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Impact of cigarette smoking on the outcomes of ST-elevation myocardial infarction after primary percutaneous coronary intervention in metropolitan Tehran

Babak Geraiely[1], Mojtaba Salarifar[2], Aida Hadizadeh[1], Elnaz Shahmohamadi[2,3], Arash Jalali[2], Tara Moghaddasfar[1], Farnoosh Larti[1]*

1. Cardiology Department, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
2. Tehran Heart Center, Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran.
3. School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

***Corresponding author:** Farnoosh Larti; **Email:** Farnooshlarti@gmail.com

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Abstract: **Objective:** Although the adverse effects of smoking are well-established, evidence shows a longer survival rate following an acute myocardial infarction (MI) among smokers or the so-called "smoker's paradox". This study aimed to determine the impact of smoking on the one-year clinical outcomes of ST-elevation myocardial infarction (STEMI) after primary percutaneous coronary intervention (PPCI) in a large registry of the Iranian population.

Methods: A total of 3087 patients diagnosed with acute STEMI who underwent PPCI between 2013 and 2018 were enrolled in the study. Patients' smoking status was determined based on self-reported history and categorized into two groups: current smokers and non-smokers. Clinical and angiographic data were collected from the Tehran Heart Center (THC) registry. The primary outcome was one-year of major adverse cardiac and cerebrovascular events (MACCE). The effect of smoking on MACCE was evaluated using a Cox model.

Results: From the study population, 1967 (63.7%) were non-smokers, and 1120 (36.3%) were current smokers. Non-smokers had higher rates of prior CABG (5.3%) as well as a higher history of co-morbidities, including a history of diabetes mellitus (46.0%), hypertension (52.7%) and hyperlipidemia (55.4%) than smokers (2.3%, 30.4%, 35.7%, and 49.8% respectively). Smokers had a higher reference vessel diameter than non-smokers (P=0.005). The unadjusted hazard ratios (HRs) for MACCE within one year were significantly lower in smokers than non-smokers (0.73, 95% CI: [0.58,0.92]; P=0.009); however, after adjustment for confounders, the HRs for MACCE in smokers were similar to non-smokers (HR: 1.00, 95% CI: [0.73,1.38]).

Conclusion: The study found that smoking had no significant impact on the one-year clinical outcomes of STEMI patients after PPCI in the Iranian population. This study is the first of its kind to assess the effect of smoking on STEMI patients in Iran and highlights the need for further research in this area.

Keywords: Myocardial Infarction; Outcome; Primary Percutaneous Coronary Intervention; Smoking; ST Elevation

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1. Introduction

Cigarette smoking is a well-recognized modifiable risk factor for coronary artery disease (CAD) with considerable morbidity and mortality (1,2). Although the adverse effects of smoking are well-established, evidence for a "smoker's paradox"emerged more than 40 years ago when it was reported that following an acute myocardial infarction (MI), smokers had a longer survival rate on average than nonsmokers (3). This favorable outcome after acute MI is partly attributed to the younger age of smokers, fewer co-morbidities, and a more significant thrombus burden in them (4,5). Later, various research conducted during the thrombolytic eras also described this phenomenon (6-8). Recent studies on patients treated with primary percutaneous coronary intervention (PPCI) are less confirmatory (9).

No study in Iran described the impact of smoking on patients who underwent PCI; therefore, the phenomenon of the "smoker's paradox" is uncertain, whether or not it exists in the Iranian population. This is while, according to the most recent global burden of the disease (GBD) study, Iran has the highest age-standardized prevalence of death due to ischemic heart disease in the world (10). Secondary preventive care has paramount importance in improving cardiovascular outcomes in CAD patients.

As far as we know, this is the first study to analyze a sizeable single-center sample in Iran to assess the effect of smoking on the clinical outcomes of ST-elevation myocardial infarction (STEMI) after PPCI. We aimed to determine the

composite endpoint of cardiovascular death, MI, stroke, re-infarction, target lesion/vessel revascularization or need for coronary artery bypass grafting (CABG) during a one-year follow-up.

2. Methods

2.1. Study population

For this single-center, retrospective cohort study, 3087 patients with the diagnosis of STEMI who underwent PPCI between January 2013 and January 2018 at Tehran Heart Center (THC) were enrolled. Data was collected from the THC registry. The study protocol was approved by the research ethics committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1399.427). All treatment methods were carried out in accordance with relevant guidelines and regulations.

2.2. Inclusion and exclusion criteria

Only patients with all the necessary items regarding cardiac risk factors and one-year patient follow-up available in the database were enrolled in the study. Patients were included if they had electrocardiographic changes consistent with acute STEMI and underwent PPCI with stent implantation. Patients who were treated with just balloon angioplasty were excluded.

2.3. Definition of the smoking status

Smoking status was based on the patient's self-reported history and the last smoking time, which was available in the data registry. The database did not record the cigarette type or the smoking amount. Patients were categorized into two groups: current smokers and non-smokers.

- Current smokers were patients who reported smoking during the last year before hospital admission due to STEMI.
- Non-smokers were patients who had never smoked or had quit smoking for more than one year before STEMI.

2.4. Clinical and angiographic data for patient allocation

Data regarding gender, age, left ventricular ejection fraction, history of CAD risk factors (hypertension, diabetes mellitus, family history of CAD, and hyperlipidemia), congestive heart failure, previous CABG, or previous PCI were collected from the THC registry. Also, the administration of glycoprotein IIb/IIIa inhibitors during PCI, the number of involved coronary arteries, and the incidence of cardiac rupture were obtained. "Angiographic success" was defined as achieving the final thrombolysis in myocardial infarction (TIMI) score 3 flow.

2.5. Study outcomes

Data from a one-year follow-up was obtained from THC's data bank. Primary outcomes were defined as major adverse cardiac and cerebrovascular events (MACCE), a composite of cardiovascular death, MI, stroke, re-infarction, target lesion/vessel revascularization, or need for CABG, which one occurred first. The secondary outcomes were the components of MACCE. Target lesion/vessel revascularization and CABG were considered "revascularization" for analysis.

2.6. Statistical analysis

The continuous variables were described as mean with standard deviation (SD) and were compared between the smoker and non-smoker groups using student's t-test. Serum creatinine level was not normally distributed, so it was expressed as a median with 25th and 75th percentiles and was compared between the two groups applying the Mann-Whitney U-test. Categorical variables were described as the frequency with percentages and were compared between the smoker and non-smoker groups using the chi-squared test.

The smoker and non-smoker groups were balanced based on the variables: age, body mass index (BMI), reference vessel diameter, stent length, sex, previous PCI, previous CABG, positive family history of CAD, diabetes mellitus, hypertension, dyslipidemia, treatment with IIb/IIIa inhibitor, number of diseased vessels, lesion complexity (AHA B2 or C grade) number of stents, and using the stabilized inverse probability weighting (sIPW). The effect of being a current smoker on MACCE was evaluated by applying a Cox model considering IPW weights. It was reported as a hazard ratio (HR) with a 95% confidence interval (CI). Also, the effect of current smoking on each component of the MACCE was assessed in competing for risk setting and was reported through subdistribution hazards ratio (sHR) with 95% CI. All statistical analyses were conducted using Stata statistical software, release 14.0 (College Station, TX: StataCorp LP).

3. Results

3.1. Baseline clinical data

From the study population of 3087 patients, 1967 (63.7%) were non-smokers, and 1120 (36.3%) were current smokers. The average age of non-smokers was 64.6±11.99 at the time of primary PCI, significantly higher than that of current smokers (57.9±10.26, P<0.001). The majority (95.4%) of smokers were male, and it was significantly higher than 69.5% of males in the non-smoker group (P<0.001). Non-smokers had significantly higher BMI than smokers (28.1±4.51 vs. 27.3±4.29, P<0.001).

Non-smokers had higher rates of prior CABG (5.3%) as well as a higher history of co-morbidities, including a history of diabetes mellitus (46.0%), hypertension (52.7%), and hyperlipidemia (55.4%) than smokers (2.3%, 30.4%, 35.7%, and 49.8% respectively).

3.2. Angiographic and procedural data

There was no difference in lesion complexity, number of diseased vessels, and number of stents between the two groups; however, smokers had a higher reference vessel diameter

Table 1 Baseline clinical andangiographic characteristics based on smoking status

		Total (N=3087)	Non-smoker (N=1967)	Current smoker (N=1120)	P-value
Clinical characteristics					
Age, median (SD)		62.2 (11.83)	64.6 (11.99)	57.9 (10.26)	<0.001
Male, n (%)		2436 (78.9)	1367 (69.5)	1069 (95.4)	<0.001
BMI, kg/m^2, median (SD)		27.8 (4.47)	28.1 (4.53)	27.4 (4.3)	<0.001
Prior PCI, n (%)		340 (11)	224 (11.4)	116 (10.4)	0.379
Prior CABG, n (%)		131 (4)	105 (5.3)	26 (2.3)	<0.001
History of CHF, n (%)		93 (3)	56 (2.8)	37 (3.3)	0.475
Family history of CVD, n (%)		477 (15.5)	293 (14.9)	184 (16.4)	0.257
DM, n (%)		1245 (40.3)	905 (46)	340 (30.4)	<0.001
HTN, n (%)		1436 (46.5)	1036 (52.7)	400 (35.7)	<0.001
HLP, n (%)		1647 (53.4)	1089 (55.4)	558 (49.8)	0.003
GP IIb/IIIa inhibitors, n (%)		2139 (69.3)	1332 (67.7)	807 (72.1)	0.012
LVEF, % (%)		41.7 (8.37)	41.8 (8.34)	41.6 (8.42)	0.567
Angiographic characteristics					
Number of diseased vessels, n (%)	1	2563 (83)	1617 (82.2)	946 (84.5)	0.179
	2	476 (15.4)	315 (16)	161 (14.4)	
	3	48 (1.6)	35 (1.8)	13 (1.2)	
Reference vessel diameter, mean (SD)		3.1 (0.62)	3.1 (0.67)	3.2 (0.52)	0.005
Stent length, mm (95% CI)		26 (20,35)	28 (20,35)	26 (20,34)	0.376
Successful, n (%)		3062 (99.2)	1951 (99.2)	1111 (99.2)	0.977
Lesion complexity B2 or C, n (%)		2841 (92)	1815 (92.3)	1026 (91.6)	0.512
Number of stents, n (%)	1	2795 (90)	1776 (90.3)	1019 (91)	0.715
	2	280 (9.1)	184 (9.4)	96 (8.6)	
	3	12 (0.4)	7 (0.4)	5 (0.4)	

BMI: Body mass index; CABG: Coronary artery bypass graft; CHF: Chronic heart failure; CVD: Cardiovascular disease; DM: Diabetes mellitus; HTN: Hypertension; HLP: Hyperlipidemia; LVEF: Left ventricle ejection fraction; PCI: Primary cardiac intervention; CI: Confidence interval; SD: Standard deviation

Table 2 Compared unadjusted and adjusted MACCE components in current smokers vs. non-smokers

Outcomes	Total population		Current smokers		Non-smokers		Unadjusted HR/sHR* (95% CI)	P-value	IPW HR/sHR* (95% CI)	P-value
MACCE	328		97		231		0.73 (0.58,0.92)	0.009	1.00 (0.73,1.38)	0.973
MI	74		32		42		1.36 (0.86,2.16)	0.188	1.54 *(0.85,2.75)	0.151
Death	161		41		120		0.60 (0.42,0.85)	0.004	0.98 *(0.58,1.66)	0.938
Revascularization CABG	90	26	26	9	66	17	0.64 (0.40,1.02)	0.063	0.76* (0.42,1.35)	0.342
TVR/TLR		64		15		49				
Stroke	3		0		3		-		-	

MACCE: Major adverse cardiac and cerebrovascular events; MI: Myocardial infarction; CABG: Coronary artery bypass graft; TVR/TLR: Target vessel revascularization/ target lesion revascularization; HR: Hazard ratio; sHR: Smoker hazard ratio
*: The effect of current smoking on MACCE components was reported with sub-distribution hazards ratio (sHR)

than non-smokers (P=0.005). Glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa) were administered more in the smokers' group compared to non-smokers (72.1% vs. 67.7%, P=0.012). Despite differences in mean age, comorbidities, and use of the GP IIB/IIIai, procedural success did not differ between these two groups. The clinical and angiographic findings are shown in table 1.

As shown in figure 1, in the current smokers' group, the unadjusted HRs for MACCE within one year were significantly lower than non-smokers (0.73, 95% CI: [0.58,0.92]; P=0.009). Inverse probability weighting (IPW) was developed to allow adjustment for the lower age of smokers and other differences in baseline variables between smoker and non-smoker groups. In this produced model, the HRs for MACCE in smokers were similar to non-smokers (HR: 1.00, 95% CI: [0.73,1.38]). The unadjusted HR for death was significantly lower for current smokers (0.65, 95% CI: [0.48,0.88]; P=0.006) than non-smokers. However, after applying the IPW model, the protective impact of smoking disappeared (Table 2).

4. Discussion

In this retrospective study of a large cohort of STEMI patients undergoing primary PCI, we found that current smokers had a decreased unadjusted HR for 1-year death and MACCE events compared to non-smokers. However, when adjusting for confounding variables, this protective effect of

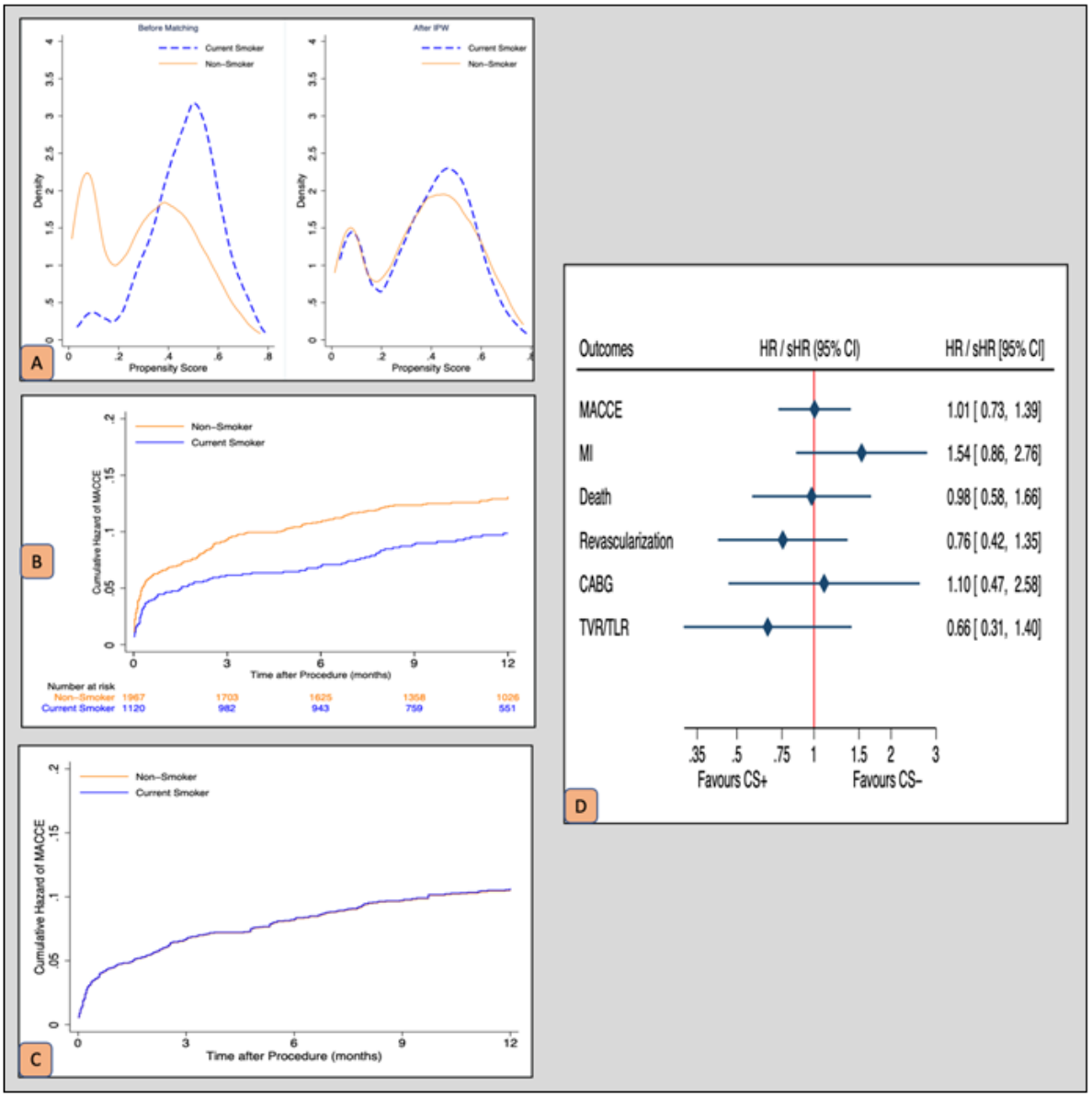

Figure 1 The coverage plot of the current smokers and non-smokers groups before and after applying the IPW method (A), the unadjusted (B), and the adjusted HR of MAACE (C), the adjusted effects of current smoking on MACCE and its components through sub-distribution hazards ratio (sHR) with 95% CI (D)

smoking was no longer observed, indicating the existence of a smoker's pseudo paradox on outcomes.

Weinblatt et al. first identified the "smoker's paradox" in 1968 as an unexpected outcome since smokers had a lower 1-month death rate after their MI incidents than non-smokers (3). Since then, numerous studies have assessed this association in different study populations.

In the presenting study, non-smokers were nearly seven years older than smokers, and this group had a greater prevalence of hypertension.

Consistent with prior research, this data may suggest that current smokers had less arterial stiffness and vascular resistance than non-smokers due to their younger age (11). In addition, non-smokers had a higher prevalence of DM and prior CABG, which may be associated with adverse outcomes after PCI in this group. Both opposing sides of the "smoker's paradox" observed that smokers were connected with a younger age, more male gender, and fewer comorbidities than non-smokers. Some researchers suggested that the "smoker's paradox" phenomenon could be partially explained by fewer concomitant high-risk characteristics in AMI patients who smoke (12,13).

In the present retrospective cohort, the number of diseased vessels, length and the number of stents, lesion complexity, and successful PCI results were similar in the smokers and non-smokers groups. At the same time, the use of the

GPIIb/IIa inhibitors was more significant in smokers compared to the non-smoker group. This difference existed despite the larger reference vessel diameter in smokers. These findings may underscore the important role of smoking as a risk factor in creating a milieu of accelerated atherosclerosis and producing angiographic and 1-year clinical outcomes similar to older non-smokers patients.

The effect of smoking on different presentations of acute coronary syndromes was reassessed in 2019 by a pooled analysis of 18 randomized controlled trials (14). Among 24,354 patients with available data on smoking status, 6,722 (27.6%) were current smokers. In one year, death, cardiac death, MI, and target vessel revascularization (TVR) had no difference in current smokers compared to non-current smokers. Probable or definite stent thrombosis was observed more in the current smokers' group, while target lesion failure (TVF) occurred more in the non-current smokers' group. After five years, death and cardiac death were the same in the smokers and non-smokers groups, but MI and stent thrombosis occurred more in the smokers' group. After adjusting for confounding factors, smoking was associated with increased death, cardiac death, MI and stent thrombosis with no effect on TVR and TVF at five years. In this analysis, the only included trial that specifically assessed STEMI patients was "HORIZONS-AMI" (15) published in 2009, compared Paclitaxel vs. BMS. The remaining STEMI patients were included in "COMPARE" (16), "TWENTE" (17), "COMPARE II" (18), and "TWENTE II" (19) trials that recruited all acute coronary syndrome (ACS) patients. No specific conclusion was drawn in STEMI patients in this pooled analysis. Meanwhile, the main limitation of the above comment was inadequate data on cigarette smoking. The smoking status of the study populations was available only at the baseline, and no information on the amount of cigarette consumption and any change in their habitual history has been analyzed.

Moreover, the definition of the current smoker vs. ex-smoker needed to be clarified. In our database, the amount of cigarette consumption and detailed data on any change in smoking status has yet to be recorded. Still, the current smokers and non-smokers were clearly defined.

5. Limitations

The data registry did not contain information regarding the type of cigarette or the amount of cigarette smoking, so figuring out the potential dose-response relationship between tobacco and outcomes was impossible. Moreover, the exact distinction between recreational and habitual smoking was not possible as the data registry included self-reporting of the smoking status based on the provided definitions, and did not interrogate occasional smoking.

6. Conclusion

The "smoker's paradox" is currently being interpreted from another perspective. The crucial role of cigarette smoking in increasing atherosclerosis burden should be reviewed in the context of the differences in age and traditional coronary artery disease risk factors. In acute MI patients who underwent primary PCI, the MACCE, MI, revascularization, and stroke were the same among younger smokers with fewer traditional risk factors compared to the older nonsmokers with multiple cardiac risk factors. The above findings underscore the role of smoking in atherosclerosis and the importance of measures to help smoking cessation.

7. Declarations

7.1. Acknowledgement

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7.2. Authors' contribution

BG and MS conceived and designed the study. TM, ES, and AH were involved in clinical study execution and data collection. FL and ES wrote the original and final draft of the manuscript. AJ and FL were involved with data analysis. All authors contributed to the manuscript.

7.3. Conflict of interest

There are no conflicts of interest.

7.4. Funding

None.

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