

## Absence of Smoker's Paradox in Middle Eastern Patients with Acute Coronary Syndrome

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### Abstract

Studies have shown that smokers admitted with acute coronary syndrome (ACS) have an apparent lower in-hospital and long term mortality rates compared with nonsmokers ("smoker's paradox"). This study was done to test if the "smoker's paradox" exists in Middle Eastern ACS patients. A 1618 consecutive patients admitted with acute coronary syndrome in 4 tertiary hospitals were enrolled. We compared clinical and coronary angiographic features and mortality during admission and after one year among smokers vs. non-smokers. Of the whole group (N=1618); smokers (N=859; 53%) were younger than non-smokers (Mean age 50+7 vs. 63+9 year; P=0.005), more likely to be male (96% vs. 69%; P<0.001), and less likely to have hypertension (33% vs. 67%; P<0.001) and diabetes mellitus (29% vs. 50%; P<0.001). Smokers were more likely to have ST-segment elevation myocardial infarction (STEMI) than non-smokers (35% vs. 24%; P<0.001) and less likely to have non ST-segment elevation ACS (65% vs. 76%; P=0.005). Compared with non-smokers; smokers had similar incidence of anterior wall MI (51.7% vs. 53.9%; P=NS), higher incidence of single vessel disease (54% vs. 47%; P=0.002) and lower incidence of multi vessel disease (44% vs. 51%; P=0.005). There were no statistically significant differences between the in-hospital (3.2% vs. 2.2%; P=0.29) and 1-year (6.5% vs. 7.0%; P=0.92) mortality rates in smoker and non-smokers; respectively. Despite being younger with less prevalence of comorbid diseases, multivessel coronary artery disease, and low TIMI risk scores; smokers in the Middle East with ACS did not have a better in-hospital or 1 year outcome compared with non-smokers.

**Keywords:** Non-smokers; Angiographic; Hypertension; Atherosclerotic; Coronary artery

### Introduction

Cigarette smoking is a well-established modifiable risk factor for atherosclerotic coronary artery disease (CAD) [1-3]. It is known for its role in impairing endogenous fibrinolysis, enhancing platelet aggregation and thrombus formation, and promoting the development of a thin fibrous cap in atherosclerotic coronary plaques, thus predisposing the plaque to erosion and subsequent thrombosis leading to acute coronary syndrome (ACS) [4-7]. However, various studies have shown that smokers have lower mortality rates following ACS than non-smokers, suggesting that smoking has a protective effect in ACS giving rise to the concept of the "smoker's paradox", in which smokers are more likely to suffer ACS but also more likely to survive [8-10]. Subsequently, various studies have demonstrated that smokers tended to be younger, with fewer comorbidities, and less extensive coronary disease. These differences were suggested to explain the difference in mortality [11-16]. According to data from Jordanian and regional studies, patients with ACS are an average 10 years younger than those in developed countries and have high prevalence of smoking [17-19]. However, the "smoker's paradox", has not been evaluated in patient with ACS in the Middle East before. We therefore undertook this study to examine the clinical characteristics, presentation, in-hospital treatment, angiographic features, prognosis, and the in-hospital and one-year mortality of patients with and without a history of smoking admitted with ACS.

### Method

A 1618 consecutive patients admitted with acute coronary syndrome in 4 tertiary hospitals were enrolled. We analyzed the clinical characteristics, coronary angiographic findings, risk stratification and mortality during admission and after one year among smokers and non-smokers. The whole group included 759 smokers and 859 non-

smokers. Inclusion criteria included: adults  $\geq 18$  years of age admitted with ACS and agreeing to sign an informed consent to be enrolled in the study. Exclusions criterion was refusal to sign the consent. Smoking was defined as current cigarette smoking at the time of enrollment. ACS was classified as (1) STEMI defined by the presence of typical chest pain suggestive of myocardial ischemia associated with ST-segment elevation of  $\geq 1$  mm in at least 2 contiguous leads on the 12-lead electrocardiogram (EKG), and elevated cardiac troponin T or CPK-MB ( $\geq 2$  upper limit of normal for both tests), (2) Non ST-segment elevation ACS (NSTACS) was diagnosed as either NSTEMI or unstable angina (UA). NSTEMI was defined by the presence of typical chest pain and ST-segment depression, inverted T wave or normal EKG and elevated cardiac troponin T or CPK-MB ( $\geq 2$  upper limit of normal for both tests), or unstable angina (UA) defined by the presence of typical chest pain and ST-segment depression, inverted T wave or normal EKG and normal cardiac enzymes on admission and 8-12 hours later. Diabetes mellitus (DM) was defined as known history of the disease made by a physician, or patient using antidiabetic treatment. Hypercholesterolemia was defined as fasting serum total cholesterol level  $\geq 240$  mg/dl or using hypolipemic agents. Obesity was defined as a body mass index  $\geq 30$  kg/m<sup>2</sup>. Left ventricular (LV) systolic function was assessed by contrast ventriculography or 2-D echocardiography and was considered normal

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when the LV ejection fraction was  $\geq 50\%$ . Patients were treated according to the discretion of the treating physician by conservative or invasive strategy. The TIMI risk score in each of the 502 patients with NSTEMACS was determined by the sum of the presence of 7 variables at admission; 1 point was given for each of the following variables: age  $\geq 65$  years;  $\geq 3$  coronary artery disease (CAD) risk factors; past history of CAD ( $\geq 50\%$  stenosis); ST segment deviation; use of aspirin in the prior 7 days;  $\geq 2$  episodes of angina in the past 24 hours; and elevated serum cardiac biomarkers. 12 Scores were classified as low (0-2 points), intermediate (3-4 points), or high ( $\geq 5$  points). The TIMI risk score in each of the 265 patients with STEMI was computed by the sum of points (total of 13-14) of the following variables: age  $\geq 75$  years (3 points) or 56-74 years (2 points); presence of diabetes mellitus, hypertension or angina (1 point); systolic blood pressure  $< 100$  mm Hg (3 points); heart rate  $\geq 100$  beats per minute (2 points); Killip class II-IV (2 points); weight  $< 67$  kg (1 point); anterior ST elevation or left bundle branch block (1 point); and time to reperfusion therapy  $\geq 4$  hours (1 point). 13 Scores were classified as low (0-3 points), low intermediate (4-6 points), high intermediate (7-9 points), or high ( $\geq 10$  points). Coronary revascularization (percutaneous or surgical) was undertaken depending on the severity and complexity of the coronary disease and comorbid diseases. Demographic, clinical, laboratory, echocardiographic and angiographic data were collected. Incidence of clinical events during hospitalization (cardiac death, ventricular tachycardia or fibrillation, heart failure, bleeding and stroke) and the 1-, 6- and 12-month mortality rates were compared between smokers and non-smokers. The main outcome analyzed was overall mortality during hospital stay and one year. One year follow-up was achieved in all of the patients, through clinic consultation or telephone contact. The study protocol was approved by the ethics committees of the participating hospitals.

### Statistical Analysis

The chi-square test was used to compare categorical variables, expressed as percentages and frequency. Continuous variables, expressed as means  $\pm$  standard deviation, were compared using the Student's t test for those with a normal distribution, or the Mann-Whitney test otherwise. Multivariate logistic regression analysis was used to identify variables independently associated with smoking, as well as independent predictors of in-hospital and 12-month mortality. A value of  $P < 0.05$  was considered statistically significant.

### Results

Baseline clinical and coronary angiographic characteristics of the patients are shown in Table 1. Smokers were younger and more frequently male, and less often had diabetes and hypertension ( $P < 0.001$ ). They also less often had a positive family history of IHD and aspirin use prior to ACS ( $P < 0.05$ ), with no statistically significant differences with regard to other cardiovascular risk factors. Patients with smoking history more frequently presented with ST elevation and were less frequently in NSTEMACS ( $P < 0.05$ ). The incidence of anterior wall MI and impaired left ventricular systolic function was similar in the two groups (51.7% vs. 53.9%,  $P = NS$ ). The clinical variables showing statistically significant differences between the two groups were included in a logistic regression multivariate analysis in order to identify independent associations between these variables and smoking. This showed that age (odds ratio [OR]=0.96; 95% confidence interval [CI]: 0.94-0.98;  $P < 0.001$ ), diabetes (OR=0.58; 95% CI: 0.38-0.89;  $P < 0.001$ ) and HT (OR=0.52; 95% CI: 0.37-0.75;  $P < 0.001$ ) were independently and negatively associated with smoking, while male gender (OR=15.50; 95% CI: 7.82-30.70;  $P < 0.001$ ) was independently and positively associated.

In Table 2 shows the TIMI risk scores in patients with NSTEMACS and STEMI at admission according to smoking status. High TIMI risk scores in patients with non ST elevation ACS were less prevalent in smokers compared with nonsmokers (60% vs. 75%,  $P = 0.003$ ). In STEMI patients, high TIMI scores occurred similarly in smokers and nonsmokers (11.1% vs. 9.8%,  $P = 0.201$ ).

Angiographic and echocardiographic data, are shown in Table 3. Coronary stenosis of  $\geq 50\%$  was considered significant disease. Of those undergoing coronary angiography, patients with a history of smoking had higher incidence of single vessel disease and less incidence of proximal left anterior descending (LAD), left main (LM), or multi-vessel CAD.

Treatment strategies are shown in Table 4. During hospital stay and on discharge, smokers and non-smokers were medicated with Standard

	Smokers	Non-smokers	Significance
N (%)	756 (46.8%)	859 (53.2%)	
Age (mean)	50	63	$p < 0.001$
Male	688 (91%)	567 (66%)	$p < 0.001$
Diabetes	144 (19%)	378 (44%)	$p < 0.001$
Hypertension	401 (53%)	576 (67%)	$p < 0.001$
Family history of CHD	83 (11%)	155 (18%)	$p = 0.009$
Dyslipidemia	431 (57%)	550 (64%)	ns
Obesity	265 (35%)	318 (37%)	ns
Past Cardiovascular history	91 (12%)	112 (13)	ns
Prior Aspirin	325 (43%)	462 (54%)	$p < 0.004$
Prior angina	76 (10%)	120 (14%)	ns
Presentation			
STEMI	265 (35%)	206 (24%)	$p = 0.01$
NSTEMI	174 (23%)	258 (30%)	$P = 0.03$
UA	318 (42%)	395 (46%)	$P = 0.01$

ns: non-significant; CHD: Coronary heart disease; STEMI: ST-Segment Elevation Myocardial Infarction; NSTEMI: Non-ST-Segment Elevation Myocardial Infarction.

**Table 1:** Baseline clinical characteristics stratified by smoking status at the time of admission.

ACS	Smoker	Non-smoker	p value
NSTEMACS	492 (%)	653 (%)	
Low score	195 (39.6%)	166 (25.4%)	0.003
Intermediate score	203 (41.2%)	295 (45.2%)	0.003
High score	94 (19.2%)	192 (29.4%)	0,003
STEMI	265 (%)	206 (%)	
Low score	171 (64.4%)	107 (51.9%)	0,03
Low intermediate score	85 (32.2%)	97 (46.9%)	0.004
High score	9 (3.4%)	2 (1.2%)	ns

**Table 2:** TIMI risk scores at admission among patients with acute coronary syndrome.

	Smokers	Non-smokers	Significance
N	756 (46.8%)	859 (53.2%)	-
Aspirin	748 (99%)	851 (99%)	ns
Clopidogrel	529 (70%)	653 (76%)	ns
Heparin	748 (99%)	851 (99%)	ns
B-blocker ns	272 (36%)	326 (38%)	ns
Statins	643 (85%)	713 (84%)	ns
PCI	348 (46%)	412 (48%)	ns
CABG	18 (2.4%)	28 (3.3%)	ns
Reintervention	1 (0.001%)	3 (0.003%)	ns

LAD: Left Anterior Descending; LVF: Left Ventricular Function; ns: Non-Significant.

**Table 3:** Angiographic characteristics of smokers and non-smokers.

cardiovascular medications (aspirin, beta blockers, renin-angiotensin system blockers, statins and heparin) with no statistically significant differences. Diagnostic coronary angiography and revascularization procedures using percutaneous intervention or surgical bypass were used in similar frequencies in both the groups.

On univariate analysis, patients with a history of smoking had numerically higher in-hospital mortality and lower one year mortality although this did not reach statistical significance (3.2% vs. 2.2%; P=0.4), (6.5% vs. 7.8%; P=0.4) respectively. However, after adjustment for variables with prognostic impact (age, left ventricular dysfunction, TIMI risk scores, diabetes and gender), smoking was not associated with better one year prognosis.

Except for heart failure; which was less frequent in smokers; other in-hospital complications (bleeding, stroke and ventricular tachyarrhythmia's) occurred in similar frequency in both groups. Mortality among smokers was not different from non-smokers during hospitalization, after 1, 6, and 12 months of follow up. In Table 5 shows the in-hospital complications and mortality.

## Discussion

To our knowledge; this is the first study that evaluated the potential presence of smoker's paradox in patients admitted with ACS in the Middle East. Despite being younger and having less prevalence of comorbid disease or LV systolic dysfunction, less prevalence of high TIMI risk scores, less prevalence of thromboses, proximal LAD or LM CAD; we have demonstrated that smoker's paradox does not exist in our patients. We did not demonstrate lower incidence of anterior wall MI or major in-hospital complications in smokers compared with non-smokers. Furthermore and most importantly, smokers did not have a better survival rate during index admission or up to 1 year of follow up.

Cigarette smoking adversely affects the cardiovascular system through several mechanisms: arterial endothelium injury, low-grade

inflammation, increase in plasma fibrinogen, enhanced platelet aggregation, catecholamine release and increase in heart rate and arterial blood pressure, vasoconstriction, and reduction in myocardial oxygen delivery [4-7,20-22]. "Smoker's paradox" describes the observations that smokers experience decreased mortality when they sustain NSTEMI or STEMI, or when they undergo percutaneous coronary intervention (PCI) compared with non-smokers. It is postulated that this may be due to the younger age and less comorbid disease in smokers rather than a benefit of smoking [23,24]. Other explanations include higher incidence of right coronary artery involvement and non-anterior wall MI, with potentially less incidence of life threatening ventricular arrhythmias and LV systolic dysfunction compared with LAD involvement and anterior wall MI. Moreover, smokers have a higher incidence of hypercoagulable state than non-smokers and this may lead to acute coronary thrombosis in the presence of less severe atherosclerosis thus predicting a better response to thrombolytic therapy [25]. Registries and clinical studies have found a significantly lower in-hospital mortality in acute MI and NSTEMI among smokers than non-smokers [26,27]. The term "smoker's paradox" was coined in the thrombolysis era when the use of fibrinolytic agents was the main strategy for STEMI reperfusion, and the high thrombogenicity state in smokers might have predicted a more favorable response to fibrinolysis [28]. However, this response was not confirmed by all thrombolysis trials, such as the GUSTO-1 trial which did not find any difference in the prevalence of thrombi or residual stenosis between smokers and non-smoker receiving thrombolysis [29]. In the contemporary era of primary PCI the studies are less supportive of the presence of this paradox when correction for differences in baseline variables was considered [30,31]. The absence of smoker's paradox that we observed in our study was similar to other more recent studies that showed a similar 1-year crude mortality among smokers and non-smokers with ACS. Furthermore, some studies demonstrated a significant mortality excess (in the adjusted analysis) among smokers vs. non-smokers supporting the unfavorable effect of current smoking at baseline [32]. Absence of the paradox was also confirmed in STEMI patients undergoing primary PCI suggesting that the possible existence of a smoker's paradox does not extend into the invasive era [33]. Our study is a contemporary one where the majority of STEMI patients undergo primary PCI with an almost non-existing role for thrombolysis in the participating hospitals, and 60-70% of NSTEMI patients undergo coronary angiography and coronary revascularization. Absence of smoker's paradox; despite younger age and better clinical profile of smokers; strengthens the notion that smoking per se adversely affects the atherosclerotic disease severity, despite the fact that a minority of smokers in quit smoking after sustaining ACS [34]. The increasing frequency of studies refuting "smoker's paradox" during the last decade supports the argument that the paradox was due to confounding factors that were not adjusted for. Thus, the use of the term "smoker's paradox" itself does not seem to be fully justified and it would be wise to encourage smoking cessation rather than relying on the "positive effects" of the so-called paradox [23,30,31,35]. The present study has few limitations. We did not evaluate the clinical, angiographic or mortality data according to the number of cigarettes smoked or number of years of smoking. This may have had some influence on characterization of the patient groups and assessment of prognosis. In addition, patients who died before arrival in the hospital were not included, which may also have affected some of the results obtained. It is estimated that the form of presentation of MI in around 20% of patients is sudden death, which is also associated with smoking. Thus, many smokers may have died before being admitted and only those with better prognosis surviving. The hospitals that participated in the study were private and university medical centers

	Smokers	Non-smokers	Significance
N	756 (46.8%)	859 (53.2%)	-
Aspirin	748(99%)	851(99%)	ns
Clopidogrel	529(70%)	653(76%)	ns
Heparin	748 (99%)	851 (99%)	ns
B-blocker ns	272(36%)	326(38%)	ns
Statins	643 (85%)	713 (84%)	ns
PCI	348(46%)	412(48%)	ns
CABG	18(2.4%)	28 (3.3%)	ns
Reintervention	1(0.001%)	3(0.003%)	ns

PCI: Percutaneous Intervention; CABG: Coronary Artery Bypass Graft; ns: Non-significant.

Table 4: Treatment strategies according to smoking status.

	Smoker 756 (%)	Non-smoker 859 (%)	p value
Complication			
Heart failure	27 (3.6%)	70(8.1%)	0.019
Bleeding	29(3.8%)	38(4.4%)	ns
Ventricular arrhythmia	1(0.1%)	4(0.5%)	ns
Mortality			
During admission	24(3.2%)	19(2.2%)	ns
One Month	36(4.7%)	30(3.5%)	ns
Six Month	49(6.5%)	49(6.5%)	ns
One-year	49(6.5%)	67(7.8%)	ns

ns: Non-Significant.

Table 5: In-hospital complications and Mortality rate during admission, at one-month, six-months, and one-year.

with high accessibility to catheterization and thus the study does not reflect the care of ACS at a national level. Future studies involving a larger number of patients are needed to confirm our findings.

## Conclusions

Despite the younger age and less prevalence of comorbid diseases, smokers in Jordan who were admitted with ACS did not have better outcome during the index admission and up to 1 year of follow up compare with non-smokers. Thus, in our population we didn't find a real "smoker's paradox", and the use of this term should be avoided. Smoking in the Middle East is a major cardiovascular risk factor, and should be a central target in primary and secondary prevention of atherosclerotic disease.

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