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Original Article

Is female gender associated with worse outcome after ST elevation myocardial infarction?

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ABSTRACT

Objectives: To investigate the impact of gender in outcomes of patients with ST segment myocardial infarction in a setting with limited access to primary percutaneous coronary intervention
Methods: In 1017 consecutive patients hospitalized with ST segment myocardial infarction during years 2008–2013, distribution of risk factors, therapeutic methods, heart failure and in-hospital mortality were compared between males and females. Association of gender and primary outcomes was determined after adjustment for confounding factors.
Results: Females were significantly older (66 ± 12.1 years vs. 59.5 ± 12.7 years, $p < 0.001$). Prevalence of hypertension, hyperlipidemia and diabetes was significantly higher in females (72.2% vs. 39%, $p < 0.001$, 36.1% vs. 20.3%, $p < 0.001$, 46.5% vs. 32.1%, $p < 0.001$, respectively). Presentation delay was similar in males and females. Females received reperfusion therapy more than males (63.2%vs. 55.8%, $p = 0.032$). Development of heart failure and in-hospital mortality were significantly higher in females (36.5% vs. 27.2%, $p = 0.003$ and 19.4% vs. 12.1%, $p = 0.002$, respectively).
However in multivariate analysis, female gender was not independently associated with increased rate of heart failure and in-hospital mortality
Conclusion: In a center with low rate of primary percutaneous coronary intervention, crude rates of heart failure and in-hospital mortality are higher in females; however, the association is lost after adjustment for baseline characteristics

1. Introduction

ST segment elevation myocardial infarction (STEMI) remains the leading cause of morbidity and mortality worldwide despite widely use of evidence-based guidelines and novel reperfusion therapies.[1] Although males are generally at a greater risk for developing the disease, clinical complications and mortality of STEMI may be higher in females.[2–5] Whether biological characteristics or socioeconomic gender disparities lead to the different outcomes is a matter controversy.[3,6–10]

The rate of undergoing reperfusion therapies, which are one of the best therapeutic methods to improve the prognosis in STEMI, may vary between males and females. According to some studies, females are more likely to receive conservative therapy.[8,11] In line with this, the higher mortality rate of females after STEMI is attributed to underutilization of standard treatments.[11,12] In contrary, similar rate of reperfusion therapies in males and females is also reported in literature.[13,14] Additionally, the trend of using treatment strategies may change over time.[13]

There is also a debate on the independent role of gender in clinical outcomes of patients with STEMI.[3,9,15] Although female gender was demonstrated as an independent risk factor for mortality after STEMI in some of the studies,[7,9,15] others have reported no independent impact of gender on clinical outcomes.[2,3] The fact that female patients are generally older with more concurrent diseases, higher mortality in females may result from other confounding factors, rather than gender itself.[16,17]

Considering the ambiguity of the evidence about the possible role of gender in clinical implications of the patients with STEMI, we designed this cohort study to investigate the potential differences in risk factor distribution, therapeutic approaches and clinical outcomes between males and females, treated for STEMI in our hospital. This study was took place in the main cardiovascular center of North-West of Iran, which is a middle-

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income country with low primary angioplasty rate at the time of present study. After adjusting for other co-morbidities, the association of gender with heart failure and in-hospital mortality was determined.

2. Methods and materials

2.1. Study sample

This is a retrospective registry based observational-analytical study of patients discharged from our cardiovascular hospital, the principal cardiac center in northwest of Iran, with a final diagnosis of STEMI during years 2008–2013. The study proposal was reviewed and approved by the Institutional Review Board at Tabriz University of Medical Sciences. The study was assigned proposal registration number 82/1231, and waiver of consent was granted due to its retrospective chart review design and absence of intervention. Extreme caution was taken to assure patient privacy during the whole study process. A total number of 1017 consecutive patients diagnosed with STEMI were included in the study. The mean age of study sample was 61.41 ± 12.93 years. Among the study population, 729 out of 1017 patients (71.7%) were male and 288 out of 1017 patients (28.3%) were female.

2.2. Study variables

Complete demographic and serum biochemical data, coronary risk factors including history of hypertension, hyperlipidemia, diabetes, active smoking and family history of premature cardiovascular diseases, history of acute coronary syndrome, coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) and history of stroke were collected and entered into prepared questionnaires.

Based on first admission electrocardiogram (ECG) in the emergency department, the location of myocardial infarction was determined to confirm the registered data. Whether the patient received reperfusion therapy including intravenous fibrinolysis, primary PCI, rescue PCI or was managed conservatively was recorded. The rate of late in-hospital angioplasty during hospitalization was also investigated.

By evaluating all ECGs of the patients during hospitalization, development of arrhythmia and cardiac bundle branch blocks were all determined. Left ventricular ejection fraction (LVEF), presence of significant mitral regurgitation (MR) and any other post myocardial infarction cardiac abnormalities were recorded based on the reports of trans-thoracic echocardiographic examination performed after myocardial infarction.

Study primary endpoints, which were development of heart failure (HF) during hospitalization period and in-hospital mortality, were also documented for each patient.

STEMI was defined as documentation for the presence of cardiac chest pain lasting more than 30 min with ST elevation of more than 0.2 mV from the J point at least in two consecutive precordial leads or more than 0.1 mV in two limb leads on the admission ECG with an increase in cardiac enzymes. An increase of one point above the 99 percentile cut off point for MB isoenzyme of creatine kinase (CK-MB) and Cardiac-Troponin I (cTNI) was considered elevated cardiac enzymes.

2.3. Study design

Patients were allocated into two groups based on their gender. All recorded demographic data, risk factors, electrocardiographic disturbances, primary reperfusion therapy and clinical complications including emergence of heart failure and in-hospital mortality were compared between males and females. To determine independent role of gender on study primary outcomes, adjustment for other confounding factors were performed.

2.4. Statistical analysis

The statistical analysis of the data was performed by statistical software SPSS (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago, United States). Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were stated as frequencies and percentages. Independent *t*-test or equivalent non-parametrical Mann-Whitney U-Test was used to compare continuous variables between two study groups. Fisher's exact test or Chi-square analysis was done as appropriate to compare the frequencies of the categorical variables.

Multivariate logistic regression analysis was performed to determine the independent role of gender on development of heart failure and in-hospital mortality after controlling for other confounding variables. Odds ratios with 95% confidence intervals for developing primary endpoints were stated for female gender. A p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Risk factors

Among 1017 patients, 729(71.7%) were male and 288 (28.3%) were female. The mean age of females was significantly higher than males (66 ± 12.1 years vs. 59.5 ± 12.7 years, $p < 0.001$). Females had significantly higher prevalence of hyperlipidemia ($p < 0.001$), hypertension ($p < 0.001$) and diabetes ($p < 0.001$). Active smoking was significantly less prevalent in females ($p < 0.001$). Family history of premature cardiovascular diseases was similar in males and females. History of stroke and unstable angina were more common in females. The comprehensive data is presented in Table 1.

The mean hemoglobin level was significantly higher in males than females (14.54 ± 3.96 mg/dl vs. 13.52 ± 4.57 mg/dl, $p = 0.001$). Mean creatinine level was not significantly different between males and females (1.23 ± 0.98 mg/dl vs. 1.21 ± 1.05 mg/dl, $p = 0.7$).

3.2. Reperfusion therapy and pharmacologic treatments

In our study population, 589 out of 1017 patients (57.9%) treated with reperfusion therapy. Out of 1017 patients, only 51 (5.01%) had

Table 1
Comparison of Demographic factors and Coronary Risk Factors in Males and Females.

	Total Patients N = 1017		P Value
	Male N = 729	Female N = 288	
Age	59.5 ± 12.7	66 ± 12.1	<0.001
Hyperlipidemia	148(20.3%)	104(36.1%)	<0.001
Hypertension	284(39.0%)	208(72.2%)	<0.001
Diabetes	234(32.1%)	134(46.5%)	<0.001
Smoker	277(38.0%)	23(8.0%)	<0.001
Family History	41(5.6%)	25(8.7%)	0.067
History of:			
CABG	16(2.2%)	3(1.0%)	0.221
Coronary Angioplasty	21(2.9%)	9(3.1%)	0.838
Stroke	22(3.0%)	19(6.6%)	0.015
Central Sleep Apnea	6(0.8%)	8(2.8%)	0.016
Unstable Angina	32(4.4%)	20(6.9%)	0.046
Myocardial Infarction	58(8.0%)	24(8.3%)	0.842

CABG; Coronary Artery Bypass Graft.

Table 2
Comparison of revascularization strategy and medications between males and females.

	Male N = 729	Female N = 288	P-value
Reperfusion Therapy	407(55.8%)	182(63.2%)	0.032
Intravenous Fibrinolysis	373(51.2%)	165(57.3%)	0.077
Primary PCI	34(4.7%)	17(5.9%)	0.427
PCI during hospitalization	150(20.6%)	52(18.1%)	0.384
Unfractionated Heparin	488(66.9%)	223(77.4%)	0.004
Low Molecular weight Heparin	202(27.7%)	61(21.2%)	0.032
Aspirin	693(95.1%)	261(90.6%)	0.005
Beta-Blocker	537(73.7%)	201(69.8%)	0.229
Calcium-Channel-Blocker	384(52.7%)	140(48.6%)	0.263
Intravenous Nitrate	344(47.2%)	134(46.5%)	0.835
Oral Nitrate	322(44.2%)	133(46.2%)	0.576
ACE-Inhibitor	289(39.6%)	134(46.5%)	0.048
Diuretics	227(31.1%)	115(39.9%)	0.008
Lidocaine	27(3.7%)	18(6.3%)	0.076
Amiodarone	41(5.6%)	23(8.0%)	0.196
Dopamine	10(1.4%)	7(2.4%)	0.277

Angiotensin-Converting-Enzyme inhibitors (ACE-Inhibitors), Percutaneous coronary intervention (PCI).

undergone primary PCI. Presentation delay after initiation of chest pain was not significantly different between males and females. (Median [25%–75% interquartile]: 240(120–360) min in males vs. 240(180–420) min in females, p = 0.757). Reperfusion therapy including intravenous fibrinolysis and primary percutaneous coronary intervention was used more commonly in females than males (63.2% vs. 55.8%, p = 0.032). Considering only primary PCI, there was no significant difference between males and females (5.9% of females vs. 4.7%, of males, p = 0.427). Intravenous fibrinolysis was administered in 57.3% of females and in 51.1% of males, p = 0.072. Undergoing angioplasty on the following days was slightly higher in males but it was not significantly different (18.1% of females vs. 20.6% of males, p = 0.384).

Administration of aspirin and low molecular weight heparin was lower in females than males (90.6% vs. 95.1%, p = 0.005 and 21.2% vs. 27.7%, p = 0.032, respectively). Females received un-fractionated heparin more than males. (77.4% vs. 66.9%, p = 0.004). Detailed data about the medications used in males and females are presented in Table 2. In reperfused subgroup of patients females were older than males with higher frequency of risk factors. Female patients undergoing reperfusion therapy had higher rate of diabetes and heart failure compared with males undergoing reperfusion, such a difference was not seen between males and females in non-reperfused group. In both reperfused and nonreperfused groups females had higher mortality compared with males (Table 3).

3.3. Clinical features

Anterior myocardial infarction was significantly higher in females than males. It was present in 66.3% of females and in 59.1% of males (p = 0.038). LVEF of less than 40% was present in 57.6% of females and 60.2% of males without significant difference. Development of heart failure was significantly higher in females than in males. Heart failure was developed in 36.5% of females vs. 27.2% of males, p = 0.003. In-hospital mortality was significantly higher in females than males (19.4% vs. 12.1%, p = 0.002).

Among patients who underwent coronary angiography, the number of involved vessels was not significantly different between males and females [single vessel disease 25.7% vs. 24.4%, P = 0.866; two vessel disease 34.2% vs. 29.3%, P = 0.360; three vessel disease 31.5% vs. 35%, P = 0.547; more than 50% left main stenosis, 4.6% vs. 2.8%, P = 0.586]. There was no significant difference in the rate of ventricular fibrillation/tachycardia within first 24 h after presentation or beyond this time window between two genders. The occurrence of new left bundle branch block (LBBB), right bundle branch block (RBBB) and atrial fibrillation were not significantly different between males and females. After excluding deceased patients, hospital stay duration was similar in males and females (Table 4).

3.4. Heart failure and in-hospital mortality with adjustment for other variables

Independent role of gender on heart failure and in-hospital mortality was investigated in multivariate model. After adjustment for age, hyperlipidemia, hypertension, diabetes, smoking, history of ischemic diseases, and reperfusion therapy, female gender was not an independent risk factor for developing heart failure as well as for the in-hospital mortality. (Odds Ratio for developing heart failure: 1.14, 95% confidence interval [0.82–1.59], Odds Ratio for in-hospital mortality: 1.19, 95% confidence interval [0.77–1.80]). (Table 5).

4. Discussion

This community-based study illustrates the gender differences in clinical practice and outcomes in patients with STEMI. The results revealed that despite higher crude rate of heart failure and in-hospital mortality after STEMI in females compared with males, female gender does not independently predict a poor prognosis after controlling for age, coronary risk factors and reperfusion methods.

Table 3
Comparison of males and females based on receiving reperfusion therapy.

	Reperfusion Group N = 589		P value	No Reperfusion group N = 428		P–Value
	Male N = 407	Female N = 182		Male N = 322	Female N = 106	
Age	59.2 ± 12.4	65.6 ± 11.6	<0.001	59.9 ± 13.2	66.8 ± 12.9	<0.001
Hyperlipidemia	113(27.8%)	78(42.9%)	<0.001	35(10.9%)	26(25.0%)	<0.001
Hypertension	177(43.5%)	145(79.7%)	<0.001	107(33.3%)	63(59.4%)	<0.001
Diabetes	206(50.6%)	122(67.0%)	<0.001	28(8.7%)	12(11.7%)	0.484
Smoker	135(33.2%)	13(7.1%)	<0.001	142(44.1%)	10(9.4%)	<0.001
Family History	28(6.9%)	21(11.6%)	0.082	13(4.0%)	4(3.9%)	0.940
Anterior MI	230(56.5%)	117(64.3%)	0.093	201(62.4%)	74(69.8%)	0.208
Heart Failure	110(27.0%)	69(37.9%)	0.011	88(27.3%)	36(34.0%)	0.217
In-Hospital Mortality	46(11.4%)	33(18.3%)	0.032	42(13.1%)	23(21.7%)	0.042

MI; Myocardial Infarction.

Table 4
Clinical features and in hospital outcome of both genders.

	Male N = 729	Female N = 288	P Value
Anterior MI	431(59.1%)	191(66.3%)	0.038
EF < 40	439(60.2%)	166(57.6%)	0.494
Mitral Regurgitation (>2+)	257(35.3%)	112(38.9%)	0.311
Heart-Failure	198(27.2%)	105(36.5%)	0.003
In-Hospital-Mortality	88(12.1%)	56(19.4%)	0.002
GI bleeding	9(1.2%)	3(1%)	1
CVA	3(0.4%)	4(1.4%)	0.105
Recurrent ischemia or re-MI	71(9.7%)	29(10.1%)	0.907
VF/VT within 24 h	37(5.1%)	18(6.3%)	0.454
VF/VT after 24 h	35(4.8%)	15(5.2%)	0.750
Left Bundle Branch Block	23(3.2%)	15(5.2%)	0.141
Right Bundle Branch Block	35(4.8%)	19(6.6%)	0.277
Atrial Fibrillation	22(3.0%)	5(1.7%)	0.288
Hospital stay (Days)	6.60 ± 6.46	6.83 ± 4.80	0.101
One Vessel disease	105(25.7%)	30(24.4%)	0.866
Two Vessel Disease	140(34.2%)	36(29.3%)	0.360
Three Vessel Disease	128(31.5%)	43(35%)	0.547
Left Main stenosis ≥50%	17(4.6%)	3(2.8%)	0.586

MI, Myocardial Infarction; EF, Ejection fraction; GI; Gastrointestinal, CVA; Cerebrovascular Accident, VF/VT; Ventricular fibrillation/Tachycardia.

4.1. Risk factors

In our patients, females were significantly older than males. In addition, they had higher prevalence of diabetes, hypertension and hyperlipidemia, compared with males. Similar pattern is described in other investigations, performed in different populations of the world.[7,13,18,19] Cardio protective effects of estrogen in younger females lead to lower incidence of coronary artery disease in this population.[20] As a result, in patients with STEMI mean age of females are generally higher than males. Older age may partly account for higher prevalence of other comorbidities in females.[7,8,13,16–18] However, it is also proposed that males have higher mortality rate before hospital presentation. As a result, high-risk patients with more severe disease on presentation to the hospital are more likely to be the survived females.[21] Even though accurate pre-hospital mortality data for STEMI is not available in our population.

According to the results, there was a notable difference in prevalence of hypertension in females compared with males. As shown before, the prevalence of hypertension in patients with acute myocardial infarction is increasing in this region.[22] Since hypertension is one of the major risk factors for developing cardiovascular diseases,[23] prevention, early detection and effective treatment of hypertension need prominent attention, especially in females. As reported before, the prevalence of smoking in patients with acute myocardial infarction has been decreased in recent years in this region.[22] However, the prevalence of active smoking in males is high. Although the effect of smoking on mortality of patients with myocardial infarction is a matter of controversy,[24,25] smoking is a well-known modifiable risk factor for developing cardiovascular diseases.[1,23]

4.2. Therapeutic patterns

Primary angioplasty, if performed shortly after arriving at an experienced center, is superior to thrombolytic therapy in treatment of STEMI. However, a delay more than 90–120 min may blunt this benefit and make thrombolytic therapy as first treatment strategy in most cases.[26] Female patients with non-STEMI who have received routine medical treatment may even have a better outcome than males.[27] In conditions like left bundle branch block in which the diagnosis of STEMI is in doubt or when the risk of bleeding with thrombolytic agents is high, strategy of primary angioplasty is preferred.[28] It has previously reported that invasive strategies are less frequently used in females.[29–31] However, the gender gap is diminished in recent years.[32] In our study, intravenous fibrinolysis was the main reperfusion therapy in both males and females. Relatively small number of both males and females underwent primary PCI. Delay in presentation to the emergency department is a major contributing factor. Lack of a dedicated primary PCI team and limited access to the required equipment which is mostly due to financial restraints in our practice also play a part. Currently optimizing our local protocols and resources for timely transfer of patients to the catheterization laboratory is our primary goal. We have recently upgraded to a 7/24 system and we perform primary angioplasty in a growing number of patients. However, improving management of patients in pre hospital phase through establishing better health care policies is necessary to achieve best results. Interestingly, in our study population there was a significantly higher overall reperfusion rate in females. Although primary PCI was used in a smaller number of patients, gender was not associated with undergoing invasive reperfusion therapy. Late in-hospital PCI was also performed in males and females without significant difference.

In our study presentation delay after initiation of chest pain was not significantly different between males and females. Similar results were reported by Zerwik et al.[33] However, in a large study in 420 US hospitals from 2001 to 2006 on patients admitted with myocardial infarction, women were less likely to receive reperfusion therapy and experienced lower rate of cardiac catheterization and angioplasty following MI.[34] This was similar to the results of the Maximal Individual TheRapy of Acute myocardial infarction (MITRA) registry.[35]

4.3. Clinical outcomes

The poor prognosis of females in comparison to males in our study population, mainly originates from the older age of females with concurrent presence of other comorbidities. Renal failure and anemia are also described as possible comorbidities that might contribute in poor short-term prognosis of patients after STEMI. Moreover, the different prevalence of these conditions in males and females may cause different outcomes regarding gender.[36,37]

Considering the possible described risk factors for a poor outcome, the association of gender and study primary outcomes, were studied after controlling for other confounding factors. The results revealed that gender was not independently associated

Table 5
Comparison of Clinical Outcomes in Males and Females.

	Male N = 729	Female N = 288	Univariate Odds Ratio (95% confidence Interval)	P Value	Multivariate Odds Ratio (95% confidence Interval)*	P Value
Heart-Failure	198(27.2%)	105(36.5%)	1.53(1.15–2.05)	0.003	1.14(0.82–1.59)	0.414
In-Hospital Mortality	88(12.1%)	56(19.4%)	1.76(1.22–2.54)	0.002	1.19(0.77–1.8)	0.407

* Odds Ratios for females adjusted for age, hyperlipidemia, hypertension, diabetes, smoking, history of ischemic heart disease and reperfusion therapy.

with either heart failure or in-hospital mortality. In a report published by Hailer et al. in which patients with STEMI were studied in German population, similar therapeutic methods was used in both genders and in-hospital mortality rate was also similar in males and females.[13] In another study from Korean population, Park et al. investigated the gender differences in patients with STEMI and showed that there was no independent role of gender on in-hospital mortality. The female patients in their study had a similarly high-risk profile at presentation.[16] Berger et al. analyzed pooled data of 11 independent, international acute coronary syndrome clinical trials in which forty percent of cases were from United States, and investigated the effect of gender on 30-day mortality. Although in unadjusted model females had about 2-fold increase in mortality after STEMI, compared to males, after adjustment for clinical characteristics and angiographic findings, females did not have increased risk for 30-day mortality.[38] Zagnoni et al. investigated sex differences in management and prognosis of patients with acute coronary syndrome in Italy and found lower rate of reperfusion therapy in females but gender was not an independent predictor of mortality at six month follow up.[31] In contrast, study by Leurent et al. on patients with STEMI, revealed that females had lower rate of reperfusion therapy as well as higher risk of in-hospital mortality even after adjustment for other factors.[7]

In our study, thrombolytic therapy was the main reperfusion strategy and primary angioplasty was applied in less than 10% of patients. However, some data from developed countries reported similar results using primary angioplasty as main reperfusion strategy. In a multicenter observational study from Germany, in which more than 90% of patients underwent primary angioplasty, adjusted mortality rate was not high in female gender.[39] In another study from Los Angeles County with primary PCI as main reperfusion strategy after multivariable logistic adjustment for baseline differences, female gender was no longer associated with higher in-hospital mortality.[40] Radovanovic et al. have investigated temporal trends in treatment of STEMI patients in Switzerland between 1997 and 2011. Although females were less likely to receive primary reperfusion treatments, there was a parallel decrease in hospital mortality of both males and females with no independent role of gender on hospital mortality after adjustment for baseline characteristics.[32]

It is important to note that other factors with a possible impact on prognosis are found to be different in males and females. Bleeding after reperfusion, which occurs more often in females, is independently associated with high mortality rate.[41] Psychological pathologies are also described as possible risk factors for a poor prognosis in patients with cardiovascular diseases.[42] Preconditioning and pre-infarction angina is reported to be associated with decreased left ventricular dysfunction after reperfusion for acute coronary syndrome in males but not in females.[43] On the other hand, myocardial salvage after primary PCI was reported to be greater in females.[4]

4.4. Limitations

Retrospective nature of our study and it's mono centric design are among major limitations. We should also mention that due to lower rate of coronary angiography and revascularization, primary outcomes of our study were not adjusted for either number of diseased vessels or severity and location of the coronary artery occlusion.

Furthermore, the lower observed rate of GI bleeding in our study was most likely due to lower rate of reperfusion therapy. We could not evaluate the impact of this finding on the clinical outcome between two genders because of the low event rate. In addition, our cardiovascular center is a tertiary level hospital, with referrals from other distinct hospitals mainly due to critical condition of the patient. As a result, presentation delay from chest pain initiation and in-hospital mortality rate may be higher than expected.

5. Conclusion

In main cardiovascular center of North-West of Iran, females constitute about one-third of hospitalized patients with STEMI; however, they are more likely to be in the high-risk group, mainly due to the older age and higher prevalence of coronary risk factors. In a setting of low reperfusion rate (57.9%) and very low primary PCI rate (5.01%) compared with western countries, the crude rates of heart failure and in-hospital mortality are higher in females; however, after adjustment for basic characteristics, female gender is not independently associated with a poor prognosis.

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