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Gender and Smoking-Related Survival Differences in Patients with ST-Elevation Myocardial Infarction

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ABSTRACT

Background: Smoking is the leading cause of preventable death. Female smokers bear a greater risk of experiencing an ST-segment elevation myocardial elevation (STEMI) than male smokers.

Objectives: This study aimed to investigate gender and smoking-related survival differences one-year post-STEMI.

Methods: This registry-based cohort study included all STEMI patients of Imam Ali Hospital, Kermanshah, Iran. All eligible adult patients with STEMI were enrolled. Baseline data and one-year post-STEMI data were collected. Cox proportional models were used to estimate crude and full-adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs). All analyses were performed using Stata.

Results: During 2080.9 person-years, 22 patients were lost to follow-up (success rate = 99%). There were 2,279 STEMI patients (22.99% women) during the study period. Men were younger than women (58.50 ± 12.22 vs. 65.26 ± 11.56 years, $P < 0.001$). In men, smoking was a protective factor against in-hospital mortality in the unadjusted model (HR = 0.49, 95% CI: 0.31 – 0.78, P = 0.002), but was not a protective factor after adjusting for age, hypertension, dyslipidemia, diabetes, creatine kinase-MB, body-mass index, LDL-cholesterol, HDL-cholesterol, glomerular filtration rate, anterior wall MI/LBBB, left ventricular ejection fraction and reperfusion therapy (HR = 0.66, 95% CI: 0.34 – 1.25, P = 0.198).

Conclusions: Although male smokers with STEMI had a lower in-hospital mortality rate, this difference did not persist in the adjusted model. Thus, the smokers' paradox phenomenon was not proven. The better outcomes of men with STEMI compared to women are probably related to their younger age and fewer risk factors at the time of presentation.

1. Background

Smoking is the leading cause of preventable death worldwide and the second leading cause of disability-adjusted life years in both men and women (1). One-fifth of the world's smokers are women (2), with smoking being a major risk factor for myocardial infarction before and after menopause (3).

Women who smoke are at a greater risk of experiencing an ST-segment elevation myocardial elevation (STEMI) than male smokers, especially when aged below 50 (4, 5). Some studies suggest that smoking is a more significant risk factor for STEMI in women than in men under 65 (6, 7). The poorer outcomes in women are explained by older age and more advanced disease (8).

Since the number of women who smoke has increased in recent decades, having enough information about the effects of smoking on women's health is desirable from a public health point of view.

2. Objectives

Gender-based studies help improve understanding of gender as a determinant of health; its interaction with other determinants contributes to the design and implementation of gender-sensitive tobacco control policies and programs.

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Therefore, this study aimed to investigate the relationship between gender, smoking status, and mortality after one year in STEMI patients.

3. Methods

3.1. Study Design, Setting, and Participants

This registry-based cohort study was conducted at Imam Ali Cardiovascular Hospital, affiliated with the Kermanshah University of Medical Sciences. This hospital is the main tertiary cardiovascular center in the Kermanshah province, west of Iran. It is also the only hospital in the province that offers primary percutaneous coronary intervention (PPCI) twenty-four hours a day, seven days a week. Therefore, patients may be directly admitted to Imam Ali Hospital or be referred from other non-PPCI-capable hospitals in the province. All eligible adult patients (≥ 18 years) with STEMI, diagnosed by current guidelines (9), were enrolled in the registry. Patients hospitalized more than 24 hours before referring to Imam Ali Hospital were excluded from the registry. In the current study, we also excluded patients with previous cardiovascular events (myocardial infarction or stroke) and interventions (percutaneous coronary intervention or coronary artery bypass graft surgery) and those with unknown cigarette smoking status. Patients were divided into four groups: ever-smokers and never-smokers, men and women.

3.2. Baseline Assessment

Two trained nurses collected data on demographic, lifestyle, and clinical characteristics from personal interviews with patients and/or their attendants. Study participants were determined to have a history of tobacco smoking based on self-report. Previous cardiovascular events, coronary intervention, diabetes, and hypertension were recorded based on physician-confirmed self-reports. Data on vital signs, early reperfusion therapy, electrocardiography, medical treatment, and laboratory tests were obtained from hospital medical records. Early reperfusion therapy status was recorded as PPCI, thrombolytic therapy, or none (no reperfusion). Body-mass index (BMI)—weight in kilograms divided by the square of height in meters—was measured using standard protocols. Lipid profile levels were measured on the first day of admission. The glomerular filtration rate (GFR) was estimated using the CKD-EPI equation. The highest levels of creatine kinase (CK-MB) after STEMI were recorded. The echocardiography results were used to record left ventricular ejection fraction (LVEF). All recorded data were quality-controlled by trained physicians.

3.3. Study Outcome and Follow-up

The primary outcome was all-cause mortality one year from STEMI events—during the index hospitalization or after discharge. In-hospital mortality was recorded using hospital documents. Upon hospital admission, the contact information of patients and family members or attendants was recorded. Patients were followed after one year by phone call. If death was reported, the research team collected and evaluated all clinical or hospital records and the cause of death. Follow-up time extended from the date of STEMI diagnosis to the date of death, loss-to-follow-up, or 365 days after STEMI, whichever came first.

3.4. Ethical Approval and Consent for Study

All patients provided written informed consent before enrolling in the study. The Research Ethics Committee of the Vice-Chancellery for Research and Technology of Kermanshah University of Medical Sciences approved the study protocol.

3.5. Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD), while categorized variables are presented as frequency (percentage). The chi-squared test and student's t-test were used to compare baseline characteristics between ever-smokers and never-smokers or men and women. We tested and confirmed the non-violation of the proportionality of hazards based on a graphical approach (log-log plots) and Schoenfeld's test. Cox proportional hazard regression analysis was performed to determine the hazard ratio (HR) and 95% confidence interval (95% CI) for the association between smoking and all-cause mortality. We reported two HRs and 95% CIs using crude and adjusted Cox models. In the adjusted model, we evaluated the association of smoking with mortality after adjusting for age (as a continuous variable), hypertension (as a binary variable: yes/no), dyslipidemia (as a binary variable: yes/no), diabetes (as a binary variable: yes/no), CK-MB (tertile), BMI (as a continuous variable), LDL-cholesterol, HDL-cholesterol, GFR (as a continuous variable), anterior wall MI/LBBB (as a binary variable: yes/no), LVEF (as a categorical variable: < 35, 35 - 50, ≥ 50%), and reperfusion therapy (as a categorical variable: PPCI, thrombolytic, no reperfusion). In subgroup analyses, we analyzed the association of smoking with all-cause mortality based on age and death time (at index hospitalization or after discharge). In this study, the numbers of missing values for the covariates were relatively small (diabetes, 41; hypertension, 20; dyslipidemia, 76; BMI, 52; LDL, 115; HDL,152; LVEF, 70; GFR, 7; CK-MB, 6). We performed all analyses on complete case data. Twenty-two (0.96%) patients were lost to follow-up. All analyses were performed using Stata version 14.0 (Stata Corp, College Station, TX, USA). A P-value < 0.05 was considered statistically significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (10).

4. Results

A total of 2,816 patients were enrolled in the registry. However, 526 (18.68%) patients had a history of cardiovascular events, and 11 (0.39%) had unknown smoking status, so they were excluded from the analysis, leaving 2,279 patients. Of the 2,279 patients, 524 (48.1%) were women, and 1,755 (51.6%) were men. During 759,553 person-days of follow-up, 216 (9.48%) patients died: 120 (5.27%) had in-hospital mortality, and 96 (4.21%) had out-of-hospital mortality during the one-year follow-up. The baseline clinical characteristics of the study population are displayed in Table 1. Age, BMI, HDL, hypertension, dyslipidemia, and diabetes were lower or less in male smokers than male non-smokers but similar among female

Table 1. Baseline Characteristics of the Study Population according to Gender and Smoking Status

Variable	Women (n = 524)		P-value	Men (n = 1,755)		P-value
	Ever-smoker (n = 58, 11.07%)	Never-smoker (n = 466, 8.93%)		Ever-smoker (n = 1033,8.86%)	Never-smoker (n = 722,41.14%)	
Age (SD), years	66.46 ± 11.58	65.11 ± 11.57	0.402	57.09 ± 11.42	60.52 ± 13.04	< 0.001
Diabetes	19 (33.93%)	172 (37.47)	0.604	112 (10.99%)	131 (18.61)	< 0.001
Hypertension	40 (70.18)	301 (64.87)	0.427	269 (26.32%)	275 (38.41)	< 0.001
Dyslipidemia	20 (35.71)	171 (38.00)	0.739	132 (13.20)	151 (21.66)	< 0.001
BMI (kg/m^2)	25.93 ± 4.82	27.01 ± 4.52	0.073	25.75 ± 4.05	26.44 ± 3.64	< 0.001
LDL-cholesterol	109.09 ± 35.81	110.33 ± 32.37	0.793	103.63 ± 28.62	105.75 ± 31.68	0.154
HDL-cholesterol	42.93 ± 8.69	44.46 ± 10.54	0.243	40.04 ± 8.46	41.78 ± 9.05	0.001
GFR (mL/min/1.73m^2)	56.95 ± 18.13	57.95 ± 15.83	0.657	75.03 ± 16.75	69.76 ± 17.05	< 0.001
Anterior MI/ LBBB	8 (13.79)	93 (19.96)	0.262	235 (22.75)	166 (22.99)	0.905
CK-MB (IU/L)						
< 56	17 ± 29.31	177 ± 37.98	0.329	306 ± 29.68	215 ± 29.94	0.982
57 - 140	21 ± 36.21	165 ± 35.41		352 ± 34.14	242 ± 33.70	
> 141	20 ± 34.48	124 ± 26.61		373 ± 36.18	261 ± 36.35	
LVEF						
< 35%	14 ± 25.00	126 ± 28.06	0.445	259 ± 25.69	197 ± 28.30	0.468
35 - 50 %	35 ± 62.50	243 ± 54.12		580 ± 57.54	390 ± 56.03	
> 50%	7 ± 12.50	80 ± 17.82		169 ± 16.77	109 ± 15.66	
Reperfusion therapy						
PPCI	29 (50.00)	257 (55.15)	0.114	615 (59.54)	428 (59.28)	0.171
Thrombolytic	21 (36.21)	113 (24.25)		283 (27.40)	179 (24.79)	
No reperfusion	8 (13.79)	96 (20.60)		135 (13.07)	115 (15.93)	

Values are mean ± standard deviation (SD) or n (%).
Abbreviations: BMI, body mass index; LDL-cholesterol, low-density lipoproteins cholesterol; HDL-cholesterol, high-density lipoproteins cholesterol; GFR, glomerular filtration rate; MI: myocardial infarction; LBBB, left bundle branch block; CK-MB, creatine kinase-MB; PPCI, primary percutaneous coronary intervention; LVEF, left ventricular ejection fraction.

Table 2. Non-Adjusted and Adjusted In-Hospital Mortality Risk Ratios of Ever-Smokers and Never-Smokers

	Death, n (%)	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Men					
Never-smoker	64 (8.94%)	Reference		Reference	
Ever-smoker	68 (6.65%)	0.73 (0.52 – 1.02)	0.067	1.15 (0.74 – 1.78)	0.526
Women					
Never-smoker	72 (15.58%)	Reference		Reference	
Ever-smoker	12 (21.43%)	1.41 (0.76 – 2.59)	0.273	1.93 (0.95 – 3.94)	0.071

Hazard Ratios were adjusted for age, hypertension, dyslipidemia, diabetes
Abbreviations: CK-MB, BMI, LDL-cholesterol, HDL-cholesterol, GFR, anterior wall MI/LBBB, LVEF, and reperfusion therapy (PPCI, thrombolytic, no reperfusion).

Table 3. Subgroup Analyses for the Relationship between Smoking and Mortality according to Age and Death Time

	Women				Men			
	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age < 60	0.70 (0.09 - 5.35)	0.731	1.86 (0.09 - 39.19)	0.689	1.00 (0.52 - 1.92)	0.998	1.35 (0.57 - 3.20)	0.492
Age > 60	1.52 (0.80 - 2.90)	0.201	1.64 (0.77 - 3.53)	0.201	0.77 (0.51 - 1.15)	0.198	0.97 (0.59 - 1.60)	0.918
Mortality								
In hospital	1.34 (0.57 - 3.16)	0.508	2.29 (0.71 - 7.43)	0.166	0.49 (0.31 - 0.78)	0.002	0.66 (0.34 - 1.25)	0.198
Out of hospital	1.55 (0.65 - 3.71)	0.321	2.08 (0.83 - 5.23)	0.119	1.25 (0.73 - 2.16)	0.414	1.70 (0.92 - 3.13)	0.092

Data are hazard ratios (HRs) with 95% confidence intervals (95% CIs) for ever-smokers versus never-smokers.

smokers and non-smokers. However, the GFR was higher in male smokers than in male non-smokers.

As illustrated in Table 2, there was no association between smoking and mortality in men and women in the crude model; however, the male gender tended to be protective. After the model was fully adjusted for all variables (age, BMI, diabetes, hypertension, dyslipidemia, LDL-cholesterol, HDL-cholesterol, CK-MB, GFR, anterior wall MI/LBBB, LVEF, and reperfusion therapy), there was no association between smoking and mortality in both men and women.

Subgroup analyses are reported in Table 3. The mortality risk was similar at < 60 and ≥ 60 years old for men and women. In men, smoking was a protective factor for in-hospital mortality in the unadjusted model. After the model

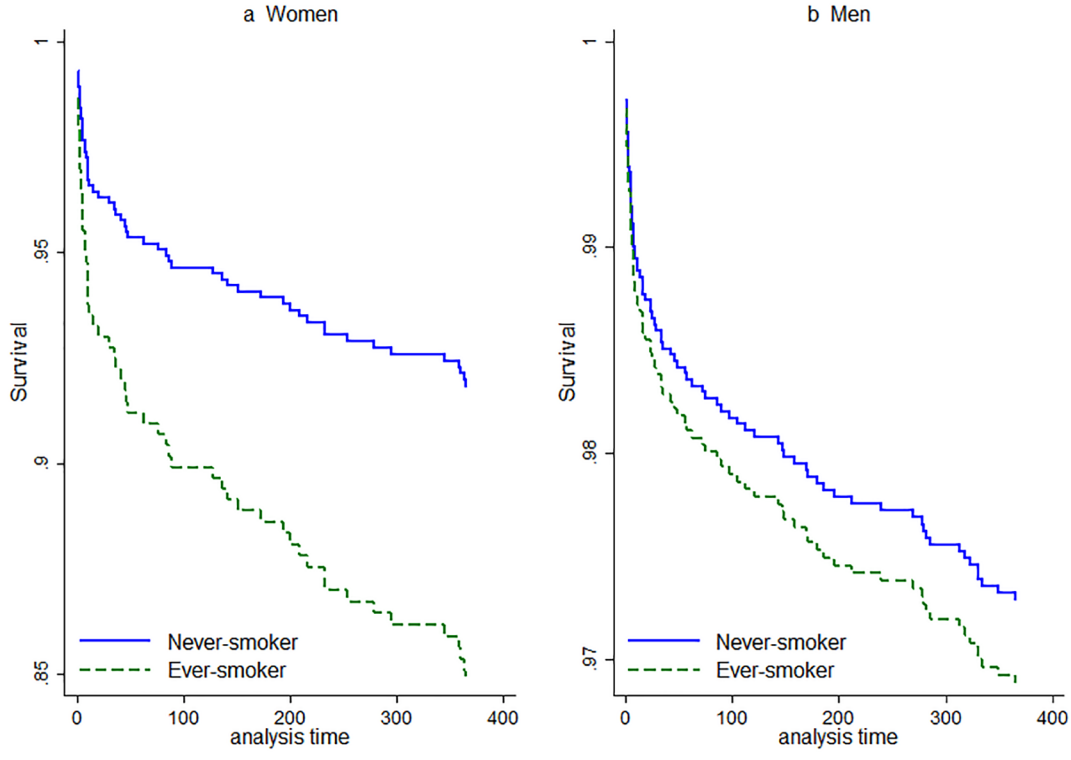

Figure 1. The Adjusted Survival Curves for Ever-Smokers and Never-Smokers.

was fully adjusted, this protection disappeared.

Although the prevalence of smoking was higher in men (94.68%), the rate of both in-hospital and out-of-hospital mortality was higher in female smokers (10.71% and 10.71%, respectively) than men (3.62% and 3.03%, respectively). In non-smokers, the mortality rate in women was higher than in men, but this relationship was insignificant in in-hospital mortality. Figure 1 Shows the Survival Curves in Men and Women for Ever-Smokers Versus Never-Smokers based on the Fully-Adjusted Cox Regression Model.

5. Discussion

The current investigation examined the relationship between sex, smoking status, and one-year mortality in patients with STEMI. Results showed that women were at a greater risk of mortality than men. Although the prevalence of smoking was higher in men, the mortality rate and HR were higher in female smokers. This study quantifies the differential impact of smoking between genders, with women having a significantly increased mortality risk than men.

As illustrated in Table 3, under unadjusted conditions, a smoker's paradox existed in the male gender, where smoking was protective against mortality. However, this paradox was resolved after adjustment with the variables presented in Table 1. The effect of smoking on the female gender was different, and there was no smoker's paradox. This may be because women started smoking at a later age. In fact, male smokers developed STEMI a few years earlier than women. In our study, women were older and had more risk factors due to their older age, which confirms the age hypothesis about the paradox.

Some studies reported the survival benefit of smokers in the setting of STEMI, ranging from in-hospital mortality to three-year mortality (11, 12). Consistent with previous studies (13, 14), this paradox was observed in in-hospital mortality. In our study, the smoker's paradox was not recorded after a one-year follow-up. It was reported that smokers suffer more out-of-hospital death, thus creating a selection bias when assessing in-hospital mortality (15).

Previous studies reported that women tend to have significantly higher in-hospital mortality for STEMI events than men (16, 17). The increased mortality in women is likely explained by their increased age and a more complex set of medical problems (15). Furthermore, socioeconomic status is widely understood to shape health disparities, and women with STEMI return to the hospital later and receive less standard treatment (18, 19).

Male smokers had significantly fewer coronary risk factors compared with female smokers; these results can predict a better outcome and put the male smoker at an advantage. These findings underscore the fact that male smokers are prone to coronary artery disease even with a lower prevalence of risk factors.

Estrogen has a protective effect on the heart by reducing the serum lipid concentration and minimizing the effect of lipids on the vessel wall (20-22). The production or activity of estrogen is inhibited by smoking (23, 24). Therefore, smoking is an important risk factor for atherosclerosis in women. This information encourages continued efforts to prevent smoking uptake and promote cessation, especially in women.

5.1. Study Strengths and Limitations

This study had several strengths and limitations. The strengths of our study were the one-year follow-up and the low rate of loss to follow-up. Our study's main limitation was its single-center nature, so caution should be exercised in extending the findings to other communities. Self-reported data (e.g., hypertension) represented another limitation.

5.2. Conclusion

The current study investigated the effects of smoking on post-STEMI mortality in men and women. Our study showed that male smokers had a better clinical outcome (fewer in-hospital mortalities) after STEMI, but upon adjustment, the seemingly beneficial effects of smoking on mortality disappeared. So, in our population, there was no actual smokers' paradox for men—the better outcomes may be related to the younger age and fewer risk factors at the time of presentation with STEMI compared with women. Women who smoke have a higher risk of in-hospital mortality than their male counterparts. However, sex alone was not a significant predictor of in-hospital mortality in these patients. This information encourages continued efforts to prevent smoking uptake and promote cessation, especially in women.

5.3. Ethical Approval

This study is approved under the ethical approval code IR.KUMS.REC.1400.252, documented online at https://ethics.research.ac.ir/PortalProposalList.php?code=IR.KUMS.REC.1400.252&title=&name=&stat=&isAll=&GlobalBackPage=https%3A%2F%2Fwww.google.com%2F

5.4. Informed Consent

Written informed consent was obtained from the participants.

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Authors' Contribution

PJ and AA: Writing - original draft, NS: Conceptualization and modification, SM: Analyzing the findings of patients, YS and SS Writing and editing. All authors read and approved the final manuscript.

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