

## Article

# Obesity Is Associated with Higher Odds of In-Hospital Mortality but Lower Risk of 5-Year Mortality in ST-Segment Elevation Myocardial Infarction Patients

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## Abstract

**Background:** The ‘obesity paradox’, whereby obese patients demonstrate better clinical outcomes compared to normal-weight patients, has been reported in acute myocardial infarction, including ST-segment elevation myocardial infarction (STEMI). However, potential sex differences in this association remain largely unexplored. **Methods:** Using a prospective registry-based multicenter cohort of consecutive STEMI presentations, we evaluated the association between body mass index (BMI) and mortality in patients with STEMI. Patients were divided into three groups based on BMI: normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25–29.9 kg/m<sup>2</sup>), and obese (≥30.0 kg/m<sup>2</sup>). We studied the odds of in-hospital, hospital discharge-to-5-year, and presentation to 5-year all-cause mortality by BMI groups in the overall cohort and in sex-stratified analyses. **Results:** Among 4682 consecutive STEMI patients, 30.1% were female, and 22.2% were normal weight, 36.2% overweight, and 41.6% obese. In the overall cohort, compared to normal-weight patients, the odds of in-hospital mortality were higher in obese patients (aOR 1.73, 95% CI 1.08–2.8) and the risk of discharge-to-5-year mortality was lower in overweight (aHR 0.69, 95% CI 0.57–0.85) and obese (aHR 0.66, 95% CI 0.53–0.82) patients. In sex-stratified analysis, compared to normal-weight males, obese males had higher odds of in-hospital mortality (aOR 2.25, 95% CI 1.18–4.51). Overweight and obese males (aHR 0.63, 95% CI 0.49–0.82, aHR 0.64, 95% CI 0.48–0.85) and obese females (aHR 0.68, 95% CI 0.49–0.94) had a lower discharge-to-5-year mortality risk. **Conclusions:** In this large STEMI cohort, obesity was associated with higher odds of in-hospital mortality but lower risk of discharge-to-5-year mortality. Sex-stratified analyses demonstrated that obese males were at high odds of in-hospital mortality and both obese males and females were at lower risk of discharge-to-5-year mortality.

**Keywords:** STEMI; obesity; sex difference; mortality



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## 1. Introduction

ST-segment elevation myocardial infarction (STEMI) remains a leading cause of global morbidity and mortality worldwide [1,2]. Obesity, a well-established and increasingly prevalent cardiovascular disease risk factor, is projected to affect over 51% of the U.S. population by 2030 [2–4]. Obesity significantly impacts STEMI outcomes; however, the relationship between obesity and STEMI outcomes is complex, with potential sex-specific differences.

The ‘obesity paradox’, characterized by better outcomes in obese patients compared to their non-obese counterparts, has been observed in various cardiovascular conditions [5], including acute coronary syndromes [6]. This phenomenon has been attributed to various mechanisms such as increased metabolic reserve, cardioprotective adipokines, and lower access site complications. Studies examining the influence of obesity on outcomes in STEMI have yielded conflicting findings. Many studies demonstrated a lower in-hospital and long-term mortality among obese patients compared to their normal-weight counterparts, consistent with the ‘obesity paradox’ [7–11], while others reported no significant differences [12,13], and some indicated an increased in-hospital mortality in extremely obese patients [14,15]. There are significant sex differences in fat composition and distribution [16,17]. However, the extent to which these sex-specific variations influence the relationship between obesity and STEMI outcomes, particularly long-term mortality, remains largely unexplored.

This study aimed to investigate the relationship between body mass index (BMI) and all-cause mortality in a large, registry-based prospective cohort of consecutive STEMI patients in the United States.

## 2. Methods

### 2.1. Study Population

This study was conducted at two tertiary percutaneous coronary intervention (PCI) centers in the United States, The Minneapolis Heart Institute in Minneapolis, MN, and The Christ Hospital in Cincinnati, OH, which are part of the Midwest STEMI Consortium [18]. We included all STEMI activations within 24 h of symptom onset, based on ischemic symptoms and ST-segment elevation or new (presumed new) left bundle branch block. All patients included in this study were treated with similar standardized treatment protocols, including pre-treatment with anti-platelets and anticoagulants and immediate referral to the cardiac catheterization laboratory for primary PCI. No exclusion criteria were applied. The study population and the protocol have been previously described in detail [18]. The study protocol and data-sharing agreement between centers were approved by the institutional review boards of each center.

We included 4682 consecutive STEMI patients presenting between January 2010 and December 2020. Patients were divided into three different groups based on their BMI at time of presentation: normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25.0–29.9 kg/m<sup>2</sup>), and obese (30.0 kg/m<sup>2</sup> or above). Demographic and clinical characteristics, angiographic details, laboratory markers, and discharge medications were abstracted by reviewing electronic medical records. All-cause mortality was collected in-hospital and at 1-year follow-up from the electronic medical records and at 5-year follow-up from the national death index.

### 2.2. Statistical Analysis

Continuous variables are summarized with median and interquartile range (IQR) and compared by using Wilcoxon-rank sum tests. Categorical variables are summarized with count and percentage and compared by using Chi-square tests or Fisher’s exact tests. Survival rates were estimated by using the Kaplan–Meier method and compared by using

log-rank tests. Odds ratio (OR) and their corresponding 95% confidence intervals (CIs) of in-hospital mortality for the overweight and obese groups compared to the normal BMI group were estimated using logistic regression models adjusting for age, race/ethnicity, study site, year of STEMI, hypertension, diabetes, dyslipidemia, smoking history, stroke, ejection fraction, out-of-hospital cardiac arrest (OHCA), and percutaneous coronary intervention (PCI) at time of presentation. Analysis of long-term mortality was performed for presentation to 5-year mortality, calculated from the date of presentation to the date of event (all-cause death), and discharge-to-5-year mortality for patients surviving to discharge, with length of follow-up calculated from the date of hospital discharge to the date of event (all-cause death). Hazard ratio (HR) and 95% CI for long-term mortality were estimated using Cox proportional hazard models, adjusting for the same variables as the in-hospital mortality models. To investigate potential differences between BMI groups based on sex, the interaction between BMI group and sex was tested. This interaction term was not found to be significant. Although the interaction effect for sex and BMI was not statistically significant, it had a meaningful trend that drove us to decide to pursue subgroup analysis by sex. All analyses were performed in the overall cohort and repeated separately in the females and males in the cohort. The proportional hazards assumption was evaluated by visually inspecting plots of scaled Schoenfeld residuals. Incidence of missing data for primary variables (BMI and sex) was <0.5%. All computations were performed using R version 4.4.2 (R Core Team, 2024) and RStudio 2024.9.1.394 (Posit team, 2024).

### 3. Results

#### 3.1. Characteristics of STEMI Patients Stratified by BMI Groups

Among 4682 consecutive STEMI patients, 30.1% were female. When assessed by BMI categories, 22.2% were normal weight, 36.2% overweight, and 41.6% obese (Table 1).

**Table 1.** Baseline characteristics of STEMI patients by BMI groups.

| Demographics and Characteristic | Normal BMI,<br>n = 1038 | Overweight,<br>n = 1697 | Obese,<br>n = 1947 | p-Value |
|---------------------------------|-------------------------|-------------------------|--------------------|---------|
| Sex, n (%)                      |                         |                         |                    | <0.001  |
| Female                          | 399 (38%)               | 418 (25%)               | 591 (30%)          |         |
| Male                            | 639 (62%)               | 1279 (75%)              | 1356 (70%)         |         |
| Age, y, median (IQR)            | 67 (58, 79)             | 63 (55, 73)             | 61 (53, 70)        | <0.001  |
| Race/Ethnicity, n (%)           |                         |                         |                    | <0.001  |
| Non-Hispanic White              | 927 (91%)               | 1523 (91%)              | 1794 (93%)         |         |
| Black                           | 47 (4.6%)               | 89 (5.3%)               | 90 (4.7%)          |         |
| Asian                           | 26 (2.5%)               | 15 (0.9%)               | 6 (0.3%)           |         |
| Hispanic                        | 8 (0.8%)                | 25 (1.5%)               | 17 (0.9%)          |         |
| Other                           | 15 (1.5%)               | 24 (1.4%)               | 16 (0.8%)          |         |
| Comorbidities, n (%)            |                         |                         |                    |         |
| Hypertension                    | 564 (55%)               | 929 (55%)               | 1366 (70%)         | <0.001  |
| Diabetes                        | 151 (15%)               | 323 (19%)               | 606 (31%)          | <0.001  |
| Dyslipidemia                    | 479 (46%)               | 922 (55%)               | 1163 (60%)         | <0.001  |
| Smoking History                 | 632 (61%)               | 1040 (62%)              | 1163 (60%)         | 0.6     |
| History of CAD                  | 315 (30%)               | 540 (32%)               | 619 (32%)          | 0.7     |
| History of Stroke               | 76 (7.4%)               | 79 (4.7%)               | 94 (4.8%)          | 0.005   |
| History of MI                   | 213 (21%)               | 376 (22%)               | 442 (23%)          | 0.4     |
| Medications on Admission, n (%) |                         |                         |                    |         |
| ASA                             | 404 (39%)               | 668 (40%)               | 854 (44%)          | 0.009   |
| Anti-platelet                   | 92 (9.0%)               | 145 (8.7%)              | 204 (11%)          | 0.12    |
| Statins                         | 329 (32%)               | 587 (35%)               | 733 (38%)          | 0.006   |

Table 1. Cont.

| Demographics and Characteristic       | Normal BMI,<br>n = 1038 | Overweight,<br>n = 1697 | Obese,<br>n = 1947 | p-Value |
|---------------------------------------|-------------------------|-------------------------|--------------------|---------|
| Beta Blockers                         | 292 (28%)               | 482 (29%)               | 663 (34%)          | <0.001  |
| RAAS-I                                | 261 (25%)               | 445 (27%)               | 703 (36%)          | <0.001  |
| <i>Clinical Characteristics</i>       |                         |                         |                    |         |
| BMI, kg/m <sup>2</sup> , median (IQR) | 23.1 (21.5, 24.2)       | 27.5 (26.3, 28.7)       | 33.8 (31.6, 37.1)  | <0.001  |
| SBP, mmHg, mean (SD)                  | 136 (31)                | 140 (33)                | 143 (34)           | <0.001  |
| DBP, mmHg, mean (SD)                  | 81 (20)                 | 85 (21)                 | 86 (22)            | <0.001  |
| HR, bpm, median (IQR)                 | 77 (64, 92)             | 76 (64, 91)             | 81 (68, 96)        | <0.001  |
| LVEF, % median (IQR)                  | 50 (37, 58)             | 52 (40, 60)             | 51 (40, 60)        | <0.001  |
| OHCA, n (%)                           | 96 (9.2%)               | 163 (9.6%)              | 234 (12%)          | 0.02    |
| CS Pre-PCI, n (%)                     | 100 (9.6%)              | 165 (9.7%)              | 202 (10%)          | 0.7     |
| Killip Class, n (%)                   |                         |                         |                    | 0.3     |
| 1 or 2                                | 951 (92%)               | 1533 (90%)              | 1755 (90%)         |         |
| 3 or 4                                | 85 (8.2%)               | 162 (9.6%)              | 191 (9.8%)         |         |
| <i>Laboratory Markers</i>             |                         |                         |                    |         |
| Peak Trop, ng/mL, median (IQR)        | 8 (1, 41)               | 9 (1, 40)               | 9 (1, 42)          | 0.7     |
| Peak Cr, mg/dL, median (IQR)          | 0.98 (0.82, 1.23)       | 1.04 (0.87, 1.26)       | 1.05 (0.89, 1.32)  | <0.001  |
| <i>Angiographic Characteristics</i>   |                         |                         |                    |         |
| Door-to-Balloon Time, median (IQR)    | 92 (65, 122)            | 88 (60, 117)            | 95 (67, 126)       | <0.001  |
| Culprit Artery, n (%)                 |                         |                         |                    | <0.001  |
| Left Main                             | 12 (1.2%)               | 24 (1.5%)               | 17 (0.9%)          |         |
| LAD                                   | 340 (33%)               | 541 (33%)               | 608 (32%)          |         |
| LCx                                   | 107 (11%)               | 208 (13%)               | 271 (14%)          |         |
| RCA                                   | 349 (34%)               | 606 (37%)               | 727 (38%)          |         |
| Multiple                              | 14 (1.4%)               | 21 (1.3%)               | 37 (1.9%)          |         |
| Graft                                 | 21 (2.1%)               | 43 (2.6%)               | 37 (1.9%)          |         |
| None                                  | 172 (17%)               | 211 (13%)               | 210 (11%)          |         |
| TIMI Flow Pre-PCI, n (%)              |                         |                         |                    | 0.002   |
| 0 or 1                                | 511 (58%)               | 894 (60%)               | 1123 (65%)         |         |
| 2 or 3                                | 371 (42%)               | 595 (40%)               | 618 (35%)          |         |
| TIMI Flow Post-PCI, n (%)             |                         |                         |                    | 0.5     |
| 0 or 1                                | 15 (1.7%)               | 30 (2.0%)               | 41 (2.4%)          |         |
| 2 or 3                                | 867 (98%)               | 1455 (98%)              | 1699 (98%)         |         |

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; ASA, aspirin; RAAS-I, renin–angiotensin–aldosterone system inhibitors; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricle ejection fraction; OHCA, outside hospital cardiac arrest; CS, cardiogenic shock; Trop, troponin; Cr, creatinine; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; PCI, percutaneous coronary intervention.

Compared to patients with normal weight or overweight, obese patients were younger and had a higher proportion of cardiovascular risk factors (hypertension, diabetes, dyslipidemia, and family history of coronary artery disease [CAD]). Obese patients had a higher proportion of medications on admission (aspirin, anti-platelet therapy, statins, beta blockers, and renin–angiotensin–aldosterone inhibitors [RAAS-I]). Obese patients had a higher proportion of out-of-hospital cardiac arrest and longer door-to-balloon time compared to normal-weight or overweight patients. The incidence of cardiogenic shock was similar in the different BMI groups (Table 1).

### 3.2. Outcomes of STEMI Patients Stratified by BMI Groups

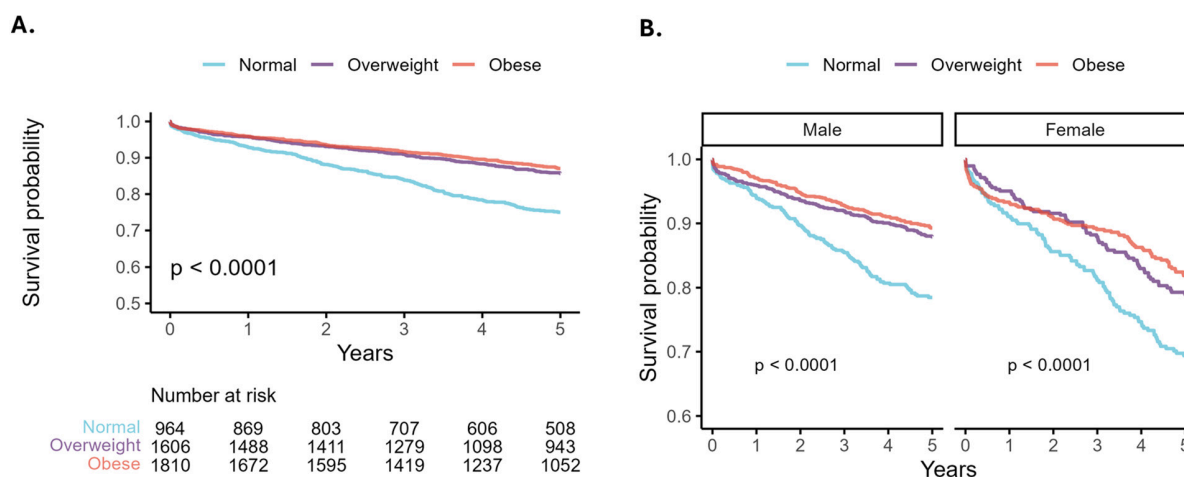
Among patients presenting with STEMI, obese patients were more likely to receive PCI and were discharged on P2Y12 inhibitors, statins, beta-blockers, and RAAS-I at a higher rate compared to patients with normal weight or overweight (Table 2).

**Table 2.** Outcomes of STEMI patients by BMI groups.

| Outcomes                            | Normal BMI,<br>n = 1038 | Overweight,<br>n = 1697 | Obese,<br>n = 1947 | p-Value |
|-------------------------------------|-------------------------|-------------------------|--------------------|---------|
| <i>Discharge Medications, n (%)</i> |                         |                         |                    |         |
| ASA                                 | 879 (91%)               | 1512 (94%)              | 1701 (94%)         | 0.003   |
| Anti-platelet                       | 801 (84%)               | 1362 (86%)              | 1593 (89%)         | 0.002   |
| Statins                             | 845 (88%)               | 1466 (92%)              | 1667 (93%)         | <0.001  |
| Beta Blockers                       | 829 (86%)               | 1422 (89%)              | 1652 (92%)         | <0.001  |
| RAAS-I                              | 655 (69%)               | 1162 (73%)              | 1358 (76%)         | <0.001  |
| <i>Treatment, n (%)</i>             |                         |                         |                    |         |
| PCI                                 | 812 (78%)               | 1388 (82%)              | 1632 (84%)         | <0.001  |
| Medical Management                  | 133 (13%)               | 175 (10%)               | 172 (9.0%)         | 0.003   |
| <i>Outcomes, n (%)</i>              |                         |                         |                    |         |
| In-Hospital Death                   | 59 (5.7%)               | 77 (4.5%)               | 123 (6.3%)         | 0.062   |
| In-Hospital MACE                    | 68 (6.6%)               | 90 (5.3%)               | 139 (7.1%)         | 0.073   |
| 5-year Mortality                    | 274 (27%)               | 274 (16%)               | 324 (17%)          | <0.001  |

Abbreviations: ASA, aspirin; RAAS-I, renin-angiotensin-aldosterone system inhibitors; PCI, percutaneous coronary intervention; MACE, major adverse cardiovascular events.

In the overall cohort, obese patients had a 1.73-fold higher risk of in-hospital mortality compared to normal-weight patients in adjusted models (aOR 1.73, 95% CI 1.08–2.8). There was a significant difference in 5-year survival probability with higher survival rates in overweight and obese patients (Figure 1A). Compared to normal-weight patients, overweight and obese patients had a lower odds of mortality from hospital discharge to 5 years (aHR 0.69, 95% CI 0.57–0.85 and aHR 0.66, 95% CI 0.53–0.82, respectively) and lower risk of presentation-to-5-year mortality in unadjusted and adjusted models (aHR 0.73, 95% CI 0.61–0.88 and aHR 0.80, 95% CI 0.66–0.97, respectively) (Table 3).

**Figure 1.** 5-year survival probability by BMI groups in (A) overall cohort and (B) by sex in male and female STEMI patients.

### 3.3. Characteristics of STEMI Patients Stratified by BMI Groups and Sex

Among 1408 female STEMI patients, 22.2% were normal weight, 36.2% were overweight and 41.6% were obese (Table 4). Compared to female patients with normal weight or overweight, obese female patients were younger and had a higher proportion of hypertension, dyslipidemia, and diabetes. The proportion of patients on cardiac medications on admission was similar among the three BMI groups, except for RASS-I, which was highest in obese female patients. Similar proportions of OHCA, cardiogenic shock and similar door-to-balloon times were seen in female patients across the three BMI groups.

**Table 3.** Association with in-hospital, discharge-to-5-year and 5-year mortality by BMI groups in overall STEMI cohort and by sex.

|                                              | Unadjusted Model | Adjusted Model   |
|----------------------------------------------|------------------|------------------|
| <b>Overall STEMI Cohort</b>                  |                  |                  |
| In-Hospital Mortality [(OR), 95% CI]         |                  |                  |
| Normal BMI                                   | 1.0 (Reference)  | 1.0 (Reference)  |
| Overweight                                   | 0.79 (0.56–1.12) | 1.1 (0.67–1.8)   |
| Obese                                        | 1.12 (0.82–1.55) | 1.73 (1.08–2.8)  |
| Discharge-to-5-Year Mortality [(HR), 95% CI] |                  |                  |
| Normal BMI                                   | 1.0 (Reference)  | 1.0 (Reference)  |
| Overweight                                   | 0.54 (0.44–0.65) | 0.69 (0.57–0.85) |
| Obese                                        | 0.48 (0.4–0.58)  | 0.66 (0.53–0.82) |
| 5-Year Mortality [(HR), 95% CI]              |                  |                  |
| Normal BMI                                   | 1.0 (Reference)  | 1.0 (Reference)  |
| Overweight                                   | 0.59 (0.5–0.7)   | 0.73 (0.61–0.88) |
| Obese                                        | 0.61 (0.52–0.72) | 0.8 (0.66–0.97)  |
| <b>Female STEMI Cohort</b>                   |                  |                  |
| In-Hospital Mortality [(OR), 95% CI]         |                  |                  |
| Normal BMI                                   | 1.0 (Reference)  | 1.0 (Reference)  |
| Overweight                                   | 0.74 (0.42–1.3)  | 0.8 (0.35–1.78)  |
| Obese                                        | 0.8 (0.48–1.34)  | 1.31 (0.64–2.73) |
| Discharge-to-5-Year Mortality [(HR), 95% CI] |                  |                  |
| Normal BMI                                   | 1.0 (Reference)  | 1.0 (Reference)  |
| Overweight                                   | 0.64 (0.47–0.87) | 0.79 (0.57–1.08) |
| Obese                                        | 0.55 (0.41–0.73) | 0.68 (0.49–0.94) |
| 5-Year Mortality [(HR), 95% CI]              |                  |                  |
| Normal BMI                                   | 1.0 (Reference)  | 1.0 (Reference)  |
| Overweight                                   | 0.66 (0.51–0.86) | 0.77 (0.57–1.03) |
| Obese                                        | 0.61 (0.47–0.78) | 0.77 (0.58–1.03) |
| <b>Male STEMI Cohort</b>                     |                  |                  |
| In-Hospital Mortality [(OR), 95% CI]         |                  |                  |
| Normal BMI                                   | 1.0 (Reference)  | 1.0 (Reference)  |
| Overweight                                   | 0.89 (0.57–1.43) | 1.42 (0.74–2.81) |
| Obese                                        | 1.41 (0.93–2.19) | 2.25 (1.18–4.51) |
| Discharge-to-5-Year Mortality [(HR), 95% CI] |                  |                  |
| Normal BMI                                   | 1.0 (Reference)  | 1.0 (Reference)  |
| Overweight                                   | 0.53 (0.42–0.69) | 0.63 (0.49–0.82) |
| Obese                                        | 0.47 (0.36–0.6)  | 0.64 (0.48–0.85) |
| 5-Year Mortality [(HR), 95% CI]              |                  |                  |
| Normal BMI                                   | 1.0 (Reference)  | 1.0 (Reference)  |
| Overweight                                   | 0.61 (0.49–0.76) | 0.71 (0.56–0.91) |
| Obese                                        | 0.65 (0.53–0.8)  | 0.83 (0.64–1.06) |

Adjusted Model: BMI, body mass index. Normal BMI (18.5–24.9 kg/m<sup>2</sup>), overweight (25.0–29.9 kg/m<sup>2</sup>), and obese (30.0 kg/m<sup>2</sup> or above). Models adjusted for age, race/ethnicity, study site, year of STEMI, hypertension, diabetes, dyslipidemia, smoking history, stroke, ejection fraction, out-of-hospital cardiac arrest (OHCA), and treatment with percutaneous coronary intervention (PCI). Logistic regression was used for in-hospital mortality represented as odds ratio (OR) and Cox proportional hazard models for 5-year mortality represented as hazard ratio (HR).

**Table 4.** Baseline characteristics of female and male STEMI patients by BMI groups.

| Demographics and Characteristics      | Female                |                       |                  | <i>p</i> -Value | Male                  |                        |                   | <i>p</i> -Value |
|---------------------------------------|-----------------------|-----------------------|------------------|-----------------|-----------------------|------------------------|-------------------|-----------------|
|                                       | Normal BMI<br>n = 399 | Overweight<br>n = 418 | Obese<br>n = 591 |                 | Normal BMI<br>n = 639 | Overweight<br>n = 1279 | Obese<br>n = 1356 |                 |
| Age, y, median (IQR)                  | 72 (61, 83)           | 68 (59, 78)           | 65 (55, 74)      | <0.001          | 65 (54, 76)           | 62 (54, 71)            | 60 (52, 68)       | <0.001          |
| Race/Ethnicity, n (%)                 |                       |                       |                  | <0.001          |                       |                        |                   | <0.001          |
| Non-Hispanic White                    | 367 (93%)             | 369 (90%)             | 528 (91%)        |                 | 560 (89%)             | 1154 (91%)             | 1266 (94%)        |                 |
| Black                                 | 8 (2.0%)              | 29 (7.0%)             | 47 (8.1%)        |                 | 39 (6.2%)             | 60 (4.7%)              | 43 (3.2%)         |                 |
| Asian                                 | 6 (1.5%)              | 3 (0.7%)              | 2 (0.3%)         |                 | 20 (3.2%)             | 12 (0.9%)              | 4 (0.3%)          |                 |
| Hispanic                              | 1 (0.3%)              | 5 (1.2%)              | 5 (0.9%)         |                 | 7 (1.1%)              | 20 (1.6%)              | 12 (0.9%)         |                 |
| Other                                 | 11 (2.8%)             | 6 (1.5%)              | 1 (0.2%)         |                 | 4 (0.6%)              | 18 (1.4%)              | 15 (1.1%)         |                 |
| Comorbidities, n (%)                  |                       |                       |                  |                 |                       |                        |                   |                 |
| Hypertension                          | 248 (63%)             | 258 (62%)             | 448 (76%)        | <0.001          | 316 (50%)             | 671 (53%)              | 918 (68%)         | <0.001          |
| Diabetes                              | 57 (14%)              | 104 (25%)             | 236 (40%)        | <0.001          | 94 (15%)              | 219 (17%)              | 370 (27%)         | <0.001          |
| Dyslipidemia                          | 191 (48%)             | 240 (58%)             | 365 (62%)        | <0.001          | 288 (45%)             | 682 (54%)              | 798 (59%)         | <0.001          |
| Smoking history                       | 207 (52%)             | 218 (52%)             | 344 (59%)        | 0.065           | 425 (67%)             | 822 (65%)              | 819 (61%)         | 0.019           |
| History of CAD                        | 109 (28%)             | 128 (31%)             | 170 (29%)        | 0.6             | 206 (32%)             | 412 (32%)              | 449 (33%)         | 0.9             |
| History of Stroke                     | 26 (6.6%)             | 23 (5.5%)             | 49 (8.3%)        | 0.2             | 50 (7.8%)             | 56 (4.4%)              | 45 (3.3%)         | <0.001          |
| History of MI                         | 71 (18%)              | 95 (23%)              | 122 (21%)        | 0.2             | 142 (22%)             | 281 (22%)              | 320 (24%)         | 0.5             |
| Medications on Admission, n (%)       |                       |                       |                  |                 |                       |                        |                   |                 |
| ASA                                   | 156 (39%)             | 182 (44%)             | 266 (45%)        | 0.2             | 248 (39%)             | 486 (39%)              | 588 (44%)         | 0.024           |
| Anti-platelet                         | 37 (9.3%)             | 30 (7.2%)             | 64 (11%)         | 0.13            | 55 (8.7%)             | 115 (9.1%)             | 140 (10%)         | 0.4             |
| Statins                               | 132 (33%)             | 147 (35%)             | 231 (39%)        | 0.13            | 197 (31%)             | 440 (35%)              | 502 (37%)         | 0.032           |
| Beta Blockers                         | 127 (32%)             | 133 (32%)             | 223 (38%)        | 0.064           | 165 (26%)             | 349 (28%)              | 440 (33%)         | 0.003           |
| RASS-I                                | 101 (26%)             | 127 (31%)             | 230 (39%)        | <0.001          | 160 (25%)             | 318 (25%)              | 473 (35%)         | <0.001          |
| Clinical Characteristics              |                       |                       |                  |                 |                       |                        |                   |                 |
| BMI, kg/m <sup>2</sup> , median (IQR) | 23 (21, 24)           | 28 (26, 29)           | 34 (32, 39)      | <0.001          | 23 (22, 24)           | 28 (26, 29)            | 34 (31, 37)       | <0.001          |
| SBP, mmHg, mean (SD)                  | 137 (32)              | 137 (33)              | 142 (35)         | 0.007           | 135 (31)              | 141 (32)               | 144 (33)          | <0.001          |
| DBP, mmHg, mean (SD)                  | 80 (20)               | 81 (21)               | 83 (22)          | 0.015           | 82 (20)               | 86 (21)                | 88 (22)           | <0.001          |
| Heart rate, bpm, median (IQR)         | 78 (66, 94)           | 80 (65, 95)           | 83 (69, 100)     | 0.015           | 76 (63, 90)           | 75 (64, 90)            | 80 (67, 95)       | <0.001          |
| LVEF, %, median (IQR)                 | 50 (35, 60)           | 52 (40, 60)           | 50 (40, 60)      | 0.2             | 50 (38, 58)           | 51 (40, 60)            | 52 (40, 60)       | 0.003           |
| OHCA, n (%)                           | 33 (8.3%)             | 37 (8.9%)             | 52 (8.8%)        | >0.9            | 63 (9.9%)             | 126 (9.9%)             | 182 (13%)         | 0.007           |
| CS pre-PCI, n (%)                     | 42 (11%)              | 53 (13%)              | 66 (11%)         | 0.6             | 58 (9.1%)             | 112 (8.8%)             | 136 (10%)         | 0.5             |
| Killip class, n (%)                   |                       |                       |                  | 0.3             |                       |                        |                   | 0.6             |
| 1 or 2                                | 361 (91%)             | 367 (88%)             | 520 (88%)        |                 | 590 (92%)             | 1166 (91%)             | 1235 (91%)        |                 |
| 3 or 4                                | 37 (9.3%)             | 51 (12%)              | 71 (12%)         |                 | 48 (7.5%)             | 111 (8.7%)             | 120 (8.9%)        |                 |
| Laboratory Markers                    |                       |                       |                  |                 |                       |                        |                   |                 |
| Peak Trop, ng/mL, median (IQR)        | 5 (1, 28)             | 7 (1, 30)             | 9 (1, 35)        | 0.14            | 10 (1, 54)            | 10 (1, 43)             | 9 (1, 44)         | 0.9             |
| Peak Cr, mg/dL, median (IQR)          | 0.9 (0.8, 1.1)        | 0.9 (0.8, 1.1)        | 0.9 (0.8, 1.3)   | <0.001          | 1.0 (0.9, 1.3)        | 1.1 (0.9, 1.3)         | 1.1 (0.9, 1.3)    | 0.001           |
| Angiographic Characteristics          |                       |                       |                  |                 |                       |                        |                   |                 |
| Door-to-Balloon Time, median (IQR)    | 94 (71, 127)          | 90 (65, 123)          | 96 (64, 132)     | 0.2             | 90 (62, 119)          | 87 (59, 116)           | 94 (69, 123)      | <0.001          |
| Culprit Artery, n (%)                 |                       |                       |                  | 0.046           |                       |                        |                   | 0.020           |
| LAD                                   | 124 (32%)             | 118 (29%)             | 185 (32%)        |                 | 216 (35%)             | 423 (34%)              | 423 (32%)         |                 |
| LCx                                   | 34 (8.7%)             | 50 (12%)              | 80 (14%)         |                 | 73 (12%)              | 158 (13%)              | 191 (14%)         |                 |
| Left Main                             | 5 (1.3%)              | 3 (0.7%)              | 8 (1.4%)         |                 | 7 (1.1%)              | 21 (1.7%)              | 9 (0.7%)          |                 |
| Multiple                              | 8 (2.1%)              | 5 (1.2%)              | 10 (1.7%)        |                 | 6 (1.0%)              | 16 (1.3%)              | 27 (2.0%)         |                 |
| None                                  | 83 (21%)              | 70 (17%)              | 77 (13%)         |                 | 89 (14%)              | 141 (11%)              | 133 (10%)         |                 |
| Graft                                 | 5 (1.3%)              | 12 (2.9%)             | 9 (1.5%)         |                 | 16 (2.6%)             | 31 (2.5%)              | 28 (2.1%)         |                 |
| TIMI Flow Pre-PCI, n (%)              |                       |                       |                  | 0.11            |                       |                        |                   | 0.017           |
| 0 or 1                                | 183 (56%)             | 201 (56%)             | 321 (62%)        |                 | 328 (59%)             | 693 (61%)              | 802 (66%)         |                 |
| 2 or 3                                | 146 (44%)             | 156 (44%)             | 197 (38%)        |                 | 225 (41%)             | 439 (39%)              | 421 (34%)         |                 |
| TIMI Flow Post-PCI, n (%)             |                       |                       |                  | 0.031           |                       |                        |                   | 0.5             |
| 0 or 1                                | 6 (1.8%)              | 2 (0.6%)              | 16 (3.1%)        |                 | 9 (1.6%)              | 28 (2.5%)              | 25 (2.0%)         |                 |
| 2 or 3                                | 323 (98%)             | 353 (99%)             | 501 (97%)        |                 | 544 (98%)             | 1102 (98%)             | 1198 (98%)        |                 |

Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; ASA, aspirin; RAAS-I, renin-angiotensin-aldosterone system inhibitors; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricle ejection fraction; OHCA, outside hospital cardiac arrest; CS, cardiogenic shock; Trop, troponin; Cr, creatinine; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; PCI, percutaneous coronary intervention.

Among 3274 male STEMI patients, 19.5% were normal weight, 39.1% were overweight, and 41.4% were obese (Table 4). Compared to male patients with normal weight or overweight, obese male patients were younger and had a higher prevalence of hypertension, dyslipidemia, and diabetes, with a lower prevalence of smoking. Obese patients had a higher proportion of medications on admission (aspirin, statins, beta blockers, RASS-I). Additionally, obese males experienced a higher incidence of OHCA and longer door-to-balloon times compared to males with normal weight or overweight.

### 3.4. Outcomes of STEMI Patients Stratified by BMI Groups and Sex

Among female patients presenting with STEMI, compared to patients with normal weight or overweight, obese female patients had a higher proportion of PCI treatment (Table 5).

**Table 5.** Outcomes of STEMI patients in females and males by BMI groups.

| Outcomes                            | Female                |                       |                  |         | Male                  |                        |                   |         |
|-------------------------------------|-----------------------|-----------------------|------------------|---------|-----------------------|------------------------|-------------------|---------|
|                                     | Normal BMI<br>n = 399 | Overweight<br>n = 418 | Obese<br>n = 591 | p-Value | Normal BMI<br>n = 639 | Overweight<br>n = 1279 | Obese<br>n = 1356 | p-Value |
| <i>Discharge Medications, n (%)</i> |                       |                       |                  |         |                       |                        |                   |         |
| ASA                                 | 327 (89%)             | 375 (96%)             | 507 (93%)        | 0.002   | 552 (92%)             | 1137 (94%)             | 1194 (95%)        | 0.13    |
| Anti-platelet                       | 292 (80%)             | 318 (83%)             | 465 (86%)        | 0.1     | 509 (86%)             | 1044 (87%)             | 1128 (90%)        | 0.031   |
| Statins                             | 309 (84%)             | 347 (89%)             | 492 (90%)        | 0.017   | 536 (90%)             | 1119 (93%)             | 1175 (94%)        | 0.02    |
| Beta Blockers                       | 320 (88%)             | 344 (88%)             | 499 (92%)        | 0.1     | 509 (85%)             | 1078 (89%)             | 1153 (92%)        | <0.001  |
| RASS-I                              | 230 (64%)             | 263 (68%)             | 388 (72%)        | 0.025   | 425 (72%)             | 899 (75%)              | 970 (77%)         | 0.029   |
| <i>Treatment</i>                    |                       |                       |                  |         |                       |                        |                   |         |
| PCI, n (%)                          | 288 (72%)             | 324 (78%)             | 483 (82%)        | 0.002   | 524 (82%)             | 1064 (83%)             | 1149 (85%)        | 0.2     |
| <i>Medical Management, n (%)</i>    |                       |                       |                  |         |                       |                        |                   |         |
| Management, n (%)                   | 65 (16%)              | 56 (14%)              | 62 (11%)         | 0.033   | 68 (11%)              | 119 (9.4%)             | 110 (8.2%)        | 0.2     |
| <i>Outcomes, n (%)</i>              |                       |                       |                  |         |                       |                        |                   |         |
| In-Hospital Death                   | 29 (7.3%)             | 23 (5.5%)             | 35 (5.9%)        | 0.5     | 30 (4.7%)             | 54 (4.2%)              | 88 (6.5%)         | 0.026   |
| In-Hospital MACE                    | 31 (7.8%)             | 28 (6.7%)             | 39 (6.6%)        | 0.8     | 37 (5.8%)             | 62 (4.8%)              | 100 (7.4%)        | 0.024   |
| 5-year Mortality                    | 128 (33%)             | 93 (22%)              | 120 (21%)        | <0.001  | 146 (23%)             | 181 (14%)              | 204 (15%)         | <0.001  |

Abbreviations: ASA, aspirin; RAAS-I, renin-angiotensin-aldosterone system inhibitors; PCI, percutaneous coronary intervention; MACE, major adverse cardiovascular events.

Among females, the obese patients also received RASS-I and statins upon discharge at higher rates compared to those with normal weight or overweight. The in-hospital mortality risk was not statistically different in females among the three BMI groups. There was a significant difference in the 5-year survival probability in females, with higher survival rates in overweight and obese patients (Figure 1B). Compared to normal-weight females, overweight females had a significantly lower hospital discharge-to-5-year mortality and 5-year mortality in unadjusted models that was not significant in adjusted models (Table 3). Obese females had a lower risk of mortality at discharge to 5 years (aHR 0.68, 95% CI 0.49–0.94) and a lower risk of 5-year mortality that was attenuated in adjusted models (aHR 0.77, 95% CI 0.58–1.03).

Among male patients presenting with STEMI, the PCI utilization rates were similar across the three BMI groups (Table 5). Obese males had a higher proportion of beta blockers, P2Y12 inhibitors, statins, and RASS-I prescribed at discharge compared to normal or overweight males. Obese males had higher odds of in-hospital mortality compared to normal-weight males (aOR 2.25, 95% CI 1.18–4.51) (Table 3). There was a significant difference in the survival probability in males, with higher survival rates in overweight and obese patients (Figure 1B). Compared to normal-weight males, there was a lower mortality risk in overweight males in unadjusted and adjusted models from discharge-to-5-years (aHR 0.63, 95% CI 0.49–0.82) and 5-year mortality (aHR 0.71, 95% CI 0.56–0.91) (Table 3). There was a lower mortality risk in obese males in unadjusted models that remained significant in adjusted models for discharge-to-5-years mortality (aHR 0.64, 95% CI 0.48–0.85) but not 5-year mortality (aHR 0.83, 95% CI 0.64–1.06) (Table 3).

## 4. Discussion

This prospective cohort study enhances our understanding of the relationship between body weight and short- and long-term outcomes in STEMI and potential differences by sex. In the overall cohort, while obesity was associated with a higher risk of in-hospital

mortality, the discharge-to-5-year mortality risk was significantly lower in overweight and obese patients, consistent with the ‘obesity paradox’. Sex-stratified analyses demonstrated that obese males were at high odds of in-hospital mortality and both obese males and females were at lower risk of discharge-to-5-year mortality (Graphic Abstract).

This study demonstrated the importance of analyzing in-hospital and discharge-to-long-term mortality separately when studying the effects of body weight on mortality. In this study, obese patients had 1.73-fold higher odds of in-hospital mortality. Our results are consistent with other studies that showed higher odds of in-hospital mortality in obese patients, however prior work demonstrated this in obesity defined by a higher BMI of greater than 40 kg/m<sup>2</sup> [12,13]. However, the majority of studies to date report lower in-hospital mortality in obese patients [7–10], or similar outcomes across BMI group categories [14,15,19]. The differences in results may be in part attributed to how obesity was defined across studies, differences in patient populations and high-risk features at the time of presentation, such as an OHCA and cardiogenic shock.

We found evidence of the well-described ‘obesity paradox’ in STEMI patients at 5 years, driven by the discharge-to-5-year outcomes. Overweight STEMI patients had a 31% lower risk and obese patients had a 34% lower risk of discharge-to-5-year mortality compared to normal-weight patients. Our findings align with the NCDR ACTION Registry-GWTG analysis of 19,499 STEMI patients, where obesity defined as BMI between 30 and 34.9 kg/m<sup>2</sup> was associated with a 23% lower risk of death compared to normal weight at 3-year follow-up [20]. A meta-analysis of 12 studies in STEMI patients also showed that obese patients had a 41% lower risk of long-term mortality than normal-weight patients [7]. The observed long-term survival benefit may be attributable in part to the younger age, more aggressive revascularization strategy, and more frequent administration of cardiovascular medications at discharge in the obese patients compared to normal-weight patients. This is supported by the attenuation observed in the adjusted models; however, the association between overweight and obesity and long-term mortality remained significant.

Few studies to date have examined sex differences in the relationship between body weight and in-hospital and long-term mortality, with conflicting results in STEMI patients [21,22]. Although the interaction between sex and BMI was not statistically significant, the sex-stratified analysis showed differences in the risk of mortality in males and females based on the timing of the outcome. Compared to normal-weight males, obese males had a 2.25-fold higher odds of in-hospital mortality, whereas overweight and obese males had a lower risk of discharge-to-5-year mortality. It is important to consider that the “obesity paradox” observed discharge-to-5-year mortality in males could be artificially amplified by the higher in-hospital mortality in males, since the analysis was restricted to survivors. In females, in-hospital mortality was similar across the BMI groups. Compared to normal-weight females, overweight and obese females had a lower risk of discharge-to-5-year mortality that was attenuated in adjusted models and only remained significant in obese females. Our results on long-term outcomes differ from Zhang et al., who demonstrated in a STEMI cohort that obesity was an independent protective factor for MACE in male patients, but not associated with prognosis in female patients [22].

There are important sex differences in adiposity and body fat distribution [16,17,23,24]. Compared to obese women, obese men have higher glucose levels and insulin resistance and lower adiponectin levels, promoting intra-abdominal adiposity and visceral adipose tissue (VAT). VAT is associated with increased systemic inflammation, which has been shown to increase plaque instability and promote thrombosis. Conversely, the subcutaneous adipose tissue (SAT) distribution, more prevalent in females, is not associated with inflammation in obesity and absorbs circulating free fatty acids and triglycerides, resulting in a protective effect that may contribute to the observed long-term survival benefit [25–27].

Additionally, hormonal differences, particularly the protective effects of estrogen in the distribution of adipose tissue in subcutaneous regions in premenopausal women, may further modulate the impact of obesity on STEMI outcomes [28]. Further mechanistic research is needed to fully elucidate the complex interplay of these factors on sex-differences in short- and long-term outcomes related to obesity in STEMI patients.

## 5. Limitations

Our study has limitations that are important to take into account when interpreting the results of two large STEMI centers with more than 40 non-PCI center referral sites. Confounding is inherent to observational studies, and despite multivariable adjustment in our models there are additional significant baseline differences between the groups, such as medications, which may result in residual confounding. Additionally, there are potential unmeasured confounders that could affect the results. While BMI is commonly used, it does not directly measure body fat or its distribution. Parameters like waist-to-hip ratio or body composition analysis may provide additional insights. We lacked data on cause-specific mortality and did not track changes in BMI after hospital discharge. Additionally, this is a predominantly non-Hispanic White cohort, limiting the ability to look at differences by race/ethnicity.

## 6. Conclusions

To our knowledge, this is the first study examining the association of body weight on both short- and long-term outcomes in STEMI patients stratified by sex. The ‘obesity paradox’ was observed at discharge-to-5-year mortality in males and females. However, obesity was associated with higher odds of in-hospital mortality, particularly in males. The differences in mortality by timing of outcome (in-hospital vs. long-term), sex and adjustment of key variables highlight the importance of all of these factors in future analyses.

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**Informed Consent Statement:** Patient consent was waived by the IRB for this registry as the data collected was already created as part of routine medical care.

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## Abbreviations

|     |                         |
|-----|-------------------------|
| BMI | Body mass index         |
| CAD | Coronary artery disease |

|        |                                            |
|--------|--------------------------------------------|
| MACE   | Major adverse cardiovascular events        |
| MI     | Myocardial infarction                      |
| OHCA   | Out-of-hospital cardiac arrest             |
| PCI    | Percutaneous coronary intervention         |
| RASS-I | Renin–angiotensin–aldosterone inhibitors   |
| STEMI  | ST-segment elevation myocardial infarction |

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