, left atrial; LDL, low-density lipoprotein; LVEDD, Left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-pro BNP, aminoterminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SGLT2, sodium glucose linked transporter 2; TAPSE, tricuspid annular plane systolic excursion; VCI, Vena cava inferior; WBC, white blood cells.

regurgitation (16.7% vs 6.0%; p = 0.001) and moderate-to-severe tricuspid regurgitation (22.8% vs 8.0%) were higher in patients with BMI 18.5 - <25 kg/m^2 compared to patients with BMI ≥ 35 kg/m^2. A higher proportion of patients with BMI 30 - <35 kg/m^2 underwent invasive coronary angiography during index hospitalization compared to patients with the lowest BMI (47.1% vs 33.5%; p = 0.001). However, no significant difference was found in the distribution of CAD type or percutaneous coronary intervention (PCI) rates across the BMI categories (p = 0.271 and p = 0.180 respectively). Levels of NT-pro-BNP were significantly higher in patients with lowest BMI compared to patients with BMI ≥ 35 kg/m^2 (3874 vs 1602 pg/mL; p = 0.001).

Finally, patients with BMI ≥ 35 kg/m^2 were more frequently discharged with an angiotensin receptor blocker (ARB) (28.9% vs 20.1%; p = 0.016), sodium-glucose cotransporter 2 (SGLT2) inhibitor (11.9% vs 1.9%; p = 0.001) or loop diuretics (57.7% vs 46.8%; p = 0.032) compared to patients with BMI 18.5 - <25 kg/m^2.

Prognostic Impact of BMI in Patients with HFmrEF

During a median follow-up of 30 months (IQR 390–1634 days), the primary endpoint all-cause mortality occurred in 40.0% of patients with BMI 18.5 - <25 kg/m^2, 29.0% of patients with BMI 25 - <30 kg/m^2, 21.4% of patients with BMI 30 - <35 kg/m^2, and 20.9% of patients with BMI ≥ 35 kg/m^2 (p = 0.001) (Figure 2). Accordingly, a higher BMI was associated with a lower risk of 30-months all-cause mortality (HR = 0.721; 95% CI 0.656–0.793; p = 0.001). The risk of HF-related rehospitalization at 30 months did not differ across the BMI groups (12.9% vs 12.7% vs 15.0% vs 18.0%; log rank p = 0.219; HR = 1.116; 95% CI 0.983–1.268; p = 0.093).

Regarding key secondary endpoints, the rates of coronary revascularization were higher in patients with BMI 30 - <35 kg/m^2 compared to patients with BMI 18.5 - <25 kg/m^2 (10% vs 4.9%; log rank p = 0.032; HR = 1.200; 95% CI 1.007–1.430; p = 0.041) (Table 3), whereas the rates of MACCE were higher in patients with BMI 18.5 - <25 kg/m^2 compared to patients with BMI ≥ 35 kg/m^2 (44.8% vs 29.9%; log rank p = 0.001; HR = 0.818; 95% CI 0.754–0.887; p = 0.001).

After multivariable adjustment for patients' characteristics and comorbidities, higher BMI was associated with lower risk of 30-months all-cause mortality as compared to lower BMI values (HR = 0.963; 95% CI 0.943–0.985; p = 0.001) (Table 4). Furthermore, higher age (HR = 1.050; 95% CI 1.039–1.060; p = 0.001), male sex (HR = 1.347;

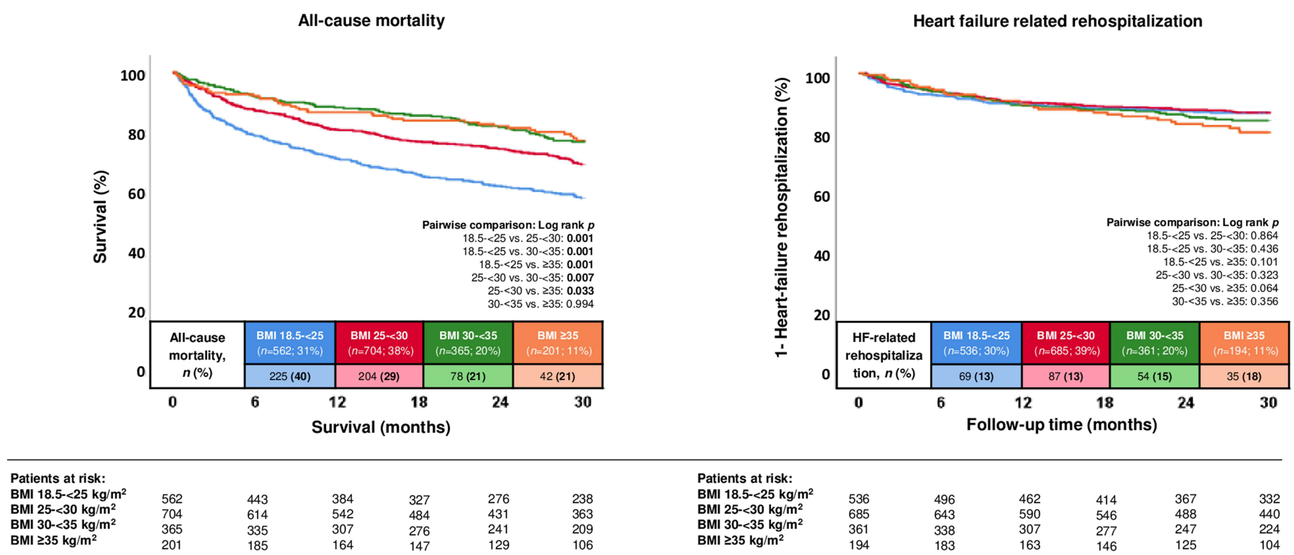

Figure 2 Kaplan-Meier analyses comparing the prognostic impact of BMI on the risk of all-cause mortality (left panel) and hospitalization for worsening HF (right panel) in patients with HFmrEF.

95% CI 1.098–1.652; p = 0.004), the presence of diabetes mellitus (HR = 1.243; 95% CI 1.015–1.522; p = 0.035), pre-existent malignancy (HR = 3.045; 95% CI 2.472–3.751; p = 0.001) and acute decompensated HF (HR = 1.994; 95% CI 1.629–2.442; p = 0.001) increased the risk of 30-months all-cause mortality, whereas the presence of hyperlipidaemia (HR = 0.702; 95% CI 0.561–0.880; p = 0.002) and ischemic cardiomyopathy (HR = 0.783; 95% CI 0.645–0.951; p = 0.014) were associated with lower risk of 30-months all-cause mortality.

Even when stratified by important pre-selected subgroups, higher BMI levels were associated with lower risk of all-cause mortality in patients >75 years of age (HR = 0.961; 95% CI 0.934–0.988; p = 0.005), males (HR = 0.955; 95% CI 0.927–0.984; p = 0.003) and patients NYHA functional class ≤2 (HR = 0.953; 95% CI 0.925–0.982; p = 0.001) and TAPSE ≥18 mm (HR = 0.967; 95% CI 0.942–0.993; p = 0.014) (Table 5). In contrast, the risk of rehospitalization for worsening HF at 30 months was higher in patients with higher BMIs and NYHA functional class ≤2 (HR 1.044; 95% CI 1.005–1.084; p = 0.027).

Table 3 Follow-Up Data, Primary and Secondary Endpoints

	BMI 18.5 - <25 kg/m^2 (n=562)	BMI 25 - <30 kg/m^2 (n=704)	BMI 30 - <35 kg/m^2 (n=365)	BMI ≥35 kg/m^2 (n=201)	p value
Primary endpoint, n (%)					
All-cause mortality, at 30 months	225 (40.0)	204 (29.0)	78 (21.4)	42 (20.9)	**0.001**
Secondary endpoints, n (%)					
All-cause mortality, in-hospital	26 (4.6)	19 (2.7)	4 (1.1)	7 (3.5)	**0.020**
All-cause mortality, at 12 months	163 (29.0)	136 (19.3)	43 (11.8)	27 (13.4)	**0.001**
Heart-failure related rehospitalization, at 30 months	69 (12.9)	87 (12.7)	54 (15.0)	35 (18.0)	0.219
Cardiac rehospitalization, at 30 months	104 (19.4)	151 (22.0)	88 (24.4)	55 (28.4)	0.056
Revascularization, at 30 months	26 (4.9)	50 (7.3)	36 (10.0)	13 (6.7)	**0.032**
Acute myocardial infarction, at 30 months	16 (3.0)	19 (2.8)	11 (3.0)	10 (5.2)	0.402
Stroke, at 30 months	17 (3.2)	16 (2.3)	9 (2.5)	5 (2.6)	0.833
MACCE, at 30 months	252 (44.8)	263 (37.4)	115 (31.5)	60 (29.9)	**0.001**
Follow-up data, median (IQR)					
Hospitalization time, days	10 (6–17)	8 (5–14)	8 (5–14)	8 (6–14)	**0.001**
ICU time, days	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0.258
Follow-up time, days	694 (259–1493)	929 (401–1733)	1063 (547–1682)	971 (504–1705)	**0.001**

Notes: Level of significance p≤0.05. Bold type indicates statistical significance.
Abbreviations: ICU, intensive care unit; MACCE, major adverse cardiac and cerebrovascular events.

Table 4 Multivariable Cox Regression Analyses with Regard to All-Cause Mortality and Heart-Failure Related Rehospitalization at 30 Months

	30-Months All-Cause Mortality			Heart-Failure Related Rehospitalization		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Age	1.050	1.039–1.060	**0.001**	1.021	1.008–1.035	**0.002**
Males	1.347	1.098–1.652	**0.004**	0.944	0.702–1.269	0.702
Arterial hypertension	0.970	0.747–1.259	0.819	1.395	0.887–2.193	0.149
Diabetes mellitus	1.243	1.015–1.522	**0.035**	1.320	0.984–1.769	0.064
Hyperlipidemia	0.702	0.561–0.880	**0.002**	0.975	0.721–1.319	0.868
Prior malignancy	3.045	2.472–3.751	**0.001**	0.846	0.555–1.289	0.436
Ischemic cardiomyopathy	0.783	0.645–0.951	**0.014**	1.274	0.946–1.715	0.111
Acute decompensated heart failure	1.994	1.629–2.442	**0.001**	2.708	1.023–3.625	**0.001**
LVEDD, mm	0.998	0.995–1.002	0.333	1.003	1.000–1.005	0.057
TAPSE, mm	0.997	0.983–1.011	0.641	0.967	0.937–0.998	**0.037**
BMI 25-<30 kg/m^2	0.758	0.610–0.941	**0.012**	1.065	0.748–1.516	0.726
BMI 30-<35 kg/m^2	0.634	0.475–0.845	**0.002**	1.259	0.836–1.895	0.271
BMI ≥35 kg/m^2	0.628	0.425–0.929	**0.020**	1.475	0.906–2.401	0.118
BMI 18.5-<25 kg/m^2	(reference group)			(reference group)		
BMI *	0.963	0.943–0.985	**0.001**	1.025	0.997–1.054	0.080

Notes: *Multivariable Cox regression were additionally performed including BMI as continuous variable. Level of significance p≤0.05. Bold type indicates statistical significance.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; LVEDD, left ventricular end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion.

Table 5 Hazard Ratios for BMI Within Pre-Specified Subgroups After Multivariable Adjustment

	30-Months All-Cause Mortality			Heart-Failure Related Rehospitalization		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Age >75	0.961	0.934–0.988	**0.005**	1.016	0.977–1.056	0.427
Age ≤75	0.974	0.940–1.010	0.158	1.027	0.987–1.069	0.189
Male sex	0.955	0.927–0.984	**0.003**	1.031	0.990–1.074	0.141
Female sex	0.973	0.943–1.004	0.088	1.013	0.975–1.052	0.520
Ischemic cardiomyopathy	0.979	0.949–1.009	0.174	1.009	0.970–1.050	0.654
No ischemic cardiomyopathy	0.950	0.920–0.980	**0.001**	1.041	1.003–1.082	0.036
NYHA functional class ≤ 2	0.953	0.925–0.982	**0.001**	1.044	1.005–1.084	**0.027**
NYHA functional class >2	0.980	0.947–1.014	0.242	0.997	0.958–1.039	0.902
TAPSE ≥ 18 mm	0.967	0.942–0.993	**0.014**	1.028	0.994–1.063	0.108
TAPSE <18 mm	0.966	0.928–1.005	0.084	1.009	0.957–1.064	0.737

Notes: Multivariable Cox regression models were adjusted for age, sex, arterial hypertension, diabetes mellitus, hyperlipidemia, malignancy, ischemic cardiomyopathy, acute decompensated heart failure, left ventricular end-diastolic diameter, and tricuspid annular plane systolic excursion. Level of significance p≤0.05. Bold type indicates statistical significance.

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion.

Discussion

The present study investigates the prognostic impact of BMI in patients hospitalized with HFmrEF using a large registry-based dataset from 2016 to 2022. The data suggests that more than two-thirds (69%) of patients with HFmrEF were overweight or obese. A higher BMI was independently associated with a lower risk of all-cause mortality at 30 months, which was still evident after multivariable Cox regression analyses, suggesting an obesity paradox in patients hospitalized with HFmrEF. Specifically, in older patients and in males, a higher BMI was associated with a lower risk of all-cause death. In contrast, the risk of HF-related rehospitalization was not affected by BMI.

The high metabolic activity of excessive fat tissue and lipotoxicity in obese patients leads to myocardial remodeling and diastolic dysfunction, which may contribute to the development and progression of congestive HF.[28] Although epidemiologic data suggest a strong link between obesity and HF, even after adjustment for demographics and commonly prevalent risk factors such diabetes mellitus, hypertension, and hypercholesterolemia, many studies have suggested that patients with higher BMI levels generally had a better prognosis.[29,30] The underlying causes of this phenomenon called obesity paradox are still unclear, however several potential explanations exist. From this perspective, obese patients may cope better with the chronic catabolic state of HF due to higher metabolic reserves and attenuated neurohormonal response to stress.[15,29,31] Increased production of leptin and soluble receptor of tumor necrosis factor in adipose tissues may reduce the effect of the proinflammatory cytokine.[31] Furthermore, obese patients show an attenuated sympathetic nervous system and renin–angiotensin response leading to higher systolic blood pressure, which results in a better prognosis for HF and may permit a higher titration of cardioprotective medication.[32] In addition, a positive correlation between higher cholesterol levels and improved survival in HF has been observed.[32] Obesity also influences circulating NT-proBNP levels, whereas obese HF patients showed significantly lower levels.[33] This phenomenon was observed within the present study including patients with HFmrEF. Finally, patients with higher BMI may manifest symptoms of HF at a younger age with consequent longer survival after diagnosis (lead-time bias),[31] however, within the present study, the rates of prior congestive HF and the proportion of patients with hospitalization for acute decompensated HF <12 months did not differ among patients with different BMI categories.

Several studies reported the existence of the obesity paradox in HFrEF and HFpEF, underlying the non-linear relation between BMI and mortality, but data regarding the prognostic impact of BMI in patients with HFmrEF is limited.[31,34,35] According to Kenchaiah et al, obesity has a high prevalence in patients with HF, regardless of LVEF,[31] which was in line with the present study, demonstrating a prevalence of overweight and obesity of 69%. The examination of patients from the CHARM program showed that lower BMI values were associated with increased risk of cardiovascular and non-cardiovascular death, whereas the risk of hospitalization for worsening of heart failure or due to all causes was not affected by baseline BMI.[31] Zhang et al suggested an inverse association between BMI and all-cause mortality in patients with HFpEF based on a systematic review including 59,263 patients; the meta-analysis showed a U-shaped association with the lowest mortality at a BMI of 32–33 kg/m^2.[35] Similar results were found when examining studies of patients with HFrEF, whereas the meta-analysis showed a flatter U-shaped association than for HFpEF with the lowest mortality at a BMI of 32 kg/m2.[35] According to the U-shaped association, it was shown that BMI <18.5 kg/m^2 is associated with a high risk of mortality, whereas very underweight patients with HF had a higher risk than obese patients.[36] This effect was not investigated in our study, due to the low proportion of underweight patients (0.02%) with HFmrEF. It should be noted that the proportion of patients with BMI <18.5 kg/m^2 is generally very low in most HFmrEF registries.[8]

While recent studies showed a strong association of higher BMI with the risk for HFpEF more than for HFrEF, little is known about the prognostic value of BMI in HFmrEF.[37] Within the CHARM Program, the BMI of patients with HFmrEF was intermediate betweenHFrEF and HFpEF, while in the TOPCAT, PARAGON-HF and DELIVER trials the BMI of the HFmrEF group resembled more the BMI of the HFpEF group.[8,9,31,38] Liu et al demonstrated that obesity increased the 1-year risk for cardiovascular death in female patients with HFmrEF but not in male patients.[13] In line with this, our study found a lower risk of all-cause mortality at 30 months in obese male patients compared to females. Furthermore, Liu et al showed that obesity had a 57% overall increased risk of cardiovascular death.[13] This was not confirmed in the study based on the DELIVER-Trial, where the risks of all-cause mortality and cardiovascular death were significantly higher in patients with lower BMI.[37] Regardless of the obesity paradox, obesity remains a relevant risk factor for heart failure and must not be attributed to a protective effect. Studies should focus on more obesity parameters such as fat distribution and waist-to-hip ratio and consider cardiorespiratory fitness as a modulating factor. While extreme obesity is linked to a negative outcome, it is still unclear how weight loss influences the prognosis of HF and requires further investigation.

Study Limitations

The study has several limitations. Due to the retrospective and single-centre study design, results may be influenced by measured and unmeasured confounding. Related to the retrospective study design, data concerning weight changes after index hospitalization was not available. In line, increased mortality in patients with lower BMI may be attributed to an older age, higher incidence of comorbidities (ie, aortic valve disease, anemia), although this was adjusted within multivariable Cox regression analyses. Furthermore, only BMI was used as a parameter for obesity, without taking into account other valid obesity parameters such as fat distribution and body composition and does not provide information on the nutritional status of patients. HF-related and cardiac rehospitalization were assessed at our institution only. Finally, causes of death beyond during index hospitalization were not available for the present study.

Conclusions

The present study found that most HFmrEF patients are overweight and obese. A lower BMI was associated with an increased risk of all-cause mortality at 30 months, which was still evident after multivariable Cox regression analyses, suggesting an obesity paradox in HFmrEF. This may be further attributed to a higher age and an increased burden with cardiovascular comorbidities in patients with lower BMI.

Data Sharing Statement

The dataset used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Funding

This manuscript did not receive any funding.

Disclosure

The authors declare that they do not have any conflicts of interest for this work.

References

1. Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2023;118(17):3272–3287. doi:10.1093/cvr/cvac013
2. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392 (10159):1789–1858. doi:10.1016/S0140-6736(18)32279-7
3. Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet*. 2018;391(10120):572–580. doi:10.1016/S0140-6736(17)32520-5
4. Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol*. 2017;70(20):2476–2486. doi:10.1016/j.jacc.2017.08.074
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18(8):891–975. doi:10.1002/ejhf.592
6. Carbone S, daSilva-deAbreu A, Lavie CJ. The sodium-glucose co-transporter 2 inhibitor dapagliflozin improves prognosis in systolic heart failure independent of the obesity paradox. *Eur J Heart Fail*. 2021;23(10):1673–1676. doi:10.1002/ejhf.2336
7. Thorvaldsen T, Ferrannini G, Mellbin L, et al. Eligibility for dapagliflozin and empagliflozin in a real-world heart failure population. *J Card Fail*. 2022;28(7):1050–1062. doi:10.1016/j.cardfail.2022.04.011
8. Solomon SD, Vaduganathan M, Claggett BL, et al. Baseline characteristics of patients with hf with mildly reduced and preserved ejection fraction: DELIVER trial. *JACC Heart Fail*. 2022;10(3):184–197. doi:10.1016/j.jchf.2021.11.006
9. Savarese G, Stolfo D, Sinagra G, et al. Heart failure with mid-range or mildly reduced ejection fraction. *Nat Rev Cardiol*. 2022;19(2):100–116. doi:10.1038/s41569-021-00605-5
10. McDonagh TA, McDonagh TA, Metra M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;24(1):4–131. doi:10.1002/ejhf.2333
11. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. *Metabolism*. 2022;133:155217. doi:10.1016/j.metabol.2022.155217
12. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;143(21):e984–e1010. doi:10.1161/CIR.0000000000000973

13. Liu Z, Peng Y, Zhao W, et al. Obesity increases cardiovascular mortality in patients with HFmrEF. *Front Cardiovasc Med*. 2022;9:967780. doi:10.3389/fcvm.2022.967780
14. Benn M, Marott SCW, Tybjærg-Hansen A, et al. Obesity increases heart failure incidence and mortality: observational and Mendelian randomization studies totalling over 1 million individuals. *Cardiovasc Res*. 2023;118(18):3576–3585. doi:10.1093/cvr/cvab368
15. Simati S, Kokkinos A, Dalamaga M, et al. Obesity Paradox: fact or Fiction? *Curr Obes Rep*. 2023;12(2):75–85. doi:10.1007/s13679-023-00497-1
16. Tutor AW, Lavie CJ, Kachur S, Milani RV, Ventura HO. Updates on obesity and the obesity paradox in cardiovascular diseases. *Prog Cardiovasc Dis*. 2022;78:2–10.
17. Zeng S, Cai X, Zheng Y, et al. Associations of body mass index with mortality in heart failure with preserved ejection fraction patients with ischemic versus non-ischemic etiology. *Front Cardiovasc Med*. 2022;9:966745. doi:10.3389/fcvm.2022.966745
18. Kim SE, Lee CJ. The paradox in defining obesity in patients with heart failure. *Int J Heart Fail*. 2022;4(2):91–94. doi:10.36628/ijhf.2022.0010
19. Giri Ravindran S, Saha D, Iqbal I, et al. The obesity paradox in chronic heart disease and chronic obstructive pulmonary disease. *Cureus*. 2022;14(6):e25674. doi:10.7759/cureus.25674
20. Li S, Zheng Y, Huang Y, et al. Association of body mass index and prognosis in patients with HFpEF: a dose-response meta-analysis. *Int J Cardiol*. 2022;361:40–46. doi:10.1016/j.ijcard.2022.05.018
21. Dong B, Yao Y, Xue R, et al. Distinct implications of body mass index in different subgroups of nonobese patients with heart failure with preserved ejection fraction: a latent class analysis of data from the TOPCAT trial. *BMC Med*. 2022;20(1):423. doi:10.1186/s12916-022-02626-4
22. Tadic M, Cuspidi C. Obesity and heart failure with preserved ejection fraction: a paradox or something else? *Heart Fail Rev*. 2019;24(3):379–385. doi:10.1007/s10741-018-09766-x
23. Alrob OA, Sankaralingam S, Alazzam S, et al. Obesity paradox among heart failure with reduced ejection fraction patients: a retrospective cohort study. *Medicina*. 2022;59(1):60. doi:10.3390/medicina59010060
24. Wenzel JP, Nikorowitsch J, Bei der Kellen R, et al. Heart failure in the general population and impact of the 2021 European Society of Cardiology Heart Failure Guidelines. *ESC Heart Fail*. 2022;9(4):2157–2169. doi:10.1002/ehf2.13948
25. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2021;42(36):3599–3726. doi:10.1093/eurheartj/ehab368
26. Popescu BA, Andrade MJ, Badano LP, et al. European Association of Echocardiography recommendations for training, competence, and quality improvement in echocardiography. *Eur J Echocardiograp*. 2009;10(8):893–905. doi:10.1093/ejechocard/jep151
27. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14(7):611–644. doi:10.1093/ehjci/jet105
28. Badimon L, Bugiardini R, Cenko E, et al. Position paper of the European Society of Cardiology-working group of coronary pathophysiology and microcirculation: obesity and heart disease. *Eur Heart J*. 2017;38(25):1951–1958. doi:10.1093/eurheartj/ehx181
29. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol*. 2009;53(21):1925–1932. doi:10.1016/j.jacc.2008.12.068
30. Horwich TB, Fonarow GC, Clark AL. Obesity and the Obesity Paradox in Heart Failure. *Prog Cardiovasc Dis*. 2018;61(2):151–156. doi:10.1016/j.pcad.2018.05.005
31. Kenchaiah S, Pocock SJ, Wang D, et al. Body mass index and prognosis in patients with chronic heart failure: insights from the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation*. 2007;116(6):627–636. doi:10.1161/CIRCULATIONAHA.106.679779
32. Oreopoulos A, Padwal R, Kalantar-Zadeh K, et al. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J*. 2008;156(1):13–22. doi:10.1016/j.ahj.2008.02.014
33. Madamanchi C, Alhosaini H, Sumida A, et al. Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. *Int J Cardiol*. 2014;176(3):611–617. doi:10.1016/j.ijcard.2014.08.007
34. Padwal R, McAlister FA, McMurray JJV, et al. The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. *Int J Obes*. 2014;38(8):1110–1114. doi:10.1038/ijo.2013.203
35. Zhang J, Begley A, Jackson R, et al. Body mass index and all-cause mortality in heart failure patients with normal and reduced ventricular ejection fraction: a dose-response meta-analysis. *Clin Res Cardiol*. 2019;108(2):119–132. doi:10.1007/s00392-018-1302-7
36. Milajerdi A, Djafarian K, Shab-Bidar S, et al. Pre- and post-diagnosis body mass index and heart failure mortality: a dose-response meta-analysis of observational studies reveals greater risk of being underweight than being overweight. *Obes Rev*. 2018;20(2):252–261. doi:10.1111/obr.12777
37. Adamson C, Kondo T, Jhund PS, et al. Dapagliflozin for heart failure according to body mass index: the DELIVER trial. *Eur Heart J*. 2022;43(41):4406–4417. doi:10.1093/eurheartj/ehac481
38. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370(15):1383–1392. doi:10.1056/NEJMoa1313731