Sex Differences in Mortality after Myocardial Infarction: A Retrospective Cohort Study

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Research Article

Keywords: Sex difference, myocardial infarction, in-hospital mortality, STEMI

Posted Date: August 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-349531/v1>

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Abstract

BACKGROUND: We aimed to examine sex differences in mortality after myocardial infarction.

METHODS: This retrospective cohort study included all first admitted patients 50 years or older with acute myocardial infarction hospitalized in Rajaei hospital of Karaj city, Iran, between 23th March 2013 and 1th January 2020. Data was retrieved from the hospital information system (HIS) database, including patient's demographic and socioeconomic characteristics, medical history, acute myocardial infarction (AMI) type, treatment and procedures, and outcome of hospitalization. Simple and multivariate cox regression models were used to assess the association of gender with in-hospital mortality after AMI. Results were presented as crude and adjusted hazard ratios along with their 95% confidence interval (HR (95% CI)).

RESULTS: Results from the multivariable Cox regression analysis revealed that females had a higher risk of death than males after ST segment Elevation MI (STEMI) (adjusted HR (95% CI): 1.64 (1.15 – 2.36), $P=0.007$). However, in subgroup analysis by age groups, this significant increased risk was observed only in female patients aged 50 to 64 years than their male counterparts. There was no significant differences between males and females after non-STEMI and unspecified MI.

CONCLUSIONS: Based on our findings, women aged 50 to 64 years may be more likely to die during hospitalization after STEMI than men.

Introduction

Cardiovascular disease (CVD) is a main cause of death worldwide, especially in developing countries [1]. In Iran, CVD is the first cause of death, accounted for about half of all-cause mortality [2]. Although, like some other countries [3] a decreasing trend of mortality rate for CVDs has been observed in both sexes during two last decades [4], partly explained by better management of the diseases after implementation of novel revascularization strategies [3] but it remains high.

Furthermore, contradicting evidence suggest that women compared to men may experience a higher rate of mortality after myocardial infarction (MI), a major form of CVDs [5]. However, most of these evidence comes from the studies performed before the widespread use of revascularization strategies [6].

Up to our knowledge, a few studies have addressed sex differences in mortality after myocardial infarction in Iranian patients, especially within last 5 years [7]. Hence, we aimed to examine if there is a sex differences in mortality after myocardial infarction using data from a large sample of patients.

Materials And Methods

Study design

We conducted a single-center retrospective cohort study using data of first-admitted patients 50 years or older with ICD-10-CM codes of acute myocardial infarction (AMI) (ICD- 10 code I21) that extracted from the hospital information system (HIS) of Shahid Rajaei hospital in Karaj city, Iran, over a 4-year period.

The study population

The study population was all inpatients 50 years or older who were admitted for the first time with a diagnosis of AMI (with or without ST segment elevation) in our hospital from 23th March 2013 to 1th January 2020. As novel revascularization techniques including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have been performed in our hospital since 2013, the study was restricted to this period.

Karaj city is the center of Alborz Province, Iran. Karaj, with about 1.97 million inhabitants as recorded in the 2016 census, is the fourth-largest city in Iran. Also, Karaj is located 20 kilometers (12 mi) west of Tehran and is a large suburb of it.

Shahid Rajaei is a referral hospital providing outpatient, inpatient and emergency services for patients with AMI in Karaj city.

Management of acute myocardial infarction in Shahid Rajaei hospital is according to the most updated guidelines of the American College of Cardiology and American Heart Association and of the European Society of Cardiology.

Data Sources and Collection

Data on demographic characteristics, medical history, and ICD-10-CM codes of diagnoses and procedures for each patient are recorded and stored in the hospital information system (HIS) by trained staffs.

In this study, we retrieved some baseline characteristic of included patients, including age (years), gender, presence of comorbidities, type of MI, performed procedures, discharge status (dead or alive), date of admission, discharge or death from the HIS database. Patient's age was categorized into three groups: 50–64, 65–74, and ≥ 75 years. Length of the stay in the hospital was calculated in days for each patient.

The clinical data were extracted by using International Classification of Diseases, tenth Revision, Clinical Modification (ICD-10-CM) codes.

The type of MI was determined according to the ICD-10-CM classification as follows: STEMI (codes I21.0-3), unspecified (code I21.9) and NSTEMI (code I21.4)

Using the ICD-10- CM codes, we identified the presence or absence of specific comorbidities at the time of the admission including heart failure (code I50), hypertension (code I10), diabetes (codes E10–E14), and chronic kidney disease (code N18). Besides, we also used ICD-10-CM codes 00.66 and 36.01 to 36.09 to identify patients who underwent PCI, and ICD-9-CM codes 36.10 to 36.19 to identify patients who underwent CABG surgery.

The outcome measurement

The main outcome was in-hospital mortality in patients with AMI. As data on the exact cause of death was not available, in-hospital death was defined as death due to any cause during the hospital stay.

Statistical analyses

We used descriptive statistics, mean (SD) for continuous variables and as number (percentage) for categorical variables to summarize demographic and clinical data of the cohort. Characteristics of males and females were compared using two-tailed t-tests or chi-square tests, as appropriate.

We also used Univariable and Multivariable Cox proportional hazard regression models to assess the effect of being female on the in-hospital mortality after AMI. The results is presented as a hazard ratio (HR) 95% confidence interval [CIs]). Proportional hazard assumption was evaluated using both graphical methods (ln-ln S [t] graphs) and statistical tests containing continuous time-interaction terms (Cox tests) [8].

Various cox regression models were constructed according to adjustment strategy: model I, unadjusted; model II, adjusted for patient age; and model III, adjusted for age, diabetes, arterial hypertension.

We also compared the survival distribution between males and females using the log-rank test. Follow-up period defined as time (days) from the date of admission until the date of discharge or in-hospital death whichever occurred first. The probability of survival for males and females was depicted in Kaplan-Meier plots. For all analyses a p-value < 0.05 (two-tailed) was considered statistically significant. Analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL, USA) and STATA V.12.0 (Stata Corp, College Station, Texas, USA).

Results

Patient Characteristics

A total of 1,730 first-admitted patients with AMI older than 50 years were recorded in our HIS database from March 2013 through January 2019. The mean age (standard deviation (SD)) of patients was 64.5 (10.4) and 455 (26.3%) were female. In order by frequency, type of MI was STEMI in 1,176 patients (68.0%), NSTEMI in 330 (19.1%), and unspecified MI in 224 (12.9%).

Overall, 7 patients (0.4%) dead in the early hours of hospitalization, 1,430 (82.6%) underwent angiography, and 293 (17.0%) received medical therapies. Among patients who underwent angiography, the performed procedure was PCI in 1,069 patients (74.8%), CABG in 73 (5.1%), PCI & CABG in 13 (0.9%), and “only angiography” in 275 (19.2%).

Table 1 shows the patients’ characteristics and treatment and procedures performed for them during hospitalization according to the gender. The mean age (SD) of females was significantly higher than males (68.3 (10.9) vs. 63.3 (9.9), respectively; $P<0.001$). Compared to males, a higher percentage of females had a history of hypertension and diabetes. (Both $P < 0.001$) There was no significant difference between both sexes regarding prevalence of comorbidities CHF and CKD.

Table 1

Main patients' characteristics according to gender

Variables		Male N= 1275 % (N)	Female N= 455 % (N)	P-value
Age (years)	50-64	62.6% (798)	41.3% (188)	< 0.001
	65-74	21.6% (276)	30.5% (139)	
	75 ≤	15.8% (201)	28.1% (128)	
Hypertension		10.7% (136)	23.5% (107)	< 0.001
Diabetes		4.4% (56)	10.3% (47)	< 0.001
CHF		0.2%(3)	0.7%(3)	0.187
CKD		0.2%(3)	0.7%(3)	0.187
STEMI		70.1%(894)	62.9%(282)	0.001
- Anterior STEMI location		44.7%(400)	34.4%(97)	0.002
Non - STEMI		17.0%(216)	25.1%(114)	<0.001
Unspecified MI		12.9%(165)	13.0%(59)	0.989
Length of hospital stay (days), mean (sd)		4.5 (3.7)	4.8 (3.9)	0.166
Management of MI	Medical N= 293	13.8% (175)	26.0% (118)	<0.001
	Coronary angiography	PCI	76.4% (836)	0.003
		CABG	5.3% (58)	
		PCI + CABG	1.1% (12)	
	N=1430	None	17.2%(188)	25.9% (87)
	Male, N: 1094			
	Female, N: 336			

CHF: Chronic heart failure. CKD: Chronic kidney disease. MI: myocardial infarction. STEMI: ST segment Elevation MI.

Besides, a higher percentage of males compared to females diagnosed by STEMI (70.1% vs. 62.9% respectively, $P=0.001$). Males also significantly showed a higher rate of the anterior location of STEMI in comparison with females (44.7% vs. 34.4% respectively, $P= 0.002$)

In subgroup of patients who underwent angiography, males were more likely to receive PCI, CABG, or PCI & CABG. ($P= 0.003$)

A total of 218 (12.6%) deaths happened among patients during hospitalization, of which 50% occurred within the first 2 days in the hospital. Females had a higher in-hospital mortality compared to males (17.8% vs. 10.7%, $P < 0.001$); by subgroups age and MI type, this significant excess mortality in females was observed in the age group 50-64 years and in STEMI category.

Table 3 presents the results of the univariate and multivariate Cox regression analysis for the effect of gender on the in-hospital mortality in first-admitted patients with AMI, overall and in subgroups of MI type. Overall, based on results of the univariable Cox regression analysis, females had a higher in-hospital mortality rates than males after AMI (Crude HR (95% CI): 1.58 (1.20- 2.08), $P=0.001$). These findings were not confirmed by the multivariate Cox regression analysis after considering potential confounder age (adjusted HR (95% CI): 1.30 (0.98 – 1.74), $P= 0.067$) However, in subgroup analysis by age group, the significant adjusted effect of being female on in-hospital mortality after AMI was observed only in patients aged 50 to 64 years. (Figure 1)

Table 2

Comparison of the all-cause mortality between males and females, totally and by subgroups

Subgroups		Males % (N)	Females % (N)	P-value
Total		10.7% (137)	17.8% (81)	< 0.001
Age Group (years)	50-64	6.0% (48)	12.2% (23)	0.003
	65-74	15.6% (46)	14.4% (20)	0.750
	75 ≤	22.9% (46)	29.7% (38)	0.168
MI type	STEMI	9.4% (84)	18.1% (51)	<0.001
	Non-STEMI or un-specified MI	13.9% (53)	17.3% (30)	0.294
Intervention	Angiography	5.2% (57)	7.4%(25)	0.124
	PCI	4.8% (40)	6.9% (16)	0.207
	CABG	5.2% (3)	6.7% (1)	0.821
	PCI & CABG	16.7% (2)	0.0%(0)	0.657
	Only Angiography	6.4% (12)	9.2% (8)	0.404
	Medical	42.3% (74)	46.6% (55)	0.465
CABG: coronary artery bypass grafting. MI: myocardial infarction. PCI: percutaneous coronary intervention. STEMI: ST segment Elevation MI.				

Table 3**Effect of gender on in-hospital mortality in first-admitted patients with AMI : Cox regression analysis**

Variable	Crude HR (95 %CI)	Adjusted HR ^a (95 %CI)	Adjusted HR ^B (95 %CI)
	Model I	Model II	Model III
Female / Male, All	1.58 (1.20- 2.08)	1.28 (0.97 – 1.69)	1.30 (0.98 – 1.74)
P value	0.001	0.084	0.067
Female / Male, STEMI group	1.93 (1.36-2.74)	1.58 (1.11 -2.26)	1.64 (1.15 – 2.36)
P value	<0.001	0.011	0.007
Female / Male, Non-STEMI and unspecified MI group	1.30 (0.80 -2.12)	0.99 (0.59-1.66)	0.93 (0.54 -1.57)
P value	0.295	0.979	0.773
a. Adjusted for age; b. Adjusted for age, diabetes, and hypertension			
CI: confidence interval. HR: hazard ratio. MI: myocardial infarction. PCI: percutaneous coronary intervention. STEMI: ST segment Elevation MI			

Furthermore, in the STEMI subgroup, the results from the Cox regression analysis revealed a gender difference in the risk of in-hospital mortality. Being female increased the hazard of death by 1.93 times in the crude model (Crude HR (95% CI): 1.93 (1.36-2.74), $P < 0.001$). In the model involving potential confounders age, diabetes, and hypertension, the in-hospital mortality rate remained significantly higher in females than males (adjusted HR (95% CI): 1.64 (1.15 – 2.36), $P = 0.007$). However, in subgroup analysis by age group, this significant effect of being female on in-hospital mortality after AMI was observed only in patients aged 50 to 64 years. (Figure 1)

We also performed a log-rank test to determine if there were differences in the survival distribution for males and females in the different age groups: 50-64, 65-74, and 75 + years. The survival distributions for males and females were significantly different in the age group 50-64 years ($\chi^2_{(1)} = 7.689$, $p = 0.006$), but not in the older age groups. (Figure 2& 3)

Discussion

In this study, we evaluated sex differences in in-hospital mortality following AMI in first admitted patients. Based on our findings, female patients aged 50 to 64 years were more likely to die following STEMI, considering potential confounders age, presence of diabetes and hypertension, than males in the same

age group; however, this gender effect was no longer seen in older age groups. Also, in patients hospitalized for non-STEMI, both sexes revealed similar risk for in-hospital mortality.

Some other studies confirm our findings [6, 9]. Recently, in line with our research, Zhang et al. have reported that higher in-hospital mortality risk in females compared to males is more evident in younger patients with STEMI [10]. Also, a systematic review evaluated gender differences in short and long term mortality in patients after STEMI. Six out of eleven included studies focused on in-hospital mortality as the main outcome reported adjusted results, of which two studies found significant effects of female gender on higher in-hospital mortality [9b].

The gender differences in the early clinical manifestations of STEMI, more prominent in younger age groups [11] may explain the higher mortality rate in females than males. While specific symptoms are believed to play a key role in patients' help-seeking behavior, early diagnosis, and timely treatment [12], but based on the available evidence, female patients are more likely to present with atypical symptoms compared to males [13].

However, we were unable to examine this justification in the present study due to the lack of data on the initial symptoms, and the time interval between the onset of symptoms and treatment.

There is evidence that physicians are less likely to comply with current guidelines recommendations on treatment options for female mi patients due to the underscoring of their risk [9c]. Indeed higher prevalence of micro-vascular involvement in females makes them less likely to undergo angiography and receive specific medications [9c]. Leurent et al., accounted "under treatment or conservative treatment of female patients" as the main explanation for higher in-hospital mortality in them compared to males [12].

During perimenopause and early post-menopause, being female may be an independent predictor of in-hospital mortality following STEMI. At this age, more involvement of microvascular than macrovascular, and having different etiology of STEMI in females compared to males could put them at a higher risk of death [9].

Noteworthy, while routine practice and guidelines are mainly determined based on the findings of clinical trials, a systematic review recently revealed the underrepresentation of females in contemporary acute coronary syndrome (ACS) trials, limiting the generalizability of their finding to the male than female population [14].

In line with our studies, previous studies also found that patients hospitalized for non-STEMI, both sexes had similar risk for in-hospital mortality [15].

In contrast to STEMI that is mainly caused by acute plaque rupture, NSTEMI often resulted from a moderate coronary stenosis [16].

Conclusions

Our findings suggest that female inpatients aged 50 to 64 years may be more likely to die than males following STEMI, considering potential confounders age, presence of diabetes, and hypertension.

Declarations

Funding

The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Ethics approval and consent to participate

We performed this research in line with the Declaration of Helsinki guidelines. Research and Ethics Committee of Alborz University of Medical Sciences (ABZUMS) reviewed the study proposal and waived the requirement for informed consent. A unique identifier number was assigned to each patient at HIS database to protect confidentiality. Also Informed consent was obtained from all individual participants included in the study

Consent for Publication

Written consent for publication was obtained from all individual participants included in the study.

Availability of data and material

Files for the raw analysis can be made available upon request

Code availability

Not applicable.

Authors' contributions

Neda Shafiabadi Hassani and Hadith Rastad had the idea and designed the study with Reza Pirdehghan and Parham Mardi. Mohammadhossein Mozafarybazargany, Roya Sepahvandi, Zeynab Khodaparast, Fatemeh Karimi, Fatemeh Rahimi, Akram Zakani, Parham Mardi collected the clinical data. Zeinab Kamipoor, Mahya dorri, Arya Bamrafie summarized all data. Hadith Rastad and Neda Shafiabadi Hassani analyzed and interpreted the information. All authors have participated to drafting the manuscript. Hadith Rastad, Neda Shafiabadi revised it critically. All authors read and approved the final version of the manuscript

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Figures

Figure 1

Forest plot of the effect of the being female on in-hospital mortality by type of MI in different age groups, considering potential confounder diabetes, and hypertension: Cox regression analysis CI: confidence interval. ES: hazard ratio. STEMI: ST segment elevation myocardial infarction. AMI: acute myocardial infarction

Figure 2

Survival Curve in patients with acute myocardial infarction (AMI) by gender in different age groups (Kaplan Meier survival curve & log rank test)

Figure 3

Survival Curve in patients with ST segment elevation myocardial infarction (STEMI) by gender in different age groups (Kaplan Meier survival curve & log rank test)

Supplementary Files

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