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Predictors of In-hospital Mortality after Primary Percutaneous Coronary Intervention for ST-segment Elevation Myocardial Infarction

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Abstract

Introduction: Treatment of myocardial infarction (MI) has been successfully developed, especially after introducing primary percutaneous coronary intervention (PPCI) as it nowadays is the recommended treatment for ST-segment elevation myocardial infarction (STEMI).

Objective: This study aimed to evaluate the in-hospital mortality of STEMI patients treated with PPCI according to gender and other likely risk factors.

Methods: This cross-sectional study presents a part of the results of a single-center registry in Imam Ali cardiovascular center affiliated to Kermanshah University of medical science (KUMS). From June 2016 to December 2017, 731 consecutive patients undergoing PPCI registered. Data were collected using a case report form developed by European Observational Registry Program (EORP). The relationship between in-hospital mortality and predicting variables was assessed using the Chi-square test, t-test, and univariate and multivariate logistic regression models (Forward LR).

Results: Totally, 155 patients (approximately 21%) were female. The mean age of women and men was 65.2 and 57.5, respectively (p=0.001). There were differences between women and men in hypertension (58.1% vs. 30.4%, respectively, p=0.001), diabetes mellitus (26.5% vs. 14.9%; p=0.001), hypercholesterolemia (37.4% vs. 18.6%; p=0.001), and history of prior congestive heart failure (5.2% vs. 2.0%; p=0.016). Although more men were current smokers (58.7% (men) vs. 15.5% (women); p=0.001). Women had a significantly greater incidence of multi-vessel disease, thrombolysis in myocardial infarction (TIMI) flow grade of 0/1 before PPCI, and longer symptom-to-balloon time. In-hospital mortality was higher in women than in men (5.2% vs. 1.9%; p=0.024). Multivariate analysis identified age ≥ 60 years, Killip class≥ II, and post-procedural TIMI flow grade < 3, but not female sex, as independent predictors of in-hospital mortality.

Conclusion: In-hospital mortality after PPCI in women was higher than men, though this difference was likely due to the severe clinical profile in women. Also, female gender was not identified as an independent predictor of death.

Key words: Iran; Mortality; Myocardial Infarction; Percutaneous Coronary Intervention; Registries; Sex

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INTRODUCTION

Acute coronary syndromes (ACS), including myocardial infarction (MI), is well recognized as one of the most common causes of mortality worldwide. Also, it needs well-established protocols and management of human and technological capacities, which require ever-increasing financial resources (1). Various factors, including therapeutic strategies, cardiovascular risk factors, and demographic characteristics may affect MI outcomes. Previous studies have reported differences in outcome between women and men after MI; however, the results have remained conflicting (2). Furthermore, it has been consistently reported that women are at increased risk of traditional risk factors for MI, such as diabetes mellitus (DM) (3). Several studies have demonstrated that women with ST-segment elevation myocardial infarction (STEMI) experience worse clinical outcomes and higher mortality than men (4, 5), whereas some researchers have identified no difference in the mortality rate between men and women after the adjustment for differences in baseline characteristics (6, 7).

Treatment for MI has been successfully developed, especially after introducing primary percutaneous coronary intervention (PPCI) as it nowadays is the

recommended treatment for STEMI in high-income countries (8). However, STEMI care provided for women lags behind that offered to men. Generally, women are less likely to be undertreated with lifesaving therapy compared to men (9). Besides, compared with men, women are less likely to be treated by PPCI, although women can derive significant benefits from PPCI (10). Moreover, the treatment delay in women with STEMI has been well established. Despite improving the door-to-balloon (DTB) time, the gender-related disparity in D2BT performance has not been ceased yet (11). Thus, 4-steps STEMI protocol was designed to improve STEMI care and outcomes for both men and women, as well as enhancing women's contribution towards the reduction of gender-related disparity (12).

Despite that studies have shown improvement in outcomes of patients treated with PPCI, gender-related differences in mortality rate after this treatment have not been sufficiently addressed yet, especially in low- and middle-income countries (13, 14). Furthermore, mortality has been reported to be higher in women treated with PPCI compared with men, though some other studies showed no difference in the mortality rate between men and women after adjustment for possible confounders (e.g., age) (15-18). Therefore, the disparity in mortality rate between women and men treated with PPCI has not been well recognized (14). Moreover, it is not evident whether female gender or differences in baseline characteristics can account for the potential differences in the mortality rate (14).

The PPCI network should be founded on the needs of both current and future populations to make an optimal balance. As population demographics are shifting, gender-specific risks of mortality after PPCI become prerequisites for future planning. Therefore, this study aims to evaluate the baseline and clinical characteristics and the potential disparity in mortality, as well as other likely associated factors, between women and men with STEMI treated with PPCI.

Methods

Study setting

This cross-sectional study was included in a registry of consecutive patients with STEMI in Imam Ali Cardiovascular Center, Kermanshah University of Medical Sciences (KUMS), which is the leading cardiovascular center in western Iran covering about two million population (mostly Kurdish with the Caucasian race). All data were adjudicated using the standards of the European Observational Research Program (EORP). The Research Ethics Committee at the Deputy of Research of KUMS had approved the study protocol in June 2017 (Ethics registration cod= KUMS.REC.1395.252). Further, the participants had been given the participant information statement and had signed the written consent form. Also, the personal information of individuals was kept confidential.

Study population

All patients who underwent PPCI for STEMI from July 1, 2016, to December 1, 2017, were assessed. The inclusion criteria considered in the study were as follows: age ≥ 18-year-old; clinical symptoms of STEMI including chest pain or equivalent symptoms of more than 20 minutes during the last 24 hours before admission and electrocardiographic (ECG) changes consistent with new or presumed new ST-segment elevations or left bundle branch block (LBBB) according to third universal definition of MI defined by the European Society of Cardiology/ACCF/AHA/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction (19). Quality control, in particular validation of diagnosis, was supervised by a physician. The patients with the following conditions were excluded from the study: patients admitted in the hospital for another reason and then developed STEMI; and/or patients hospitalized in another medical center more than 24 hours; and/or patients who did not sign the consent form to participate in the study.

Data collection

Data were collected using case report forms (developed by the EORP) by a nurse and research assistant - well trained regarding protocols for patient entry and data gathering - working in the Kermanshah Cardiovascular Research Center (KCRC). All case report forms were checked and approved by a physician responsible for quality control, followed by being forwarded online to the EORP website. Patients' national identification numbers were used to avoid duplicate admissions to this registry. Variables included in the analyses were as follows: demographic information (e.g., age); clinical histories (e.g., prior MI); cardiovascular risk factors (e.g., smoking); admission process (e.g., DBT time); biochemical findings (e.g., serum cholesterol), ECG results (e.g., heart rate); treatment strategies (e.g., PPCI); clinical outcomes (e.g., vital status).

Statistical methods

Quantitative Variables (e.g., age) were described using mean ± standard deviation (SD) and qualitative/categorical variables (e.g., smoking)

were expressed as frequencies and percentages. Differences between groups were assessed using the chi-square test (or Fisher exact tests) for categorical variables, and independent t-tests were performed for continuous and normally distributed variables. The univariate regression analysis was performed followed by multivariate regression analysis to identify independent predictors of in-hospital mortality. It is worth noting that the univariate analysis was conducted for all independent variables, whereby three univariate significant predictors were then selected for multiple regression. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for variables. In the univariate model, age ≥ 60 years old, body mass index (BMI) ≥ 25, hypertension (HTN), DM, current smoking, hypercholesterolemia, congestive heart failure (CHF), Killip class (at first presentation) ≥ II, prior PCI, radial access, symptom-to-balloon (STB) time > 360 minutes and door-to-balloon (DTB) time > 90 minutes (20), thrombolysis in myocardial infarction (TIMI) grade < 3 after PCI, TIMI grade pre 0-1, multi-vessel (culprit vessel ≥ 2), and drug-eluting stent (DES) were used as independent variables, whereas in-hospital mortality was assumed as the dependent variable. All of the analyses were considered significant at P<0.05 and performed using the statistical package for social science (SPSS) software, version 22 (IBM Corp., Armonk, NY USA).

RESULTS

Baseline characteristics

A total of 1209 patients with STEMI (957 (79.2%) men and 252 (20.8%) women) met the inclusion

Table 1: **Baseline characteristics stratified by sex**

Variable	Men (n=576)	Women (n=155)	P-value
Age (y)*	57.57±12.16	65.18±9.94	0.001
Body mass index	26.24±3.77	27.00±4.13	0.083
Current smoker	338 (58.7)	24 (15.5)	0.001
Diabetes mellitus	86 (14.9)	41 (26.5)	0.001
Hypercholesterolemia	107 (18.6)	58 (37.4)	0.001
Hypertension	175 (30.4)	90 (58.1)	0.001
Prior congestive heart failure	11 (2.0)	8 (5.2)	0.016
Killip class ≥ II	46 (8.0)	10 (6.5)	0.504
Prior percutaneous coronary intervention	37 (6.5)	9 (5.8)	0.779

* Continuous variables expressed as mean ± SD, otherwise n (%).

Table 2: Procedural and angiographic characteristics according to sex

Variable	Men (n=576)	Women (n=155)	P-value
Door-to-balloon time (min)*	110.91±104.71	133.07±131.79	0.303
Symptom-to-balloon time (min)	316.63±273.37	394.30±320.77	0.001
Vascular access site			
Femoral	312 (54.2)	95 (61.3)	0.061
Radial	264 (45.8)	60 (38.7)	
Number of culprit vessels			
1-Vessel	179 (31.1)	40 (25.8)	0.048
2-Vessel	213 (37.0)	48 (31.0)	
3-Vessel	184 (31.9)	66 (43.2)	
Culprit vessel			
Left anterior descending	317 (55.0)	75 (48.4)	
Left main stem	11 (2.0)	2 (1.3)	0.309
Circumflex	73 (12.7)	20 (12.9)	
Right coronary artery	184 (32.0)	59 (38.1)	
Lesion treated at PCI	24 (4.2)	11 (7.1)	0.126
Thrombolytic therapy	258 (44.8)	52 (33.5)	0.013
Stent use			
Bare metal stents	14 (2.4)	5 (3.2)	0.638
Drug- eluting stents	499 (97.6)	139 (96.8)	
Pre-procedural TIMI flow grade			
0/1	533 (92.5)	136 7.7)	0.021
2	40 (6.9)	16 (10.3)	
3	2 (0.6)	3 (2.0)	
Post-procedural TIMI flow grade			
0/1	7 (1.2)	1 (0.6)	0.301
2	23(4.0)	11`(7.1)	
3	545 (94.8)	143 (92.3)	

* Continuous variables expressed as mean ± SD, otherwise n (%).

criteria for the present study. Among them, 731 (60.5%) patients (576 (78.8%) men and 155 (21.2%) women) were treated with PPCI. Also, there was no difference in treatment with PPCI between the women (155/252, 61.2%) and men (576/957, 60.2%). Women were older than men on average, i.e., the mean (±SD) age for women was 65.79±11.34 years, and it was 59.04±12.39 years for the men (p=0.001). The prevalence of some comorbidities such as DM, hypercholesterolemia, HTN, and prior CHF was significantly higher in women, though substantially fewer women were current smokers. Moreover, the Killip classifications (p=0.504) and prior PCI (p=0.779) showed negligible differences between men and women (Table 1).

Procedural and angiographic characteristics

The median STB time (or treatment delay) was dramatically longer for women than men (p=0.001). Women were more likely to have PCI via femoral rather than the radial approach. Also, women had a higher incidence of multi-vessel disease with 2 or 3 culprit vessels compared with men (p=0.048). The left anterior descending (LAD) and right coronary artery (RCA) were the most often culprit vessel in both groups, respectively. The performance of thrombolytic therapy was more prevalent and significant in men than women (45% vs. 33%; p=0.013). Moreover, TIMI flow grade 0/1 before PPCI was much more frequent in men (p=0.021), whereas it was similar between men and women after PPCI (p= 0.301) (Table 2).

In-hospital and discharge medication

Similar treatment patterns existed for in-hospital medication use, thought, at discharge, prescription of aspirin (p=0.041) and clopidogrel (p=0.026) was significantly lower in women (Table 3).

In-hospital mortality

In-hospital mortality of the total sample was 2.6%. Higher in-hospital mortality was observed among women than men (5.2% vs. 1.9%; p=0.024). The analytical results of logistic regression (Forward LR) identified age ≥ 60 years (OR 4.81, 95% CI 1.20-19.23; p=0.031), Killip class ≥ II (OR 12.39, 95%, CI 3.72-40.89; p<0.001), and post-procedural TIMI flow grade < 3 (OR 11.87, 95% CI 3.36-41.88;

Table 3: In-hospital and discharge medication according to sex

Variable	Men (n=576)	Women (n=155)	P-value
In-hospital therapy			
Aspirin	576 (100.0)	154 (99.4)	0.205
Clopidogrel	573 (99.5)	155(100.0)	0.305
Unfractionated heparin	554 (96.2)	152 (98.0)	0.306
Low molecular weight heparin	175 (30.4)	46 (29.7)	0.802
Warfarin	4 (0.7)	1 (0.7)	0.926
Discharge therapy			
Aspirin	559 (97.0)	145 (93.5)	0.041
Clopidogrel	561(97.4)	145(93.5)	0.026
Warfarin	11 (1.9)	1(0.7)	0.203
β-Blocker	444 (77.1)	119 (76.8)	0.935
Angiotensin Converting Enzyme inhibitors	331(57.5)	78 (50.4)	0.061
Statin	554(96.2)	145(93.5)	0.125

Table 4: Univariable and multivariate (Forward LR) analysis of in-hospital mortality, all patients

Risk factor	Univariable		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Female gender	1.78 (0.35-8.88)	0.475		
Age≥ 60 y	2.98 (1.06-8.36)	0.038	4.81 (1.20-19.23)	0.031
Body mass index ≥ 25	1.03 (0.40-2.66)	0.943		
Current smoker	0.46 (0.17-1.23)	0.121		
Diabetes mellitus	1.24 (0.41-3.81)	0.702		
Hypercholesterolemia	0.60 (0.17-2.08)	0.417		
Hypertension	1.26 (0.50-3.16)	0.628		
Previous congestive heart failure	1.71 (0.00-10.86)	1.000		
Killip class ≥ II	7.89 (2.97-20.95)	<0.001	12.39 (3.72-40.89)	<0.001
Prior PCI	0.54 (0.00-3.21)	0.571		
Radial access	0.44 (0.16-1.23)	0.119		
Door-to-balloon time ≥ 90	1.13 (0.45-2.84)	0.798		
Symptom-to-balloon Time ≥ 360	1.28 (0.48-3.42)	0.620		
Post-procedural TIMI flow < 3	6.51 (2.22-19.03)	0.001	11.87 (3.36-41.88)	<0.001
Pre-procedural TIMI flow 0-1	2.51 (0.42-+Inf)	0.3729		
Multi-vessel	1.63 (0.54-4.98)	0.388		
Drug- eluting stents	0.60 (0.17-2.11)	0.426		

p<0.001) as factors independently associated with in-hospital mortality (Table 4).

Discussion

This study revealed that women have presented STEMI in older ages with a higher prevalence of traditional risk factors. Women have suffered STEMI as frequently as men treated with PPCI, although the post-PCI mortality rate was higher in women. After adjustment for baseline characteristics, it was observed that female gender could not independently predict mortality in patients treated with PCI for STEMI.

Prior studies have shown a mean age range of 58.8–60.9 years for men and 65.5-67.5 years for women (2, 21, 22), which are consistent with the findings of the present study (57.57and 65.18 for men and women, respectively). The later development of cardiovascular disease, i.e., STEMI, in women is attributed to differences in endogenous sex hormones, especially the protective effect of estrogen until menopause starts (23). Mean age of women with STEMI was almost eight years older than men. Also, the incidence of some comorbidities such as hypercholesterolemia, DM, HTN, and prior CHF was markedly higher in women. Other studies have also reported that women with STEMI are older, have HTN and DM, and have higher comorbidities more often (24, 25). Since the prevalence of DM and HTN increases by aging and the vardiovascular disease (CVD) starts in women at an older age compared with men, women are more susceptible to suffering DM and HTN at presentation.

Moreover, the obtained results demonstrated some key gender differences in procedural and angiographic characteristics. As shown by Wijnbergen et al. (26), Matthijs et al. (27), and Barbosa et al. (2), STB time (or treatment delay) was considerably longer in women. Furthermore, lack of awareness about cardiovascular risk factors and failure to recognize symptoms might be a potential explanation for the longer STB time in women and, in turn, longer time between onsets of symptoms until arrival in the cat lab. Besides, STB time was not an independent risk factor for mortality in multivariate analysis, which was most likely due to the difference between the patient's median STB time and standard STB time by approximately 30 min that might not be long enough to affect mortality significantly.

Moreover, consistent with the study conducted by Wei et al. (28), the men were more likely to have pre-procedural TIMI flow grade 0/1. Also, Zhang et al. (29) observed that female patients had a higher incidence of Multivessel disease with 2 or 3 culprit vessels compared to men, agreeing well with the results of the present study. However, to the contrary, Akhter et al. (30) reported a higher prevalence of single-vessel disease in women.

Previous studies have shown that, based on the American College of Cardiology and the American Heart Association, medical therapies are given less commonly to women at the time of admission and discharge (31, 32). In the present study, discharge-recommended medical therapies were given less often to women. The most significant differences were observed in the administration of antiplatelet therapies such as aspirin and Clopidogrel at the time of discharge, which may be due to the higher incidence of adverse bleeding events and vascular complications after PPCI among females (24, 33).

In the past, women had higher in-hospital mortality after PPCI (2, 25). Nowadays, fortunately, there has been a trend toward improvement in post-PPCI mortality rates in women (34). However, in the present study, higher rates of in-hospital mortality have been reported in women; conversely, Zhang et al. (35) stated that women with STEMI treated with sirolimus-eluting-stent based primary PCI had the same in-hospital mortality as their male counterparts. The higher in-hospital mortality observed in women may be attributed to several factors. Firstly, in our society, older age and baseline risk factors in women have increased their in-hospital mortality rates, and if these factors are adjusted, the risk of in-hospital mortality will be equalized for both genders, which is consistent with the results of earlier studies (36, 37). Secondly, a higher incidence of PCI failure was reported in women, despite similar angiographic characteristics. Besides, as previously reported, the incidence of major bleedings was higher in women (24).

Consistent with a trend toward improved in-hospital mortality rates after PPCI in women (34), a significant gender difference in adjusted mortality rates was not observed in this study as well. In other words, the female gender was not an independent predictor of in-hospital mortality in the multivariate analysis, which agrees properly with the findings of previous studies. Birkemeyer et al. (24) reported that the female gender failed to be predictive as an independent variable for in-hospital mortality after PPCI. Kanic et al. (38) showed that the female gender was not an independent prognostic factor in in-hospital mortality in patients with STEMI treated with PCI. De Luca et al. (39) investigated 1548 patients with STEMI and illustrated that the female gender was

not an independent risk factor in in-hospital mortality.

However, many studies reported converse results. For instance, Matthijs et al. (27) concluded that the female gender independently predicted the mortality of patients with STEMI treated with PCI. Also, Pu et al. (40) demonstrated that female gender was an independent predictor of mortality in patients with STEMI. Likewise, Benamer (25) conducted a study identical to the present work, showing that female gender was an independent risk factor for in-hospital mortality after PPCI for STEMI.

Furthermore, Killip class≥ II at admission, age ≥ 60 years, and post-procedural TIMI flow<3 were identified as independent factors associated with the in-hospital mortality, indicating that elderly patients and those with high clinical severity have been at higher risk of death. Similar results were obtained for these variables in other researches. Barbosa et al. (2) showed that Killip class≥ II at admission and age ≥ 70 years were independent predictors of in-hospital mortality after PCI. Also, in another study conducted in the Netherlands (2013), post-procedural TIMI flow < 3 was recognized as an important predictor of in-hospital mortality after PCI for STEMI (27).

Limitations

The most important limitation of the current study, as an observational registry, was non-randomized nature and confounding factors, which cannot be controlled. However, the dataset of this work included all basic variables influencing mortality, which would support the validity of our findings. Furthermore, since only patients with STEMI treated with PCI were evaluated, this analysis cannot be generalized to different treatment patterns among patients who were not treated with PCI. Also, since the data were derived from a single-center, the results may not express the whole community.

Conclusions

In conclusion, women with STEMI have shown higher mortality rates after primary PCI compared with men, fairly due to older age and a higher prevalence of traditional risk factors at presentation. Indeed, post-PCI mortality was not independently associated with female gender after adjustment for baseline characteristics. Despite that the women with STEMI were at higher risk, the discharge-recommended medical therapies were used less frequently in women, which entails more investigation. Moreover, quality efforts geared toward decreasing mortality in general, with a specific focus on women, are required to help decrease post PCI mortality and reduce gender-related disparity in this adverse event.

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Authors' contribution

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

Conflict of interest

None declared.

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