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ORIGINAL ARTICLE

# U-shaped association between body mass index and ejection fraction in intensive care unit patients with heart failure

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## Abstract

**Aims** There are limited data about the relationship between body mass index (BMI) and left ventricular ejection fraction (EF) in patients with heart failure (HF). The study aims to assess the correlation between BMI and left ventricular EF under HF conditions.

**Methods and results** We derived the data from the Dryad Digital Repository for analysis, and the information of the original patients was obtained from the MIMIC-III database by the data uploader. We performed smooth curve and two piecewise linear regression analyses to evaluate the association between BMI and EF in HF patients. A total of 962 participants were included in this study, with age of 73.7 ± 13.5 years, and 475 participants were male (49.4%). The results of the smooth curve supported a U-shaped relationship between BMI and EF, and the inflection point was found to be a BMI of 23.3 kg/m$^2$ in these HF patients. After adjusting for potential confounders, we found that EF decreased with increasing BMI up to the inflection point ($\beta = -0.7$, 95% CI $-1.3$ to $-0.1$, $P = 0.028$), whereas beyond the turning point, the relationship between EF and BMI showed a positive correlation ($\beta = 0.2$, 95% CI 0.1–0.3 $P < 0.001$). Importantly, ischaemic heart disease (interaction $P = 0.0499$) and hyperlipidaemia (interaction $P = 0.0162$) affected the association between BMI and EF in the lower BMI group (BMI $<$ 23.3 kg/m$^2$), although only diabetes mellitus (interaction $P = 0.0255$) altered the association between BMI and EF in the higher BMI group (BMI $\geq$ 23.3 kg/m$^2$).

**Conclusions** In addition to higher BMI, we also found that lower BMI is related to higher EF in intensive care unit patients with HF, supporting a U-shaped association between BMI and EF.

**Keywords** body mass index; ejection fraction; heart failure; association

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## Introduction

Heart failure (HF) is an end-stage clinical manifestation of organic heart disease, and it has become a major public health problem worldwide. According to the latest guidelines, the current incidence of HF in Europe is approximately 5/1000 person-years in adults.[1] In China, the prevalence rate of adult HF is 0.9%, and the fatality rate of hospitalized patients with HF is 4.1%.[2]

Left ventricular ejection fraction (EF) is generally used as a classification criterion for HF[3]: HF with reduced EF (HFrEF, EF $\leq$ 40%), HF with mildly reduced EF (HFmrEF, EF 41–49%), and HF with preserved EF (HFpEF, EF $\geq$ 50%). HF with improved EF (HFimpEF) is classified separately as EF $\leq$ 40% at baseline, EF $>$ 40% at second measurement, and a $\geq$10% point increase from baseline EF,[3] respectively. Therefore, the discovery of some modifiable risk factors that are associated with EF can help to better determine the status of HF for aggressive treatment.

Body mass index (BMI) is the most commonly used index to measure the degree of obesity. Obesity, a modifiable cardiovascular disease risk factor,[4] has been shown to be

associated with an increased risk of HF and cardiovascular disease,[5,6] whereas other studies have shown that patients with HF with an overweight BMI have a better prognosis.[7,8] There is a phenomenon called the 'obesity paradox' in many diseases, such as diabetes,[9] chronic kidney disease,[10] atrial fibrillation (AF),[11] hypertension,[12] and stroke[13]; that is, the prognosis of overweight or moderately obese patients seems to be better than that of patients with a normal BMI. Several studies have found that all-cause mortality of patients with HFrEF is generally higher than that of patients with HFpEF,[14,15] and for HFrEF patients, improving left ventricular systolic function through some treatments can improve the prognosis.[16,17] Other studies have also found that patients with improved EF have better outcomes than those with persistent EF reduction.[18,19] The above evidence suggests that EF is closely related to the risk of death in patients with HF. Recently, a higher BMI was found to be closely related to EF recovery in patients with dilated cardiomyopathy.[20] As the relationship between obesity and EF is unclear, further confirmation is needed. The aim of our study was to further evaluate the association between BMI and EF in HF patients to provide additional evidence.

# Materials and methods

## Data source

We used the data downloaded from the Dryad Digital Repository for secondary analysis (Dryad data package: Zhou, Jingmin *et al*. (2021), Prediction model of in-hospital mortality in intensive care unit (ICU) patients with heart failure: machine learning-based, retrospective analysis of the MIMIC-III database, Dryad, Dataset, https://doi.org/10.5061/dryad.0p2ngf1zd). Dyrad is a non-profit repository that stores research data in the fields of medicine, biology, and ecology. It is open to the world and can be downloaded and reused free of charge. Dyrad is committed to promoting the flow of scientific data and providing researchers with easy access to high-quality data resources. Because this was a post hoc study using existing research data, informed consent was waived.

## Study population and handling of missing data

The original information of HF patients was obtained from the MIMIC-III database (V.1.4, 2016), a public critical care database that contains records of 46 520 patients and 58 976 admissions at Beth Israel Deaconess Medical Center from 2001 to 2012.[21] The data uploaded by Zhou *et al*. on Dryad included 1177 adult patients with HF, all of whom had left ventricular EF data. We conducted further data screening according to the study design, excluding 215 patients with missing BMI data. Ultimately, 962 patients were enrolled in this study. To handle missing data, according to the description of Li *et al*.,[22] we retained variables with less than 25% missing values, and for the continuous variables of normal distributions, the missing values were replaced by the mean value. For the continuous variables with skewed distributions, the missing values were replaced by the median value. There were no missing dichotomous variables in this study.

## Covariates

Variables that might be related to BMI and EF needed to be adjusted to increase the reliability of the results. This mainly included demographic data (age and gender), clinical co-morbidities [hypertension, AF, ischaemic heart disease, diabetes mellitus, hypoferric anaemia, depression, hyperlipidaemia, chronic renal insufficiency, and chronic obstructive pulmonary disease (COPD)].

## Statistical analysis

Normally distributed data are presented as the mean (SD), skewed distributions are expressed as the median [interquartile range (IQR)], and categorical variables are expressed as *n* (%). To compare the differences between groups, we used independent *t*-tests (normal distribution), Mann–Whitney *U* tests (skewed distribution), and chi-square tests (categorical variables) for analysis.

First, we implemented a smooth curve to estimate BMI and EF. Then, according to the fitting result of the smooth curve and log likelihood ratio test, a two-piecewise linear regression model was performed to evaluate the relationship between BMI and EF. We used adjusted models to make the results more reliable (crude model: adjusted for no. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, hypertension, AF, ischemic heart disease, diabetes mellitus, hypoferric anaemia, depression, hyperlipidaemia, and COPD). Finally, subgroup analysis and interaction analysis were performed to identify potential modifiers.

We used the statistical packages R for all data analyses (The R Foundation; http://www.r-project.org; version 3.4.3) and Empower (R) (www.empowerstats.com, X&Y Solutions, Inc. Boston, MA). $P < 0.05$ was considered a statistically significant criterion.

# Results

## Characteristics of participants

A total of 962 participants were enrolled in this study, with an age of 73.7 ± 13.5 years old, and 475 participants were male

(49.4%). We divided all participants into two groups based on the BMI turning points shown in *Figure 1* (BMI $< 23.3$ kg/m$^2$, BMI $\geq 23.3$ kg/m$^2$). Compared with the high-BMI participants (BMI $\geq$ 23.3 kg/m$^2$), participants with a low BMI (BMI $<$ 23.3 kg/m$^2$) had significantly higher age and higher levels of platelet count, neutrophils, and NT-proBNP, as well as a lower male ratio, decreased urine output (first 24 h), and lower levels of creatinine, blood urea nitrogen, glucose, and bicarbonate. In addition, compared with high-BMI participants, low-BMI participants tended to have a lower rate of AF, diabetes mellitus, and chronic renal insufficiency. More details are shown in *Table 1*.

## Association of BMI with EF

The non-linear association between EF and BMI was examined before and after adjustment for confounding factors. After fully adjusting for the confounding factors of age, gender, hypertension, AF, ischaemic heart disease, diabetes mellitus, hypoferric anaemia, depression, hyperlipidaemia, chronic renal insufficiency, and COPD, the smooth curve supported a U-shaped relationship between serum BMI and EF in these HF patients ($P = 0.009$) (*Figure 1*), and the turning point was BMI = 23.3 kg/m$^2$. $P$ for the log-likelihood ratio test was less than 0.05, indicating that the two-piecewise linear regression model was suitable for fitting the association between BMI and EF. After adjusting for the above confounding factors, the EF decreased with increasing BMI up to the inflection point ($\beta = -0.7$, 95% CI $-1.3$ to $-0.1$, $P = 0.028$). However, beyond the inflection point, EF and BMI showed a positive correlation ($\beta = 0.2$, 95% CI 0.1–0.3 $P < 0.001$) (*Table 2*).

## Subgroup analysis and interaction analysis

Stratified analyses were performed using gender, hypertension, AF, ischaemic heart disease, diabetes mellitus, hypoferric anaemia, depression, hyperlipidaemia, chronic renal insufficiency, and COPD as stratification variables to assess the association between BMI and EF, as shown in *Table 3*. Interestingly, we found interactions for ischaemic heart disease (interaction $P = 0.0499$) and hyperlipidaemia (interaction $P = 0.0162$) in the low-BMI group (BMI $<$ 23.3 kg/m$^2$), whereas there was an interaction for diabetes mellitus (interaction $P = 0.0255$) in the high-BMI group (BMI $\geq$ 23.3 kg/m$^2$). In the low-BMI group (BMI $<$ 23.3 kg/m$^2$), a stronger association between BMI and EF was present in patients without hyperlipidaemia ($P = 0.0190$). In the high-BMI group (BMI $\geq$ 23.3 kg/m$^2$), a stronger positive correlation between BMI and EF was present in patients with diabetes mellitus ($P = 0.0004$).

# Discussion

In this study of 962 participants, we found a U-shaped association between BMI and EF in HF patients after adjusting for important identified confounders. The inflection point for the curve was found to be a BMI of 23.3 kg/m$^2$. To the best of our knowledge, we are the first to find that a lower BMI is related to higher EF in ICU patients with HF, in addition to a previous report relating to a higher BMI.

Obesity is an important risk factor for cardiovascular diseases.[23] Previous studies have focused on the relationship between obesity and mortality. There was a J-shaped or U-shaped relationship between BMI and mortality in the

**Figure 1** Smooth curve on association between BMI and EF. Adjustment factors included age, gender, hypertension, atrial fibrillation, ischaemic heart disease, diabetes mellitus, hypoferric anaemia, depression, hyperlipidaemia, chronic renal insufficiency, and chronic obstructive pulmonary disease.

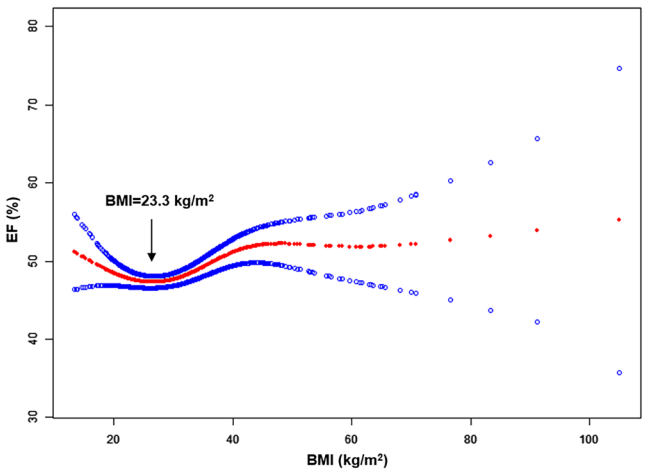

**Table 1** Clinical characteristics of patients with heart failure during the ICU

| Variables | Total | BMI < 23.3 | BMI ≥ 23.3 | *P*-value |
|---|---|---|---|---|
| *N* | 962 | 188 | 774 | |
| Age, mean (SD), years | 73.7 (13.5) | 79.2 (11.6) | 72.4 (13.6) | <0.001 |
| Heart rate, mean (SD), bpm | 84.1 (16.0) | 86.2 (16.2) | 83.6 (16.0) | 0.049 |
| Systolic blood pressure, mean (SD), mmHg | 117.6 (17.1) | 117.9 (17.5) | 117.5 (17.0) | 0.741 |
| Diastolic blood pressure, mean (SD), mm Hg | 59.6 (10.5) | 58.7 (10.6) | 59.8 (10.5) | 0.189 |
| Respiratory rate, mean (SD), bpm | 20.8 (4.0) | 21.3 (4.2) | 20.6 (3.9) | 0.078 |
| Temperature, mean (SD), °C | 36.7 (0.6) | 36.6 (0.6) | 36.7 (0.6) | 0.177 |
| $SPO_2$, mean (SD), % | 96.2 (2.3) | 96.6 (2.0) | 96.2 (2.4) | 0.016 |
| Urine-output (first 24 h), median (Q1–Q3), mL | 1685.0 (1009.2–2540.0) | 1360.0 (897.8–1897.5) | 1753.0 (1067.5–2665.0) | <0.001 |
| Haematocrit, mean (SD), % | 31.9 (5.2) | 31.6 (4.9) | 32.0 (5.3) | 0.414 |
| Red cells, mean (SD), ×10^12/L | 3.6 (0.6) | 3.5 (0.6) | 3.6 (0.6) | 0.180 |
| MCH, mean (SD), pg | 29.5 (2.6) | 29.7 (2.7) | 29.4 (2.6) | 0.225 |
| MCHC, mean (SD), % | 32.9 (1.4) | 32.9 (1.4) | 32.9 (1.4) | 0.589 |
| MCV, mean (SD), fL | 89.7 (6.5) | 90.2 (6.4) | 89.6 (6.6) | 0.275 |
| RDW, mean (SD), % | 15.9 (2.1) | 15.7 (2.0) | 16.0 (2.1) | 0.089 |
| White cells, mean (SD), ×10^9/L | 10.6 (5.3) | 11.1 (5.3) | 10.5 (5.3) | 0.186 |
| Platelet count, median (Q1–Q3), ×10^9/L | 222.4 (166.9–303.5) | 246.6 (187.7–318.7) | 217.8 (163.2–296.7) | 0.001 |
| Neutrophils, mean (SD), % | 79.9 (10.5) | 81.0 (12.0) | 79.7 (10.0) | 0.011 |
| Lymphocytes, median (Q1–Q3), % | 10.6 (7.2–15.0) | 10.6 (6.3–13.0) | 10.6 (7.5–15.3) | 0.016 |
| PT, mean (SD), s | 17.6 (7.5) | 17.4 (6.7) | 17.6 (7.7) | 0.771 |
| INR, median (Q1–Q3) | 1.3 (1.1–1.7) | 1.3 (1.1–1.7) | 1.3 (1.1–1.7) | 0.886 |
| NT-proBNP, median (Q1–Q3), pg/mL | 5953.0 (2276.5–15077.0) | 8579.5 (3197.5–17819.9) | 5402.5 (2092.4–13652.1) | 0.030 |
| Creatine kinase (CK), median (Q1–Q3), IU/L | 91.0 (51.8–173.7) | 86.8 (42.7–145.4) | 91.0 (56.0–175.0) | 0.006 |
| Creatinine, median (Q1–Q3), mg/dL | 1.3 (1.0–1.9) | 1.2 (0.9–1.7) | 1.4 (1.0–2.0) | 0.009 |
| Blood urea nitrogen, median (Q1–Q3), mg/dL | 31.2 (21.5–45.4) | 29.0 (20.1–39.9) | 31.9 (21.9–46.9) | 0.018 |
| Glucose, mean (SD), mEq/L | 150.0 (51.1) | 142.1 (43.6) | 152.0 (52.6) | 0.017 |
| Potassium, mean (SD), mEq/L | 4.2 (0.4) | 4.1 (0.4) | 4.2 (0.4) | 0.054 |
| Sodium, mean (SD), mEq/L | 138.9 (4.0) | 138.9 (4.4) | 138.9 (3.9) | 0.899 |
| Calcium, total, mean (SD), mg/dL | 8.5 (0.6) | 8.5 (0.6) | 8.5 (0.6) | 0.198 |
| Chloride, mean (SD), mEq/L | 102.2 (5.2) | 103.1 (5.4) | 102.0 (5.2) | 0.012 |
| Anion gap, mean (SD), mEq/L | 14.0 (2.7) | 14.0 (2.5) | 13.9 (2.7) | 0.675 |
| Magnesium, mean (SD), mg/dL | 2.1 (0.2) | 2.1 (0.2) | 2.1 (0.3) | 0.107 |
| Bicarbonate, mean (SD), mEq/L | 26.9 (5.2) | 25.9 (4.7) | 27.2 (5.3) | 0.003 |
| Lactate, median (Q1–Q3), mmol/L | 1.6 (1.3–2.0) | 1.6 (1.3–2.1) | 1.6 (1.3–2.0) | 0.735 |
| LVEF, mean (SD), % | 48.5 (12.9) | 49.8 (13.0) | 48.2 (12.9) | 0.120 |
| Gender | | | | 0.010 |
| Male (*n*, %) | 475 (49.4%) | 77 (41.0%) | 398 (51.4%) | |
| Female (*n*, %) | 487 (50.6%) | 111 (59.0%) | 376 (48.6%) | |
| Hypertension | | | | 0.408 |
| No (*n*, %) | 269 (28.0%) | 48 (25.5%) | 221 (28.6%) | |
| Yes (*n*, %) | 693 (72.0%) | 140 (74.5%) | 553 (71.4%) | |
| Atrial fibrillation | | | | 0.007 |
| No (*n*, %) | 535 (55.6%) | 88 (46.8%) | 447 (57.8%) | |
| Yes (*n*, %) | 427 (44.4%) | 100 (53.2%) | 327 (42.2%) | |
| Ischaemic heart disease | | | | 0.421 |
| No (*n*, %) | 879 (91.4%) | 169 (89.9%) | 710 (91.7%) | |
| Yes (*n*, %) | 83 (8.6%) | 19 (10.1%) | 64 (8.3%) | |
| Diabetes mellitus | | | | <0.001 |
| No (*n*, %) | 546 (56.8%) | 132 (70.2%) | 414 (53.5%) | |
| Yes (*n*, %) | 416 (43.2%) | 56 (29.8%) | 360 (46.5%) | |
| Hypoferric anaemia | | | | 0.438 |
| No (*n*, %) | 637 (66.2%) | 129 (68.6%) | 508 (65.6%) | |
| Yes (*n*, %) | 325 (33.8%) | 59 (31.4%) | 266 (34.4%) | |
| Depression | | | | 0.326 |
| No (*n*, %) | 839 (87.2%) | 168 (89.4%) | 671 (86.7%) | |
| Yes (*n*, %) | 123 (12.8%) | 20 (10.6%) | 103 (13.3%) | |
| Hyperlipidaemia | | | | 0.167 |
| No (*n*, %) | 587 (61.0%) | 123 (65.4%) | 464 (59.9%) | |
| Yes (*n*, %) | 375 (39.0%) | 65 (34.6%) | 310 (40.1%) | |
| Chronic renal insufficiency | | | | 0.017 |

(*Continues*)

**Table 1** (continued)

| Variables | Total | BMI < 23.3 | BMI ≥ 23.3 | *P*-value |
|---|---|---|---|---|
| No (*n*, %) | 592 (61.5%) | 130 (69.1%) | 462 (59.7%) | |
| Yes (*n*, %) | 370 (38.5%) | 58 (30.9%) | 312 (40.3%) | |
| COPD | | | | 0.155 |
| No (*n*, %) | 893 (92.8%) | 170 (90.4%) | 723 (93.4%) | |
| Yes (*n*, %) | 69 (7.2%) | 18 (9.6%) | 51 (6.6%) | |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; NT-proBNP, N-terminal pro-brain natriuretic peptide; PT, lymphocytes, prothrombin time; RDW, red blood cell distribution width; SPO2, saturation pulse oxygen.
Data are presented as mean ± SD, median (IQR), or %.

**Table 2** Two-piecewise linear regression for relationship between BMI and EF

| Variables | | β | β 95% CI | P-value |
|---|---|---|---|---|
| Crude Mode | Inflection point (23.4) | | | |
| | <23.4 | −1.0 | −1.6, −0.4 | 0.002 |
| | ≥23.4 | 0.2 | 0.1, 0.3 | 0.002 |
| | Likelihood ratio test | | | <0.001 |
| Mode1 | Inflection point (23.3) | | | |
| | <23.3 | −0.8 | −1.4, −0.2 | 0.015 |
| | ≥23.3 | 0.2 | 0.1, 0.3 | <0.001 |
| | Likelihood ratio test | | | 0.004 |
| Mode2 | Inflection point (23.3) | | | |
| | <23.3 | −0.7 | −1.3, −0.1 | 0.028 |
| | ≥23.3 | 0.2 | 0.1, 0.3 | <0.001 |
| | Likelihood ratio test | | | 0.009 |

Crude model: adjusted for no. Model 1: adjusted for age and gender. Model 2: adjusted for age, gender, hypertension, atrial fibrillation, ischaemic heart disease, diabetes mellitus, hypoferric anaemia, depression, hyperlipidaemia, chronic renal insufficiency, and chronic obstructive pulmonary disease.

general population, and a BMI range of 20–25 kg/m$^2$ was associated with the lowest risk of mortality.[24,25] The relationship between BMI and mortality in patients with cardiovascular disease is still U-shaped, but the nadir of mortality risk occurs in the range of overweight (BMI range of 25.0–30.0 kg/m$^2$).[26] Currently, there is ample evidence to support the 'obesity paradox' in patients with cardiovascular disease.[27]

EF is a common indicator of cardiac function and is used as a classification criterion for HF. In our study, we found that lower and higher BMI was associated with higher EF in patients with HF. According to the 'obesity paradox' in the prognosis of patients with HF, it is well understood that higher BMI is related to higher EF. A study of HF patients diagnosed with dilated cardiomyopathy showed that higher BMI was closely related to recovered EF and that BMI was a valid predictor of EF improvement in HFrEF.[20] The conclusions of this study are consistent with some of our results. The driving mechanism of this association is unclear, and the underlying cause may be the neutralizing inflammatory endotoxins by higher-level lipoproteins,[28] the reduced response of renin–angiotensin–aldosterone system,[29] and the higher nutritional and metabolic reserves in obesity patients.[30] Also, obese patients may seek medical treatment in time due to earlier onset of symptoms.[31]

Another interesting result was that we found that lower BMI was also associated with higher EF, which might be the first time this phenomenon has been reported in ICU patients. This finding might be supported by several studies. Results from the Swedish Obese Subjects cohort study showed that bariatric surgery was related to a reduced risk of HF in obese patients, and the risk of HF appeared to decrease with increased weight loss.[32] A systematic review based on randomized controlled trials and observational studies indicated that weight loss can improve left ventricular function and quality of life in obese patients with HF.[33] In a case report, a 27-year-old male who weighed 245 kg significantly reversed HF after weight loss of 146 kg, with systolic EF improved from 30 to 51%.[34] The possible mechanisms of weight loss and improvement of HF symptoms have also been explored. In obese mice with HF, after induced weight loss, EF was significantly improved, and left ventricular mass was significantly decreased. Further analysis showed that weight loss can enhance cardiac insulin signalling, reduce the cardiac fatty acid oxidation rate, and improve related metabolic pathways.[35] In addition, weight loss might play a beneficial role by improving the gene richness, composition, and function of gut microbes associated with cardiovascular disease.[36]

**Table 3** Subgroup analyses by potential effect modifiers

| | BMI < 23.3 | | | BMI ≥ 23.3 | | |
|---|---|---|---|---|---|---|
| Subgroup | β, 95% CI | *P* | Interaction *P* | β, 95% CI | *P* | Interaction *P* |
| Gender | | | | | | |
| Male | −0.5 (−2.1, 1.0) | 0.4842 | 0.9155 | 0.1 (−0.0, 0.3) | 0.1672 | 0.1317 |
| Female | −0.5 (−1.5, 0.6) | 0.4188 | | 0.3 (0.1, 0.4) | 0.0005 | |
| Hypertension | | | | | | |
| No | −0.4 (−2.3, 1.4) | 0.6365 | 0.9627 | 0.1 (−0.1, 0.2) | 0.4313 | 0.0626 |
| Yes | −0.5 (−1.5, 0.5) | 0.3367 | | 0.3 (0.1, 0.4) | 0.0002 | |
| Atrial fibrillation | | | | | | |
| No | 0.5 (−1.7, 0.8) | 0.4707 | 0.9645 | 0.2 (0.1, 0.3) | 0.0010 | 0.3695 |
| Yes | −0.5 (−1.7, 0.7) | 0.4237 | | 0.1 (−0.1, 0.3) | 0.1879 | |
| Ischaemic heart disease | | | | | | |
| No | −0.7 (−1.6, 0.2) | 0.1464 | 0.0499 | 0.2 (0.1, 0.3) | 0.0008 | 0.6113 |
| Yes | 3.4 (−0.7, 7.4) | 0.1078 | | 0.0 (−0.6, 0.7) | 0.9613 | |
| Hyperlipidaemia | | | | | | |
| No | −1.4 (−2.6,-0.2) | 0.0190 | 0.0162 | 0.2 (0.1, 0.3) | 0.0027 | 0.8254 |
| Yes | 0.6 (−0.7, 1.9) | 0.3517 | | 0.2 (−0.0, 0.4) | 0.0857 | |
| Diabetes mellitus | | | | | | |
| No | −0.1 (−1.2, 1.0) | 0.8335 | 0.2551 | 0.1 (−0.0, 0.2) | 0.1915 | 0.0255 |
| Yes | −1.1 (−2.6, 0.3) | 0.1306 | | 0.3 (0.1, 0.5) | 0.0004 | |
| Hypoferric anaemia | | | | | | |
| No | −0.2 (−1.3, 0.9) | 0.7253 | 0.3672 | 0.2 (0.0, 0.3) | 0.0141 | 0.4251 |
| Yes | −1.0 (−2.5, 0.5) | 0.1840 | | 0.2 (0.1, 0.4) | 0.0094 | |
| Depression | | | | | | |
| No | −0.6 (−1.5, 0.4) | 0.2311 | 0.5260 | 0.2 (0.1, 0.3) | 0.0012 | 0.7554 |
| Yes | 0.2 (−2.2, 2.6) | 0.8677 | | 0.1 (−0.1, 0.4) | 0.3060 | |
| Chronic renal insufficiency | | | | | | |
| No | −0.6 (−1.7, 0.4) | 0.2507 | 0.6193 | 0.2 (0.1, 0.3) | 0.0049 | 0.6430 |
| Yes | −0.1 (−1.8, 1.5) | 0.8704 | | 0.2 (0.0, 0.4) | 0.0400 | |
| COPD | | | | | | |
| No | −0.2 (−1.2, 0.8) | 0.6883 | 0.1480 | 0.2 (0.1, 0.3) | 0.0028 | 0.2063 |
| Yes | −1.9 (−4.0, 0.3) | 0.0885 | | 0.4 (0.0, 0.9) | 0.0380 | |

Adjusted for age, gender, hypertension, atrial fibrillation, ischaemic heart disease, diabetes mellitus, hypoferric anaemia, depression, hyperlipidaemia, chronic renal insufficiency, and chronic obstructive pulmonary disease (COPD) except the subgroup variable.

We used stratification analyses to evaluate interactions with the independent association between BMI and EF by adding 'gender', 'hypertension', 'AF', 'ischaemic heart disease', 'hyperlipidaemia', 'diabetes mellitus', 'hypoferric anaemia', 'depression', 'chronic renal insufficiency', and 'COPD' as covariates. In the low-BMI group, 'ischaemic heart disease' and 'hyperlipidaemia' were found to be effect modifiers on the relationship between BMI and EF. The results showed that in the lower-BMI group, there was a strong negative correlation between BMI and EF in patients without hyperlipidaemia, but the correlation disappeared in patients with hyperlipidaemia. Lower BMI is generally associated with a lower risk of hyperlipidaemia; therefore, hyperlipidaemia might be a strong factor that modifies the association between BMI and EF in low-weight patients. Interestingly, 'diabetes mellitus' was a significant effect modifier on the relationship between BMI and EF in the high-BMI group, and there was still a strong correlation between BMI and EF in patients with diabetes. We found that increased BMI was still associated with higher EF in HF patients with co-morbid diabetes, whereas several studies have confirmed that obesity has a survival benefit for HF patients without diabetes but not for those with diabetes.[37,38] Another study showed that the 'obesity paradox' still existed in HFpEF patients with co-morbid diabetes without insulin treatment.[39] The underlying mechanisms of these controversial phenomena require further study.

There are several strengths in our study. First, the original information of patients came from the MIMIC-III database, an intensive care dataset established by professional researchers, which ensured the reliability and standardization of the data. Second, this study adjusted for many confounding factors, including various medical histories, to improve the reliability of the conclusions. Finally, this study found for the first time that there was a U-shaped correlation between BMI and EF in HF patients and found an inflection point, providing a further theoretical basis for the controversial topic of the 'obesity paradox'.

There are also some limitations in this study. First, the included HF patients were not distinguished by the specific types of HF; additionally, whether the patients had an acute episode of chronic HF was unclear, indicating that further research is needed to determine whether HF type affects the correlation between BMI and EF. Second, some other echocardiographic data that can be helpful for the better phenotype characterization were lacked, such as the left ventricle wall thickness and dimensions, the left atrium diameter, and the estimation of the right ventricle systolic pressure.

Third, this study was based on the secondary analysis of published data, so the variables that were not included in the dataset could not be adjusted for as confounding factors. Finally, our subjects were mainly ICU patients, so it is not clear whether the results can be applied to other populations. Further investigation in other populations is needed.

## Conclusions

In summary, both lower BMI and higher BMI are related to higher EF in ICU patients with HF. Our study suggests that the relationship between BMI and EF is non-linear and takes on a U-shaped curve. When BMI was lower than 23.3 kg/m$^2$, it had a significantly negative correlation with EF; when BMI was higher than 23.3 kg/m$^2$, it had a significantly positive correlation with EF. Going forward, further analyses are needed to elucidate this association between BMI and EF and to explore the underlying biological mechanisms.

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## Conflict of interest

None.

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## References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, Group ESCSD. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021; **2021**: 3599–3726.
2. Heart Failure Group of Chinese Society of Cardiology of Chinese Medical A, Chinese Heart Failure Association of Chinese Medical Doctor A, Editorial Board of Chinese Journal of C. Chinese guidelines for the diagnosis and treatment of heart failure 2018. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2018; **46**: 760–789.
3. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Bohm M, Butler J, Drazner MH, Michael Felker G, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa JE, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferovic P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. 2021; **23**: 352–380.
4. Karasoy D, Bo Jensen T, Hansen ML, Schmiegelow M, Lamberts M, Gislason GH, Hansen J, Torp-Pedersen C, Olesen JB. Obesity is a risk factor for atrial fibrillation among fertile young women: A nationwide cohort study. *Europace*. 2013; **15**: 781–786.
5. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: The Framingham experience. *Arch Intern Med*. 2002; **162**: 1867–1872.
6. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med*. 2002; **347**: 305–313.
7. Sharma A, Lavie CJ, Borer JS, Vallakati A, Goel S, Lopez-Jimenez F, Arbab-Zadeh A, Mukherjee D, Lazar JM. Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. *Am J Cardiol*. 2015; **115**: 1428–1434.
8. Mehta T, Smith DL Jr, Muhammad J, Casazza K. Impact of weight cycling on risk of morbidity and mortality. *Obes Rev*. 2014; **15**: 870–881.
9. Carnethon MR, De Chavez PJ, Biggs ML, Lewis CE, Pankow JS, Bertoni AG, Golden SH, Liu K, Mukamal KJ, Campbell-Jenkins B, Dyer AR. Association of weight status with mortality in adults with incident diabetes. *JAMA*. 2012; **308**: 581–590.
10. Rhee CM, Ahmadi SF, Kalantar-Zadeh K. The dual roles of obesity in chronic kidney disease: A review of the current literature. *Curr Opin Nephrol Hypertens*. 2016; **25**: 208–216.
11. Zhu W, Wan R, Liu F, Hu J, Huang L, Li J, Hong K. Relation of body mass index with adverse outcomes among patients with atrial fibrillation: A meta-analysis and systematic review. *J Am Heart Assoc*. 2016; **5**: e004006.
12. Uretsky S, Messerli FH, Bangalore S, Champion A, Cooper-Dehoff RM, Zhou Q, Pepine CJ. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med*. 2007; **120**: 863–870.
13. Andersen KK, Olsen TS. The obesity paradox in stroke: lower mortality and lower risk of readmission for recurrent stroke in obese stroke patients. *Int J Stroke*. 2015; **10**: 99–104.
14. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Nielsen OW, Zannad F, Tavazzi L, Heart Failure Association of the European Society of C. EURObservational research programme: Regional differences and 1-year follow-up results of the heart failure pilot survey (ESC-HF pilot). *Eur J Heart Fail*. 2013; **15**: 808–817.
15. Iorio A, Senni M, Barbati G, Greene SJ, Poli S, Zambon E, Di Nora C, Cioffi G,

Tarantini L, Gavazzi A, Sinagra G, Di Lenarda A. Prevalence and prognostic impact of non-cardiac co-morbidities in heart failure outpatients with preserved and reduced ejection fraction: a community-based study. *Eur J Heart Fail*. 2018; **20**: 1257–1266.
16. Florea VG, Rector TS, Anand IS, Cohn JN. Heart failure with improved ejection fraction: Clinical characteristics, correlates of recovery, and survival: Results from the valsartan heart failure trial. *Circ Heart Fail*. 2016; **9**: e003123.
17. Jorgensen ME, Andersson C, Vasan RS, Kober L, Abdulla J. Characteristics and prognosis of heart failure with improved compared with persistently reduced ejection fraction: A systematic review and meta-analyses. *Eur J Prev Cardiol*. 2018; **25**: 366–376.
18. Lupon J, Diez-Lopez C, de Antonio M, Domingo M, Zamora E, Moliner P, Gonzalez B, Santesmases J, Troya MI, Bayes-Genis A. Recovered heart failure with reduced ejection fraction and outcomes: A prospective study. *Eur J Heart Fail*. 2017; **19**: 1615–1623.
19. Ghimire A, Fine N, Ezekowitz JA, Howlett J, Youngson E, McAlister FA. Frequency, predictors, and prognosis of ejection fraction improvement in heart failure: An echocardiogram-based registry study. *Eur Heart J*. 2019; **40**: 2110–2117.
20. Ye LF, Li XL, Wang SM, Wang YF, Zheng YR, Wang LH. Body mass index: An effective predictor of ejection fraction improvement in heart failure. *Front Cardiovasc Med*. 2021; **8**: 586240.
21. Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, Moody B, Szolovits P, Celi LA, Mark RG. MIMIC-III, a freely accessible critical care database. *Sci Data*. 2016; **3**: 160035.
22. Li F, Xin H, Zhang J, Fu M, Zhou J, Lian Z. Prediction model of in-hospital mortality in intensive care unit patients with heart failure: Machine learning-based, retrospective analysis of the MIMIC-III database. *BMJ Open*. 2021; **11**: e044779.
23. Carbone S, Canada JM, Billingsley HE, Siddiqui MS, Elagizi A, Lavie CJ. Obesity paradox in cardiovascular disease: Where do we stand? *Vasc Health Risk Manag*. 2019; **15**: 89–100.
24. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, Romundstad P, Vatten LJ. BMI and all cause mortality: Systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ*. 2016; **353**: i2156.
25. Global BMIMC, Di Angelantonio E, Bhupathiraju SN, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, Cairns BJ, Huxley R, Jackson CL, Joshy G, Lewington S, Manson JE, Murphy N, Patel AV, Samet JM, Woodward M, Zheng W, Zhou M, Bansal N, Barricarte A, Carter B, Cerhan JR, Smith GD, Fang X, Franco OH, Green J, Halsey J, Hildebrand JS, Jung KJ, Korda RJ, McLerran DF, Moore SC, O'Keeffe LM, Paige E, Ramond A, Reeves GK, Rolland B, Sacerdote C, Sattar N, Sofianopoulou E, Stevens J, Thun M, Ueshima H, Yang L, Yun YD, Willeit P, Banks E, Beral V, Chen Z, Gapstur SM, Gunter MJ, Hartge P, Jee SH, Lam TH, Peto R, Potter JD, Willett WC, Thompson SG, Danesh J, Hu FB. Body-mass index and all-cause mortality: Individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet (London, England)*. 2016; **388**: 776–786.
26. Antonopoulos AS, Tousoulis D. The molecular mechanisms of obesity paradox. *Cardiovasc Res*. 2017; **113**: 1074–1086.
27. Antonopoulos AS, Oikonomou EK, Antoniades C, Tousoulis D. From the BMI paradox to the obesity paradox: The obesity-mortality association in coronary heart disease. *Obes Rev*. 2016; **17**: 989–1000.
28. Horwich TB, Fonarow GC, Clark AL. Obesity and the obesity paradox in heart failure. *Prog Cardiovasc Dis*. 2018; **61**: 151–156.
29. Okoshi MP, Capalbo RV, Romeiro FG, Okoshi K. Cardiac cachexia: Perspectives for prevention and treatment. *Arq Bras Cardiol*. 2017; **108**: 74–80.
30. Josiak K, Jankowska EA, Piepoli MF, Banasiak W, Ponikowski P. Skeletal myopathy in patients with chronic heart failure: Significance of anabolic-androgenic hormones. *J Cachexia Sarcopenia Muscle*. 2014; **5**: 287–296.
31. Mebazaa A, Gheorghiade M, Pina IL, Harjola VP, Hollenberg SM, Follath F, Rhodes A, Plaisance P, Roland E, Nieminen M, Komajda M, Parkhomenko A, Masip J, Zannad F, Filippatos G. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. *Crit Care Med*. 2008; **36**: S129–S139.
32. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Karason K. Surgical obesity treatment and the risk of heart failure. *Eur Heart J*. 2019; **40**: 2131–2138.
33. McDowell K, Petrie MC, Raihan NA, Logue J. Effects of intentional weight loss in patients with obesity and heart failure: A systematic review. *Obes Rev*. 2018; **19**: 1189–1204.
34. Zuber M, Kaeslin T, Studer T, Erne P. Weight loss of 146 kg with diet and reversal of severe congestive heart failure in a young, morbidly obese patient. *Am J Cardiol*. 1999; **84**: 955–956, A8.
35. Karwi QG, Zhang L, Altamimi TR, Wagg CS, Patel V, Uddin GM, Joerg AR, Padwal RS, Johnstone DE, Sharma A, Oudit GY, Lopaschuk GD. Weight loss enhances cardiac energy metabolism and function in heart failure associated with obesity. *Diabetes Obes Metab*. 2019; **21**: 1944–1955.
36. Aron-Wisnewsky J, Prifti E, Belda E, Ichou F, Kayser BD, Dao MC, Verger EO, Hedjazi L, Bouillot JL, Chevallier JM, Pons N, Le Chatelier E, Levenez F, Ehrlich SD, Dore J, Zucker JD, Clement K. Major microbiota dysbiosis in severe obesity: Fate after bariatric surgery. *Gut*. 2019; **68**: 70–82.
37. Zamora E, Lupon J, Enjuanes C, Pascual-Figal D, de Antonio M, Domingo M, Comin-Colet J, Vila J, Penafiel J, Farre N, Alonso N, Santesmases J, Troya M, Bayes-Genis A. No benefit from the obesity paradox for diabetic patients with heart failure. *Eur J Heart Fail*. 2016; **18**: 851–858.
38. Lee KS, Moser DK, Lennie TA, Pelter MM, Nesbitt T, Southard JA, Dracup K. Obesity paradox: Comparison of heart failure patients with and without comorbid diabetes. *Am J Crit Care*. 2017; **26**: 140–148.
39. Ye M, Choy M, Liu X, Huang P, Wu Y, Dong Y, Zhu W, Liu C. Associations of BMI with mortality in HFpEF patients with concomitant diabetes with insulin versus non-insulin treatment. *Diabetes Res Clin Pract*. 2022; **185**: 109805.