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Unfolding the reality of the smoking paradox in a South Asian cohort of patients presenting with ST-elevation acute coronary syndrome undergoing primary percutaneous coronary intervention

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Abstract

Objectives: Smoking is a potent risk factor for coronary artery disease, but there is controversy about its protective nature in terms of prognosis in ST-elevation acute coronary syndrome patients undergoing primary percutaneous coronary intervention. So, the main objective of this study is to unfold this controversy in a South Asian population in terms of clinical angiographic parameters and its in-hospital outcomes.

Methods: In this study, we included 1756 consecutive patients diagnosed with ST-elevation acute coronary syndrome undergoing primary percutaneous coronary intervention. Patients were classified into smokers and non-smokers, and the in-hospital mortality rate was compared. Multivariable logistic regression analysis was performed to evaluate the paradoxical role of smoking.

Results: Smokers were younger (53.78 ± 11.16 years vs 56.43 ± 11.17 years; $p < 0.001$) and more frequently men (98.7% vs 69.9%; $p < 0.001$) and had less diabetes (19.6% vs 44.8%; $p < 0.001$) and hypertension (38.5% vs 64.9%; $p < 0.001$). Smokers presented less frequently in Killip III (5.6% vs 8.1%; $p < 0.001$) and Killip IV (2.5% vs 4.8%; $p < 0.001$). Smokers mostly had single vessel disease (41.7% vs 34.4%; $p = 0.013$), whereas non-smokers had the multi-vessel disease and frequently presented with total occlusion of the culprit vessel (64.6% vs 58.8%; $p = 0.040$). Smokers have significantly lesser mortality (1.8% vs 4.3%; $p = 0.009$) compared to non-smokers with an odds ratio of 0.41 (95% confidence interval (CI): 0.21–0.82, $p = 0.011$); however, adjusted odds ratio on multivariable analysis was 0.67 (95% CI: 0.31–1.41, $p = 0.290$).

Conclusions: The paradoxical protective role of smoking is the confounding effect of mainly younger age, less coronary artery disease burden, lower prevalence of diabetes and hypertension, and lower Killip III/IV at presentation.

Keywords
STE-ACS, primary PCI, smoking paradox, South Asian

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Introduction

The smoking paradox in patients with acute coronary syndrome (ACS) is a phenomenon that has been difficult to understand and, even more so, explained by the scientific community for more than three decades. It implies that patients suffering from ACS have a better treatment outcome, mostly on a short-term basis, among smokers compared to non-smokers or ex-smokers. A number of studies from selective review[1–6] have reported contradictory results on the effect of smoking on the outcome of ACS, with some studies showing a protective effect.[5] While others simply report it to be a result of potential confounders and other covariates.[7]

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Pakistan ranks as one of the most prominent countries with a large number of active smokers. Recent studies have indicated that adults aged 15 and above, out of which 27% were males and 5.5% were females, are active daily smokers.[8] In spite of the vigorous cessation programs, mass media campaigns, and increased taxation, the prevalence of smoking in Pakistan is expected to increase by the year 2025.[8]

The studies indicating a protective effect of smoking and lower mortality in individuals with ST-elevation myocardial infarction (STEMI) have mainly cited age as a contributory factor to this paradox. These studies concluded smokers present with myocardial infarction at a younger age as compared to non-smokers[9,10]; however, the paradox is eliminated after adjustment for the age of participants.[7] Interestingly, several studies, including more than 20,000 participants, dispelled the nonexistence of the paradox by showing that it persists even after adjustment of age.[11,12]

The protective effect of smoking has also been attributed to other factors, starting with the nature of myocardial infarction, which is thrombotic in nature in the case of smokers, while it is atherosclerotic in non-smokers. The pathogenesis has a temporal relationship with the treatment; therefore, a better response has been observed in the smokers group to thrombolytic therapy as compared to non-smokers, further supporting the paradox.[13] On the other hand, the spectrum of the current most commonly used modality of treatment, that is, primary percutaneous coronary intervention (PPCI), is taken into account, and the paradox is found to be inconsistent.[14] It has been theorized that clopidogrel may have a useful effect on patients with STEMI,[15] but contrasting evidence showing no healthy impact of preconditioning of the heart has also been reported.[14] Recent studies have taken into account the relationship between smoking status and other variables in patients treated with aspirin and clopidogrel followed by PPCI. The results showed that both smokers and non-smokers had similar left ventricle ejection fraction and micro-vessel obstruction in both adjusted and non-adjusted analyses. Age was found to be the major confounder, and smokers were eventually associated with a higher rate of re-infarction and hospitalization after adjusted analysis.[14,16]

The phenomenon of the smoking paradox is complex and has serious implications. Pakistan is one of the many countries in the world where not only smoking is prominent but also significant steps are being taken for its cessation. In light of these factors. This study, which is the first prospective study of the country, aims to further unfold the reality of the smoking paradox using purely research-oriented data with a large dataset.

Methods

Study population and design

This is a descriptive cross-sectional study conducted at the largest cardiac care center in Pakistan, namely the "National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan" between January 2022 and June 2022. The study proposal was approved by the ethical review board of the hospital (ERC-01/2022), and verbal consent was obtained from all the patients or attendants as per the Declaration of Helsinki. In this study, we analyzed prospectively collected data from the cohort of patients diagnosed with STEMI undergoing PPCI. This contemporary cohort of STEMI patients consisted of adult patients ($\geq$18 years) of either gender shifted to the cardiac catheterization laboratory for PPCI as per the hospital protocol. There were no specific exclusion criteria except for the patients who did not consent to participate in the study, or primary PCI procedures were not included in this study.

The minimum sample size of 1118 was calculated for this descriptive cross-sectional study with an expected in-hospital mortality rate of 3%, a 1% margin of error, and a 95% confidence level. Considering the monthly flow of patients, we have included consecutive patients during the 6 months of the study period.

Assessments and definitions

STEMI was diagnosed based on history and a 12-lead electrocardiogram (ECG). Patients with a history of "typical chest pain for at least 20 min" and 12-lead ECG finding of "ST-elevation in at least two contiguous leads $>$2 mm in men or $>$1 mm in women in leads V2 to V3 and/or $>$1 mm in other contiguous chest leads or limb leads." Random blood sugar (RBS) was obtained as a pre-procedure assessment for all the patients. Smokers were considered as individuals who self-reported a history of smoking at least one packet a day for at least the last 1 year. The Killip class at presentation was categorized for all the patients as per the criteria defined by Killip III and Kimbal.[17]

Management and data collection

As per the hospital policy, all the PPCI procedures were performed in accordance with standard clinical practice guidelines. All the patients were premeditated with dual antiplatelet therapy (DAPT), which included aspirin and clopidogrel, unfractionated heparin. The demographic, clinical, and angiographic characteristics were obtained using a pre-defined self-designed proforma (provided as a Supplemental Material). The proforma was pre-tested on 30 patients and finalized for the data collection and all the performa were filled by the attending physician. All the patients were observed during their hospital course, and post-procedure complications and outcomes, including mortality, were recorded.

Statistical analysis

Patients were stratified into two groups based on their smoking status as smokers and non-smokers. The clinical characteristics and in-hospital outcomes were compared by

conducting chi-square/Fisher's exact test or independent sample *t*-test/Mann–Whitney *U* Test. Furthermore, multivariable and univariate binary logistic regression was performed to identify the predictors of in-hospital outcomes and to quantify the smoking paradox. All the factors with p-value < 0.20 in the univariate analysis were considered for the multivariable regression analysis, and significance criteria were taken at 5%. To compensate for confounders among the studied group, propensity score matching was performed by taking age (years), total ischemic time in minutes, Killip class at presentation, heart rate (bpm), RBS level (mg/dl), body mass index (kg/m^2), hypertension, diabetes mellitus, left ventricular ejection fraction (%), left ventricular end-diastolic pressure (LVEDP mmHg), and pre-procedure thrombolysis in myocardial infarction (TIMI) flow grade as propensity score matching parameters. Data analysis was performed with the help of IBM SPSS (Statistics for Windows, Version 21.0. Armonk, NY IBM Corp).

Results

Baseline characteristics

The number of male participants (98.7%) was significantly higher than females (1.3%) in the smokers group, and the opposite was present in the non-smokers group. The smokers were predominantly younger (53.78 ± 11.78) as compared to non-smokers (56.43 ± 11.17) (Table 1).

RBS and other comorbid conditions

Smokers had significantly lower levels of RBS than non-smokers. ($p < 0.001$) when brought to the emergency department. They had RBS in the range of 150 (126–179) mg/dl, while non-smokers had RBS in the range of 160 (130–226) mg/dl (Table 1).

There was a significantly high occurrence in non-smokers as compared to smokers of co-morbidities strongly associated with the onset of STEMI, including diabetes (44.8% vs 19.6%) and hypertension (64.9% vs 38.5%; $p < 0.001$).

Killip's criteria

Higher Killips class, which indicates poor prognosis and left ventricular systolic dysfunction (LVSD) in individuals with STEMI, was found in non-smokers as compared to smokers. Both Killips class III (8.1% vs 5.6%) and class IV (4.8% vs 2.5%) were more common in the non-smokers than smokers group (Table 1).

Cardiovascular factors

Smokers had significantly reduced left ventricular compliance than non-smokers, as indicated by the low LVEDP (20.06 ± 6.77 vs 18.82 ± 6.09) (p-value: 0.001). The majority of smokers had single-vessel disease as compared to non-smokers (41.7% vs 34.4%; p-value: 0.013). Complete occlusion of vessels was more common in non-smokers than in smokers (64.6% vs 58.8%; p-value: 0.040) (Table 1).

Complications and outcomes

Pre-procedure TIMI flow grade 0 was found to be significantly higher in smokers than non-smokers (64.6% vs 58.8%, p-value: 0.040). Post-STEMI complications were more significantly associated with non-smokers as compared to smokers, such as slow flow/no-flow (33.2% vs 24.3%; p-value: 0.001) and cardiogenic shock (4.6% vs 2.3%; p-value < 0.001). Mortality rate during hospital stay was also lower in smokers than non-smokers (4.3% vs 1.8%; p-value: 0.009) (Table 1).

Multivariable analyses and adjustments of potential confounders

Smokers had a significantly lesser mortality rate (1.8% vs 4.3%; $p = 0.009$) compared to non-smokers with an odds ratio (OR) of 0.41 (95% CI: 0.21–0.82, $p = 0.011$); however, adjusted OR on multivariable analysis was 0.67 (95% CI: 0.31–1.41, $p = 0.290$). In addition to this, independent predictors of mortality were found to be a history ofcerebral vascular accident (CVA)/stroke, pre-procedure LVEDP, multi-vessel diseases, and RBS in emergency room (ER) adjusted OR of 3.83 (95% CI: 1.24–11.79; $p = 0.019$), 1.07 (95% CI: 1.03–1.12; $p = 0.002$), 2.2 (95% CI: 1.07–4.54; $p = 0.033$), and 1 (95% CI: 1.0–1.01; $p = 0.032$), respectively (Table 2).

Compensating confounders among the studied group using propensity score matching

After propensity matching for the baseline characteristics, the difference in the rate of in-hospital mortality was not statistically significant between the smokers and non-smokers group, with a mortality rate of 1.8% versus 2.5%; $p = 0.409$, respectively. However, the incidence of slow flow/no-flow remained low for smokers compared to non-smokers, with a rate of 24.3% versus 30.9%; $p = 0.013$, respectively (Table 3).

Discussion

We aimed at further understanding the smoking paradox through so far the largest prospectively collected research-oriented data in the Pakistani population so that maximum potential variables can be adjusted and we can find the actual direction of association between smoking and outcome among patients presenting with ST-elevation acute coronary syndrome (STE-ACS) undergoing PPCI. We found an insignificant association between smoking and the outcome, on multivariable analysis, among patients presenting with STE-ACS undergoing PPCI. The smoker's paradox is created

Table 1. Baseline characteristics of patients ($n = 1756$) describing the distribution of patients as per different variables.

Characteristics	Total	Smoking		*p*-Value
		No	Yes	
Total (*N*)	1756	68.3% (1200)	31.7% (556)	—
Gender				
Male	79% (1388)	69.9% (839)	98.7% (549)	<0.001
Female	21% (368)	30.1% (361)	1.3% (7)	
Age (years)	55.59 ± 11.23	56.43 ± 11.17	53.78 ± 11.16	<0.001
18–40	10.4% (182)	8.3% (99)	14.9% (83)	<0.001
41–65	74% (1300)	74.7% (896)	72.7% (404)	
>65	15.6% (274)	17.1% (205)	12.4% (69)	
Total ischemic time (min)	355 (240–490)	355 (240–500)	346.5 (230–480)	0.111
Systolic blood pressure (mmHg)	131.63 ± 25.91	131.27 ± 26.44	132.4 ± 24.74	0.395
Heart rate (bpm)	85.45 ± 20.33	86.13 ± 20.95	83.98 ± 18.87	0.033
Random blood sugar (mg/dl)	160 (130–213)	160 (130–226)	150 (126–179)	<0.001
Killip class				
I	75.5% (1326)	73.3% (879)	80.4% (447)	0.006
II	13.1% (230)	13.8% (166)	11.5% (64)	
III	7.3% (128)	8.1% (97)	5.6% (31)	
IV	4.1% (72)	4.8% (58)	2.5% (14)	
Comorbid conditions				
Hypertension	56.5% (993)	64.9% (779)	38.5% (214)	<0.001
Diabetes	36.8% (647)	44.8% (538)	19.6% (109)	<0.001
Ischemic heart diseases	7.6% (134)	8.2% (98)	6.5% (36)	0.214
Cerebrovascular accident/stroke	2% (35)	2% (24)	2% (11)	0.976
Congestive heart failure	0% (0)	0% (0)	0% (0)	—
Body mass index (BMI)	26.46 ± 3.22	26.6 ± 3.3	26.17 ± 3.03	0.009
Obesity	11.2% (196)	12% (144)	9.4% (52)	0.101
Pre-procedure LVEDP (mmHg)	19.66 ± 6.58	20.06 ± 6.77	18.82 ± 6.09	<0.001
Pre-procedure ejection fraction (%)	39.55 ± 9.27	39.54 ± 9.33	39.55 ± 9.17	0.981
Number of involved vessels				
Single vessel disease	36.7% (645)	34.4% (413)	41.7% (232)	0.013
Two vessel disease	34.2% (600)	35.5% (426)	31.3% (174)	
Three vessel disease	29.1% (511)	30.1% (361)	27% (150)	
Culprit vessel				
Left main	1.3% (23)	1.5% (18)	0.9% (5)	0.055
Proximal LAD	36% (633)	35.1% (421)	38.1% (212)	
Non-proximal LAD	19% (334)	18.8% (226)	19.4% (108)	
Right coronary artery	31.3% (550)	33.3% (400)	27% (150)	
Left circumflex	11.3% (198)	10.4% (125)	13.1% (73)	
Diagonal	1% (18)	0.8% (10)	1.4% (8)	
Ramus	0% (0)	0% (0)	0% (0)	
Pre-procedure TIMI (thrombolysis in myocardial infarction) flow				
0	62.8% (1102)	64.6% (775)	58.8% (327)	0.040
I	9.6% (168)	8.7% (104)	11.5% (64)	
II	15.6% (274)	15.7% (188)	15.5% (86)	
III	12.1% (212)	11.1% (133)	14.2% (79)	
Complications and outcomes				
Slow flow/no-flow	30.4% (533)	33.2% (398)	24.3% (135)	<0.001
Heart failure	3.9% (68)	4.6% (55)	2.3% (13)	<0.001
Contrast-induced nephropathy	9.6% (169)	10.4% (125)	7.9% (44)	0.098
Major bleeding	0.9% (16)	1.2% (14)	0.4% (2)	0.098
Cerebrovascular accident/stroke	0.2% (4)	0.1% (1)	0.5% (3)	0.062
Access site complications	0.7% (13)	0.8% (9)	0.7% (4)	0.945
In-hospital mortality	3.5% (61)	4.3% (51)	1.8% (10)	0.009

LVEDP: left ventricular end-diastolic pressure; LAD: left anterior descending artery.

Table 2. Univariate and multivariable results show before and after adjustment of important covariates to detect the potential effect of smoking on ACS treatment outcome.

Characteristics	Univariate		Multivariable	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Female	1.89 (1.09–3.26)	0.023	1.26 (0.69–2.32)	0.454
Age (year)	1.03 (1–1.05)	0.022	1.01 (0.99–1.04)	0.400
Total ischemic time (hours)	1.05 (1.02–1.09)	0.003	1.03 (0.99–1.07)	0.202
Killip class III/IV	4.45 (2.56–7.71)	<0.001	1.23 (0.59–2.54)	0.582
Hypertension	1.6 (0.93–2.75)	0.090	0.91 (0.5–1.65)	0.763
Diabetes	3.41 (1.99–5.84)	<0.001	1.46 (0.73–2.9)	0.280
Smoking	0.41 (0.21–0.82)	0.011	0.67 (0.31–1.41)	0.290
History of cerebrovascular accident/stroke	3.77 (1.29–11.03)	0.016	3.83 (1.24–11.79)	0.019
Obesity	1.03 (0.46–2.3)	0.937	—	—
Pre-procedure LVEDP (mmHg)	1.11 (1.07–1.14)	<0.001	1.07 (1.03–1.12)	0.002
Pre-procedure ejection fraction (%)	0.94 (0.92–0.97)	<0.001	0.98 (0.95–1.02)	0.302
Multi-vessel diseases	3.06 (1.54–6.06)	0.001	2.2 (1.07–4.54)	0.033
Random blood sugar (mg/dl)	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.01)	0.032

LVEDP: left ventricular end-diastolic pressure; OR: odds ratio; CI: confidence interval.

because different observational studies and trials have reported contradictory findings in terms of the role of smoking on ACS treatment outcomes, including survival, duration of hospital stay, and other related outcomes. A number of studies have confirmed the long-known finding that smoking can be considered an independent risk factor for cardiovascular disease, and it is associated with higher mortality and heart failure post-follow-up.[18–20] Several other studies,[1] five have provided completely different results highlighting that smoking has a protective effect in patients with STE-ACS undergoing PPCI; these studies, however, have been conducted on retrospective data with each using no standard set of covariates that need to be adjusted before an inference regarding the protective role of smoking can be made. The large number of prospective participants and consideration of all possible relevant confounders in our study can serve as a key to overcoming these limitations.

It has been observed that several studies with extensive data and analysis conducted to decipher the exact role of smoking in myocardial infarction, albeit indicating the same results, have used varied definitions as to who can be identified as smokers and non-smokers. A retrospective study done in Malaysia concluded that the smoker's paradox is, in fact, a reality that considered smokers as individuals who actively used tobacco-based products, including not only cigarettes but also pipes and cigars, while non-smokers were people who never smoked their entire lives.[5] Another study that also favored the impact of paradox in patients suffering from STEMI used a completely different methodology that used specific codes such as ICD-9-CM code 305.1 or V15.82 to identify both active and former smokers to be categorized in the smokers' category.[21]

There has not only been a contrast in the definition of smokers and non-smokers but also in the outcome variables. Some of the studies have only observed the immediate clinical outcome, that is, up to 30 days of hospital stay,[5] while others have reported that smoking has a long-term protective outcome.[22] This extreme variation in methods used by different studies warrants the need to develop a standard to classify study participants as smokers and non-smokers and to set a definite period of time to assess the outcome.

The concept of the smoking paradox can be considered manifold, which needs to be critically viewed from different aspects. Beginning with the pathogenesis of myocardial infarction, a major distinction lies in the pathogenesis of myocardial infarction between smokers and non-smokers. Both smokers and non-smokers on the outlook may present with decreased coronary blood flow, but the underlying pathology behind this clinical finding is different. Smoking is associated with an increase in hematocrit and clotting factors,[23] leading to the formation of intracoronary thrombi with minimal atherosclerotic thickening. Non-smokers, on the other hand, have significant atherosclerotic thickening.

This difference in the mechanism of myocardial infarction is also reflected in terms of its treatment, where smokers are more responsive to anti-thrombotic therapy, resulting in a paradoxical favorable prognosis as compared to non-smokers presenting with atherosclerotic narrowing of the blood vessels.[13,24] A study by Ramotowski et al.[25] reported a greater risk of high platelet reactivity among clopidogrel-treated patients after PCI, *P2Y12* inhibitors can be an alternative option for patients who stop smoking after PCI.

Another possible factor considered responsible for the paradox is the pretreatment of smokers with clopidogrel.[26] This factor is aligned with cigarette smoke-induced levels of cytochrome P4501A2. The increased level of the enzyme is an ambiguous finding since it can be the result of only a laboratory artifact.[27] Preconditioning of the myocardium has no

Table 3. Comparison of smokers with propensity-matched non-smoker group for baseline characteristics and in-hospital outcomes.

Characteristics	Non-smoker	Smoker	*p*-Value
Total (*N*)	556	556	
Gender			
Male	75.4% (419)	98.7% (549)	<0.001
Female	24.6% (137)	1.3% (7)	
*Age (years)	54.37 ± 12.01	53.78 ± 11.16	0.391
18–40	13.5% (75)	14.9% (83)	0.459
41–65	71.8% (399)	72.7% (404)	
>65	14.7% (82)	12.4% (69)	
*Total ischemic time (minutes)	330 (234–456)	346.5 (230–480)	0.468
Systolic blood pressure (mmHg)	130.64 ± 24.59	132.4 ± 24.74	0.234
*Heart rate (bpm)	85 ± 20.22	83.98 ± 18.87	0.384
*Random blood sugar (mg/dl)	146 (126.5–178.5)	150 (126–179)	0.997
*Killip class			
I	78.1% (434)	80.4% (447)	0.616
II	12.4% (69)	11.5% (64)	
III	5.8% (32)	5.6% (31)	
IV	3.8% (21)	2.5% (14)	
Comorbid conditions			
*Hypertension	40.5% (225)	38.5% (214)	0.500
*Diabetes	22.8% (127)	19.6% (109)	0.187
Ischemic heart diseases	6.7% (37)	6.5% (36)	0.904
Cerebrovascular accident/Stroke	1.6% (9)	2% (11)	0.652
*Body mass index (BMI)	26.22 ± 3.01	26.17 ± 3.03	0.761
Obesity	9.2% (51)	9.4% (52)	0.918
*Pre-procedure LVEDP (mmHg)	19.2 ± 6.17	18.82 ± 6.09	0.304
*Pre-procedure ejection fraction (%)	38.85 ± 9.14	39.55 ± 9.17	0.200
Number of involved vessels			
Single-vessel disease	43% (239)	41.7% (232)	0.329
Two-vessel disease	33.8% (188)	31.3% (174)	
Three-vessel disease	23.2% (129)	27% (150)	
Culprit vessel			
Left main	2.2% (12)	0.9% (5)	0.121
Proximal LAD	37.9% (211)	38.1% (212)	
Non-proximal LAD	20.3% (113)	19.4% (108)	
Right coronary artery	29.7% (165)	27% (150)	
Left circumflex	8.8% (49)	13.1% (73)	
Diagonal	1.1% (6)	1.4% (8)	
Ramus	0% (0)	0% (0)	
*Pre-procedure TIMI (thrombolysis in myocardial infarction) flow			
0	61.9% (344)	58.8% (327)	0.320
I	10.3% (57)	11.5% (64)	
II	16.9% (94)	15.5% (86)	
III	11% (61)	14.2% (79)	
Complications and outcomes			
Slow flow/no-flow	30.9% (172)	24.3% (135)	0.013
Heart failure	3.4% (19)	2.3% (13)	0.282
Contrast-induced nephropathy	9.4% (52)	7.9% (44)	0.393
Major bleeding	1.1% (6)	0.4% (2)	0.156
Cerebrovascular accident/stroke	0.2% (1)	0.5% (3)	0.316
Access site complications	0.5% (3)	0.7% (4)	0.705
In-hospital mortality	2.5% (14)	1.8% (10)	0.409

LVEDP: left ventricular end-diastolic pressure; LAD: left anterior descending artery.
*Propensity score matching parameter.

significant impact on infarct size between smokers and non-smokers, therefore further diminishing the alleged beneficial effect of antiplatelet drugs.[14]

Both of these factors abolishing any protective effect of smoking, that is, the use of PPCI and the insignificant role of antiplatelet therapy, have themselves been rendered insignificant by the results of studies where smokers tend to have a lower mortality and hospitalization rate even if after adjustment of age, treatment methods, and presence of comorbidities.[1,5]

As we progress from the pathology toward the clinical factors that form an important layer of the protective impact of smoking, the young age of smokers at the time of STEMI is the primary factor contributing to the smoker's paradox, this is supported by the findings of our studies according to which smokers were significantly younger than smokers. However, in other studies, the paradox remains even after adjustment for age.[18]

There are several other possible contributory conditions, such as hypertension, dyslipidemia, and diabetes mellitus, which are found to be contrary to expectations in a higher proportion of non-smokers than smokers, further supporting the paradox.[4,27] Our study has also reported similar results.

One of the features of STEMI is decreased pumping activity of the heart, resulting in decreased LVSD. Killip criteria were used to assess the loss of LVSD and to predict prognosis. It has been studied that poor LVSD, that is, Killip criteria III and IV, occurs in smokers compared to non-smokers.[5] Our results also indicate a higher frequency of non-smokers presenting with Killip class III and IV.

The studies that report the protective role of smoking after ACS have several limitations ranging from small sample size, retrospectively collected data not intended for research, and a number of methodological drawbacks. Saad et al.,[3] in a study conducted on 772 German population, reported a significantly lower 12-month mortality rate among smokers after Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) (43% vs 59%; $p < 0.001$).

Another recently published study from Pakistan by Ashraf et al.[28] on 3255 patients' hospital's retrospective records, claiming it to be the largest study from Pakistan, reported insignificant no association between smoking and poor outcomes in-hospital mortality in both univariate and multivariate analyses, therefore failing to establish the harmful effects on the outcomes of smoking on outcomes of PPCI.

There has been extensive research regarding the ultimate impact of the paradox on post-infarction complications and mortality. Numerous studies have now disregarded the protective effect of smoking after adjusting for confounders. Haig et al.[18] established that smoking is strongly associated with inflammation and can be considered an independent causative factor of mortality or heart failure event. Similarly, smokers had a higher all-cause mortality and risk of re-hospitalization once the covariates were adjusted in a study conducted by Oh et al.[29] Smoking was to be associated with higher mortality and risk of re-infarction.[16]

Similarly, our study, on the other hand, prospectively enrolled STEMI patients, especially aiming at including all the covariates to control for that results in this paradoxical effect. In univariate analyses, we did find a protective association between smoking and outcomes of PPCI. However, controlling for all the possible confounders, including age and comorbidities at multivariate analyses (Table 2), the association between smoking and decreased mortality was found to be insignificant. We also think that with this robust methodology and larger sample size, we could possibly have proven the negative impact of smoking on treatment outcomes. The difference in the results between our study and the study reported by Ashraf et al.[28] is the effect of sampling bias (inferring from non-research-oriented data) and also their inability to find any significant association even at the univariate analysis level. This is in accordance with the findings of a very recent meta-analysis published by White[6] who tried to debunk the paradox and ultimately concluded that the improper use of data and potential flaws in the methodologies have resulted in authors reporting the protective role of smoking after ACS treatment outcomes.

In summary, in this study, we have observed that the paradoxical protective role of smoking on in-hospital mortality after PPCI was mainly a confounding effect of differences in clinical and demographic characteristics. After appropriate adjustment through multivariable analysis and propensity score matching, the protective effect remains no longer significant. It is important to note that, in our population, as a cultural phenomenon, smoking is not a common practice among females, a similar observation has been reported by Ashraf et al.[28] in their study of our local population.

Certain limitations need to be highlighted: the study was a single-center study in one country, and selection bias may affect the generalizability of the results. The observational nature of the study with risk of confounder bias, the type of tobacco used was not assessed among the study subjects, and other factors related to the coronary lesion characteristics and the PPCI procedure may have affected the results. Finally, in the context of the smoking paradox, the dose-dependent effect of passive smoking, ex-smokers, and the quantum of smoking in terms of duration and number of cigarettes/packs can be relevant; in addition, assessment of in-hospital mortality without follow-up and lack of data on pre-hospital mortality. The lack of these details can be the major limitation of our current study. Further studies are warranted to delineate the role of these factors in the context of the smoking paradox.

Conclusion

This research paves the theoretical way for further investigations into the phenomenon of the smoker's paradox in STEMI.

Smoker's paradox can be likened to the iceberg phenomenon, where the tip of the berg apparently shows a protective association between smoking and the outcome of myocardial infarction. However, deeper investigation into the factors supporting this paradoxical relationship, when adjusted for, is found to be inconsistent. Therefore, emergent and rigorous attempts should be continued to promote smoking cessation in our country.

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Author's contribution

RK, JAS, TS, SK, and NQ contributed to the concept and design of study; RK, AHS, RA, MNS, KR, and KC contributed to the analysis and interpretation of data; RK, KC, MQK, MS, AU, and ABN collected data and drafted the manuscript; and TS, and MQK critically analyzed for content. All author approved the final draft to the manuscript.

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Ethics approval

Ethical approval for this study was obtained from the ethical review committee of the National Institute of Cardiovascular Diseases (NICVD) (ERC-01/2022).

Informed consent

Verbal informed consent was obtained from all subjects before the study. Due to the observational nature of the study, written consent was waived by the Institutional Ethics Committee (ERC-01/2022).

Trial registration

Not applicable.

Animal welfare

The present study followed international, national, and/or institutional guidelines for humane animal treatment and complied with relevant legislation.

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Supplemental material

Supplemental material for this article is available online.

References

1. Papazisis A, Koreli A and Misouridou E. Heavy smoking is associated with low depression and stress: a smokers' paradox in cardiovascular disease? *Mater Sociomed* 2019; 31(4): 268–272.
2. Ramotowski B, Gurbel PA, Tantry U, et al. Smoking and cardiovascular diseases: paradox greater than expected? *Pol Arch Intern Med* 2019; 129(10): 700–706.
3. Saad M, Fuernau G, Desch S, et al. "Smoker's paradox" in patients with cardiogenic shock complicating myocardial infarction—a substudy of the IABP-SHOCK II-trial and registry. *Int J Cardiol* 2016; 222: 775–779.
4. Stokes A and Preston SH. Smoking and reverse causation create an obesity paradox in cardiovascular disease. *Obesity (Silver Spring)* 2015; 23(12): 2485–2490.
5. Venkatason P, Salleh NM, Zubairi Y, et al. The bizzare phenomenon of smokers' paradox in the immediate outcome post acute myocardial infarction: an insight into the Malaysian National Cardiovascular Database-Acute Coronary Syndrome (NCVD-ACS) registry year 2006–2013. *Springerplus* 2016; 5: 534.
6. White HD. Deconstructing the paradox of smoking and improved short-term cardiovascular outcomes after myocardial infarction. *J Am Coll Cardiol* 2020; 75(15): 1755–1757.
7. Sia C-H, Ko J, Zheng H, et al. Association between smoking status and outcomes in myocardial infarction patients undergoing percutaneous coronary intervention. *Sci Rep* 2021; 11(1): 6466.
8. Zubair F, Zhao T, Ahmad H, et al. A gender-specific assessment of tobacco use risk factors: evidence from the latest Pakistan demographic and health survey. *BMC Public Health* 2022; 22(1): 1133.
9. Jørgensen S, Køber L, Ottesen MM, et al. The prognostic importance of smoking status at the time of acute myocardial infarction in 6676 patients. *J Cardiovasc Risk* 1999; 6(1): 23–7.
10. Lisa KT, Gilpin E, Ahnve S, et al. Smoking status at the time of acute myocardial infarction and subsequent prognosis. *Am Heart J* 1985; 110(3): 535–541.
11. Steele L, Lloyd A, Fotheringham J, et al. A retrospective cross-sectional study on the association between tobacco smoking and incidence of ST-segment elevation myocardial infarction and cardiovascular risk factors. *Postgrad Med J* 2015; 91(1079): 492–496.
12. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364(9438): 937–952.
13. Grines CL, Topol EJ, O'Neill WW, et al. Effect of cigarette smoking on outcome after thrombolytic therapy for myocardial infarction. *Circulation* 1995; 91(2): 298–303.
14. Steele L, Palmer J, Lloyd A, et al. The impact of smoking on mortality after acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: a retrospective cohort outcome study at 3 years. *J Thromb Thrombolysis* 2019; 47(4): 520–526.
15. Desai NR, Mega JL, Jiang S, et al. Interaction between cigarette smoking and clinical benefit of clopidogrel. *J Am Coll Cardiol* 2009; 53(15): 1273–1278.
16. Redfors B, Furer A, Selker HP, et al. Effect of smoking on outcomes of primary PCI in patients with STEMI. *J Am Coll Cardiol* 2020; 75(15): 1743–1754.
17. Killip T 3rd and Kimball JT. Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. *Am J Cardiol* 1967; 20(4): 457–464.

18. Haig C, Carrick D, Carberry J, et al. Current smoking and prognosis after acute ST-segment elevation myocardial infarction: new pathophysiological insights. *JACC Cardiovasc Imaging* 2019; 12(6): 993–1003.
19. Symons R, Masci PG, Francone M, et al. Impact of active smoking on myocardial infarction severity in reperfused ST-segment elevation myocardial infarction patients: the smoker's paradox revisited. *Eur Heart J* 2016; 37(36): 2756–2764.
20. Larsen GK, Seth M and Gurm HS. The ongoing importance of smoking as a powerful risk factor for ST-segment elevation myocardial infarction in young patients. *JAMA Intern Med* 2013; 173(13): 1261–122.
21. Gupta T, Kolte D, Khera S, et al. Smoker's paradox in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *J Am Heart Assoc* 2016; 5(4): e003370.
22. Takagi H and Umemoto T. Is alice still in wonderland of the "smoker's paradox"? A meta-analysis of mortality following ACS. *Br J Cardiol* 2014; 21: 117.
23. Alarabi AB, Lozano PA, Khasawneh FT, et al. The effect of emerging tobacco related products and their toxic constituents on thrombosis. *Life Sci* 2021; 290: 120255.
24. Zahger D, Cercek B, Cannon CP, et al. How do smokers differ from non-smokers in their response to thrombolysis? (the TIMI-4 trial). *Am J Cardiol* 1995; 75(4): 232–236.
25. Ramotowski B, Gurbel PA, Tantry U, et al. Effect of smoking cessation on the pharmacokinetics and pharmacodynamics of clopidogrel after PCI: the smoking cessation paradox study. *Thromb Haemost* 2020; 120(3): 449–456.
26. Park KW, Park JJ, Jeon K-H, et al. Enhanced clopidogrel responsiveness in smokers: smokers' paradox is dependent on cytochrome P450 CYP1A2 status. *Arterioscler Thromb Vasc Biol* 2011; 31(3): 665–671.
27. Kim YG, Suh J-W, Kang S-H, et al. Cigarette smoking does not enhance clopidogrel responsiveness after adjusting VerifyNow P2Y12 reaction unit for the influence of hemoglobin level. *JACC Cardiovasc Interv* 2016; 9(16): 1680–1690.
28. Ashraf T, Afaque SM, Aziz R, et al. Clinical, angiographic characteristics and in-hospital outcomes of smoker and non-smoker patients after primary percutaneous coronary intervention. *Glob Heart* 2019; 14(3): 335–3341.
29. Oh S, Kim JH, Cho KH, et al. Association between baseline smoking status and clinical outcomes following myocardial infarction. *Front Cardiovasc Med* 2022; 9: 918033.