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Original Article

ST-elevation myocardial infarction in a real world population - An observational retrospective study with a sex perspective

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ABSTRACT

Background: Mortality after myocardial infarction is higher in women than in men. Data on the association between sex and mortality are conflicting and inconclusive. We evaluated whether there is a sex difference in survival and if sex is associated with the outcome in patients with ST-elevation myocardial infarction (STEMI).
Methods: We analyzed 3671 STEMI patients. Long-term and 30-day mortality in men and women were compared.
Results: Unadjusted mortality at day 30 was higher in women [221 (8.7%) men died compared to 147 (13.1%) women; $p < 0.0001$]. After multivariate adjustments, this became insignificant (OR 1.65; 95% CI; 0.81 to 1.40). The long-term, unadjusted mortality was also higher in women [674 (26.3%) men died compared to 382 (34%) women; $p < 0.0001$]. After multivariable adjustments, female sex (adjusted HR 0.81; 95% CI 0.71 to 0.93; $p = 0.002$), bleeding (adjusted HR 1.79; 95% CI 1.52 to 2.10; $p < 0.0001$), renal dysfunction adjusted HR (1.60; 95% CI 1.40 to 1.84; $p < 0.0001$), hyperlipidemia (adjusted HR 1.61; 95% CI 1.40 to 1.85; $p < 0.0001$), arterial hypertension (adjusted HR 1.17; 95% CI 1.03 to 1.33; $p = 0.015$), diabetes (adjusted HR 1.55; 95% CI 1.35 to 1.78; $p < 0.0001$), age (adjusted HR 1.05; 95% CI 1.04 to 1.06; $p < 0.0001$), anemia on admission (adjusted HR 1.38; 95% CI 1.23 to 1.58; $p < 0.0001$), and heart failure (adjusted HR 2.40; 95% CI 2.09 to 2.75; $p < 0.0001$) predicted long-term mortality.
Conclusion: Female sex was associated with a lower risk of dying in the long term. However, risk factors, age, and comorbidities associated with female patients affected the worse outcome.

1. Introduction

Many studies have observed a higher mortality in women with myocardial infarction compared to men [1–8]. This may be explained by their higher cardiovascular risk profile, differences in treatment or it may be related to sex per se [1,9] The data on sex as a predictor of a worse outcome are still inconclusive and conflicting [2–5,8,10–12]. Moreover, there is a persistent belief that after primary percutaneous coronary intervention (PCI), women have a worse prognosis. [4,13]. A limited number of studies have reported results on the medium or long-term mortality in women with ST-elevation myocardial infarction (STEMI) receiving modern treatment [1,5,10,12,13].

We evaluated the 30-day and long-term survival of STEMI patients undergoing PCI and the possible association of sex with the outcome.

2. Materials and methods

A retrospective, single-center observational study was performed at the University Medical Center Maribor, a tertiary referral hospital with a 24/7 primary PCI service. We reviewed 3706 consecutive STEMI patients with a diagnosis of acute STEMI who were treated with PCI between January 2007 and December 2016. The diagnosis of STEMI was established in accordance with published guidelines, including a typical history of chest pain, diagnostic electrocardiographic changes, and serial elevation of cardiac biomarkers [14] We excluded patients with incomplete data (35), leaving 3671 for further analysis. Otherwise, this was an all-comers study.

Primary PCI was performed in patients with symptoms ≤12 h in duration as well as in patients with symptoms lasting 12–24 h if the symptoms persisted at the time of admission. Patients were treated according to the guidelines for STEMI management [14,15]. All

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therapeutic decisions were left to the operators' discretion. Patients were pretreated with aspirin and P2Y12 inhibitors with the recommended loading doses; aspirin was continued indefinitely and P2Y12 inhibitors were recommended for 12 months. Unfractionated heparin (initial bolus of 5000 IU) or bivalirudin (with a bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg/h) were given according to the operator's preference. All medical records were obtained from the hospital information system to complete the data collection. Mortality was assessed over a median period of 5 years (25th, 75th percentile: 3,8) up to January 1, 2018. The study was approved by the local ethics committee. Data on dates of death were provided by the Slovenian National Cause of Death Registry.

Anemia was defined as proposed by the World Health Organization: a serum hemoglobin level < 130 g/L for men and < 120 g/L for women [16]. The Bleeding Academic Research Consortium (BARC) bleeding criteria and BARC 3a bleeding (Hb drop of 30–50 g/L or any transfusion) were used [17]. Renal dysfunction on admission was defined as an estimated glomerular filtration rate (GFR) ≤60 mL/kg/1.73m^2.

Heart failure was defined according to clinical criteria (bilateral pulmonary rales, S_3 gallop, edema or cardiogenic shock) and/or pulmonary edema on chest X-ray and/or ejection fraction < 30%. The ventricular ejection fraction was assessed by bedside echocardiography in the first 48 h after admission.

2.1. Outcome

The end point was all-cause 30-day and long-term mortality in male and female patients.

2.2. Statistical methods

We counted end point events that occurred during the follow-up period and compared their rates between men and women. The cumulative incidence rates of the unadjusted long-term mortality were estimated by the Kaplan–Meier method and compared by the log-rank test. Binary logistic regression models were performed using the Enter mode to identify independent predictors of 30-day mortality. Cox proportional hazards regression was used to compute hazard ratios (HRs) as estimates of long-term mortality. The models were adjusted for variables that significantly differed in univariant analysis: age, diabetes, hypertension, hyperlipidemia, heart failure, renal dysfunction, anemia, bleeding, PCI of the circumflex artery, the usage of bivalirudin, and sex.

Differences between the groups in baseline clinical, angiographic, and procedural characteristics were compared using the independent samples *t*-test or the Mann-Whitney *U* test for continuous variables, and the chi-square test for categorical variables, as appropriate.

Data were analyzed with SPSS 23.0 software for Windows (IBM Corp., Armonk, NY). All p-values were two-sided and values < 0.05 were considered statistically significant.

3. Results

3.1. Descriptive data for patients

Out of 3671 STEMI patients, 1123 (30.6%) were female. Women were, on average, seven years older. They suffered more often from hypertension, diabetes, anemia, and renal dysfunction. On the contrary, they had less hyperlipidemia. Bivalirudin was less frequently used and fewer PCIs of the circumflex artery were performed in women. They bled more, and suffered more heart failure.

Tables 1 and 2 show the basic clinical and procedural characteristics of patients enrolled in the study.

3.2. Mortality

Unadjusted mortality at day 30 was higher in women [221 (8.7%) men died compared to 147 (13.1%) women; p < 0.0001]. However, after multivariate adjustments, this became insignificant (OR 1.65; 95% CI; 0.81 to 1.40). Long-term, all-cause unadjusted mortality was also higher in women [665 (26.1%) men died compared to 382 (34%) women; p < 0.0001] (Fig. 1A). Surprisingly, after multivariable adjustments, women had a better long-term prognosis (adjusted HR 0.81; 95% CI 0.71 to 0.93; p = 0.002) (Fig. 1B). Besides female sex (which predicted lower mortality), heart failure, bleeding, renal dysfunction on admission, hyperlipidemia, arterial hypertension, diabetes, age, and anemia predicted higher long-term mortality (Table 3).

Table 1
Basic demographic characteristics of patients with ST-elevation myocardial infarction.

	Men N = 2548	Women N = 1123	p
Age, years[a]	61.6 (11.8)	68.6 (12.3)	< 0.0001
Diabetes, N (%)[b]	471 (18.5)	272 (24.2)	< 0.0001
Hypertension, N (%)[b]	1259 (49.4)	663 (59.0)	< 0.0001
Dyslipidemia, N (%)[b]	1241 (48.7)	485 (41.4)	< 0.0001
Renal dysfunction on admission, N (%)[b]	446 (17.5)	363 (32.3)	< 0.0001
Anemia, N (%)[b]	719 (28.2)	416 (37.0)	< 0.0001

[a] Mean (standard deviation); comparison made using the t-test.
[b] Comparison made using the chi-square test; N = number.

Table 2
Procedural data of patients with ST-elevation myocardial infarction.

	Men N = 2548	Women N = 123	p
Dual antiplatelet therapy, N (%)[a]	2329 (91.4)	1017 (90.6)	0.41
Bivalirudin, N (%)[a]	366 (14.4)	127 (11.3)	0.013
GPIIb/IIIa receptor inhibitors, N (%)[a]	1423 (55.9)	616 (54.9)	0.59
PCI left main coronary artery, N (%)[a]	63 (2.5)	37 (3.3)	0.19
PCI left anterior descending artery, N (%)[a]	1088 (42.7)	512 (45.6)	0.11
PCI circumflex artery, N (%)[a]	513 (20.1)	185 (16.5)	0.009
PCI right coronary artery, N (%)[a]	914 (35.9)	405 (36.1)	0.91
Drug-eluting stent, N (%)[a]	957 (37.6)	404 (36.0)	0.37
Intra-aortic balloon pump, N (%)[a]	52 (2.0)	33 (2.9)	0.097
TIMI flow 0/1 after PCI, N (%)[a]	133 (5.2)	72 (6.4)	0.16
Multivessel PCI, N (%)[a]	348 (13.7)	146 (13.0)	0.60
Radial access, N (%)[a]	403 (15.8)	174 (15.5)	0.84
Bleeding, N (%)[a]	199 (7.8)	132 (11.8)	< 0.0001
Heart failure, N (%)[a]	483 (19.0)	258 (23.0)	0.007

N = number; PCI = percutaneous coronary intervention; TIMI flow 0/1 after PCI = Thrombolysis in Myocardial Infarction grade flow 0/1.
[a] Comparison made using the chi-square test.

4. Discussion

There are limited data on sex differences in long-term mortality in patients with STEMI [1,2,5,10,12,13]. In our long-term follow-up study, we followed patients for up to 11 years, with a median of 5 years. We found a higher unadjusted mortality but a 19% lower multivariable-adjusted risk for long-term mortality in women compared to men. In other words, women have a 19% lower risk of dying in the long-term after STEMI than their age-matched male peers who have the same comorbidities. This was rather a surprising finding, which, however, is in line with previous observations [1]. However, data on sex as a predictive factor for outcome are inconclusive, conflicting and partly contradictive [2–5,8,10–12,18,19]. Even our previous observations are conflicting. We found that sex did not predict the two-year outcome in STEMI patients [18], and in propensity-matched all-comers with myocardial infarction who underwent PCI [19].

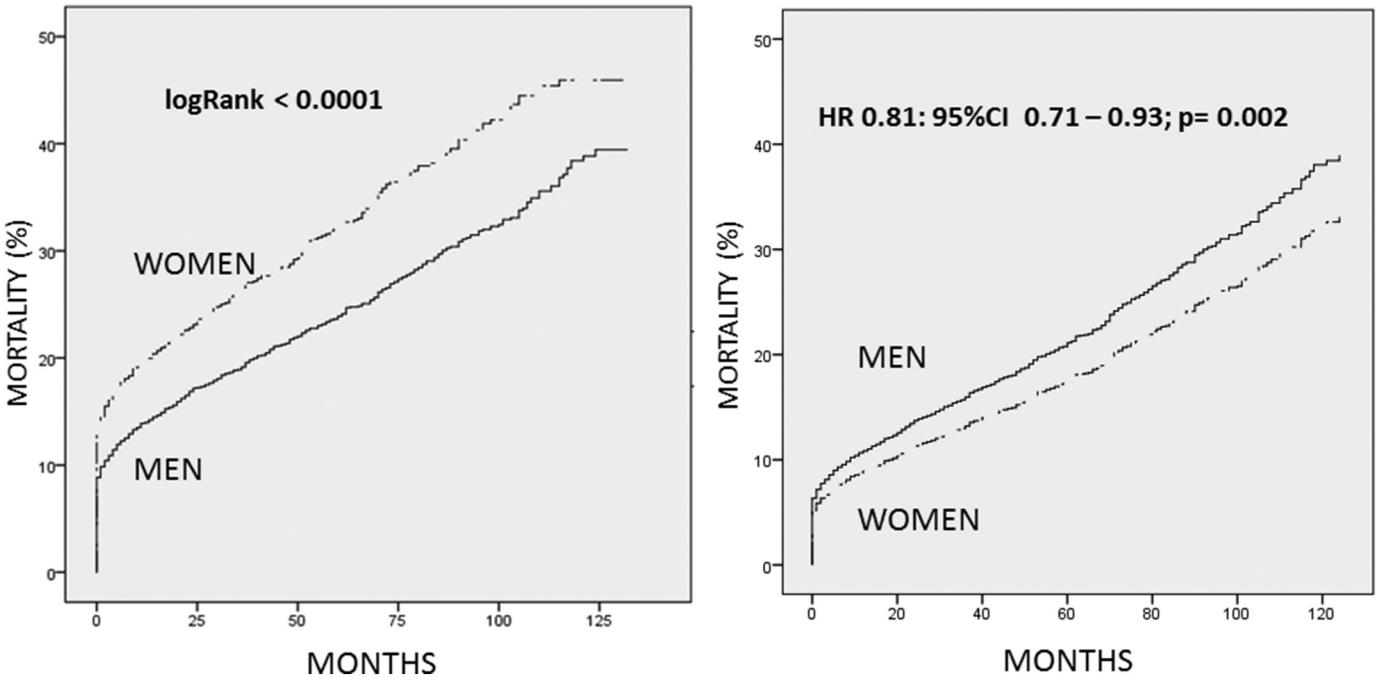

Fig. 1. Unadjusted (A) and adjusted (B) long-term mortality among men and women with ST-elevation myocardial infarction. Long-term, all-cause unadjusted mortality was higher in women (Fig. 1A). After multivariable adjustments, women had a better long-term prognosis (Fig. 1B).

Table 3
Predictors of long-term mortality in patients with ST-elevation myocardial infarction.

Predictors	Long-term mortality	
	Multivariable-adjusted hazard ratios	p
Heart failure	2.40 (2.10–2.75)	< 0.0001
Bleeding	1.79 (1.52–2.10)	< 0.0001
Renal dysfunction	1.60 (1.40–1.84)	< 0.0001
Hyperlipidemia	1.61 (1.40–1.85)	< 0.0001
Arterial hypertension	1.17 (1.03–1.33)	0.015
Diabetes	1.55 (1.35–1.78)	< 0.0001
Age	1.05 (1.04–1.06)	< 0.0001
Anemia	1.39 (1.23–1.58)	< 0.0001
Female sex	0.81 (0.71–0.93)	0.002

There were several differences between our observations. In the previous analysis, we lacked the data on anemia on admission, bleeding, and heart failure [18,19]. We were unable to include the data on time-to-reperfusion in the present analysis because of insufficient data. All these parameters are well known to influence the outcome [14]. The propensity-matching technique used in previous analysis cannot adjust for residual confounders [19]. Furthermore, the number of patients and the observation time were different. Comparisons must be made in light of these differences and, in our opinion, these differences could explain the different results.

We found, as have others before us, that women were older, with more comorbidities, tended to have a worse clinical presentation on admission and had a higher unadjusted short and long-term mortality [1,10,18,20–22]. Similar to previous studies, we found that bleeding, renal dysfunction, hyperlipidemia, age, arterial hypertension, diabetes, heart failure, and anemia were associated with higher mortality [14,18,20,23–27]. Dyslipidemia was less frequently found in women in our analysis. However, sex-specific data on lipids at admission and outcome after myocardial infarction are lacking [20].

In contrast to most studies, there was no difference in treatment between the sexes with regard to reperfusion therapy and dual antiplatelet therapy in our study [1]. Unadjusted long-term mortality was much higher, which sounds paradoxical, with the adjusted lower long-term risk of dying in women.

It is necessary to take into account the fact that this unadjusted mortality was almost entirely due to the age difference, heart failure, anemia, renal dysfunction, diabetes, hypertension, and bleeding after PCI, which are all well-known risk factors for mortality [14,20,23–27].

The multivariable-adjusted risk of dying, in the long run, was lower in women. Our result suggests that the anemic woman with diabetes and hypertension, who suffers a STEMI with consequent heart failure and bleeds after PCI, is expected to have a higher long-term mortality risk than a man who is seven years younger without comorbidities even though she is just as likely to have received reperfusion therapy as the man. According to our data, this is not because she is a female, but because she is older and has associated illnesses, risk factors and bleeding after PCI.

Our data suggest that female sex is somehow protective, but additional comorbidities, heart failure, age, risk factors, and bleeding deleteriously affect the prognosis in STEMI in women.

The result of our study has some potential clinical implications. Women with STEMI are usually older at presentation, with more risk factors and comorbidities, and are therefore at higher risk [9]. Clinicians should be aware of this crucial difference [10]. Special attention to reducing under-treatment in the acute setting and preventive strategies to decrease bleeding (radial access, careful usage of GP IIb/IIIa receptor inhibitors) and renal function (low contrast volume, crystalloid infusions, measures to ensure optimal hemodynamics, and discontinuation of nephrotoxic drugs) might provide a long-term benefit [9,28].

In conclusion, we found that female sex predicts a lower risk of long-term mortality in STEMI. However, women suffer STEMI at an older age, with many comorbidities, which are the major determinants of their poorer outcome.

5. Limitations

Our study has some notable limitations. This was an observational, single-center study. Our data only encompassed all-cause mortality. Data on previous myocardial infarction, obesity, smoking,

hyperuricemia, glucose, and pain-to-balloon time were not available for a sufficient number of patients to be considered in the evaluation, which is certainly a limitation of the study. Data on PCI complications are also missing and data on medication (except for dual antiplatelet therapy) after PCI were not available. In addition, we did not collect data for the heart rate, and blood pressure, which are variables with a strong impact on mortality. Finally, there were no exclusion criteria regarding concomitant diseases, thus this population represents a real-world experience of high-risk patients requiring PCI.

6. Conclusion

Women with STEMI were older, with more risk factors and co-morbidities and suffered more heart failure and bleeding during hospitalization than men. Unadjusted 30-day mortality was higher in women but this disappeared after multivariable adjustments. The long-term unadjusted mortality was also higher in women. After adjustment for potential confounding factors, female sex was surprisingly associated with the lower risk of long-term mortality. Risk factors, heart failure, age, and comorbidities rather than sex per se affect the worse outcome and special attention should be paid to these factors.

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Declaration of Competing Interest

There is no conflict of interest on the part of any author.

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