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# Untangling the obesity paradox in patients with acute myocardial infarction after primary percutaneous coronary intervention (detail analysis by age)

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ABSTRACT

*Background:* Obesity is associated with increased morbidity and mortality. However, obesity paradox has been discussed in some patients with cardiovascular disease.
*Objectives:* We investigated the mechanisms of the obesity paradox in acute myocardial infarction (AMI) patients.
*Methods:* We evaluated 1634 AMI patients with primary percutaneous coronary intervention (PCI). Patients were divided into 6 subgroups according to baseline body mass index (BMI) (low BMI: <20 kg/m$^2$, normal BMI: 20–24.9 kg/m$^2$, high BMI: ≥25 kg/m$^2$) and age (the younger and elderly groups consisting of patients <70 and ≥70 years old). The primary outcome was defined as all-cause mortality.
*Results:* During the follow-up periods (median, 620 days; range, 344 to 730 days), 8.7% of patients experienced all-cause death. According to the Kaplan-Meier survival analysis, the patients in the younger age group with high BMI demonstrated significantly higher all-cause mortality compared to the other patients in the same age group ($P = 0.012$). In contrast, patients in the elderly age group with low BMI demonstrated significantly higher all-cause mortality compared to the others in the same age group ($P < 0.001$). Multivariate cox regression analyses showed that low BMI in the elderly age group (HR 1.69, 95% CI 1.12 to 2.55, $P = 0.012$) and high BMI in the younger age group (HR 2.77, 95% CI 1.19 to 6.45, $P = 0.018$) were independent predictors of all-cause mortality.
*Conclusions:* The obesity paradox was recognized only in patients in the elderly age group and not in the younger age group. The prognostic impact of BMI may differ by age in AMI patients.


## 1. Introduction

The rate of obesity is increasing in epidemic proportions and has become a social problem [1]. It plays a major role in adversely affecting major coronary heart disease (CHD) risk factors, such as hypertension (HTN), dyslipidemia (DL), and diabetes mellitus (DM), and may be an independent risk factor for atherosclerosis and CHD events [2].

In the general population, mortality is lowest at a body mass index (BMI) range of 20–24.9 kg/m$^2$; however, it increases below and above this range [3,4]. For overweight or obese patients, survival is longer in those with chronic diseases such as end-stage kidney disease, and chronic obstructive pulmonary disease [2,5,6]. In addition, previous reports have suggested that overweight or obese patients with cardiovascular disease (CVD) including chronic heart failure (HF) also have a more favorable prognosis than underweight or normal weight CVD patients [2,7]. This “obesity paradox” has also been reported in patients with acute myocardial infarction (AMI) who underwent primary percutaneous coronary intervention (PCI) [8–10]. These studies showed that overweight and obese AMI patients had a lower risk of death, recurrence of AMI, and HF hospitalization. Furthermore, other studies have suggested that the relationship between BMI and mortality in AMI patients is U-shaped, where extreme obesity increases mortality [11,12]. Although the mechanisms for this obesity paradox are difficult to reconcile, several potential mechanisms have been suggested [7]. For example, the obesity paradox may be due to the fact that overweight or obese patients were younger at the time of presentation [10,13].

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However, the impact of age on the obesity paradox and U-shaped phenomenon has not been well evaluated in patients with AMI. The purpose of this study was to clarify the mechanism of obesity paradox and evaluate the impact of age on the obesity paradox in AMI patients who underwent primary PCI in Japan.

## 2. Methods

### 2.1. Study population

We consecutively evaluated 2120 patients with AMI between January 2013 and December 2016 using data from the Mie ACS Registry, a prospective and multicenter registry in Japan [14]. This study enrolled AMI patients who underwent primary PCI within 24 h from onset. Patients who did not undergo primary PCI within 24 h after onset or lacked data for analysis were excluded from this study. Therefore, a total of 1634 patients were included in this analysis. This registry was approved by the Institutional Review Board of Mie University Graduate School of Medicine and each participating hospital ethics committee. All patients provided written informed consent.

### 2.2. Definitions

The diagnosis of AMI was based on the third universal definition of MI [15]. BMI was calculated using the ratio of body weight in kilograms and the square of the height in meters. The patients were divided into 3 groups according to baseline BMI (low BMI, <20 kg/m$^2$; normal BMI, 20–24.9 kg/m$^2$; high BMI, ≥25 kg/m$^2$). CV death was defined using the classification by the Academic Research Consortium. Briefly, all deaths caused by the heart (e.g., MI, HF, or fatal arrhythmia), deaths without witnesses, deaths in which other causes could not be identified, deaths related to procedures, and deaths caused by blood vessels other than coronary arteries (e.g., cerebrovascular disease, pulmonary embolism, rupture of aortic aneurysm, or aortic dissection) were considered CV deaths.

### 2.3. Emergency coronary angiogram and PCI for AMI

All patients in this study underwent emergency coronary angiogram and received primary PCI for the diseased artery. Device selection and the decision to employ stent implantation for the culprit artery were at the physicians' discretion. The perfusion status of the infarct-related artery was assessed according to the Thrombolysis In Myocardial Infarction (TIMI) study classification. Final TIMI flow grade was assessed on the basis of the final angiograms obtained at admission [16].

### 2.4. Follow-up and outcomes

Outcome data were collected via patient interviews at the outpatient clinic, hospital chart reviews, or telephone interviews with the patient or close relatives, and the clinical events were recorded in a web system. Patients who were lost to follow-up were censored using data from the last contact. The primary endpoint was all-cause mortality during follow-up. The secondary endpoint was defined as 30-day all-cause mortality and after 30-day all-cause mortality.

### 2.5. Statistical analyses

Continuous variables with normal distributions were expressed as the mean ± standard deviation, and those without normal distributions were expressed as the median and interquartile range. Categorical variables were expressed as a number and percentage. In order to assess differences between the 3 subgroups in each age group, a one-way analysis of variance with Bonferroni post-hoc analysis was performed. Kruskal-Wallis test and Pearson's chi-squared test for non-normally distributed data and categorical data respectively were also performed. Event analyses were displayed using Kaplan-Meier survival curves and were compared with the log-rank test. In addition, survival curves for the time-to-event variables were constructed for patients who survived the first 30 days after hospital admission (landmark analysis) using Kaplan-Meier estimates and were compared using the log-rank test. Cox regression model was used to investigate the independent predictor of all-cause mortality. The multivariate analysis was constructed by adjusting for clinically relevant factors and factors with $P < 0.05$ in univariate analysis. We performed a complete case analysis since we excluded all cases with missing variables for the multivariate analysis. Factors used in the multivariate analysis were BMI categories (normal BMI as reference), age (per 1 year), Killip classification ≥2 at presentation, multivessel disease (MVD), door to balloon time (DTB) ≤90 min, final Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, and peak creatinine phosphokinase level (per 1 IU/L). Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using SPSS Version 24.0 (SPSS, Chicago, IL, USA).

## 3. Results

A total of 1634 patients were included in this analysis (Supplemental file 1). The median age was 69 years, 78.6% were male, and the mean BMI was 23.6 ± 3.7 kg/m$^2$. All patients were divided into two age categories according to their median age and were independently assessed; 851 patients who were 69 years and younger (52.1%) were categorized in the younger age group, and 783 patients who were 70 years and older (47.9%) were categorized in the elderly age group. Among the patients in the younger age group, there were 61 patients with low BMI (7.2%), 443 with normal BMI (52.1%), and 347 with high BMI (40.7%). Among the patients in the elderly age group, there were 162 patients with low BMI (20.7%), 476 with normal BMI (60.8%), and 145 with high BMI (18.5%).

### 3.1. Patient characteristics

Baseline patient characteristics according to BMI and age are summarized in Table 1. Age and gender ratios were significantly different among the three BMI groups for both age groups. Furthermore, the high BMI group was significantly younger and had a higher prevalence of males than the low BMI group in both age groups. The prevalence of HTN and DM was significantly different among the three BMI groups only in the younger age group, and the high BMI group had a significantly higher prevalence of these two risk factors. Although the rate of previous PCI was different among the three BMI groups in only the elderly age group, there were no differences in the rate of previous coronary artery bypass grafting, previous MI, previous stroke, and hemodialysis among the three BMI groups in the two age groups. The lipid profile, hemoglobin concentration, and plasma B-type natriuretic peptide level were significantly different among the three BMI groups in both age groups, whereas creatinine levels and HbA1c were significantly different among the three BMI groups only in the younger age group. The rate of Killip classification ≥2 at presentation was different among the three BMI groups in both age groups.

### 3.2. Angiographic and treatment characteristics

Angiographic and treatment characteristics are also shown in Table 1. There were no differences in the prevalence of culprit arteries, multi-vessel disease, and initial TIMI flow grade of 0 among the three BMI groups in both age groups. DTB ≤ 90 min was significantly different among the three BMI groups only in the elderly age group, but the prevalence of the final TIMI flow grade of 3 was similar among the three BMI groups in both age groups. The frequency of calcium channel blocker use was significantly different among the three BMI groups in the younger age group. In contrast, the frequency of beta-blockers and statin use was significantly different among the three BMI groups in the elderly age group.

### 3.3. Outcomes

During follow-up, 141 patients (8.7%) died. The Kaplan-Meier curves for all-cause mortality stratified by BMI categories are shown in Fig. 1 (A). Including all the patients, the low BMI group had higher all-cause mortality compared to the other BMI groups ($P < 0.001$). However, in the younger age group, it was significantly higher for those in the high BMI group compared to the other BMI groups ($P = 0.012$). Among the patients in the elderly age group, the low BMI group showed higher all-cause mortality compared to the other BMI groups ($P < 0.001$), which was a similar result when assessing the entire study group. In addition, influence of gender difference for obesity paradox was analyzed in each subgroups. Male and female in both younger and elderly age groups showed similar trends in relation to BMI and all cause mortality (Supplemental file 2).

Multivariate cox regression analyses for all-cause mortality are summarized in Table 2. Killip classification ≥ 2 was the strongest independent poor prognostic factor for all-cause mortality. Notably, low BMI was another poor prognostic factor in all patients (HR 1.73, 95% CI 1.16–2.57, $P = 0.007$) and those in the elderly group (HR 1.69, 95% CI 1.12–2.55, $P = 0.012$). In contrast, high BMI was the second strongest

**Table 1**
Patient characteristics.

| | All patients (n = 1634) | Younger age group (<70 years old) (n = 851) | | | P-value | Elderly age group (≥70 years old) (n = 783) | | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | | BMI (kg/m$^2$) | | | | BMI (kg/m$^2$) | | | |
| | | Low | Normal | High | | Low | Normal | High | |
| | | (<20) | (20–24.9) | (≥25) | | (<20) | (20–24.9) | (≥25) | |
| | | (n = 61) | (n = 443) | (n = 347) | | (n = 162) | (n = 476) | (n = 145) | |
| Baseline characteristics | | | | | | | | | |
| Age (years) | 68 ± 13 | 62 ± 6 | 60 ± 8 | 56 ± 9[*†] | <0.001 | 82 ± 6 | 78 ± 6[*] | 77 ± 5[*] | <0.001 |
| Male | 1284 (78.6) | 47 (77.1) | 386 (87.1)[*] | 315 (90.8)[*] | 0.008 | 89 (54.9) | 342 (71.9)[*] | 105 (72.4)[*] | <0.001 |
| Hypertension | 1056 (64.6) | 25 (41.0) | 255 (57.6)[*] | 234 (67.5)[*†] | <0.001 | 102 (63.0) | 332 (69.8) | 108 (74.5) | 0.086 |
| Diabetes mellitus | 495 (30.3) | 11 (18.0) | 132 (29.8) | 122 (35.2)[*] | 0.020 | 36 (22.2) | 145 (30.5) | 49 (33.8) | 0.060 |
| Dyslipidemia | 825 (50.5) | 34 (55.7) | 228 (51.5) | 227 (65.4)[†] | <0.001 | 53 (35.7) | 202 (42.4)[*] | 81 (55.9)[*†] | <0.001 |
| Current smoker | 526 (32.2) | 31 (50.8) | 207 (46.7) | 164 (47.3) | 0.84 | 14 (8.6) | 81 (17.0)[*] | 29 (20.0)[*] | 0.013 |
| Previous PCI | 157 (9.6) | 1 (1.6) | 36 (8.1) | 32 (9.2) | 0.14 | 3 (1.9) | 63 (13.2)[*] | 15 (10.3) | 0.046 |
| Previous CABG | 16 (1.0) | 0 (0) | 1 (0.2) | 3 (0.9) | 0.37 | 3 (2.9) | 6 (1.3) | 3 (1.9) | 0.73 |
| Previous MI | 152 (9.3) | 2 (3.3) | 31 (7.0) | 31 (8.9) | 0.25 | 18 (11.8) | 56 (11.8) | 14 (9.7) | 0.78 |
| Previous stroke | 78 (4.8) | 2 (3.3) | 17 (3.8) | 5 (1.4) | 0.13 | 12 (7.4) | 27 (5.7) | 15 (10.3) | 0.15 |
| Hemodialysis | 19 (1.1) | 0 (0) | 3 (0.7) | 3 (0.9) | 0.75 | 2 (1.2) | 9 (1.9) | 2 (1.4) | 0.82 |
| Laboratory data | | | | | | | | | |
| Triglyceride (mg/dl) | 104 (70–162) | 93 (72–134) | 115 (74–173) | 142 (94–220)[*†] | <0.001 | 74 (53–107) | 93 (63–135)[*] | 102 (74–162)[*†] | <0.001 |
| LDL-C (mg/dl) | 123 ± 38 | 129 ± 34 | 127 ± 37 | 136 ± 42[†] | 0.016 | 108 ± 33 | 112 ± 33 | 121 ± 40[*†] | 0.006 |
| HDL-C (mg/dl) | 50 ± 14 | 55 ± 15 | 49 ± 14[*] | 46 ± 12[*†] | <0.001 | 55 ± 15 | 51 ± 14[*] | 47 ± 15[*†] | <0.001 |
| Creatinine (mg/dl) | 0.8 (0.7–1.0) | 0.7 (0.6–0.8) | 0.8 (0.7–0.9)[*] | 0.8 (0.7–1.0)[*] | <0.001 | 0.8 (0.6–1.1) | 0.9 (0.7–1.1) | 0.9 (0.8–1.2) | 0.15 |
| Hemoglobin (mg/dl) | 14.1 ± 2.1 | 14.1 ± 1.7 | 14.8 ± 1.6[*] | 15.5 ± 1.7[*†] | <0.001 | 12.0 ± 2.1 | 13.2 ± 2.0[*] | 14.0 ± 1.8[*†] | <0.001 |
| HbA1c (%) | 6.4 ± 1.3 | 6.1 ± 1.3 | 6.4 ± 1.5 | 6.6 ± 1.6 | 0.025 | 6.2 ± 1.3 | 6.3 ± 1.0 | 6.3 ± 1.0 | 0.43 |
| BNP (pg/ml) | 71 (26–208) | 89 (25–266) | 32 (12–86)[*] | 51 (17–141)[†] | 0.007 | 169 (63–481) | 118 (43–296)[*] | 96 (40–219)[*] | 0.017 |
| Presentation of MI | | | | | | | | | |
| STEMI | 1308 (80.0) | 55 (90.2) | 359 (81.0) | 295 (85.0) | 0.11 | 123 (75.9) | 370 (77.7) | 106 (73.1) | 0.51 |
| Killip classification ≥ 2 | 332 (20.3) | 14 (23.0) | 55 (12.4)[*] | 61 (17.6)[†] | 0.030 | 59 (36.4) | 108 (22.7)[*] | 35 (24.1)[*] | 0.002 |
| Culprit artery | | | | | | | | | |
| RCA | 622 (38.0) | 21 (34.4) | 165 (37.3) | 124 (35.7) | 0.86 | 61 (37.7) | 197 (41.4) | 54 (37.2) | 0.55 |
| LMT | 23 (1.4) | 0 (0) | 3 (0.7) | 6 (1.7) | 0.25 | 5 (3.1) | 6 (1.3) | 3 (2.1) | 0.31 |
| LAD | 761 (46.6) | 34 (55.7) | 204 (46.1) | 179 (51.6) | 0.17 | 67 (41.4) | 209 (43.9) | 68 (46.9) | 0.62 |
| LCx | 228 (14.0) | 6 (9.8) | 71 (16.1) | 38 (11.0) | 0.078 | 29 (17.9) | 64 (13.5) | 20 (13.8) | 0.37 |
| Multivessel disease | 635 (38.9) | 20 (32.8) | 163 (36.8) | 114 (32.9) | 0.48 | 78 (48.2) | 199 (41.8) | 61 (43.2) | 0.36 |
| Initial TIMI flow grade 0 | 925 (56.8) | 40 (65.6) | 261 (59.2) | 233 (67.2) | 0.065 | 83 (51.6) | 239 (50.4) | 69 (47.9) | 0.81 |
| Revascularization | | | | | | | | | |
| DTB ≤ 90 (min) | 957 (58.6) | 35 (57.4) | 280 (63.2) | 202 (58.2) | 0.31 | 79 (48.8) | 270 (56.7) | 91 (62.8)[*] | 0.045 |
| Use of stent | 1485 (90.1) | 54 (88.5) | 417 (94.1) | 311 (89.6)[†] | 0.043 | 147 (90.7) | 427 (89.7) | 129 (89.0) | 0.87 |
| Bare metal stent | 203 (12.4) | 4 (6.6) | 51 (11.5) | 58 (16.7)[*†] | 0.028 | 22 (13.6) | 53 (11.1) | 15 (10.3) | 0.62 |
| Drug eluting stent | 1287 (78.8) | 50 (82.0) | 367 (82.8) | 254 (73.2)[†] | 0.004 | 125 (77.2) | 377 (79.2) | 114 (78.6) | 0.86 |
| Final TIMI flow grade 3 | 1489 (91.1) | 53 (86.9) | 413 (93.2) | 317 (91.4) | 0.19 | 145 (89.7) | 427 (89.7) | 134 (92.4) | 0.60 |
| Peak CPK (IU/L) | 1902 (841–3690) | 3206 (1516–5694) | 2118 (964–4239)[*] | 2380 (1023–4322) | 0.044 | 1629 (610–2841) | 1495 (661–2977) | 1567 (764–3001) | 0.81 |
| Medications | | | | | | | | | |
| Antiplatelet therapy | 1622 (99.3) | 61 (100) | 440 (99.3) | 342 (98.6) | 0.40 | 161 (100) | 475 (99.8) | 143 (98.6) | 0.093 |
| ACE-I or ARB | 1403 (85.9) | 50 (82.0) | 400 (90.3) | 304 (87.6) | 0.12 | 127 (78.4) | 396 (83.2) | 126 (86.9) | 0.14 |
| Beta-blocker | 990 (60.6) | 42 (68.9) | 282 (63.7) | 222 (64.0) | 0.73 | 101 (62.4) | 250 (52.5)[*] | 93 (64.1)[†] | 0.013 |
| Calcium channel blocker | 235 (14.4) | 5 (8.2) | 40 (9.1) | 53 (15.3)[†] | 0.018 | 22 (13.7) | 91 (19.2) | 24 (16.7) | 0.27 |
| Statin | 1454 (89.0) | 58 (95.1) | 412 (93.0) | 323 (93.1) | 0.83 | 126 (78.3) | 409 (85.9)[*] | 126 (86.9)[*] | 0.046 |

Data given as mean ± standard deviation, median (interquartile range) or n (%).
BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; BNP, brain natriuretic peptide; STEMI, ST elevation myocardial infarction, RCA, right coronary artery; LMT, left main trunk; LAD, left anterior descending artery; LCx, left circumflex artery; TIMI, thrombolysis in myocardial infarction; DTB, door to balloon time; CPK, creatinine phosphokinase; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
* $P < 0.05$ between low BMI group and normal BMI group or high BMI group in post-hoc multiple comparison tests.
† $P < 0.05$ between normal BMI group and high BMI group in post-hoc multiple comparison tests.

independent prognostic factor for the patients in the younger age group. Fig. 1(B) provides the plot graph of HR of all-cause mortality obtained by multivariate Cox regression analysis. A U-shaped relationship between BMI and all-cause mortality was observed in all patients and clearly shows that the obesity paradox was recognized only in the elderly age group.

The Kaplan-Meier estimates of survival using landmark analysis stratified by BMI categories in each age group are shown in Fig. 2. In the younger age group, the high BMI group had the highest 30-day all-cause mortality ($P = 0.005$); however, there was not a significant difference in long-term mortality among the three BMI groups ($P = 0.72$). In the elderly group, both 30-day and long-term all-cause mortality were the highest in the low BMI group ($P = 0.010$ and 0.005, respectively).

Cumulative event rates of CV and non-CV deaths in each period are summarized in Supplemental file 3. The high BMI group had highest CV death for patients in the younger age group within 30 days. In contrast, the low BMI group had highest non-CV death for patients in the elderly age group during long-term follow-up.

## 4. Discussion

This study investigated the impact of age on obesity paradox in AMI patients who underwent primary PCI. The results show that the obesity

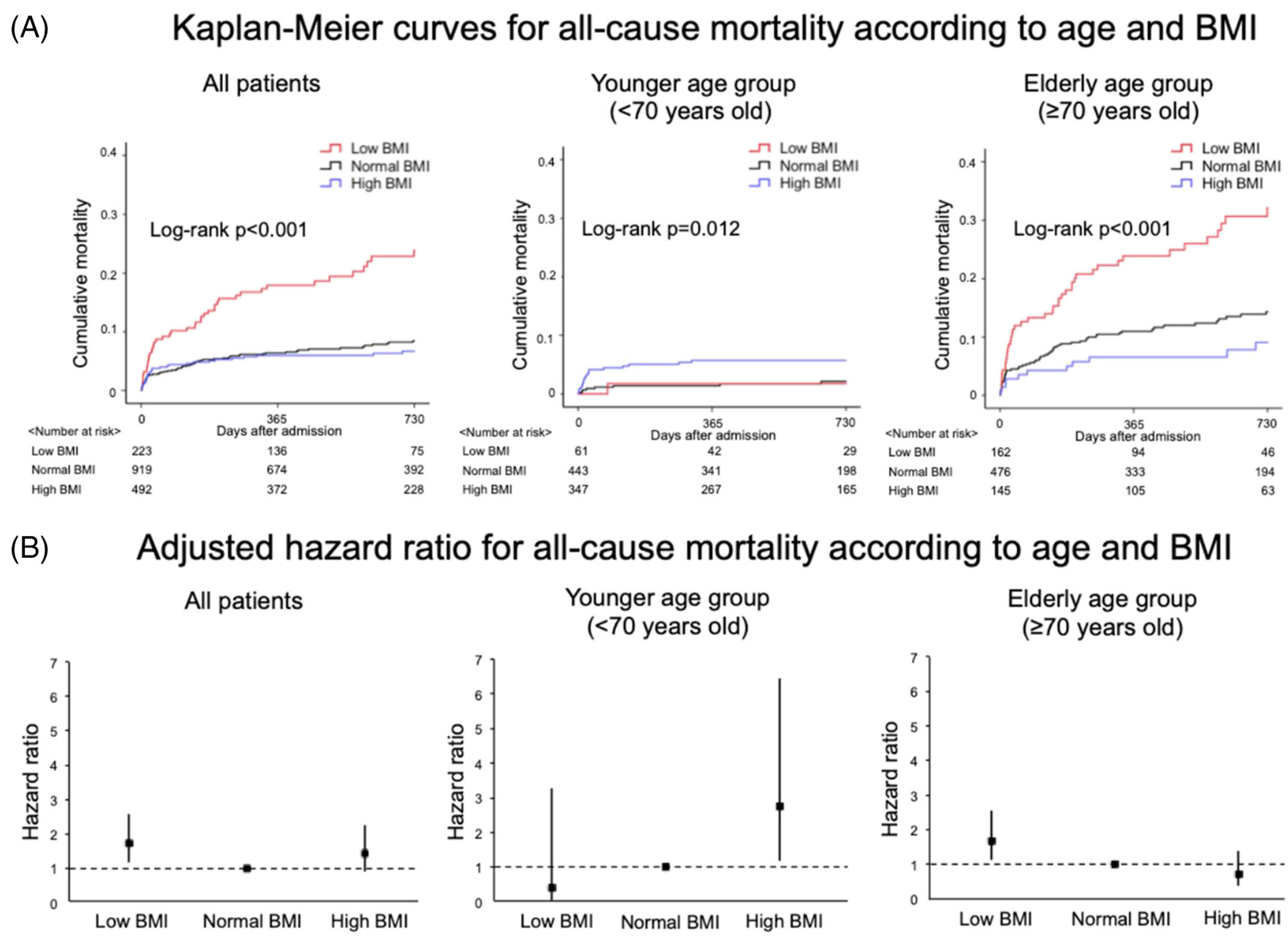


**Fig. 1.** (A) Kaplan-Meier curves for all-cause mortality according to age and BMI. (B) Adjusted hazard ratio for all-cause mortality according to age and BMI. Younger age group was defined as <70 years old, and elderly age group was defined as ≥70 years. BMI categories: low BMI (<20 kg/m$^2$), normal BMI (20–24.9 kg/m$^2$), and high BMI (≥25 kg/m$^2$). BMI, body mass index.

paradox was recognized only in the elderly age group. In other words, low and high BMI in the elderly and younger age group, respectively, were identified as poor independent prognostic factors for all-cause mortality.

A recent meta-analysis study showed that all-cause mortality was lowest in individuals with a BMI of 20–25 kg/m$^2$ when analyzed in never-smokers without pre-existing diseases [4]. In addition, guidelines for the management of weight recommend body weight reduction to the normal range (BMI 20–25 kg/m$^2$) to prevent CV disease [17,18]. In this study, high BMI worsened the short-term prognosis after AMI in younger patients. Therefore, proper weight maintenance may be important not only to prevent AMI but also to improve prognosis after it develops, especially in younger patients. However, whether BMI itself is an independent prognostic factor after AMI remains controversial [9,10,12,19]. In addition, some investigators suggested the obesity paradox in AMI patients. The mechanisms for obesity paradox in CV disease are difficult to reconcile, but there are several potential mechanisms: younger age at presentation, greater metabolic reserve, less cachexia, high blood pressure allowing for more cardiac medication, increased muscle mass and muscular strength, implications regarding cardiorespiratory fitness, and unmeasured confounding factors [7]. Previous reports showed that the obesity paradox may be explained by the fact that

**Table 2**
Multivariate cox regression analyses for all-cause mortality.

| | All patients | | Younger age group (<70 years old) | | Elderly age group (≥70 years old) | |
|---|---|---|---|---|---|---|
| | Hazard ratio (95% CI) | *P*-value | Hazard ratio (95% CI) | *P*-value | Hazard ratio (95% CI) | *P*-value |
| Low BMI (Normal BMI as reference) | 1.70 (1.10–2.62) | 0.016 | 0.43 (0.050–3.73) | 0.44 | 1.69 (1.12–2.55) | 0.012 |
| High BMI (Normal BMI as reference) | 1.60 (0.99–2.59) | 0.056 | 3.82 (1.49–9.79) | 0.005 | 0.72 (0.38–1.39) | 0.33 |
| Age, per 1 year | 1.06 (1.04–1.08) | <0.001 | – | – | 1.07 (1.04–1.11) | <0.001 |
| Killip class ≥2 at presentation | 4.55 (3.03–6.83) | <0.001 | 9.60 (3.80–24.28) | <0.001 | 4.26 (2.85–6.39) | <0.001 |
| Multivessel disease | 1.51 (1.04–2.19) | 0.031 | 3.11 (1.36–7.08) | 0.007 | – | – |
| DTB ≤ 90 (minitus) | 0.49 (0.34–0.72) | <0.001 | 0.14 (0.052–0.36) | <0.001 | – | – |
| Final TIMI flow grade 3 | 0.46 (0.30–0.70) | <0.001 | 0.18 (0.074–0.42) | <0.001 | – | – |
| Peak CPK, per 1 IU/L | 1.00 (1.00–1.00) | <0.001 | 1.00 (1.00–1.00) | 0.006 | 1.00 (1.00–1.00) | 0.001 |

DTB, door to balloon time; TIMI, thrombolysis in myocardial infarction; CPK, creatine phosphokinase.

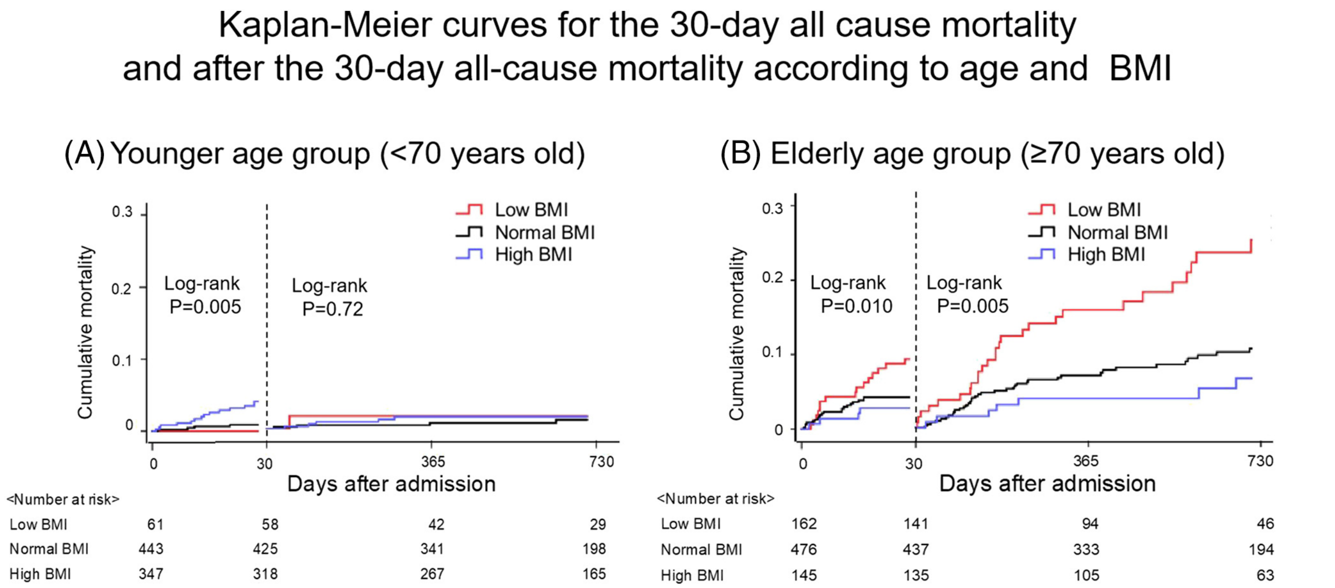


**Fig. 2.** Kaplan-Meier curves for the 30-day all-cause mortality and after the 30-day all-cause mortality according to age and BMI. (A) Younger age group (<70 years old). (B) Elderly age group (≥70 years). BMI categories: low BMI (<20 kg/m$^2$), normal BMI (20–24.9 kg/m$^2$), and high BMI (≥25 kg/m$^2$). BMI, body mass index.

overweight or obese patients were younger at presentation [10,13]. This was consistent with our data in which patients with high BMI were younger than patients with low BMI. Therefore, we separately assessed the prognostic influence of BMI among younger and elderly patients in this study and showed that high BMI and low BMI were poor independent prognostic factors in the younger and elderly groups, respectively. These findings strongly suggest that the obesity paradox with regards to prognosis was observed only in elderly AMI patients. In elderly patients, being underweight is known to be associated with frailty or cachexia caused by chronic disease such as cancer and HF. Gruberg et al. reported that post procedural complications after PCI, such as hypotension, pulmonary edema, acute renal failure, major bleeding, access site hematoma, vascular complications, and overall mortality rates, were surprisingly higher in underweight patients compared to overweight or obese patients [20]. The mechanism by which underweight patients have an excess of these complications is not clear but could be related to the excessive anticoagulation in underweight patients or the presence of severe, non-cardiovascular, underlying diseases in underweight patients, as shown in a previous study [21]. Elderly overweight or obese patients may maintain a metabolic reserve and muscle and muscle strength that lead to favorable prognosis. However, younger overweight or obese patients usually have several comorbidities; therefore, obesity may worsen the prognosis in younger patients. Another study suggested that the obesity paradox seems largely apparent in patients with low fitness, whereas those with better fitness have a good prognosis, and no clear obesity paradox. In general, elderly patients would be less fit compared to the younger population, which might lead to the obesity paradox in elderly patients.

The effects of obesity in prognosis increase with the duration of follow-up. There is an increase in mortality in underweight and obese patients during the first few years of follow-up and in subsequent years, respectively [22]. These findings support our data in which after the 30-day all-cause mortality, high BMI was not a poor prognostic factor in the younger patients within 2 years. Furthermore, even within 2 years, low BMI was a significant poor prognostic after the 30-day all-cause mortality in elderly patients.

Since previous reports have shown that weight loss in overweight patients with CV disease was associated with increased mortality, purposeful weight loss may not be beneficial and may even be detrimental in patients with CV diseases [2,23]. In contrast, other studies that assessed mortality based on body fat and lean mass rather than BMI or weight alone have suggested that subjects losing body fat rather than lean mass have lower mortality [24,25]. In addition, several studies have suggested that lifestyle interventions, including exercise training, cardiac rehabilitation, and mild weight reduction, markedly alters the relationship between obesity and prognosis in CHD [26–28]. In this study, the long-term and 30-day all-cause mortality were significantly higher in patients in the younger age group with high BMI than the other BMI groups of the same age group. Furthermore, those in the younger age group with high BMI had a higher prevalence of HTN, DM and DL as well as high levels of serum creatinine, which may cause CV organ damage. However, this study also showed that the after 30 days all-cause mortality was similar in the 3 younger age groups. Therefore, cardiac rehabilitation and intensive medication may improve the long-term prognosis of young patients with high BMI [26,27].

Peto et al. showed that, in the general population, patients with BMI above 25 kg/m$^2$ had an expected lifetime that is approximately 10 years shorter than people with normal BMI [28]. Therefore, it follows that the percentage of obese individuals in the general population decreases with increasing age. Individuals who are susceptible to the adverse effects of elevated BMI may have already died prior to old age. Therefore, elderly adults with high BMI represent individuals who are resistant to the effects of high BMI [29]. In addition, the ratio of body fat and muscle may be different in overweight younger and elderly patients who have the same BMI, which may further indicate major biological differences between these two age populations.

Patients with low BMI had higher CV and non-CV deaths compared to those in other BMI categories in the elderly group in this study. This is consistent with previous reports that showed that non-CV deaths (due to cardiac cachexia, malnutrition, malignancies and other non-CV diseases) were higher in patients post AMI with low BMI [11,30]. There is a possibility that underweight elderly patients with co-morbidities did not receive enough medication. Therefore, elderly underweight patients may indicate poor prognosis due to many factors. Finally, clarifying the obesity paradox suggests that a more aggressive treatment is received by overweight or obese patients during the index hospitalization, especially in younger patients. Physicians may recognize that overweight and obese patients have a higher risk for adverse outcomes and identify comorbidities resulting in the prescription of evidence-based therapies and interventions for patients with high BMI.

There were several strengths in this study. First, our data was derived from all-comer cohorts. Second, we performed a complete case analysis by excluding all cases with missing variables for multivariate analysis.

### 4.1. Clinical implications

In young patients with high BMI, intensive treatment after onset of AMI may improve long-term prognosis. In elderly patients with low BMI, not only the treatment of AMI but also the evaluation and care for the causes of low BMI may improve prognosis. These findings suggest that education for life style-related diseases should be adjusted for age and BMI.

### 4.2. Limitations

Several limitations of this study should be acknowledged. First, severely obese patients (BMI ≥ 30 kg/$m^2$) were analyzed together with overweight patients (25–29.9 kg/$m^2$) due to the low prevalence (5.1% in entire study population, 7.9% in younger age group and 2.0% in elder age group) of this condition in Japanese patients. Second, we used the BMI at the onset of AMI, but it was not re-evaluated during follow-up, and it may have effects on the results. Third, we did not have enough data to assess bleeding complications, which have been reported to be an independent prognostic factor [31]. Fourth, we did not evaluate frailty and nutritional status, which may be useful to explain the causal relationship between being underweight and all-cause mortality especially in the elderly age group. In addition, the patients were not assessed for whether or not they participated in cardiac rehabilitation after AMI. Fifth, influence of complete revascularization for all cause mortality was not analyzed because of lack of data. Finally, we did not include medications in the multivariate analysis since there was no follow-up data.

## 5. Conclusion

The obesity paradox was recognized only in the elderly and not in the younger age group. The prognostic impact of BMI may differ by age in AMI patients with primary PCI.

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