Original Article

Differential associations between body mass index and outcome in different age groups in patients with myocardial infarction

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ABSTRACT

Objective: To investigate the association between age and body mass index (BMI) and mortality in patients with myocardial infarction (MI). Methods We divided 6453 patients into three age groups (<60, 60–75, >75 years) and five BMI categories. Thirty-day and long-term all-cause mortality were assessed. Results: No association was found between the BMI category and 30-day mortality in any age group. The association between BMI and long-term multivariable-adjusted mortality risk was age-dependent. Overweight patients had a lower risk than patients with BMI <25 kg/m² in all age groups (HR 0.62; 95%CI 0.45–0.85; p = 0.003, HR 0.78; 95%CI 0.65–0.93; p = 0.005, HR 0.82; 95%CI 0.70–0.95; p = 0.011 for ages <60, 60–75, >75 years, respectively). The lower risk of death as a function of BMI shifted upward with age, and the risk was also lower in patients with obesity grade I (HR 0.81; 95% CI 0.66–0.98; p = 0.035 and HR 0.78; 95% CI 0.63–0.97; p = 0.023 for ages 60–75, >75 years, respectively). Excessive obesity was harmful only in the oldest group. Patients with obesity grade III had more than a 2.5 times higher mortality risk than patients with BMI <25 kg/m² only in this group (HR 2.58; 95%CI 1.27–5.24; p = 0.009). An obesity paradox was found in all age groups. Conclusion: Our results suggest that moderate weight gain with age improves long-term survival after MI and that the magnitude of this “protective” weight gain is greater in older compared to younger patients. However, excessive weight gain (obesity grade III) is particularly harmful in the oldest age group. The exact relationship between BMI, age, and mortality remains unclear.

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1. Introduction

Obesity has become a serious problem, with nearly 40% of adults in the Western Hemisphere and one billion people around the world being overweight or obese. Obesity is associated with an increased risk of premature death. However, overweight, and obese patients with established cardiovascular disease paradoxically have a more favorable prognosis, which is called the obesity paradox. Another problem affecting cardiovascular disease in society worldwide is population aging. Obesity is more prevalent among the elderly: 43%–71% of those over 65 years of age in developed countries are at least overweight, and in middle-income countries, the increase in obesity is greatest among those over 65 years of age. Cardiac function and metabolism are negatively affected by aging, but the precise role of aging in obesity-related cardiovascular disease remains elusive. The interaction between obesity and age appears to be complex and may vary by age group. Aging is associated with fat redistribution and obesity, while obesity may promote premature aging. Although obesity, body fat percentage, and fat distribution change with age, data on the possible association between age and BMI and outcome in patients with MI who have undergone percutaneous coronary intervention (PCI) are extremely sparse, inconclusive, contradictory, and sometimes controversial, and long-term data are lacking. We aimed to investigate the possible differential influences of BMI on 30-day and long-term outcomes in different age categories in patients with MI who underwent PCI.
1.1. End points

The end points were all-cause 30-day and long-term mortality in the different age groups according to BMI.

1.2. Patients and methods

A single-center retrospective observational study was performed at the University Medical Center Maribor, a tertiary referral hospital with a 24/7 PCI service. We screened all 7342 consecutive patients with MI, who underwent PCI between 2007 and 2017 and excluded patients without BMI data (848, 11.5%). The remaining 6496 patients were included in this analysis. Patients were divided into three groups according to age (<60 years, 60–75, and >75 years), and these age groups were compared. Patients were also divided into five BMI categories: BMI category <25 kg/m², overweight 25.0–29.9 kg/m², obesity grade I 30.0–34.9 kg/m², obesity grade II 35.0–39.9 kg/m², and obesity grade III ≥40 kg/m². The BMI was calculated as the weight (kg) divided by the square of the height in meters. Patient data were obtained from the patients’ electronic medical records. The definition of MI was based on current guidelines and patients were treated accordingly.7,8 Data on BMI, age, and mortality were available for all patients, whereas data on other parameters were available for at least 92.8% of patients. Data on the date of death were obtained from the Slovenian National Cause of Death Registry. The median (IQR) follow-up time was 6.0 (3–9) years. Bleeding was defined according to the Bleeding Academic Research Consortium (BARC) criteria, using category 3a bleeding (Hb drop of 30–50 g/L or any transfusion) to determine the presence of bleeding.6 Ventricular ejection fraction was determined by bedside echocardiography in the first 48 h after admission. The study was approved by the University Medical Center Maribor Committee for Medical Ethics (reference: UKC-MB-KME -59/19).

1.3. Statistical methods

Continuous variables are presented as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. Baseline characteristics of patients in the different age categories were compared using Fisher’s exact chi-square test for categorical variables and the t test for continuous variables. The characteristics of patients in the different BMI categories were compared using the chi-square test for nominal variables and the Jonckheere–Terpstra test for continuous variables. Univariable associations between BMI categories in different age groups and long-term outcomes were assessed using analysis of variance and chi-square tests. Binary logistic regression models were performed using the Enter mode to identify independent predictors of 30-day mortality. Cox proportional hazards regression analysis was used to calculate hazard ratios (HRs) as estimates of long-term mortality. Regression models were adjusted for age groups and BMI categories. Variables determined a priori for inclusion in the multivariable models were sex, diabetes, hyperlipidemia, hypertension, glomerular filtration rate (GFR) on admission, ST-elevation MI, access site, TIMI 0/1 after PCI, bleeding, dual antiplatelet therapy, and ejection fraction (EF). The variables included and retained in the model were determined on the basis of previous literature reports and experience that these factors are known to influence all-cause mortality. In addition, all included variables had a univariable association with 30-day mortality p < 0.05 and variance inflation factor (VIF) < 1.5. We calculated adjusted hazard ratios (HR) for all age and BMI categories. The HRs were calculated using a stratified model according to the BMI value. The BMI category with <25.0 kg/m² was used as the reference group. Data were analyzed using SPSS 25.0 software for Windows (IBM Corp., Armonk, NY). All p values were two-sided; p values less than 0.05 were considered statistically significant.

2. Results

The baseline and procedural characteristics of the patients according to the different age categories are shown in Table 1. Of the 6496 patients, 2216 (34.1%) were in the age group <60 years, 2793 (43.0%) were in the age group 60–75 years, and 1487 (22.9%) were in the age group >75 years. The median (IQR) BMI was 27.7 (25.0–30.9) kg/m². In terms of BMI, 1613 (22%) fell into the <25 kg/m² category, 2879 (39.2%) into the overweight category, 1509 (22.5%) into the obesity class I category, 381 (5.2%) into the obesity class II category, and 114 (1.6%) into the obesity class III category. There were fewer patients with obesity in the oldest group (>75 years) than in the younger age groups (p < 0.0001) (Fig. 1).

From the youngest to the oldest group, an increase in the incidence of diabetes and hypertension and a decrease in BMI values, EF, and GFR were observed. Among the younger patients, males outnumbered females and they suffered more frequently from hyperlipidemia. Younger patients were more frequently admitted with ST-elevation MI. Fewer PCIs were performed on the left main coronary artery, and these were more likely to be successful. They were also more likely to be treated with dual antiplatelet therapy. Younger patients were less likely to bleed after PCI.

2.1. Mortality

2.1.1. 30-Day mortality

In the first 30 days, 508 (7.8%) patients died. The mortality rate was similar in all BMI categories (p = 0.44, p = 0.056, and p = 0.61 for the age group <60, 60–75, and >75 years, respectively) (Table 2). Even after adjusting for confounding factors, there was no association between BMI category and 30-day all-cause mortality in any age group (p = 0.45, p = 0.27, and p = 0.25 for <60, 60–75 years, and >75 years age groups, respectively) (Table 3).

2.1.2. Long-term mortality

During follow-up, 1960 (30.2%) deaths were recorded. Regarding BMI categories, we observed a different long-term all-cause mortality only in the 60–75 years age group (p = 0.004) with the lowest mortality in the overweight category (27.4%), followed by the obesity grade I category (29.6%), and the highest in the obesity grade III, followed by the obesity grade II category (38.5% and 37.6%, respectively) (Table 2). In the other two age groups (<60 and >75 years), the observed long-term all-cause mortality rates were similar in all BMI categories (p = 0.10 and p = 0.092, respectively) (Table 2).

After adjustment for confounding factors, BMI categories were significantly but differently associated with long-term mortality risk in all three age groups (p = 0.026, 0.003, and 0.001 for ages <60, 60–75, and >75 years, respectively) (Table 3, Fig. 2). The BMI category with <25.0 kg/m² was used as the reference group. Overweight patients had a lower long-term multivariable-adjusted all-cause mortality risk in all age groups (HR 0.62; 95% CI 0.45 to 0.83; p = 0.003, HR 0.78; 95% CI 0.65 to 0.93; p = 0.005, HR 0.82; 95% CI 0.70 to 0.95; p = 0.011 respectively for the age groups <60, 60–75, >75 years) (Table 3, Fig. 2). We found that with increasing age the risk became lower even in higher BMI categories. In the 60–75 years and >75 years age groups, patients with obesity grade I had a lower risk (HR 0.81; 95% CI 0.66 to 0.98; p = 0.035 and HR 0.78; 95% CI 0.63 to 0.97; p = 0.023, respectively). Excessive obesity (obesity grade III) was harmful only in the oldest age group (>75 years), where these patients had more than a 2.5-fold higher risk of dying in the
A J-shaped relationship between BMI category and long-term mortality risk was observed in the oldest age group (Table 3, Fig. 2), whereas no clear relationship was seen in the younger age groups. An obesity paradox was observed in all age groups.

### Table 1

Patient and procedural characteristics by age category on admission.

| AGE (YEARS) | < 60 | 60–75 | >75 | p     |
|------------|------|-------|-----|-------|
| Number of patients, (%) | 2216 (34.1) | 2793 (43.0) | 1487 (22.9) | <0.0001 |
| AGE, (years) | 52.0 (47.0–56.0) | 67.0 (63.0–72.0) | 80.0 (78.0–83.0) | <0.0001 |
| Female sex, N (%) | 424 (19.1) | 828 (29.6) | 757 (50.9) | <0.0001 |
| Diabetes, N (%) | 349 (15.7) | 843 (30.2) | 429 (28.9) | <0.0001 |
| Hypertension, N (%) | 985 (44.9) | 1794 (64.2) | 991 (66.6) | <0.0001 |
| Hyperlipidemia, N (%) | 1284 (57.9) | 1278 (45.8) | 470 (31.6) | <0.0001 |
| BMI (kg/m2) | 28.1 (25.5–31.4) | 27.9 (25.2–31.0) | 26.5 (24.2–29.4) | <0.0001 |

**BMI** = body mass index. **EF** = ejection fraction; **GFR** = glomerular filtration rate; **DAPT** = dual antiplatelet therapy; **LAD** = left anterior descending artery; **LCX** = circumflex artery; **LMCA** = left main coronary artery; **PCI** = percutaneous coronary intervention; **RCA** = right coronary artery; **STEMI** = ST-elevation myocardial infarction; **TIMI** = Thrombolysis In Myocardial Infarction.

### Fig. 1

The proportion of patients in different BMI categories in different age groups.

Fig. 1. The proportion of patients in different BMI categories in different age groups BMI = body mass index.

### 3. Discussion

This study examined the possible differential influences of BMI on outcomes in different age categories in patients with MI who underwent PCI. The main results of our study in patients with MI are as follows:

- A J-shaped relationship between BMI category and long-term mortality risk was observed in the oldest age group (Table 3, Fig. 2), whereas no clear relationship was seen in the younger age groups. An obesity paradox was observed in all age groups.
1. Overweight patients had a lower risk of dying in the long-term compared to patients with BMI <25kg/m² in all three age groups.

2. The lower risk of death as a function of BMI shifted upward with age, especially in the oldest group, where patients with obesity grade I had the lowest risk of long-term death.

3. Patients with obesity grade III had a higher risk than patients with BMI <25kg/m² only in the age group >75 years.

4. An obesity paradox was observed in all age groups in relation to long-term mortality.

5. BMI category was not associated with 30-day mortality in any age group.

### Table 2

Thirty-day and long-term observed all-cause mortality rate according to age and BMI categories.

| Age (years) | BODY MASS INDEX CATEGORY (kg/m²) | 30-day mortality | Long-term mortality |
|-------------|----------------------------------|------------------|--------------------|
|             | <25.0                            | 25.0–29.9        | 30.0–34.9          | 35.0–39.9          | ≥40 |
| <60, N (%)  | 19 (4.1)                         | 25 (2.6)         | 18 (3.2)           | 6 (3.5)            | 3 (6.0) | 0.44 |
| 60–75, N (%)| 64 (10.0)                        | 78 (6.3)         | 46 (6.6)           | 14 (8.4)           | 4 (7.7) | 0.056|
| >75, N (%)  | 85 (16.8)                        | 99 (14.8)        | 36 (13.8)          | 8 (19.0)           | 3 (25.0) | 0.61 |

### Table 3

Risk of dying within 30 days and in the long term, according to age and BMI category.

#### 30-day mortality risk

| Age (years) | BMI (kg/m²) | OR (95% CI) | p     | BMI category in multivariable analysis |
|-------------|-------------|-------------|-------|----------------------------------------|
| <60         | <25.0       | 1.00 (referent) | 0.66 (0.31–1.41) | 0.29 |
| 60–75       | 1.00 (referent) | 0.66 (0.43–1.02) | 0.06 |
| >75         | 1.00 (referent) | 0.93 (0.63–1.36) | 0.70 |

#### Long-term mortality risk

| Age (years) | BMI (kg/m²) | HR (95% CI) | p     | HR (95% CI) | p     | HR (95% CI) | p     | HR (95% CI) | p     |
|-------------|-------------|-------------|-------|-------------|-------|-------------|-------|-------------|-------|
| <60         | <25.0       | 1.00 (referent) | 0.62 (0.45–0.85) | 0.003 |
| 60–75       | 1.00 (referent) | 0.78 (0.65–0.93) | 0.005 |
| >75         | 1.00 (referent) | 0.82 (0.70–0.95) | 0.011 |

BMI – body mass index; CI – confidence interval; HR – adjusted hazard ratio; OR – odd ratio.

### Fig. 2

Risk-adjusted mortality (95% CI) according to age and BMI

BMI – body mass index; CI – confidence interval; HR – hazard ratio.
Comparison of mortality risk between age groups showed that as age increased, the lower long-term multivariable-adjusted mortality risk associated with BMI shifted upward, especially in the oldest group. This was independent of confounding factors up to 12 years after hospitalization. However, our analysis also showed that in the oldest group, patients with obesity grade III had more than a 2.5-fold higher risk of long-term death compared to patients with BMI <25kg/m2, which was not observed in younger age groups (Table 3, Fig. 2). Previously, a J-shaped relationship between BMI and risk of death was observed in patients with MI in the entire population, whereas we observed this relationship only in the age group >75 years. This relationship was less evident in the two younger age groups.

Our finding supports existing evidence that the association between BMI and outcome varies across age groups in patients with MI. However, our result is only partially consistent with the previous finding of Fukuoka. In agreement with their results, we found that patients with the lowest BMI had the highest risk of dying in the oldest age group, but in contrast to their results, we could not confirm the higher risk of dying in younger patients (<60 years) with higher BMI. Another difference between our result and that of Fukuoka was that we found an obesity paradox in all age groups. Comparisons showed considerable differences in patient selection, BMI categories, number of patients, treatment modality, covariates in multivariable adjustments, and observation time, and these differences may explain our result.

Our result suggests that the association between obesity and cardiovascular disease may vary between age groups. This is probably related to physical changes during aging. Physiologically, appetite and average energy intake decrease with age in response to lower energy expenditure, so body weight tends to decrease in the elderly, as found in our analysis (Table 1). Changes in body composition reflect the balance of the decline in these two parameters. In general, older people have significantly more body fat than young adults for a given BMI. This is a multifactorial process, with lower physical activity and lower levels of growth and sex hormones being most important. The reduced resting metabolic rate and the thermic effect of food also play a role. We can assume that older people have more adipocytes compared with young adults for a given BMI. Adipocytes are a source of angiotensinogen and angiotensin-converting enzyme and activate the renin-angiotensin-aldosterone system, which stimulates sympathetic nervous system activity and increases afterload. Aldosterone also stimulates myocardial fibrosis. In addition to the higher body fat percentage, the distribution of fat tissue also differs from that in young adults. Older individuals have a greater proportion of intra-abdominal, intrahepatic, and intramuscular fat tissue (as opposed to subcutaneous fat tissue), resulting in greater insulin resistance. More insulin binding to insulin-like growth factor 1 receptors in the myocardium, along with angiotensin II, promotes left ventricular hypertrophy. Visceral fat tissue also produces cytokines that are proinflammatory and cardiodepressant, as well as proatherosclerotic adipokines.

It would be expected that elderly patients with more visceral fat tissue would have a higher risk of dying than normal-weight elderly patients. Paradoxically, as noted in our study, with increasing age, the longest survival is associated with moderately increased body weight. This was previously observed in healthy seniors. It has been suggested that aging somewhat attenuates the deleterious effects of increasing body fat.

Our analysis also showed that patients with excessive obesity (obesity grade III) who are >75 years have a significantly worse prognosis, which contradicts previous observations in healthy people >75 years. Any comparison must take into account that our patients suffered MI. We compared the prevalence of risk factors known to be associated with worse outcomes after MI (diabetes, hypertension, hyperlipidemia, renal dysfunction, anemia on admission in different BMI categories in the age group >75 years and found an almost linear positive association between BMI category and number of risk factors (p < 0.0001), which is consistent with previous findings. Accordingly, patients with obesity grade III had the highest cardiovascular risk in the age group >75 years. In MI there is an immediate need for additional energy due to the sudden activation of the neurohormonal system and inflammation, and patients with higher levels of obesity and age-related morbidities would require a greater metabolic reserve stored in adipose tissue to survive MI. This would explain why moderately elevated BMI becomes more important with age (Fig. 2). In patients with obesity grade III, the protective effect of obesity is most likely annulled by obesity-related conditions. This is supported in part by the observation that obesity-related cardiovascular adverse events do not occur at a BMI of less than 35 kg/m2 and that the inflection point of the survival curve is at a BMI between 35 kg/m2 and 40 kg/m2. The tendency toward higher long-term risk in patients with obesity grade III was also observed in younger age groups but was not significant (Fig. 2). Why this was significantly accentuated only in the elderly age group remains to be clarified, but this again demonstrates the differential association between BMI categories and mortality in different age groups with MI.

The difference in the treatment of patients in the different BMI categories in the age group >75 years could also be responsible for this result. When we reviewed how patients >75 years were treated in the different BMI categories, we found that they were treated similarly in terms of access site, reperfusion, frequency of P2Y12 receptor antagonist administration, and contrast volume used (unpublished data). The incidence of bleeding was also similar, so we can assume that differences in treatment were not responsible for the higher mortality risk in patients with obesity grade III. The enhanced protective effect of moderate obesity in old age could also be due to the disproportionate loss of body weight in this age group, which is mainly caused by the loss of skeletal muscle. Obesity is usually associated with an increase in muscle mass acquired to support the extra weight. As patients age, overweight and obese patients probably gain more muscle mass, which in turn allows for better mobility and cardiorespiratory fitness, leading to a better outcome. This may be another reason moderate obesity is associated with lower mortality risk after the
age of 75 years. Unfortunately, our analysis lacked data on physical activity and cardiorespiratory fitness.

Although obesity is more common in the elderly, the proportion of patients with obesity was significantly lower in the age group >75 years compared to younger age groups (Fig. 1), and selection bias could not be excluded. In addition, the effect of obesity may be attenuated by other risk factors that we could not consider in our model, such as smoking, severity, and duration of cardiovascular disease, type of obesity, cardiorespiratory fitness, other illnesses, and diseases leading to weight loss.

We also observed that patients in the age group 60–75 years with obesity grade 1 (in addition to overweight patients) had a lower risk of long-term death compared to patients with a BMI <25 kg/m2. These data suggest that the relationship between BMI category and outcome is age-dependent and also confirm the assumption that a moderately high BMI, with its caloric reserve and greater muscle mass and strength, becomes more important in the long term with age. However, the exact mechanisms by which obesity improves the prognosis after MI are not fully understood. Our results should be considered hypothesis-generating for future research, especially because we had no data on cardiorespiratory fitness and could not track data on long-term changes in BMI. Our analysis may have potential clinical implications. Previous reports have shown that purposeful weight loss in such patients may not be beneficial and may even be harmful. We, and others previously, believe that there is no clear evidence that weight loss is beneficial after MI, especially in patients aged >75 years. According to our findings, moderate weight loss should be recommended only for elderly people with obesity grade III. The preservation of muscle mass, which is associated with a higher BMI in these patients, probably allows for better physical activity, which becomes increasingly important with age.

There are still unanswered questions regarding age and BMI. Our results demonstrate that the exact mechanistic underlying the association between BMI and age remains unclear. The interaction of BMI, age, and risk of death according to MI requires further investigation to develop potentially tailored approaches for patients in different age groups and BMI categories. However, our results show that obesity has different prognostic implications in different age groups.

4. Conclusion

The prognostic significance of BMI categories differs according to age in patients with MI. Overweight patients had a lower long-term all-cause mortality risk compared to patients with a BMI <25 kg/m2 at any age. With increasing age, this risk was lower even in patients with grade I obesity. Our results suggest that moderate weight gain with age improves long-term survival after MI and that the magnitude of this “protective” weight gain is greater in older patients than in younger ones. However, excessive weight gain (obesity grade III) is particularly harmful in the oldest age group. The exact relationship between BMI, age, and mortality remains unclear.

5. Limitations

We acknowledge several limitations of the present study. It was a retrospective observational study at a single center and should be interpreted as hypothesis-generating. Cause-specific mortality data were not available, and we could not determine whether specific disease processes were responsible for the increased mortality rates. BMI alone is unable to distinguish between peripheral and abdominal obesity, which may be more important clinically than BMI itself. In addition, few patients had class III obesity, and mortality estimates for these patients were based on very few deaths. The association between BMI categories and mortality may still be overestimated due to unmeasured confounders, and our subgroup analyses are limited by the small sample size, especially in patients with obesity grade III. Multiple confounding factors such as hypertension, diabetes, and hyperlipidemia were also unevenly distributed in the baseline population, which could alter the results. Only BMI at the first hospitalization was recorded, and any subsequent changes in BMI were not followed. Data were missing on a history of MI, heart failure or revascularization, smoking, and socioeconomic status, which are known to be strong predictors of outcome. Data on physical activity before and after MI, cardiorespiratory fitness, and inflammatory biomarkers were also missing. Data on medical treatments other than P2Y12 receptor inhibitors during hospitalization were not collected. However, we adjusted the results for EF, which greatly affected the outcome. Only Caucasians were included; therefore, the generalizability of our results is questionable. We could not rule out selection bias. We did not list the data separately for each sex, as this would lead to a plethora of results that would make the article confusing, and it is beyond the scope of this analysis.

Declarations

Ethics approval

The study was approved by the Hospital Ethics Committee (UKC-MB-KME-24/19).

Consent for publication

Not applicable.

Availability of data and materials statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

VK initiated the study, analyzed, and interpreted the data, and wrote the initial manuscript. BF, GK, and DS were involved in drafting or revising the manuscript, which was critically important for the intellectual content, and approved the final manuscript. All the authors reviewed the manuscript.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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