Underweight Predicts Greater Risk of Cardiac Mortality Post Acute Myocardial Infarction

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Summary
Increased body mass index (BMI) is a well-established risk factor for cardiovascular disease; however, patients with elevated BMI, in comparison to those with low BMI, seem to have better survival, a phenomenon reported as “obesity paradox,” which remains controversial. We investigated the effect of BMI on cardiac mortality post acute myocardial infarction (AMI).

In this analysis, 3562 AMI patients were included and classified into four groups based on BMI values. The primary endpoint was cardiac death. Compared to normoweight group, overweight and obese group subjects were younger, mostly men, and more likely to receive percutaneous coronary intervention (PCI) and had higher levels of glucose and lipids, but lower level of NTproBNP. Subjects in the underweight group were older, were mostly women, had lower Barthel index (BI), were less likely to receive PCI, and had lower levels of glucose and lipids, but higher level of N-terminal pro-brain natriuretic peptide (NTproBNP) and higher rates of left ventricular ejection fraction (LVEF) < 50%. During a median follow-up period of 1.9 years, cardiac death occurred significantly more in the underweight group (30.0%, 10.6%, 7.0%, and 5.0% among the four groups from underweight to obese; \( P < 0.001 \) for trend). The Cox analysis revealed that underweight was an independent predictor of subsequent cardiac death (odds ratio (OR), 1.86; 95% confidence interval (CI), 1.07-3.25) and identified that older age, BI < 60, higher levels of cardiac troponin I (cTnI), LVEF < 50%, and not receiving PCI were independently associated with increased risk of cardiac death.

Patients who were underweight were at greater risk of cardiac death post AMI. In addition, older age, frail, higher levels of cTnI, LVEF < 50%, and not receiving PCI also independently predicted cardiac mortality post AMI. (Int Heart J 2020; 61: 658-664)

Key words: Body mass index, Obesity paradox, Acute coronary syndrome

Although obesity defined using body mass index (BMI) is an established independent risk factor for the development of coronary artery disease (CAD), recent studies have shown that higher BMI is paradoxically associated with improved clinical outcomes in patients with acute coronary syndrome (ACS). This so-called “obesity paradox” still remains controversial. Therefore, this study aims to investigate the effects of BMI on clinical cardiovascular outcomes in patients with acute myocardial infarction (AMI) by comparing underweight, overweight, and obese groups to normoweight individuals.

Methods
For this study, the inclusion criteria were patients who had a confirmed AMI diagnosis in the Cardiovascular Center Beijing Friendship Hospital Database Bank (CBDBANK) and were admitted to the Beijing Friendship Hospital between January 2013 and April 2018. AMI diagnosis was based on 1) symptoms consistent with ASC, 2) increased cardiac troponin levels consistent with acute injury, and 3) typical electrocardiographic changes or significant angiographic coronary stenosis. Patients were designated with persistent chest discomfort or other symp-
symptoms suggestive of ischemia and ST-segment elevation in at least two contiguous leads as ST-segment elevation MI (STEMI). In contrast, patients without ST-segment elevation at presentation are usually designated as having a non-ST-segment elevation MI.12) The exclusion criteria were missing weight or height data because we could not calculate BMI for these patients.

We identified 3603 patients with confirmed AMI diagnosis, of whom 3562 had BMI data available and were included in this analysis as shown in Figure 1. Baseline BMI was calculated using weight and height measured at time of hospital admission. Participants were classified into four groups based on BMI: normoweight (BMI 18.5-24.9 kg/m²), underweight (BMI < 18.5 kg/m²), overweight (BMI 25-29.9 kg/m²), and obese (BMI ≥ 30 kg/m²).

The baseline characteristics including clinical and laboratory parameters and treatment for AMI were collected during hospitalization and recorded in CBDBANK. The Barthel index (BI), a 10-item scale that assesses a patient’s ability to feed, groom, bathe, use the toilet, dress, walk, transfer, and climb stairs, as well as fecal incontinence and urinary incontinence, was used to measure the frailty, as some previous studies recommended.13-16) The BI is calculated by adding 5, 10, or 15 points for the presence of each variable (final score 0-100 points).13) In our study, the BI was calculated by experienced nurses, who were blind to the study, before discharge of the patients. Patients with a BI <60 were considered to be frail. The peak values of cardiac troponin I (cTnI) and N-terminal pro-brain natriuretic peptide (NTproBNP) after serial measurements were used as indicators of myocardial injury. The treatment of patients followed the usual CCU procedures. Patients received medical therapy according to individual need, which was determined by the attending physician. Primary, urgent, or selective percutaneous coronary intervention (PCI) was performed according to patient conditions. Echocardiography was routinely performed on the second day of hospitalization using a VIVID 7 (General Electric Medical Systems, Horten, Norway). Patients were followed up for a median of 1.9 years (interquartile range, 0.5-3.0). The primary endpoint of the study was cardiac death. The second endpoint was a composite of major adverse cardiac events (MACE) including cardiac death, recurrent nonfatal myocardial infarction, and stroke. Cardiac death was defined as death due to left ventricular failure, myocardial infarction, cardiac perforation or pericardial tamponade, arrhythmia or conduction abnormality, procedural complications, or any death in which a cardiac cause could not be excluded.17) Analysis of the etiology of death was performed by reviewing original medical records.

T-test, Kruskal-Wallis rank-sum test, and chi-square test were used to compare clinical, laboratory, and outcome variables in underweight, overweight, and obese groups to normoweight individuals. The cumulative incidences of events were calculated using the Kaplan-Meier survival method. Hazard ratio estimates with 95% confidence intervals (CIs) were calculated using the Cox proportional hazard regression models, adjusted for potential confounding factors identified to be different among the four BMI groups. These factors included age, sex, BI, hypertension, diabetes, history of heart failure, diagnosis of STEMI, PCI therapy, cTnI, left ventricular ejection fraction (LVEF) < 50%, glycosylated hemoglobin, low-density lipoprotein cholesterol, triglyceride, high-sensitive C-reactive protein (HsCRP), free triiodothyronine, creatinine, alanine aminotransferase, albumin, and medical treatment. All analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

**Results**

Of the 3562 patients included in this analysis, 2560 (72%) were men and 1002 were women. The mean age was 65 ± 13 years. The median BMI was 25.2 kg/m² (interquartile range, 23.0-27.7). These patients were classified into four groups based on BMI values: 110 (3%) were underweight, 1579 (44%) were normoweight, 1493 (42%) were overweight, and 380 (11%) were obese.

As described in Table I, compared to normoweight
patients, overweight and obese subjects were significantly younger, were more likely to be men, have more hypertension and higher BP, have more multivessel disease, and were more likely to receive PCI, whereas those in the underweight group were significantly older, were mostly women, have lower BI and higher rates of prior myocardial infarction and heart failure, have fewer diabetes, were current smokers, have lower levels of BP, and were less likely to receive PCI and medical treatment including beta-blockers, ACE inhibitors, and statins.

Table I shows biomarker comparisons. Compared to normoweight subjects, overweight and obese individuals had significantly higher levels of glucose, lipids, and HsCRP but lower level of NTproBNP. Underweight subjects had significantly lower levels of glucose and lipids but higher level of NTproBNP and higher rates of LVEF < 50%.

The median hospital stay for our study population was 8 days (interquartile range, 6–10). Inhospital cardiac death occurred significantly more frequently in the underweight group: 9.1%, 3.5%, 2.5%, and 2.6% among the four groups with \( P = 0.01 \) for trend. Inhospital MACE showed a similar trend of higher rate in the underweight group. During follow-up, cardiac death and incidence of MACE continued to cumulate significantly at higher rates in the underweight group than other weight groups. As shown in Table III, cumulative cardiac death was seen in 30%, 10.6%, 7%, and 5% among the four groups with \( P = 0.029 \). Multivariate analysis also identified that older age (OR, 1.06; 95%CI, 1.04–1.08; \( P = 0.001 \)) and BMI < 18.5 had a significantly worse survival rate than patients with lower risk of cardiac death. Patients with BMI < 18.5 had a significantly worse survival rate than patients in normoweight group (70.0% versus 89.4%; \( P < 0.001 \)). Kaplan-Meier curves for MACE-free survival also showed lowest rate in underweight group than other BMI groups (Figure 2B).

The Cox proportional hazard model revealed that underweight was an independent predictor of subsequent cardiac death (odds ratio (OR), 1.86; 95%CI, 1.07–3.25; \( P = 0.029 \)). Multivariate analysis also identified that older age (OR, 1.06; 95%CI, 1.04–1.08; \( P = 0.001 \)), BI > 60 (OR, 3.86; 95%CI, 2.69–5.52; \( P < 0.001 \)), higher levels of cTnI (OR, 1.01; 95%CI, 1.00–1.02; \( P = 0.041 \)), and LVEF

| Table I. Baseline Characteristics in the Different BMI Categories |
|-----------------|-----------------|-----------------|-----------------|
| **Normoweight** (BMI 18.5-24.9 kg/m²) | **Underweight** (BMI < 18.5 kg/m²) | **Overweight** (BMI 25-29.9 kg/m²) | **Obese** (BMI ≥ 30 kg/m²) |
| Age, years | 68 ± 12 | 77 ± 10 | < 0.001 | 64 ± 12 | < 0.001 | 61 ± 13 | < 0.001 |
| Male gender, n (%) | 1104 (69.9) | 55 (50) | < 0.001 | 1128 (75.6) | < 0.001 | 273 (71.8) | 0.461 |
| BMI, kg/m² | 23.1 (21.5-24.1) | 17.3 (16.4-17.9) | < 0.001 | 26.9 (26.0-28.1) | < 0.001 | 31.3 (30.5-32.9) | < 0.001 |
| Barthe index < 60*, n (%) | 189 (12.0) | 34 (30.9) | < 0.001 | 124 (8.3) | 0.001 | 28 (7.4) | 0.010 |
| Past history, n (%) | | | | | | | |
| Myocardial infarction | 189 (12) | 21 (19.3) | 0.026 | 179 (12) | 0.987 | 38 (10) | 0.282 |
| PCI | 251 (15.9) | 14 (12.7) | 0.377 | 245 (16.4) | 0.699 | 68 (17.9) | 0.343 |
| CABG | 3 (2.1) | 3 (2.7) | 0.506 | 34 (2.3) | 0.722 | 11 (2.9) | 0.342 |
| Hypertension | 965 (61.2) | 65 (59.1) | 0.668 | 1036 (69.5) | < 0.001 | 293 (77.1) | < 0.001 |
| Diabetes | 575 (36.4) | 16 (14.5) | < 0.001 | 521 (34.9) | 0.380 | 137 (36.1) | 0.888 |
| Heart failure | 22 (1.4) | 7 (6.4) | 0.002 | 17 (1.1) | 0.521 | 2 (0.5) | 0.203 |
| Current smoker, n (%) | 641 (40.6) | 29 (26.4) | < 0.001 | 669 (44.8) | 0.064 | 169 (44.5) | 0.106 |
| Diagnosis of STEMI | 736 (46.6) | 55 (50) | 0.491 | 709 (47.5) | 0.627 | 166 (44.5) | 0.106 |
| Systolic BP, mmHg | 127 (113-140) | 122 (105-138) | 0.016 | 130 (114-144) | 0.020 | 134 (120-150) | < 0.001 |
| Diastolic BP, mmHg | 71 (65-80) | 70 (60-80) | 0.012 | 73 (65-81) | 0.003 | 77 (69-86) | < 0.001 |
| Heart rate, bpm | 73 (65-84) | 74 (65-90) | 0.545 | 73 (65-82) | 0.069 | 75 (65-84) | 0.293 |
| Multivessel disease, n (%) | 73 (60.2) | 29 (65.9) | 0.448 | 837 (67.2) | < 0.001 | 229 (72.5) | < 0.001 |
| Left main lesion, n (%) | 191 (15.7) | 6 (13.6) | 0.707 | 158 (12.7) | 0.03 | 26 (8.2) | 0.001 |
| Pre-procedural TIMI 3 flow, n (%) | 520 (50.1) | 21 (56.8) | 0.267 | 546 (49.5) | 0.283 | 135 (49.1) | 0.982 |
| Post-procedural TIMI 3 flow, n (%) | 1012 (97.5) | 37 (100) | 0.445 | 1076 (97.5) | 0.321 | 267 (97.1) | 0.763 |
| PCI therapy, n (%) | 1038 (65.7) | 37 (33.6) | < 0.001 | 1104 (73.9) | < 0.001 | 275 (72.4) | 0.014 |
| Emergency PCI, n (%) | 408 (25.8) | 11 (10) | < 0.001 | 416 (27.9) | 0.206 | 99 (26.1) | 0.932 |
| IABP use, n (%) | 13 (1.3) | 1 (2.7) | 0.598 | 11 (1.0) | 0.494 | 5 (1.8) | 0.388 |
| Medical treatment | | | | | | | |
| Beta-blockers, n (%) | 1109 (70.2) | 64 (58.2) | 0.008 | 1106 (74.1) | 0.018 | 291 (76.6) | 0.014 |
| ACE inhibitors, n (%) | 974 (61.7) | 46 (41.8) | < 0.001 | 1029 (68.9) | < 0.001 | 298 (78.4) | < 0.001 |
| Statins, n (%) | 1334 (85.5) | 74 (67.3) | < 0.001 | 1311 (87.8) | 0.008 | 381 (87.1) | 0.199 |

Values are mean ± SD or median (interquartile range), unless otherwise indicated. BMI indicates body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pumping; NSTE-PCI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction. *Patients with a Barthel index < 60 were considered to be frail.
ACE inhibitors, and statins, significantly and independently associated with increased risk of cardiac death.

|                        | Normoweight (BMI 18.5-24.9 kg/m²) | Underweight (BMI < 18.5 kg/m²) | Overweight (BMI 25-29.9 kg/m²) | Obese (BMI ≥ 30 kg/m²) |
|------------------------|----------------------------------|---------------------------------|--------------------------------|------------------------|
|                        | (n = 1579)                       | (n = 110)                       | (n = 1493)                     | (n = 380)              |
| Fasting glucose, mmol/L| 5.4 (4.6-6.9)                    | < 0.001                         | 5.9 (5.7-6.5)                  | < 0.001                |
| HbA1c, %               | 5.9 (5.5-6.6)                    | < 0.001                         | 6.0 (5.6-6.9)                  | 0.217                  |
| GA, %                  | 14.9 (13.3-18)                   | 0.430                           | 14.9 (13.2-17.9)               | 0.783                  |
| TC, mmol/L             | 4.3 (3.6-4.9)                    | < 0.001                         | 4.5 (3.9-5.1)                  | < 0.001                |
| Triglyceride, mmol/L   | 1.3 (0.9-1.7)                    | < 0.001                         | 1.6 (1.2-2.3)                  | < 0.001                |
| LDL-C, mmol/L          | 2.4 (2.0-3.0)                    | < 0.001                         | 2.6 (2.2-3.0)                  | < 0.001                |
| HDL-C, mmol/L          | 0.99 (0.85-1.2)                  | 0.001                           | 0.99 (0.87-1.14)               | < 0.001                |
| HsCRP, mg/dL           | 5.8 (1.9-13.1)                   | 0.272                           | 7.8 (2.8-13.9)                 | 0.037                  |
| Fibrinogen, g/L        | 2.9 (2.3-3.7)                    | 0.366                           | 2.9 (2.4-3.6)                  | 0.042                  |
| WBC, x10⁹/L            | 7.9 (6.3-9.9)                    | < 0.001                         | 8.2 (6.9-10.3)                 | < 0.001                |
| Platelet, x10⁹/L       | 209 (163-251)                    | 0.001                           | 212 (180-253)                  | 0.235                  |
| Creatinine, μmol/L     | 82 (73.3-99.7)                   | 0.438                           | 85 (74.7-97.7)                 | 0.177                  |
| ALT, U/L               | 24 (15-36)                       | 0.002                           | 25 (17-42)                     | < 0.001                |
| Albumin, g/L           | 35.9 (33.6-38.7)                 | < 0.001                         | 36.9 (32.5-39)                 | < 0.001                |
| CK-MB, ng/mL           | 35.9 (6.8-139)                   | 0.004                           | 45.4 (8.8-166)                 | 0.034                  |
| cTnl, mg/L             | 4.2 (1.7-15.8)                   | 0.009                           | 4.9 (0.9-15.9)                 | 0.239                  |
| NTproBNP, pg/mL        | 2407 (841-7585)                  | < 0.001                         | 1586 (554-1469)                | < 0.001                |
| LVEF < 50%, n (%)      | 397 (25.1%)                      | 0.009                           | 308 (20.6%)                    | 0.003                  |

Values are median (interquartile range). FT3 indicates free triiodothyronine; HbA1c, glycated hemoglobin; GA, glycated albumin; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; WBC, white blood cell counts; RBC, red blood cell counts; ALT, alanine aminotransferase; CK-MB, creatine kinase-MB; cTnl, cardiac troponin I; NTproBNP, N-terminal pro-brain natriuretic peptide; and LVEF, left ventricular ejection fraction. The normal range of cTnl was 0-0.03 ng/mL.

|                        | Normoweight (BMI 18.5-24.9 kg/m²) | Underweight (BMI < 18.5 kg/m²) | Overweight (BMI 25-29.9 kg/m²) | Obese (BMI ≥30 kg/m²) | P    |
|------------------------|----------------------------------|---------------------------------|--------------------------------|------------------------|------|
|                        | (n = 1579)                       | (n = 110)                       | (n = 1493)                     | (n = 380)              |------|
| **Inhospital**         |                                  |                                 |                                |                        |      |
| Cardiac mortality, n   | 55 (3.5%)                        | 10 (9.1%)                       | 38 (2.5%)                      | 10 (2.6%)              | 0.010|
| All-cause mortality, n | 62 (3.9%)                        | 11 (10.0%)                      | 40 (2.7%)                      | 11 (2.9%)              | 0.003|
| Recurrent nonfatal MI, n | 45 (2.8%)                      | 2 (1.8%)                        | 43 (2.9%)                      | 12 (3.2%)              | 0.894|
| Stroke, n (%)          | 7 (0.4%)                         | 1 (0.9%)                        | 5 (0.3%)                       | 0 (0%)                 | 0.336|
| MACE, n (%)            | 105 (6.6%)                       | 13 (11.8%)                      | 83 (5.6%)                      | 22 (15.8%)             | 0.055|
| **Follow-up**          |                                  |                                 |                                |                        |      |
| Cardiac mortality, n   | 168 (10.6%)                      | 33 (30.0%)                      | 105 (7.0%)                     | 19 (5.0%)              | < 0.001|
| All-cause mortality, n | 255 (16.1%)                      | 48 (43.6%)                      | 155 (10.4%)                    | 29 (7.6%)              | < 0.001|
| Recurrent nonfatal MI, n | 82 (5.2%)                      | 4 (3.6%)                        | 58 (3.9%)                      | 17 (4.5%)              | 0.371|
| Stroke, n (%)          | 24 (1.5%)                        | 5 (4.5%)                        | 12 (0.8%)                      | 4 (1.1%)               | 0.012|
| MACE, n (%)            | 262 (16.6%)                      | 40 (36.4%)                      | 164 (11.0%)                    | 38 (10.0%)             | < 0.001|

MACE was defined as a composite of cardiac death, recurrent nonfatal MI, and stroke. MI, myocardial infarction.

<50% (OR, 2.66; 95%CI, 1.92-3.67; P < 0.001) were independently associated with increased risk of cardiac death. PCI and medical treatment, including beta-blockers, ACE inhibitors, and statins, significantly and independently protected AMI patients against cardiac death (Table IV).

Discussion

It is well established that overweight or obese increases the risk of cardiovascular disease. However, several studies have observed that overweight or obese was associated with a lower mortality rate in patients with CAD, which has been described as “obesity paradox.” We investigated the effect of BMI on cardiac mortality and MACE post AMI in a Chinese population and found that underweight, not overweight or obese, was significantly associated with increased cardiac death and MACE. After adjusting for potentially confounding variables, BMI < 18.5 kg/m² was an independent predictor of increased risk of cardiac death post AMI.

Previous study that generated the “obesity paradox” showed a lower adjusted 30-day mortality rate in obese than normoweight (0.9% versus 1.7%; P < 0.05) in 15071
patients with ACS treated with medical therapy for 12 months. \(^2\text{b)\) Another study showed that adjusted mortality was lower in obese than normoweight (2% versus 10%; \(P = 0.042\)) in patients undergoing cardiac rehabilitation for...

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**Figure 2.** Kaplan-Meier curves indicating the cardiac mortality and major adverse cardiovascular events (MACE) in different BMI categories among patients with AMI. Normoweight indicates BMI 18.5-24.9 kg/m\(^2\); underweight, BMI < 18.5 kg/m\(^2\); overweight, BMI 25-29.9 kg/m\(^2\); and obese, BMI ≥ 30 kg/m\(^2\).

**Table IV.** Predictors of Cardiac Death

|                       | Univariate predictors OR (95% CI) | \(P\)  | Multivariate predictors OR (95% CI) | \(P\)  |
|------------------------|----------------------------------|--------|-----------------------------------|--------|
| Age                    | 1.09 (1.08-1.10)                 | < 0.001| 1.06 (1.04-1.08)                  | < 0.001|
| Male gender            | 0.61 (0.49-0.76)                 | < 0.001| 1.25 (0.88-1.78)                  | 0.220  |
| BMI categories         |                                  |        |                                   |        |
| Normoweight            |                                  |        |                                   |        |
| Underweight            | 3.30 (2.27-4.80)                 | < 0.001| 1.86 (1.07-3.25)                  | 0.029  |
| Overweight             | 0.65 (0.51-0.83)                 | < 0.001| 1.34 (0.95-1.90)                  | 0.094  |
| Obese                  | 0.46 (0.29-0.74)                 | 0.001  | 0.67 (0.28-1.57)                  | 0.354  |
| Bartheil index < 60\*  | 13.1 (10.6-16.4)                 | < 0.001| 3.86 (2.69-5.52)                  | < 0.001|
| Hypertension           | 1.36 (1.07-1.73)                 | 0.014  | 1.24 (0.87-1.79)                  | 0.239  |
| Diabetes               | 1.57 (1.26-1.96)                 | < 0.001| 1.14 (0.78-1.69)                  | 0.501  |
| History of heart failure| 7.72 (4.99-11.93)               | < 0.001| 1.09 (0.47-2.51)                  | 0.844  |
| Diagnosis of STEMI     | 0.84 (0.68-1.05)                 | 0.129  | 0.8 (0.56-1.14)                   | 0.216  |
| PCI therapy            | 0.17 (0.13-0.21)                 | < 0.001| 0.51 (0.35-0.74)                  | < 0.001|
| cTnI                   | 1.009 (1.002-1.016)              | 0.016  | 1.01 (1.00-1.02)                  | 0.041  |
| LVEF < 50\%            | 4.62 (3.68-5.81)                 | < 0.001| 2.66 (1.92-3.67)                  | < 0.001|
| HbA1c                  | 1.11 (1.04-1.19)                 | 0.004  | 1.09 (0.97-1.22)                  | 0.145  |
| LDL-C                  | 0.60 (0.51-0.71)                 | < 0.001| 0.90 (0.72-1.12)                  | 0.325  |
| Triglyceride           | 0.68 (0.58-0.80)                 | < 0.001| 1.09 (0.93-1.28)                  | 0.277  |
| HoCRP                  | 1.03 (1.02-1.04)                 | < 0.001| 1.01 (0.99-1.02)                  | 0.473  |
| fT3                    | 0.36 (0.26-0.49)                 | < 0.001| 1.10 (0.81-1.48)                  | 0.543  |
| Creatinine             | 1.002 (1.001-1.003)              | < 0.001| 1.00 (0.999-1.002)                | 0.672  |
| ALT                    | 1.001 (1.001-1.002)              | < 0.001| 1.00 (0.998-1.002)                | 0.902  |
| Albumin                | 0.88 (0.86-0.90)                 | < 0.001| 0.997 (0.953-1.044)               | 0.902  |
| Medical treatment      |                                  |        |                                   |        |
| Beta-blockers          | 0.24 (0.19-0.30)                 | < 0.001| 0.67 (0.46-0.96)                  | 0.030  |
| ACE inhibitors         | 0.27 (0.21-0.34)                 | < 0.001| 0.50 (0.35-0.72)                  | < 0.001|
| Statins                | 0.12 (0.10-0.15)                 | < 0.001| 0.46 (0.32-0.68)                  | < 0.001|

We used Cox proportional hazards models to analyze the associations between various parameters and cardiac death. Multivariate analysis models were built to adjust for potentially confounding factors. BMI indicates body mass index; PCI, percutaneous coronary intervention; cTnI, cardiac troponin I; LVEF, left ventricular ejection fraction; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HoCRP, high-sensitivity C-reactive protein; fT3, free triiodothyronine; and ALT, alanine aminotransferase. *Patients with a Bartheil index < 60 were considered to be frail.
4 to 8 weeks.\textsuperscript{13} Our study examined the associations of cardiac death and MACE with the BMI categories post AMI. The cardiac death over a median of 1.9 years occurred in 7.0% and 5.0% in the overweight and obese groups and 10.6% in the normoweight group. This 3.6% - 5.6% lower of cardiac mortality post AMI in overweight and obese subjects than normoweight appeared to add evidence to support the “obesity paradox;” however, after adjusting for BMI-related factors, the association of higher BMI with lower risk of cardiac health became no longer statistically significant. The rates of MACE and all-cause mortality over a median of 1.9 years were also lower in the overweight and obese groups and higher in the underweight group, which was consistent with previous studies.\textsuperscript{4,21} Patients at a higher level of body fat may provide a cardiac event-free advantage compared with those at lower level post AMI.

Several other studies with further investigation of the "obesity paradox" suggested that, within the obese cohort, more severe obese patients did not have a more favorable outcome.\textsuperscript{22,23} Azimi et al. reported that patients with 27.5 ≤ BMI < 30 kg/m\textsuperscript{2} seemed to have the lowest mortality risk, but both very low (BMI <18.5 kg/m\textsuperscript{2}) and very high (BMI ≥40 kg/m\textsuperscript{2}) BMI were associated with increased mortality risk.\textsuperscript{24} Lacey et al. reported that risk of MACE was lowest at BMI of 22.5-25 kg/m\textsuperscript{2} in older men and started to increase above this range, with each 5 kg/m\textsuperscript{2} higher BMI associated with 30% increased risk.\textsuperscript{25} These suggested a "J shape" association between BMI and mortality.\textsuperscript{25} Unsurprisingly, the higher BMI effect on cardiac mortality became nonstatistically significant after adjusting for BMI-related differences in demographic and clinical factors and whether PCI was received for treatment of AMI. For example, the lower rate of cardiac death was found in the overweight and obese patients who were younger, were mostly male, had lower rates of LVEF <50%, and were more likely to receive PCI, indicating that the risk of cardiac death and outcomes post AMI were determined by some other important factors that are also related to BMI.\textsuperscript{22,30} Indeed, the multivariate analysis in our study identified that older age, frail condition, higher levels of cTnI, and LVEF <50% were significantly and independently associated with increased risk of cardiac death, and PCI protected AMI patients from cardiac death. Although whether older, female patients should receive PCI should be further studied, a recent patient-level pooled analysis of female participants from 26 randomized trials on PCI with drug-eluting stents showed that all-cause mortality was significantly higher in underweight patients and a trend toward increased risk in the severely obese patients, supporting the "J shape" relationship between BMI and mortality.\textsuperscript{53}

Our study found the highest cardiac death rate (34.7%) in the underweight subject. Survival curves for underweight and normoweight patients separated at the beginning and remained separate over time. Increased mortality rates among underweight patients after AMI have been observed before,\textsuperscript{30} but this was thought to be due to different comorbidities and chronic diseases, not the effect of being underweight alone. In a recent study,\textsuperscript{30} Emily and colleagues found that, after adjusting for comorbidities and cachexia, a considerably higher risk of death in underweight patients still existed compared to those of normoweight. Recently, Shiga and colleagues reported that increased risk of all-cause mortality post AMI was associated with lower BMI in two Japanese cohorts of 6216 patients.\textsuperscript{3} Since frail condition could increase the risk of death and the percentage of patients who are frail was significantly higher in the underweight group, we incorporated the frail condition in multivariate analysis. After adjusting for all these potential confounding factors, underweight was indeed an independent predictor of subsequent cardiac death in our study. Several reasons may explain the excess mortality seen in underweight patients post AMI. For example, underweight patients have decreased physiologic reserve, which may lower their ability to overcome the catabolic changes after AMI. These patients may also be with an underlying genetic predisposition to severe CAD and worse prognosis.\textsuperscript{30} These findings remind us that strategies to promote healthy weight and nutritional counseling in underweight patients post AMI may be beneficial.

Our study had several limitations. First, this was a single-center retrospective observational study. Prospective and multicenter studies are needed to confirm our findings. Second, we did not collect data on waist circumference and waist-to-hip ratio, which might be important measures to evaluate the degree of visceral fat accumulation for central obesity. Third, group analysis located at the ends of the distribution of BMI, low (<18.5 kg/m\textsuperscript{2}) and high (≥30 kg/m\textsuperscript{2}), was limited by the relatively small number of patients.

Conclusions

Underweight predicted greater risk of cardiac mortality in patients post AMI than normoweight, overweight, and obese. Older age, frail, higher levels of cTnI, LVEF <50%, and not receiving PCI were also independent predictors of cardiac mortality post AMI.

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Disclosure

Conflicts of interest: The authors declare that there is no conflict of interest.

References

1. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983; 67: 968-77.
2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke Statistics-2018 update: A report from the American Heart Association. Circulation 2018; 137: e67-492.
3. Shiga T, Kohro T, Yamasaki H, et al. Body mass index and sud-
den cardiac death in Japanese patients after acute myocardial infarction: Data from the JCAD study and HIJAMI-II Registry. J Am Heart Assoc 2018; 7: e008633.

4. Lamelas P, Schwalm JD, Quazi I, et al. Effect of body mass index on clinical events after acute coronary syndromes. Am J Cardiol 2017; 120: 1453-9.

5. Faggioni M, Baber U, Afshar AE, et al. Effects of body mass index on clinical outcomes in female patients undergoing percutaneous coronary intervention with drug-eluting stents: Results from a patient-level pooled analysis of randomized controlled trials. JACC Cardiovasc Interv 2018; 11: 68-76.

6. Samanta R, Poulilopoulos J, Kumar S, et al. Influence of BMI on inductive ventricular tachycardia and mortality in patients with myocardial infarction and left ventricular dysfunction: The obesity paradox. Int J Cardiol 2018; 265: 148-54.

7. Glover BM, Hong KL, Dagres N, et al. Impact of body mass index on the outcome of catheter ablation of atrial fibrillation. Heart 2019; 105: 244-50.

8. Medina-Inojosa JR, Batsis JA, Supervia M, et al. Relation of waist-hip ratio to long-term cardiovascular events in patients with coronary artery disease. Am J Cardiocardiovasc 2018; 121: 903-9.

9. Chen H, Deng Y, Li S. Relation of body mass index categories with risk of sudden cardiac death. Int Heart J 2019; 60: 624-30.

10. Xia JY, Lloyd-Jones DM, Khan SS. Association of body mass index with mortality in cardiovascular disease: New insights into the obesity paradox from multiple perspectives. Trends Cardiovasc Med 2019; 29: 220-5.

11. Thysesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012; 126: 2020-35.

12. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-77.

13. Kodama A, Koyama A, Sugimoto M, Niimi K, Banno H, Komi K. Association between preoperative frailty and mortality in patients with critical limb ischemia following infrainguinal bypass surgery—usefulness of the Barthel index. Circ J 2017; 82: 267-74.

14. Fimognari FL, Pierantozi A, De Alfieri W, et al. The severity of acute illness and functional trajectories in hospitalized older medical patients. J Gerontol A Biol Sci Med Sci 2017; 72: 102-8.

15. Maxwell CA, Dietrich MS, Minnick AF, Mion LC. Preinjury physical function and frailty in injured older adults: Self- versus proxy responses. J Am Geriatr Soc 2015; 63: 1443-7.

16. Michal M, Prochaska JH, Keller K, et al. Symptoms of depression and anxiety predict mortality in patients undergoing oral anticoagulation: Results from the thrombEMIVAL study program. Int J Cardiol 2015; 187: 614-9.

17. Stone GW, Clayton T, Deliagryis EN, Prats J, Mehran R, Pocock SJ. Reduction in cardiac mortality with bivalirudin in patients with and without major bleeding: The HORIZONS-AMI trial (Harmonizing Outcomes with revascularization and Stents in acute myocardial infarction). J Am Coll Cardiol 2014; 63: 15-20.

18. Sierra-Johnson J, Wright SR, Lopez-Jimenez F, Allison TG. Relation of body mass index to fatal and nonfatal cardiovascular events after cardiac rehabilitation. Am J Cardiol 2005; 96: 211-4.

19. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: A systematic review of cohort studies. Obset Gynecol 2006; 108: 666-78.

20. Eisenstein EL, McGuire DK, Bhapkar MV, et al. Elevated body mass index and intermediate-term clinical outcomes after acute coronary syndromes. Am J Med 2005; 118: 981-90.

21. Ma WQ, Sun XJ, Wang Y, Han XQ, Zhu Y, Liu NF. Does body mass index truly affect mortality and cardiovascular outcomes in patients after coronary revascularization with percutaneous coronary intervention or coronary artery bypass graft? A systematic review and network meta-analysis. Obes Rev 2018; 19: 1236-47.

22. Lalive CJ, De Schutter AD, Milani RV. Is there an obesity, overweight, or lean paradox in coronary heart disease? Getting to the ‘fat’ of the matter. Heart 2013; 99: 596-8.

23. Lee DH, Keum N, Hu FB, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: Prospective US cohort study. BMJ 2018; 362: k2575.

24. Azimi A, Charlot MG, Torp-Pedersen C, et al. Moderate overweight is beneficial and severe obesity detrimental for patients with documented atherosclerotic heart disease. Heart 2013; 99: 655-60.

25. Lacey B, Yeap BB, Golledge J, et al. Body mass index and vascular disease in men aged 65 years and over: HIMS (health in Men Study). J Am Heart Assoc 2017; 6: e007343.

26. Aune D, Sen A, Prasad M, et al. 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.

27. Nguyen OK, Makam AN, Clark C, Zhang S, Das SR, Halm EA. Predicting 30-day hospital readmissions in acute myocardial infarction: The AMI “READMITS” (renal function, elevated brain natriuretic peptide, age, diabetes mellitus, normale sex, intervention with timely percutaneous coronary intervention, and low systolic blood pressure) score. J Am Heart Assoc 2018; 7: e008882.

28. Freisinger E, Sehner S, Maloy NR, Suling A, Reinecke H, Wegscheider K. Nationwide routine-data analysis of sex differences in outcome of acute myocardial infarction. Clin Cardiol 2018; 41: 1013-21.

29. Champagne-Langabeer T, Kim J, Bower JK, Gardner A, Fowler R, Langabeer JR. Obesity, treatment times, and cardiovascular outcomes after ST-elevation myocardial infarction: Findings from mission: Lifeline North Texas. J Am Heart Assoc 2017; 6: e005827.

30. Bucholz EM, Krumholz HA, Krumholz HM. Underweight, markers of cachexia, and mortality in acute myocardial infarction: A prospective cohort study of elderly medicare beneficiaries. PLOS Med 2016; 13: e1001998.