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Future CARDIOLOGY

Short Communication

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The outcome of ST-elevation myocardial infarction by sex: a retrospective cohort study

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We aimed to compare in-hospital mortality (IHM) of acute myocardial infarction (AMI) between male and females. We assessed the association of sex with IHM after AMI using simple and multivariate cox regression models. Results were presented as crude and adjusted hazard ratios along with their 95% confidence interval (HR; 95% CI). Multivariable Cox regression analysis revealed females had a higher risk of death than males after ST-elevation MI (STEMI) (adjusted HR [95% CI]: 1.64 [1.15–2.36]; p = 0.007). In subgroup analysis by age group, this significantly increased risk was only observed in 50- to 64-year-old females. There were no significant differences between genders after non-STEMI and unspecified MI. Women aged 50 to 64 years had higher IHM after STEMI than men.

Plain language summary:

What is this study about? Cardiovascular diseases are one of the leading causes of death and disability in both males and females worldwide. Over the few last decades, with the development of novel techniques for the treatment of heart attacks, its prognosis has dramatically improved, although adverse outcomes remain high in female patients. Nevertheless, sex differences in death rates following heart attacks are still poorly understood. Hence, we compared the in-hospital death rate between male and female patients following a heart attack. **What were the study results?** Women are more likely to die during hospitalization following a heart attack in which the artery supplying the heart muscle was completely blocked, when compared with similarly aged men. This increased risk was most prominent between 50 to 64 years of age. However, the risk of in-hospital death was similar between men and women following a heart attack in which the artery supplying the heart muscle was not completely blocked. **What do the results of the study mean?** Women who have a heart attack with complete blockage of an artery supplying heart muscle are more likely to die during hospitalization when compared with men.

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Keywords: in-hospital mortality • myocardial infarction • NSTEMI • sex difference • STEMI

Cardiovascular disease (CVD) is the main cause of death worldwide, especially in developing countries [1]. In Iran, CVD is the most common cause of death, accounting for about half of all-cause mortality [2]. Despite the decreasing trend in CVD mortality rate which has been observed in both sexes over the last two decades [3], mortality remains high [4]. This decrease is in line with the trend observed in other countries [4] and is likely partly explained by better disease management after implementation of novel revascularization strategies. Previous studies have assessed the association of patients' sex with incidence, symptom presentation, pathophysiological characteristics, management strategies and clinical outcome [5–10]. Contradicting evidence suggests that when compared with men, women may experience a higher rate of mortality after myocardial infarction (MI), which is a major form of CVD [11]. Some studies established a significant association between sex and MI mortality even after adjustment for confounding

factors [12,13], while others failed to show such specific gender-intrinsic-causes [14,15]. However, most of the evidence comes from the studies performed before the widespread use of revascularization strategies [16].

To the best of our knowledge, few studies have addressed the sex differences in mortality following myocardial infarction in Iranian patients, especially within the last 5 years [17]. There is still insufficient data on the association between sex and in-hospital mortality of different types of MI, including ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) [18]. Hence, we aimed to compare outcome by sex in patients presenting with myocardial infarction from a large sample of patients.

Materials & methods

Study design

We conducted a single-center retrospective cohort study using data from first-admitted patients 50 years or older with ICD-10-CM codes of acute myocardial infarction (AMI) (ICD-10 code I21). This data was extracted from the health informatics system (HIS) of Shahid Rajaei Hospital (Karaj, Iran), over a 4-year period. We conducted and reported this study according to the STROBE and NIH method reporting checklists which are presented in Supplementary Tables 1 & 2, respectively.

Study population

The study population was all inpatients that were at least 50 years of age, who were admitted for the first time with a diagnosis of AMI (with or without ST segment elevation) in our hospital from the 20 March 2016 to 18 December 2019. Novel revascularization techniques including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have been performed in our hospital since 2013, but as the hospital started to utilize ICD-9/10 Codes for recoding clinical data in 2016, 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. Additionally, Karaj is located 20 kilometers (12 mi) west of Tehran which is a large suburb.

Data sources & collection

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

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

Clinical data was extracted using International Classification of Diseases, tenth Revision and 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). 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.

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) was used for continuous variables and percentage was used for categorical variables to summarize the 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 in-hospital mortality after AMI. The results are presented as a hazard ratio (HR) 95% confidence

Table 1. Main patients' characteristics according to sex.

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), median (IQR)			3 (2–5)	4 (2–6)	0.043
Management of MI	Medical n = 293		13.8% (175)	26.0% (118)	<0.001
	Coronary angiography n = 1430 Male, n: 1094 Female, n: 336	PCI	76.4% (836)	69.3% (233)	0.003
		CABG	5.3% (58)	4.5% (15)	
		PCI + CABG	1.1% (12)	0.3% (1)	
		None	17.2% (188)	25.9% (87)	

CABG: Coronary artery bypass graft; CHF: Chronic heart failure; CKD: Chronic kidney disease; IQR: Inter quartile Range; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction.

interval). 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 periods were 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, IL, USA) and STATA V.12.0 (Stata Corp, TX, USA).

Results

Patient characteristics

A total of 1,730 first-admitted patients with AMI that were older than 50 years were recorded in our HIS database from March 2016 to December 2019. The median age (interquartile range (IQR) of patients was 63.50 (56.0 to 71.0) and 45.5 (26.3%) were female. In order of frequency, the 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%) died 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, treatments and procedures performed during hospitalization, according to their sex. The median age (IQR) of males was significantly lower than females (61.0 [55.0 to 69.0] versus 67.0 [60.0 to 76.0] years, respectively; $p < 0.001$). Compared with males, a higher percentage of females had a history of hypertension and diabetes (for both $p < 0.001$). There were no significant differences between both sexes regarding prevalence of comorbidities CHF and CKD.

There was a higher percentage of males diagnosed by STEMI when compared with females (70.1% vs 62.9%, respectively; $p = 0.001$). Males also showed a significantly higher rate of anterior STEMI in comparison with females (44.7 vs 34.4%, respectively; $p = 0.002$).

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 myocardial infarction.

Table 3. Association of sex on in-hospital mortality in first-admitted patients with acute myocardial infarction: Cox regression analysis.

Variable	Crude HR (95%CI) Model I	Adjusted HR† (95%CI) Model II	Adjusted HR‡ (95%CI) 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

†Adjusted for age.
‡Adjusted for age, diabetes and hypertension.
HR: Hazard ratio; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction.

In the 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 when compared with 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 the STEMI category (Table 2).

Table 3 presents the results of the univariate and multivariate Cox regression analysis for the effect of sex on 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 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).

Furthermore, in the STEMI subgroup, the results from the Cox regression analysis revealed a sex 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).

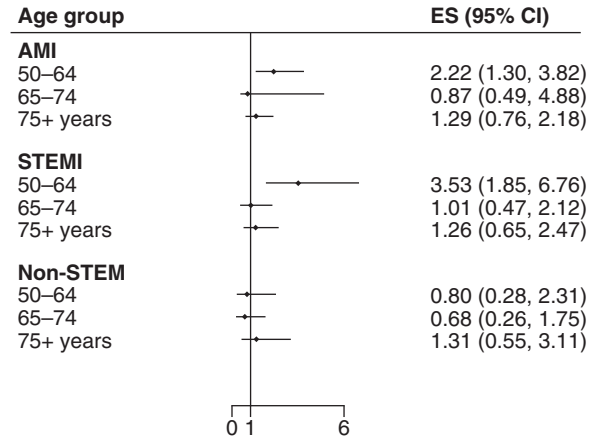

Figure 1. Forest plot of the association of being female on in-hospital mortality by type of myocardial infarction in different age groups, considering potential confounder diabetes and hypertension (Cox regression analysis).
AMI: Acute myocardial infarction; ES: Hazard ratio; STEMI: ST segment elevation myocardial infarction.

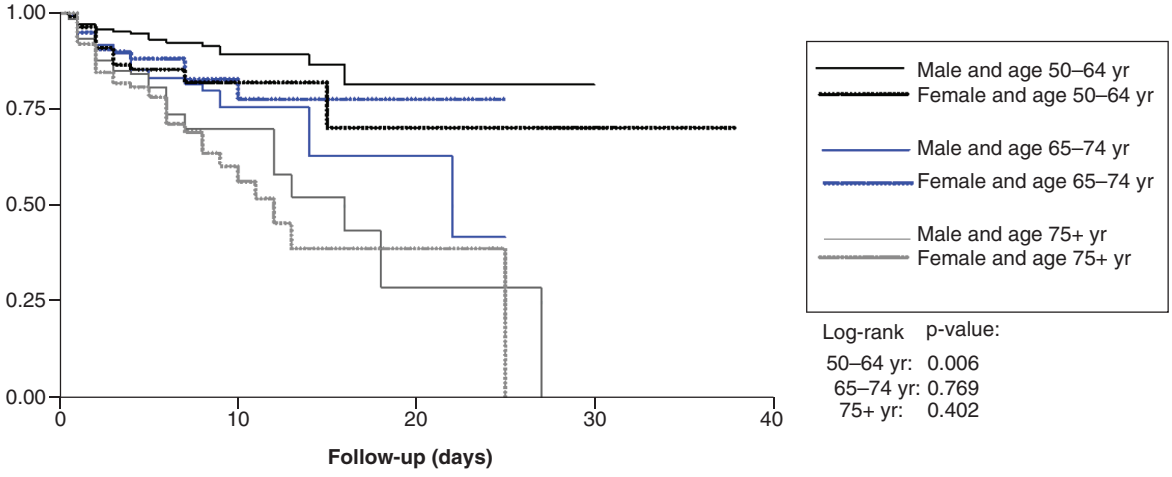

Figure 2. Survival curve in patients with acute myocardial infarction by sex in different age groups (Kaplan–Meier survival curve & log rank test).

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 (Figures 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 sex effect was no longer seen in older age groups. Also, in patients hospitalized for non-STEMI, both sexes revealed a similar risk for in-hospital mortality.

Our findings are in line with other studies [19–22]. The largest existing study of four ongoing European STEMI registries observed that when compared with males, females experienced a higher rate of in-hospital mortality, 30 days and 1 year after hospitalization in all countries [23]. Likewise, a study conducted by De Miguel-Yanes revealed that women presenting with a STEMI had 21% higher odds of in-hospital mortality. In line with our findings, they also observed a non-significant association between in-hospital mortality and sex in patients with NSTEMI [21]. Furthermore, Alkhouli *et al.* found that associations of female sex with post-MI outcomes were age specific; based on their findings, the association of females sex with most outcomes of STEMI, including in-hospital mortality, was stronger in young and middle-aged subgroups of patients in both crude and adjusted models [20].

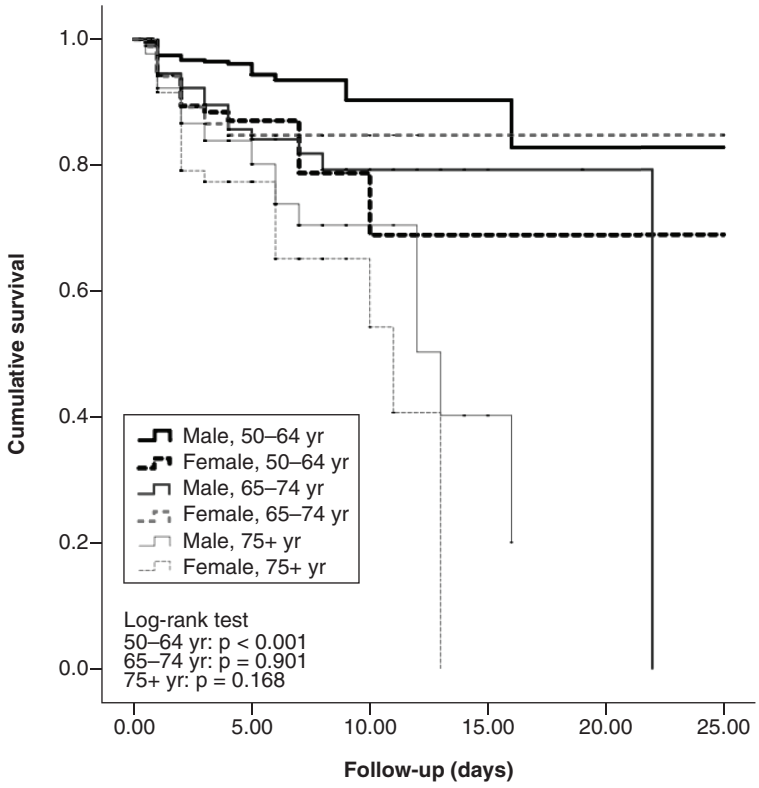

Figure 3. Survival curve in patients with ST segment elevation myocardial infarction by sex in different age groups (Kaplan–Meier survival curve & log rank test).

The sex differences in the early clinical manifestations of STEMI, were more prominent in younger age groups which may explain the higher mortality rate in females than males [24]. While specific symptoms are believed to play a key role in patients' help-seeking behavior, early diagnosis and timely treatment, based on the available evidence, female patients are more likely to present with atypical symptoms compared with males [25,26].

Also, while timely reperfusion using pPCI is critical in STEMI management, a recent systematic review revealed that female patients with a STEMI had longer door-to-balloon (D2B) and symptom-to-balloon (S2B) times than males [27].

There is evidence that physicians are less likely to comply with current guideline recommendations on treatment options for female MI patients due to the underscoring of their risk [28]. Recent studies showed that women admitted with a STEMI still received less guideline-recommended in-hospital management in different European countries [21,23]. Indeed, higher prevalence of microvascular involvement in females makes them less likely to undergo angiography and receive specific medications [28]. Leurent *et al.*, attributed 'under treatment or conservative treatment of female patients' as being the main explanation for higher in-hospital mortality in females when compared with males [25]. During perimenopause and early postmenopause, being female may be an independent predictor of in-hospital mortality following STEMI. At this age, more involvement of microvascular than macrovascular, and having a different etiology of STEMI in females when compared with males, could put females at a higher risk of death [29].

Actually, the results of randomized clinical trials guide evidence-based guidelines for management of MI. 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 findings to the male, rather than female, population [30]. More enrollment of women in related clinical trials could lead to better management of these patient by providing gender-specific data on the safety and effectiveness of available diagnostic and treatment strategies.

In line with our studies, previous studies also found that in patients hospitalized for non-STEMI, of both sexes, had similar a risk of in-hospital mortality [31]. In contrast to STEMI, which is mainly caused by acute plaque rupture, NSTEMI often resulted from a moderate coronary stenosis [32].

Shahid Rajaei Hospital is the only public hospital in Karaj with interventional cardiologists. Accordingly, nearly all STEMI cases were referred to this hospital, but NSTEMI patients can receive care in other centers. So, the proportion of STEMIs appears to be high in this study.

Shahid Rajaei Hospital 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. All patients receive medications according to guidelines at the hospital and at discharge, such as aspirin, clopidogrel, low molecular weight heparin (LMWH), atorvastatin, beta-blocker and angiotensin converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB), which is in line with international protocols. Hence, our findings are generalizable to other hospitals in other countries that adhere to these guidelines.

Limitations & strengths

Our study has a few limitations that must be considered while interpreting our findings. Our data source was an administrative database – HIS, which is primarily created for billing purposes, hence we lacked some important clinical data, such as occurrence of prehospital cardiac arrest, medications, time from symptom to PCI, time from ECG to PCI, echocardiographic assessments, left ventricular ejection fraction measurements, treatment regiment, type of MI or localization of MI, presence of atrial fibrillation and smoking status that may have confounded the observed associations. Moreover, we lacked data on treatment to perform adjustments. In the absence of follow-up data, the paper is concentrated on in hospital mortality which is related to pre- and in-hospital factors.

Cardioprotective effects of estrogen has long been known in females of fertile age (<50 years old). Too few of the patients younger than 50 years were female. Thus, we compared cardiovascular mortality between both sexes in patients over the age of 50 years old. Furthermore, we limited our study to first-admitted patients with MI because we believed considering those with a history of MI would complicate the findings and their generalizability, as we were not able to evaluate the data of patients who had sought out previous cardiovascular care. Including only first MI patients and those aged 50 to 64 years, limited the generalizability of our findings to those groups.

However, studies showed that the association of female sex with in-hospital mortality of STEMI remained significant even after adjustment for some of these potential factors [33]. Additionally, our study is one of the few studies in Iran that addressed this topic. Furthermore, some of the strengths of this study include the sample size and sound methodology.

Conclusion

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.

Executive summary

- Among patients experiencing their first episode of acute myocardial infarction (AMI), females were significantly older and more likely to have diabetes mellitus or hypertension than males.
- Male patients were significantly more likely to have ST-elevation myocardial infarction (STEMI), anterior location MI and undergo invasive procedures including percutaneous coronary intervention, coronary artery bifurcation disease or both, than females.
- All-cause mortality was significantly higher only in females aged 50 to 64 years old, and in females with STEMI, compared with counterpart males.
- There was no significant difference in all-cause mortality between males and females older than 65 years after first episode of AMI.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fca-2022-0064

Author contributions

NS Hassani and H Rastad had the idea and designed the study with R Pirdehghan and P Mardi. M Mozafarybazargany, R Sepahvandi, Z Khodaparast, F Karimi, F Rahimi, A Zakani, P Mardi collected the clinical data. Z Kamipoor, M Dorri, A Bamrafie summarized all data. H Rastad and NS Hassani analyzed and interpreted the information. All authors have participated to drafting the manuscript. H Rastad, N Shafiabadi revised it critically. All authors read and approved the final version of the manuscript.

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Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

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 the hospital EER system to protect confidentiality. Also informed consent was obtained from all individual participants included in the study.

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

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Papers of special note have been highlighted as: • of interest; •• of considerable interest

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•• **After widespread use of percutaneous coronary intervention, female gender is still an independent predictor of in hospital mortality.**

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