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Keywords:	smoking, in-hospital mortality, acute myocardial infarction

Smoking was associated with lower in-hospital mortality among patients with acute myocardial infarction—Insights from China Acute Myocardial Infarction (CAMI) registry

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Abstract

Introduction: Smoking is a well-established risk factor for cardiovascular disease. However, the impact of smoking on in-hospital mortality among patients with acute myocardial infarction (AMI) managed by contemparary treatment is still unclear.

Methods: A cohort study was conducted using data between 2013 and 2016 from China AMI (CAMI) Registry were extracted. Eligible patients were diagnosed with AMI in accordance with third Universal Definition of MI. Propensity score (PS) matching and multivariable logistic regression were used to control for confounders. Subgroup analysis was performed to examine whether the association between smoking and in-hospital mortality varies according to baseline characteristics.

Results: A total of 37614 patients were included. Smokers were younger, more often males with fewer comorbidities than non-smokers. After PS matching and multivariable log regression analysis was performed, difference in in-hospital mortality between current smokers vs. non-smokers reduced but was still statistical significant (5.1% vs.6.1%, p=0.0045; adjusted odds ratio 0.78, 95% CI 0.69–0.88, P<0.001). Among all subgroups, there was a trend toward lower in-hospital mortality in current smoker or ex-smoker group compared with non-smoker.

Conclusions: Smoking was associated with lower in-hospital mortality among AMI patients even after multiple analyses to control for potential confounders. “Smoker’s paradox” cannot be fully explained by confounding alone.

Keywords:

smoking; in-hospital mortality; acute myocardial infarction

Strength:

The study utilized data from a large-scale multicenter registry in contemporary era of PCI.

We used both propensity score matching and multivariable cox regression model to adjust confounders, which ensure the robustness of our conclusion.

Limitations:

It is still possible that we didn't adjust for potential unmeasured confounders.

INTRODUCTION

Smoking is a well-established risk factor of cardiovascular disease[1,2]. However, evidence regarding the impact of smoking on in-hospital mortality among patients with acute myocardial infarction (AMI), especially in the context of contemporary era of percutaneous coronary intervention (PCI)，is still controversial. Some studies reported that the difference in in-hospital mortality was not significant between smokers and non-smokers after accounting for age and other baseline characteristics[3-9]. Other studies reported that smokers had lower in-hospital mortality rate as compared with non-smokers even after adjustment for potential confounders, which is called "smoker's paradox"[10-14]. Thus, the aim of our study is to assess how smoking impacts the in-hospital mortality of patients receiving contemporary management of AMI. We hypothesized that smokers have lower in-hospital mortality than non-smokers.

METHODS

Data source

A cohort study was conducted by using data from China AMI (CAMI) registry between January 1, 2013 and January 31, 2016. Detailed description of the registry design was published previously[15]. Briefly, CAMI registry was a prospective, multicenter observational registry. The project included Chinese patients with acute myocardial infarction and collected data on patients' characteristics, treatments and outcomes. A total of 108 hospitals covering a broad geographic region participated the project, which assured a good representation of all the AMI patients in China and reduced selection bias[15]. Our study was approved by the institutional review board central committee at Fuwai Hospital, NCCD of China. Written informed consent was obtained from each patient included in the study. If the patient could not be communicable, informed consent was obtained from his family member. The study

protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. CAMI registry was registered on www.clinicaltrials.gov, and the registration number was NCT01874691.

Study population

We included study population from CAMI registry. Eligible patients were diagnosed with AMI and within 7 days of ischemia symptoms. Diagnostic criteria of AMI were in accordance with third Universal Definition of MI[16]. We excluded patients with age ＜18 or＞100 years old, missing or invalid data on gender, admission diagnosis and detailed smoking status.

Data were extracted by trained researchers using standard definition to reduce measure and report bias. These data included age, sex, height, weight, clinical presentation (symptoms, ST-segment elevation, anterior wall MI, blood pressure, heart rate, heart failure, cardiac shock, fatal arrhythmia, cardiac arrest, Killip classification), comorbidities (hypertension, hyperlipidemia, diabetes, heart failure, peripheral vascular disease, stroke, chronic kidney disease, COPD), medical history (family history of premature CAD, prior angina or MI, prior coronary intervention, prior CABG)，initial reperfusion strategy (prime PCI, thrombolysis, conservative therapy), lab results (creatinine, Hb, LVEF) and in-hospital outcome.

Patient and Public Involvement

We did not involve patients or the public in our work

Definition of variables

All patients were divided into three groups according to smoking status. Current smokers were defined as those who have smoked within one month before registration. Ex-smokers were defined as those who quitted smoking for at least one month. Non-smokers were defined as those who never smoked. Standard definition of the medical history and physical examination elements were well described in the ACC/AHA Task Force on clinical Data Standards and NCDR-ACTION-GWTG element dictionary[17-19]. ECG and echocardiogram were interpreted locally.

The primary endpoint was all-cause in-hospital mortality, which was defined as all cause death during hospitalization.

Statistical analysis

Baseline continuous data were presented as mean±SD or median(25th-75th percentiles) and were compared using 1-way ANOVA test. This was followed by Bonferroni t test with corrected P value 0.05/3. Categorical data were presented as counts and frequencies and were compared using X^2 test. Propensity score matching was used to control for baseline differences and to make the two groups more comparable. We used a multivariable logistic regression model to estimate propensity scores, with smoking as dependent variable and the following factors as covariates: age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI. These variables were chosen as covariates because the difference in these baseline characteristics reached statistical significance or these variables were previously reported to be associated with patients' outcome.

Matching was performed with the use of greedy nearest matching algorithm and a 1:1 fashion. We performed PS between current smokers vs. non-smokers, and ex-smokers vs. non-smokers. The caliper width was equal to 0.01 of the SD of the score. McNemar's and paired t-tests were used to compare continuous and categorical variables between the two groups after matching. For each variable in the PS model, we computed SD between the two groups with SD less than 0.1 indicating good balance.

Multivariable logistic regression analysis was used to compare in-hospital mortality between the two groups in order to adjust for potential confounders. Variables included in the model were: age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip

classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI. To determine whether the association between smoking and in-hospital mortality varied according to baseline patient characteristics, we performed the same multivariable logistic analysis in subgroups stratified by age, sex, BMI, presence or absence of hypertension, diabetes, hyperlipidemia, heart failure, prior angina, MI or coronary intervention, admission diagnosis. For interaction test, a P value less than 0.1 is considered significant. During statistical analysis phase, based on the type, pattern and amount of missing data, appropriated methods will be used to handle missing data.

RESULTS

Baseline characteristics

From January 1, 2013 to January 31, 2016, a total number of 41590 continuous patients were registered in CAMI registry. We excluded those age＜18 or＞100 years old (n=1178), with missing or invalid data on gender (n=18) , admission diagnosis (n=1237) and detailed smoking status (n=1543). The final cohort included 37614 patients (Figure 1).

Baseline characteristics before matching were shown in Table 1. A total of 16664 (44.3%) patients were current smokers, 843 (2.2%) patients quit smoking less or equal to 1 year, 3410 (9.1%) patients quit smoking greater than 1 year, and 16697 (44.4%) patients were non-smokers. Compared with non-smokers, current smokers were younger (57.99±11.81 vs. 66.59±11.82) and had higher BMI (24.39 ±2.87 vs. 23.98 ±2.95 kg/m^2). The proportion of male (93.7% vs.49.8%) and Killip I (80.5% vs. 72.1%) was higher among current smokers. Compared with non-smokers, current smokers were less likely to have hypertension, diabetes, heart failure, stroke or chronic kidney disease, but more likely to have hyperlipidemia. Among ex-smokers, the proportion of male, hyperlipidemia, heart failure, PVD, stroke was higher than

those of current smokers. Ex-smokers also had a trend towards old age, low proportion of hypertension, diabetes than current smokers, but the difference was less significant compared with the difference between current and non-smokers.

Propensity score matching

Before PS, there were differences in almost all baseline variables among different groups (Table 1). To control for potential confounding, we matched 8552 current smokers with 8552 non-smokers (supplementary table 1), as well as 4142 ex-smokers and 4142 non-smokers (supplementary table 1). The standardized differences were less than 10.0% for all variables after matching, indicating a good match between the two groups. After PS matching, current smokers still have lower in-hospital mortality than non-smokers (5.1% vs. 6.1%, p=0.0045), but difference in in-hospital mortality was not significant between ex-smokers and non-smokers (7.0% vs. 7.4%, p=0.5198) (Supplementary Table 2).

In-hospital outcomes

Overall, 2370 patients died before discharge. There were 614 deaths (3.7%) in current smokers group, 306 deaths (7.2%) in ex-smoker group and 1450 (8.7%) in non-smokers group. Unadjusted OR for in-hospital mortality was 0.4 (95% CI: 0.37-0.44, p <.0001) in current smokers and was 0.82 (95% CI: 0.72-0.93, p=0.0018) in ex-smokers relative to non-smokers (table 2). After adjustment for potential confounders, current smoking status was associated with lower in-hospital mortality relative to non-smokers (adjusted OR: 0.78, 95% CI 0.69–0.88, p<0.001) (table 2). No difference in in-hospital mortality was detected between ex- and non-smokers (OR: 0.89, 95% CI: 0.77-1.04, p=0.1443).

Subgroup analysis

Subgroup analysis indicated that a significant interaction between smoking status and age ($P_{interaction}$: 0.0986), sex ($P_{interaction}$: 0.0163), LVEF ($P_{interaction}$: 0.0149), previous MI ($P_{interaction}$: 0.0557), previous HF ($P_{interaction}$: 0.0086) on in-hospital mortality (table 3). However, compared with non-smoker group, there was a trend toward lower in-hospital mortality in current smoker or ex-smoker group among all subgroups.

DISCUSSION

Our major finding was that among patients with AMI, current-smokers had lower in-hospital mortality than non-smokers among both the whole population and almost all subgroups, after adjusting for potential confounders by using propensity score matching, multivariable logistic regression model in our analysis of CAMI registry, the largest contemporary registry of AMI patients in east Asia.

Comparison with previous study

Most previous studies were conducted in "thrombolytic era" and we only identified 4 studies enrolling patients in current "primary PCI era"[9,14,20,21]. Of these 4 studies, three studies used multivariate regression analysis to control confounders. The results of our study were in consistent with another large-scale study[14], which also demonstrated that among STEMI patients receiving primary PCI, smokers (including both current and ex-smoker) had lower adjusted in-hospital mortality risk than non-smokers. In our study, we further separated current and ex-smokers, and used PS matching to comprehensively control for potential confounders. Several mechanisms have been proposed to explain this paradox phenomenon.

First, some studies showed the suppression effect of clopidogrel on platelet was greater among smokers than non-smokers[22-24]. Potential explanation were that smoking can enhance in vivo bioactivation of clopidogrel via increasing induction of cytochrome P450 (CYP1A2 and CYP2B6) and increased active metabolite concentration of clopidogrel [25,26]. Thus, smokers may respond better to clopidogrel therapy and consequently had a lower in-hospital mortality rate than non-smokers.

Second, smoking was unexpectedly associated with lower risk of adverse LV remodeling post infarction LV remodeling. Rolf Symons et al performed cardiac MRI at 4 days and 4 months after MI. They found that smokers had improved LVEF, which was attributable to a decrease of end diastolic volume index but not an increase of systolic volume index[27].

However, the results of our study were not consistent with two studies, which found the absence of "smoker paradox" after baseline risk adjustment[9,21]. This difference

may be related to study population selection and sample size. For instance, one study enrolled patients with symptomatic CAD, including those presented with stable or unstable angina[9], while we included patients with AMI. Patients with stable angina represented a relatively "lower risk" group, thus enrollment of this patient subset may have an impact on the association between smoking and mortality. The other study had a small sample size (N=382), which may not be powered to detect the difference in mortality between smokers and non-smokers.

Interpretation of our results:

Our results should be interpreted with caution. First, even though our study had a large sample size and we adjusted many variables, we still can't assure the precision of our results. This is also the case in the interpretation of three analysis of the AFFIRM trial, in which digoxin use was associated with increase, no change or decrease in mortality risk[28-30]. In addition, it is also possible that we didn't adjust all potential confounders. Second, our results did not mean we encourage patients to smoke. Since it is well established that smoking is an independent risk factor for mortality, and recurrent myocardial infarction[31], as well as subacute stent thrombosis [32] in the long-term, and patients with CHD can benefit from smoking cessation[33], we still recommend patients to stop smoking. However, the phenomenon might give us clue about potential mechanisms underlying myocardial protection related to smoking and further exploring novel therapy. For instance, smoking might lead to chronic ischemic state (ischemic preconditioning)[34], therefore smokers might have better tolerance for acute ischemic event like an heart attack. The phenomenon can give us clue to explore whether pre-conditioning therapy or brief period of reversible ischemia) can protect myocardium and improve outcome.

Our subgroup analysis results indicated a significant interaction between smoking status and age, gender, LVEF, previous MI, previous HF. However, currently we can't reach the conclusion that these baseline characteristics had a significant impact on the relationship between smoking and in-hospital mortality because there was a similar trend among all subgroups that current smokers and ex-smokers had lower in-hospital mortality risk compared with non-smokers. A significant P value may be

attributed to different OR value between subgroups of smokers and non-smokers, as well as a large sample size of some subgroups.

Limitations

Some patients might die before reaching hospital, therefore early death might be underestimated. CAMI registry was a multicenter, large-scale study involving over 100 hospitals. Although standardized data collection procedure was emphasized, the accuracy of data still depends greatly on the expertise of local investigators. Our results require further external validation in another independent cohort. We did not account for angiographic variables or other potential unknown confounders, which could also play a role in predicting patients' outcome. Smoking status might be modified after myocardial infarction onset. However, we asked the patients about their smoking status prior to AMI onset and all patients were enrolled within 7 days of symptom onset. Therefore, this might not have a significant impact on smoking status. We only assessed the association between smoking and short-term outcome, future studies are required to investigate this association in the long-term.

Conclusions:

We demonstrated that in-hospital mortality rate was lower among smokers compared with non-smokers in a large scale contemporary cohort representing AMI patients in China. Our findings indicated that future studies should be done to further explore the potential biological mechanisms that may explain this phenomenon.

Declaration of interests:

We confirm that there are no known conflicts of interest associated with this publication.

Author contributions:

Chenxi Song and Rui fu were major contributors in writing the manuscript. Kefei Dou and Yuejin Yang contributed substantially to the conception and design of the study. Jingang Yang, Haiyan Xu, Xiaojin Gao, Hao Wang, Shuai Liu revised it critically for

important intellectual content. Wei Li, Yang Wang and Xiaoxue Fan made contribution to analysis and interpretation of data.

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Data availability statement

Data are available from corresponding author on reasonable request.

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Figure and table legends:

Table 1 Baseline characteristics according to smoking status (Before matching)

Table 2 Association between Smoking and In-hospital Mortality

Table 3 Association between smoking and in-hospital mortality according to baseline characteristics

Supplementary Table 1 Baseline characteristics between current smokers vs. non-smokers (After matching)

Supplementary Table 2 Baseline characteristics between ex-smokers vs. non-smokers (After matching)

Figure legend: Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age＜18 or ＞100 years old (n=1178), with missing or invalid data on gender (n=18) , admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

Table 1 Baseline characteristics according to smoking status (Before matching)

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Age	57.99±11.81	66.49±11.50	66.59 ±11.82	<0.0001
Male	93.7%	94.0%	49.8%	<0.0001
BMI (Kg/m²)	24.39±2.87	23.95±2.84	23.98±2.95	<0.0001
ST-elevation on ECG	74.3%	65.7%	66.7%	0.1845
Heart failure on admission	11.1%	19.2%	18.1%	0.0856
Cardiac shock	3.1%	4.1%	3.9%	0.6058
Killip classification				<0.0001

I	80.5%	68.5%	72.1%	
II	13.6%	18.8%	17.3%	
III	2.8%	7.6%	5.7%	
IV	3.0%	5.1%	4.9%	
Comorbidities				
Hypertension	43.7%	54.7%	56.5%	0.0387
Hyperlipidemia	8.0%	8.6%	6.1%	<0.0001
Diabetes	14.7%	21.7%	23.3%	0.0271
PVD	0.6%	1.2%	0.7%	0.0035
Heart failure	1.1%	4.7%	3.2%	<0.0001
Stroke	7.1%	13.4%	10.0%	<0.0001
COPD	1.7%	4.5%	1.7%	<0.0001
Chronic kidney disease	0.7%	2.4%	1.5%	<0.0001
Smoking duration (year)	30.38±11.89	26.86 ±11.99	NA	<0.0001
Number of cigarettes/ day	21.23 ±11.10	19.13 ±10.93	NA	<0.0001
Drinking history				<0.0001
Never drink	27.7%	26.9%	76.2%	
Occasionally	53.1%	60.5%	21.5%	
Frequently	19.2%	12.6%	2.2%	
Duration (years)	27.80±11.72	28.75±11.91	27.04±13.07	0.2033
Frequency/per week	5.78±2.53	6.02±3.08	5.95±2.75	0.2453
Drinking preference				0.2515
Liquor	88.3%	92.4%	88.3%	
Beer	4.6%	0.9%	3.9%	
Wine	0.2%	0.3%	0.8%	
Others	6.9%	6.4%	7.0%	
Volume (ml)/per time				0.2899
Liquor	172.91±133.18	183.30±158.05	183.60 ±142.70	
Beer	722.21±1033.0	308.50±364.87	489.58 ±527.71	
Wine	69.17±227.54	75.00±119.66	34.62 ±74.68	
In-hospital mortality	3.7%	7.2%	8.7%	0.0015

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

Table 2 Association between Smoking and In-hospital Mortality

Smoking status	**OR (95% CI)**			***p* value[b]**
	Unadjusted	**Adjusted[a]**	**PS matching**	
Current smokers vs non-smokers	0.40 (0.37, 0.44)	0.78 (0.69, 0.88)	0.80 (0.69, 0.92)	<.0001
Ex- smokers vs non-smokers	0.82 (0.72, 0.93)	0.89 (0.77, 1.04)	1.03 (1.02, 1.04)	0.1443

a: adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal

failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI.

b: adjusted p value

Table 3 Association between smoking and in-hospital mortality according to baseline characteristics

Baseline characteristics	Current smoker	Ex-smoker	Non-smoker	$P_{interaction}$
Age≥55 years	0.78 (0.69, 0.89)	0.90 (0.77, 1.05)	reference	0.0986
Age<55 years	0.72 (0.53, 0.99)	0.85 (0.48, 1.49)	reference	
Male	0.78 (0.68, 0.89)	0.94 (0.80, 1.10)	reference	0.0163
Female	0.75 (0.58, 0.98)	0.45 (0.26, 0.77)	reference	
BMI≥24 kg/m^2	0.80 (0.67, 0.94)	0.89 (0.71, 1.12)	reference	0.2063
BMI<24 kg/m^2	0.74 (0.63, 0.88)	0.89 (0.73, 1.10)	reference	

LVEF⩾50%	0.77 (0.67, 0.88)	0.98 (0.82, 1.16)	reference	0.0149
LVEF＜50%	0.87 (0.68, 1.11)	0.74 (0.54, 1.01)	reference	
Hypertension-Yes	0.85 (0.72, 1.00)	0.96 (0.78, 1.17)	reference	0.4556
Hypertension-No	0.70 (0.59, 0.83)	0.80 (0.64, 1.01)	reference	
Previous angina-Yes	0.84 (0.65, 1.07)	0.83 (0.62, 1.12)	reference	0.1833
Previous angina-No	0.76 (0.66, 0.87)	0.92 (0.78, 1.10)	reference	
Previous MI-Yes	0.67 (0.47, 0.97)	0.67 (0.45, 1.00)	reference	0.0557
Previous MI-No	0.77 (0.68, 0.87)	0.91 (0.78, 1.07)	reference	
Previous PCI-Yes	0.95 (0.44, 2.04)	1.23 (0.56, 2.72)	reference	0.7975
Previous PCI-No	0.78 (0.69, 0.88)	0.89 (0.76, 1.04)	reference	
Previous HF-Yes	0.96 (0.57, 1.60)	0.85 (0.53, 1.37)	reference	0.0086
Previous HF-No	0.77 (0.68, 0.87)	0.88 (0.76, 1.03)	reference	
Diabetes-Yes	0.78 (0.60, 1.02)	0.86 (0.63, 1.18)	reference	0.4065
Diabetes-No	0.77 (0.67, 0.88)	0.90 (0.76, 1.07)	reference	
Hyperlipidemia -Yes	0.75 (0.45, 1.24)	1.16 (0.66, 2.03)	reference	0.1239
Hyperlipidemia -No	0.77 (0.68, 0.87)	0.87 (0.74, 1.02)	reference	
Diagnosis of STEMI	0.81 (0.71, 0.93)	0.93 (0.78, 1.11)	reference	0.9700
Diagnosis of NSTEMI	0.61 (0.48, 0.78)	0.71 (0.54, 0.92)	reference	

adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI.

BMI: body mass index; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; HF: heart failure;

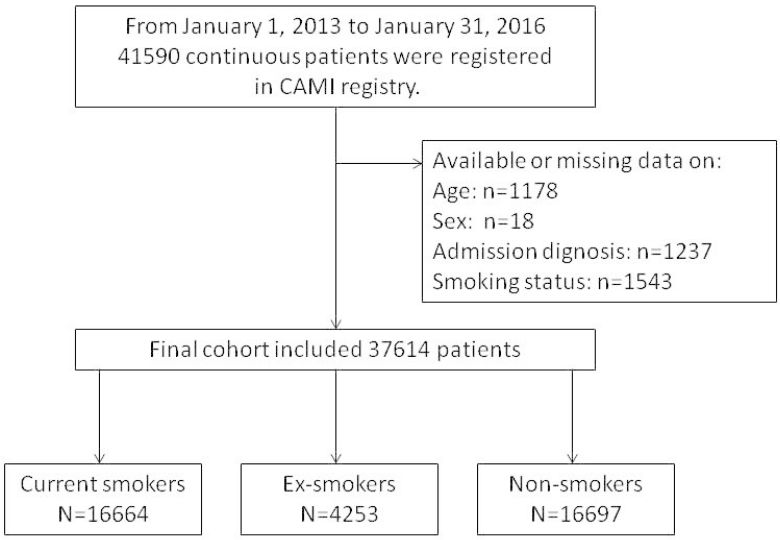

Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age＜18 or＞100 years old (n=1178), with missing or invalid data on gender (n=18) , admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

254x190mm (96 x 96 DPI)

Supplementary Table 1 Baseline characteristics between current smokers vs. non-smokers (After matching)

Variable	Current Smokers (N=8552)	Non-smokers (N=8552)	p value	SD
Age	62.80±11.53	62.84±12.04	0.6983	0.0035
Male	87.7%	87.5%	0.0995	0.0067
BMI (Kg/m^2)	24.18±2.88	24.17`±2.79	0.7580	0.0047
ST-elevation on ECG	71.1%	71.5%	0.5830	0.0083
Heart failure on admission	14.1%	13.4%	0.1448	0.0217
Cardiac shock	3.5%	3.3%	0.6165	0.0077
Killip classification			0.6823	0.0080
I	76.8%	77.1%		
II	15.3%	15.2%		
III	4.0%	3.9%		
IV	3.9%	3.8%		
Comorbidities				
Hypertension	50.4%	49.8%	0.4066	0.0124
Hyperlipidemia	6.8%	6.4%	0.3293	0.0151
Diabetes	19.0%	18.4%	0.2747	0.0162
PVD	0.8%	0.5%	0.0376	0.0319
Heart failure	1.7%	1.7%	0.8570	0.0027
Stroke	8.9%	8.8%	0.7671	0.0045
COPD	1.8%	1.8%	1.0000	0.0000
Chronic kidney disease	1.1%	1.0%	0.8206	0.0034
In-hospital mortality	5.1%	6.1%	0.0045	

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

Supplementary Table 2 Baseline characteristics between ex-smokers vs. non-smokers (After matching)

Variable	Ex-smokers (N=4142)	Non-smokers (N=4142)	p value	SD
Age	66.28±11.49	66.02±12.19	0.2242	0.0222
Male	93.8%	93.8%	0.3173	0.0010
BMI (Kg/m^2)	23.96±2.83	24.02 ±2.79	0.2900	0.0226
ST-elevation on ECG	70.4%	71.2%	0.4054	0.0175
Heart failure on admission	18.4%	18.7%	0.7158	0.0075
Cardiac shock	4.1%	3.5%	0.1701	0.0302
Killip classification			0.4505	0.0157
I	69.2%	70.0%		
II	18.5%	18.4%		
III	7.3%	6.5%		
IV	5.0%	5.1%		
Comorbidities				
Hypertension	54.4%	53.7%	0.4668	0.0155
Hyperlipidemia	8.2%	7.5%	0.2057	0.0270
Diabetes	21.5%	21.3%	0.7664	0.0065
PVD	1.1%	0.6%	0.0050	0.0611
Heart failure	4.1%	3.5%	0.1466	0.0289
Stroke	12.8%	12.8%	1.0000	0.0000
COPD	3.5%	3.0%	0.1294	0.0260
Chronic kidney disease	2.2%	2.1%	0.8108	0.0050
In-hospital mortality	7.0%	7.4%	0.5198	

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7 NA NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Association between smoking and in-hospital mortality in patients with acute myocardial infarction: a prospective, multicenter, observational study

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Secondary Subject Heading:	Cardiovascular medicine
Keywords:	smoking, in-hospital mortality, acute myocardial infarction

Association between smoking and in-hospital mortality in patients with acute myocardial infarction: a prospective, multicenter, observational study

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Abstract

Introduction: Smoking is a well-established risk factor for cardiovascular disease. However, the effect of smoking on in-hospital mortality in patients with acute myocardial infarction (AMI) who are managed by contemporary treatment is still unclear.

Methods: A cohort study was conducted using data from the China AMI registry between 2013 and 2016. Eligible patients were diagnosed with AMI in accordance with the third Universal Definition of Myocardial Infarction. Propensity score matching and multivariable logistic regression were used to control for confounders. Subgroup analysis was performed to examine whether the association between smoking and in-hospital mortality varies according to baseline characteristics.

Results: A total of 37,614 patients were included. Smokers were younger and more frequently men with fewer comorbidities than non-smokers. After propensity score matching and multivariable log regression analysis was performed, the difference in in-hospital mortality between current smokers versus non-smokers was reduced, but it was still significant (5.1% vs.6.1%, p=0.0045; adjusted odds ratio: 0.78; 95% confidence interval: 0.69–0.88, p<0.001). Among all subgroups, there was a trend toward lower in-hospital mortality in current smokers or ex-smokers compared with non-smokers.

Conclusions: Smoking is associated with lower in-hospital mortality in patients with AMI, even after multiple analyses to control for potential confounders. This "smoker's paradox" cannot be fully explained by confounding alone.

Keywords:

smoking; in-hospital mortality; acute myocardial infarction

Strengths and limitations of the study

This study used data from a large-scale multicenter registry in a contemporary era of PCI.

We used propensity score matching and the multivariable logistic regression model to adjust for confounders, which ensured the robustness of our conclusion.

The current study did not include data on patients who died before hospitalization, which may have caused index event bias (type of selection bias).

The current study did not adjust for unmeasured confounders.

INTRODUCTION

Smoking is a well-established risk factor of cardiovascular disease[1,2]. However, some previous studies have shown that smokers have a better outcome than do non-smokers following AMI. This phenomenon is referred to as "smoker's paradox". This phenomenon was first introduced in the 1970s, when Helmers found that smokers had a lower risk of mortality than did nonsmokers[3]. Some subsequent studies also showed smoker's paradox in patients with acute coronary syndrome [4]. This paradox may be explained by differences in baseline characteristics between smokers and non-smokers[5]. Additionally, the anti-platelet response may differ according to smoking status because of the effect of smoking on pharmacodynamics of clopidogrel therapy[6]. Notably, most studies regarding smoker's paradox were conducted in the era of thrombolysis, while the association between smoking and in-hospital mortality in patients who are treated with percutaneous intervention (PCI) remains controversial. Some studies have reported that the difference in in-hospital mortality was not significant between smokers and non-smokers after accounting for age and other baseline characteristics[7-13]. Other studies reported that smokers had a lower in-hospital mortality rate compared with non-smokers, even after adjustment for potential confounders (smoker's paradox)[14-18].

Examining the true effect of smoking on outcome among contemporary patients with AMI is important. If smoker's paradox is explained by confounding and smoking is not associated with favorable outcomes, physicians should disseminate this message to patients and help them quit smoking. However, if smoker's paradox still exists in the contemporary era of PCI, the biochemical basis for this phenomenon should be

investigated. This investigation may promote development of novel therapy for myocardial protection.

This study aimed to assess how smoking affects in-hospital mortality of patients receiving contemporary management of AMI. We hypothesized that smokers have lower in-hospital mortality than do non-smokers.

METHODS

Data source

A cohort study was conducted by using data from the China AMI (CAMI) registry between January 1, 2013 and January 31, 2016. A detailed description of the registry design was published previously[19]. Briefly, the CAMI registry was a prospective, multicenter, observational registry. The project included Chinese patients with AMI and data were collected on patients' characteristics, treatments, and outcomes. A total of 108 hospitals covering a broad geographic region participated in the project. This assured a good representation of all of the patients with AMI in China and reduced selection bias[19]. Our study was approved by the institutional review board central committee at Fuwai Hospital, NCCD of China (approval ID: 2012-431). Written informed consent was obtained from each patient who was included in the study. If the patient was not able to communicate, informed consent was obtained from a family member. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The CAMI registry was registered at www.clinicaltrials.gov (registration number: NCT01874691).

Study population

We included the study population from the CAMI registry. Eligible patients were diagnosed with AMI and within 7 days of ischemic symptoms. Diagnostic criteria of AMI were in accordance with the third Universal Definition of Myocardial Infarction[20]. We excluded patients who were aged <18 or >100 years, and those with missing or invalid data on sex, admission diagnosis, and smoking status.

Data were extracted by trained researchers using standard definitions to reduce measurement and reporting bias. These data included age, sex, height, weight, clinical

presentation (symptoms, ST-segment elevation, anterior wall myocardial infarction [MI], blood pressure, heart rate, heart failure, cardiac shock, fatal arrhythmia, cardiac arrest, and Killip classification), risk factors (hypertension, hyperlipidemia, diabetes), comorbidities (heart failure, peripheral vascular disease, stroke, chronic kidney disease, and chronic obstructive pulmonary disease [COPD]), medical history (family history of premature coronary artery disease [CAD], prior angina or MI, prior coronary intervention, prior coronary artery bypass grafting [CABG]), initial reperfusion strategy (primary PCI, thrombolysis, and conservative therapy), laboratory results (creatinine, hemoglobin, and left ventricular ejection fraction [LVEF]) and in-hospital outcome.

Patient and public involvement

We did not involve patients or the public in our work

Definition of variables

All patients were divided into three groups according to smoking status. Current smokers were defined as those who smoked within 1 month before registration. Ex-smokers were defined as those who quitted smoking for at least 1 month. Non-smokers were defined as those who never smoked. Standard definitions of the medical history and physical examination elements were well described in the ACC/AHA Task Force on clinical Data Standards and the NCDR-ACTION-GWTG element dictionary[21-23]. Electrocardiograms and echocardiograms were interpreted locally.

The primary endpoint was all-cause in-hospital mortality, which was defined as all-cause death during hospitalization.

Statistical analysis

Baseline continuous data are presented as mean±SD or median (25th–75th percentiles) and were compared using one-way ANOVA. This was followed by the Bonferroni t test with a corrected p value of 0.05/3. Categorical data are presented as counts and frequencies and were compared using the χ^2 test. Propensity score (PS) matching was used to control for baseline differences. We performed PS matching between current smokers and non-smokers, and between ex-smokers and non-smokers. We used a

multivariable logistic regression model to estimate propensity scores, with smoking as the dependent variable and the following factors as covariates: age, sex, body mass index (BMI), systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, Killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure, renal failure, and COPD), medical history (previous angina, PCI, and CABG), creatinine levels, hemoglobin levels, Global Registry of Acute Coronary Events (GRACE) risk score, and primary PCI. These variables were chosen as covariates because the difference in these baseline characteristics reached statistical significance or these variables were previously reported to be associated with patients' outcome.

Matching was performed using the greedy nearest matching algorithm and a 1:1 fashion. The caliper width was equal to 0.01 of the standardized difference of the score. McNemar's and paired t-tests were used to compare continuous and categorical variables between the two groups after matching. For each variable in the PS model, we computed the standardized difference between the two groups, with a standardized difference less than 0.1 indicating good balance.

The stepwise selection method was used to compare in-hospital mortality across the different groups. Baseline characteristics that significantly differed across the groups and those of clinical importance were included in the model. These variables were the same as those used for propensity matching. A p value <0.1 was used as the entry criterion and a p value <0.05 was used as the removal criterion. To determine whether the association between smoking and in-hospital mortality varied according to baseline patients' characteristics, we performed the same multivariable logistic analysis in subgroups that were stratified by age, sex, BMI, presence or absence of hypertension, diabetes, hyperlipidemia, heart failure, prior angina, MI or coronary intervention, and admission diagnosis. A two-sided p value <0.05 was considered significant. For the interaction test, a p value <0.1 was considered significant. For all variables included in our study, less than 2% of the data were missing. We used complete case analysis to deal with missing data[24] . Patients with missing data were

excluded from analysis. We presented data as "counts/total numbers available (frequencies) " for categorical variables.

RESULTS

Baseline characteristics

From January 1, 2013 to January 31, 2016, a total of 41,590 continuous patients were registered in the CAMI registry. We excluded 118 patients aged <18 or >100 years, and those with missing or invalid data on sex (n=18), admission diagnosis (n=1237), and detailed smoking status (n=1543). The final cohort included 37,614 patients (Figure 1).

Baseline characteristics before matching are shown in Table 1. A total of 16,664 (44.3%) patients were current smokers, 843 (2.2%) quit smoking before or at 1 year, 3410 (9.1%) quit smoking after 1 year, and 16,697 (44.4%) were non-smokers. Current smokers were younger (57.99±11.81 vs. 66.59±11.82 years) and had a higher BMI (24.39±2.87 vs. 23.98±2.95 kg/m^2) compared with non-smokers. The proportion of men (93.7% vs.49.8%) and Killip class I (80.5% vs. 72.1%) was higher in current smokers compared with non-smokers. Compared with non-smokers, current smokers were less likely to have hypertension, diabetes, heart failure, stroke, or chronic kidney disease, but more likely to have hyperlipidemia. Among ex-smokers, the proportions of male sex, hyperlipidemia, heart failure, peripheral vascular disease (PVD), and stroke were higher than those of current smokers. Ex-smokers also showed a trend towards old age and a low proportion of hypertension and diabetes than did current smokers, but these differences were less significant compared with the differences between current and non-smokers.

In-hospital outcomes

Overall, 2370 patients died before discharge. There were 614 (3.7%) deaths in the current smoker group, 306 (7.2%) deaths in the ex-smoker group, and 1450 (8.7%) deaths in the non-smoker group. Causes of mortality are shown in supplementary

table 1. The unadjusted odds ratio (OR) for in-hospital mortality was 0.4 (95% confidence interval [CI]: 0.37–0.44, p<0.0001) in current smokers and 0.82 (95% CI: 0.72–0.93, p=0.0018) in ex-smokers relative to non-smokers (Table 2). After adjustment for potential confounders, current smoking status was significantly associated with lower in-hospital mortality relative to non-smokers (adjusted OR: 0.78, 95% CI: 0.69–0.88, p<0.001) (Table 2). No difference in in-hospital mortality was detected between ex- and non-smokers (OR: 0.89, 95% CI: 0.77–1.04, p=0.1443).

Propensity score matching

Before PS matching, there were differences in almost all baseline variables among the different groups (Table 1). To control for potential confounding, we matched 8552 current smokers with 8552 non-smokers, as well as 4142 ex-smokers and 4142 non-smokers (Supplementary Table 2). The standardized differences were less than 10.0% for all variables after matching, which indicated a good match between two groups. After PS matching, current smokers still had lower in-hospital mortality than did non-smokers (5.1% vs. 6.1%, p=0.0045), but the difference in in-hospital mortality was not significant between ex-smokers and non-smokers (7.0% vs. 7.4%, p=0.5198) (Supplementary Table 3).

Subgroup analysis

Subgroup analysis indicated significant interactions between smoking status and age ($p_{interaction}$: 0.0986), sex ($p_{interaction}$: 0.0163), LVEF ($p_{interaction}$: 0.0149), previous MI ($p_{interaction}$: 0.0557), and previous heart failure ($p_{interaction}$: 0.0086) for in-hospital mortality (Table 3). However, there was a trend toward lower in-hospital mortality in the current smoker or ex-smoker group compared with the non-smoker group.

DISCUSSION

Our study used data from the CAMI registry, which is the largest contemporary registry of patients with AMI in East Asia. Our major finding was that in patients with AMI, current-smokers had lower in-hospital mortality than did non-smokers in the

whole population and in almost all subgroups, after adjusting for potential confounders by using PS matching.

Comparison with previous studies

Most previous studies were conducted in the thrombolytic era and we only identified four studies that enrolled patients in the current primary PCI era[13,18,25,26]. Of these four studies, three studies used multivariate regression analysis to control for confounders. Our study results are consistent with those from another large-scale study[18]. This previous study also showed that among patients with ST elevation myocardial infarction (STEMI) who received primary PCI, smokers (including current and ex-smokers) had a lower adjusted in-hospital mortality risk than did non-smokers. In our study, we further separated current and ex-smokers, and used PS matching to comprehensively control for potential confounders. Several mechanisms have been proposed to explain this paradox phenomenon.

First, some studies showed that a suppressive effect of clopidogrel on platelets was greater in smokers than in non-smokers[27-29]. A potential explanation for this finding is that smoking can enhance *in vivo* bioactivation of clopidogrel via increasing induction of cytochrome P450 (CYP1A2 and CYP2B6) and increased active metabolite concentrations of clopidogrel [30,31]. Therefore, smokers may respond better to clopidogrel therapy and consequently have a lower in-hospital mortality rate than non-smokers. Second, smoking was unexpectedly associated with a lower risk of adverse left ventricular remodeling post-infarction. Rolf Symons et al performed cardiac magnetic resonance imaging at 4 days and 4 months after MI. They found that smokers had an improved LVEF, which was attributable to a decrease in the end-diastolic volume index, but not an increase in the systolic volume index[32]. However, our results are not consistent with two studies, which found an absence of the smoker paradox after baseline risk adjustment[13,26]. This difference may be related to selection of the study population and sample size. One previous study enrolled patients with symptomatic CAD, including those who presented with stable or unstable angina[9], while we included patients with AMI. Patients with stable angina represent a relatively lower risk group. Therefore, enrollment of this patient subset

may affect the association between smoking and mortality. The other study had a small sample size (n=382), and it may not have had sufficient statistical power to detect a difference in mortality between smokers and non-smokers.

Interpretation of our results

Our results should be interpreted with caution. Although we adjusted for many common confounders, our study was still subject to selection bias as discussed below in the Limitations subsection. Our results should not be interpreted as encouraging patients to smoke. Smoking is well established as an independent risk factor for mortality and recurrent MI[33], as well as for subacute stent thrombosis [34] in the long-term, and patients with coronary heart disease can benefit from cessation of smoking[35]. Therefore, we still recommend that patients stop smoking. Our results indicated potential mechanisms underlying the protective effect of smoking. Future studies should investigate novel therapies to protect the myocardium by targeting the relevant pathways. Smoking might lead to a chronic ischemic state (ischemic preconditioning)[36]; therefore, smokers might have better tolerance for an acute ischemic event, such as a heart attack. The phenomenon could be investigated by examining whether pre-conditioning therapy or a brief period of reversible ischemia can protect the myocardium and improve outcome.

Our subgroup analysis showed a significant interaction between smoking status and age, sex, LVEF, previous MI, and previous heart failure. However, currently, we cannot reach the conclusion that these baseline characteristics had a significant effect on the relationship between smoking and in-hospital mortality. This is because there was a similar trend among all subgroups that current smokers and ex-smokers had a lower in-hospital mortality risk compared with non-smokers. A significant p value may be attributed to a different OR value between subgroups of smokers and non-smokers, as well as a large sample size of some of the subgroups.

Limitations

Our study may have been subject to selection bias. The CAMI registry did not collect data on patients who died before hospitalization. Failing to account for pre-hospital deaths may have led to selection bias. The distribution of risk factors was significantly

different between smokers and non-smokers. Although we adjusted for known and measured variables, there are likely to be other unmeasured variables leading to selection bias. The CAMI registry was a multicenter, large-scale study that involved more than 100 hospitals. Although a standardized data collection procedure was emphasized, the accuracy of data still greatly depends on the expertise of local investigators. The CAMI registry did not collect detailed data regarding smoking status. Smoking status might be modified after onset of MI. However, we asked the patients about their smoking status before onset of AMI and all patients were enrolled within 7 days of symptom onset. We only assessed the association between smoking and short-term outcome. Future studies are required to investigate this association in the long-term.

Conclusions:

Our study showed that the in-hospital mortality rate was lower in smokers compared with non-smokers in a large-scale, contemporary cohort representing patients with AMI in China. Our findings indicate that future studies should be performed to further explore the potential biological mechanisms that may explain this phenomenon.

Declaration of interests:

We confirm that there are no known conflicts of interest associated with this publication.

Author contributions:

Chenxi Song and Rui fu were major contributors in writing the manuscript. Kefei Dou and Yuejin Yang contributed substantially to the conception and design of the study. Jingang Yang, Haiyan Xu, Xiaojin Gao, Hao Wang, Shuai Liu revised it critically for important intellectual content. Xiaoxue Fan made contribution to analysis and interpretation of data.

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Data availability statement

Data are available from corresponding author on reasonable request.

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Figure and table legends:

Table 1 Baseline characteristics according to smoking status (Before matching)

Table 2 Association between Smoking and In-hospital Mortality

Table 3 Association between smoking and in-hospital mortality according to baseline characteristics

Figure legend: Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age＜18 or ＞100 years old (n=1178), with missing or invalid data on gender (n=18) , admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

Table 1 Baseline characteristics according to smoking status (Before matching)

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Age	57.99±11.81	66.49±11.50	66.59 ±11.82	<0.0001
Male	15616/16664 (93.7%)	3997/4253 (94.0%)	8317/16697 (49.8%)	<0.0001
BMI (Kg/m^2)	24.39±2.87	23.95±2.84	23.98±2.95	<0.0001
ST-elevation on ECG	12044/16330 (74.3%)	2725/4185 (65.7%)	10822/16374 (66.7%)	0.2338
SBP(mmHg)	127.82 ±24.69	129.71 ±25.17	130.58 ±25.97	<0.0001
Heart rate (bpm)	76.74 ±17.40	79.85 ±19.82	79.47 ±18.89	<0.0001
Heart failure on admission	1851/16608 (11.1%)	817 /4227 (19.2%)	3016/16620 (18.1%)	0.0781
Cardiac shock	512/16597 (3.1%)	175/4227 (4.1%)	658/16614 (3.9%)	0.5962
Killip classification				<0.0001
I	13332/16577 (80.4%)	2877 /4215 (68.3%)	11906 /16568 (71.9%)	
II	2272 /16577 (13.7%)	799/4215 (19.0%)	2892 /16568 (17.5%)	
III	472/16577 (2.8%)	324 /4215 (7.7%)	951/16568 (5.7%)	
IV	501/16577 (3.0%)	215 /4215 (5.1%)	819 /16568 (4.9%)	
Comorbidities				
Hypertension	7288/16653 (43.8%)	2328/4251(54.8%)	9434/16693 (56.5%)	0.0401
Hyperlipidemia	1329/16640 (8.0%)	367 /4247 (8.6%)	1020 /16679 (6.1%)	<0.0001
Diabetes	2451/ 16635 (14.7%)	924 /4242 (21.8%)	3893 /16672 (23.4%)	0.0295
PVD	100 /16611 (0.6%)	49 / 4234 (1.2%)	115 /16642 (0.7%)	0.0035
Heart failure	177 /16628 (1.1%)	199 /4235 (4.7%)	528 /16638 (3.2%)	<0.0001
Stroke	1176 /16616 (7.1%)	570 /4237 (13.5%)	1666 /16648 (10.0%)	<0.0001
COPD	277 /16664 (1.7%)	191 /4253 (4.5%)	277/16697 (1.7%)	<0.0001
Chronic kidney disease	121 /16588 (0.7%)	103 /4222 (2.4%)	257 /16612 (1.5%)	0.0001
Smoking duration (year)	30.38±11.89	26.86 ±11.99	NA	<0.0001

Number of cigarettes/ day	21.23 ±11.10	19.13 ±10.93	NA	<0.0001
Hb (g/L)	142.15 ±17.42	135.38 ±19.39	130.18 ±19.43	<0.0001
Creatinine (mg/L)	37.40 ±0.69	37.40 ±0.46	37.42 ±2.04	0.1842
Primary PCI	8499/16544 (51.4%)	1566/4224 (37.1%)	6369/16579 (38.4%)	0.1084
P2Y12 inhibitors	16086/16458 (97.7%)	4030/4186 (96.3%)	15837/16446 (96.3%)	0.9423
GRACE risk score	151.43 ±33.02	171.34 ±35.63	169.61 ±35.89	<0.0001
In-hospital mortality	614/16664 (3.7%)	306/4325 (7.2%)	1450/16679 (8.7%)	0.0015

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events

Table 2 Association between Smoking and In-hospital Mortality

Smoking status	OR (95% CI)			*p* value[b]
	Unadjusted	Adjusted[a]	PS matching	
Current smokers vs non-smokers	0.40 (0.37, 0.44)	0.78 (0.69, 0.88)	0.80 (0.69, 0.92)	<.0001
Ex- smokers vs non-smokers	0.82 (0.72, 0.93)	0.89 (0.77, 1.04)	1.03 (1.02, 1.04)	0.1443

a: adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI. The number of patients included in the adjusted model was 37614.
b: adjusted p value

Table 3 Association between smoking and in-hospital mortality according to baseline characteristics

Baseline characteristics	Current smoker	Ex-smoker	Non-smoker	$P_{interaction}$
Age≥55 years	0.78 (0.69, 0.89)	0.90 (0.77, 1.05)	reference	0.0986
Age<55 years	0.72 (0.53, 0.99)	0.85 (0.48, 1.49)	reference	
Male	0.78 (0.68, 0.89)	0.94 (0.80, 1.10)	reference	0.0163
Female	0.75 (0.58, 0.98)	0.45 (0.26, 0.77)	reference	
BMI≥24 kg/m²	0.80 (0.67, 0.94)	0.89 (0.71, 1.12)	reference	0.2063
BMI<24 kg/m²	0.74 (0.63, 0.88)	0.89 (0.73, 1.10)	reference	
LVEF≥50%	0.77 (0.67, 0.88)	0.98 (0.82, 1.16)	reference	0.0149
LVEF<50%	0.87 (0.68, 1.11)	0.74 (0.54, 1.01)	reference	
Hypertension-Yes	0.85 (0.72, 1.00)	0.96 (0.78, 1.17)	reference	0.4556
Hypertension-No	0.70 (0.59, 0.83)	0.80 (0.64, 1.01)	reference	
Previous angina-Yes	0.84 (0.65, 1.07)	0.83 (0.62, 1.12)	reference	0.1833
Previous angina-No	0.76 (0.66, 0.87)	0.92 (0.78, 1.10)	reference	
Previous MI-Yes	0.67 (0.47, 0.97)	0.67 (0.45, 1.00)	reference	0.0557
Previous MI-No	0.77 (0.68, 0.87)	0.91 (0.78, 1.07)	reference	
Previous PCI-Yes	0.95 (0.44, 2.04)	1.23 (0.56, 2.72)	reference	0.7975
Previous PCI-No	0.78 (0.69, 0.88)	0.89 (0.76, 1.04)	reference	
Previous HF-Yes	0.96 (0.57, 1.60)	0.85 (0.53, 1.37)	reference	0.0086
Previous HF-No	0.77 (0.68, 0.87)	0.88 (0.76, 1.03)	reference	
Diabetes-Yes	0.78 (0.60, 1.02)	0.86 (0.63, 1.18)	reference	0.4065
Diabetes-No	0.77 (0.67, 0.88)	0.90 (0.76, 1.07)	reference	
Hyperlipidemia -Yes	0.75 (0.45, 1.24)	1.16 (0.66, 2.03)	reference	0.1239
Hyperlipidemia -No	0.77 (0.68, 0.87)	0.87 (0.74, 1.02)	reference	
Diagnosis of STEMI	0.81 (0.71, 0.93)	0.93 (0.78, 1.11)	reference	0.9700
Diagnosis of NSTEMI	0.61 (0.48, 0.78)	0.71 (0.54, 0.92)	reference	

adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI.
BMI: body mass index; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; HF: heart failure;

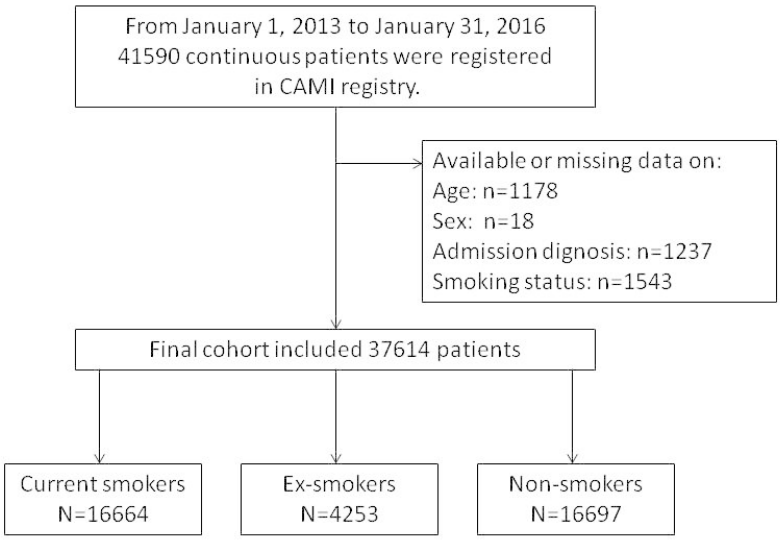

Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age＜18 or＞100 years old (n=1178), with missing or invalid data on gender (n=18) , admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

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Supplementary Table 1 Causes of mortality according to smoking status

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Sudden cardiac death	202/16664 (1.2%)	107/4253 (2.5%)	519/16697 (3.1%)	0.0387
Cardiac shock	157/16664 (0.9%)	85/4253 (2.0%)	375/16697 (2.2%)	0.3203
Heart failure	121/16664 (0.7%)	65/4253 (1.5%)	291/16697 (1.7%)	0.3277
Intracerebral hemorrhage	4/16664 (0.0%)	1/4253 (0%)	3/16697 (0%)	0.8199
Lung infection	15/16664 (0.1%)	10/4253 (0.2%)	26/16697 (0.2%)	0.2833
Ischemic stroke	3/16664 (0.0%)	2/4253 (0%)	7/16697 (0.0%)	0.8873
Major bleeding	3/16664 (0.0%)	0/4253 (0%)	6/16697 (0.0%)	0.0989
Others	25/16664 (0.2%)	9/4253 (0.2%)	47/16697 (0.3%)	0.4176

Supplementary Table 2 Baseline characteristics between current smokers vs. non-smokers (After matching)

Variable	Current Smokers (N=8552)	Non-smokers (N=8552)	p value	Standardized difference
Age	62.80±11.53	62.84±12.04	0.6983	0.0035
Male	1048/8552 (87.7%)	7485/8552 (87.5%)	0.0995	0.0067
BMI (Kg/m^2)	24.18±2.88	24.17`±2.79	0.7580	0.0047
ST-elevation on ECG	71.1%	71.5%	0.5830	0.0083
SBP(mmHg)	129.01±25.75	128.90±24.68	0.7767	0.0043
Heart rate(bpm)	77.88±18.55	77.61±17.40	0.3279	0.0147
Heart failure on admission	1208 (14.1%)	1144 (13.4%)	0.1448	0.0217
Cardiac shock	297 (3.5%)	285 (3.3%)	0.6165	0.0077
Killip classification			0.6823	0.0080
I	6564/8552 (76.8%)	6593/8552 (77.1%)		
II	1312/8552 (15.3%)	1301 /8552 (15.2%)		
III	341 /8552 (4.0%)	330/8552 (3.9%)		
IV	335 /8552 (3.9%)	328 /8552 (3.8%)		
Comorbidities				
Hypertension	4309/8552 (50.4%)	4256 /8552 (49.8%)	0.4066	0.0124
Hyperlipidemia	582/8552 (6.8%)	550 /8552 (6.4%)	0.3293	0.0151
Diabetes	1629 /8552 (19.0%)	1575/8552 (18.4%)	0.2747	0.0162
PVD	67 /8552 (0.8%)	45/8552 (0.5%)	0.0376	0.0319
Heart failure	146 /8552 (1.7%)	143 //8552 (1.7%)	0.8570	0.0027
Stroke	762/8552 (8.9%)	751 /8552 (8.8%)	0.7671	0.0045
COPD	150/8552 (1.8%)	150 /8552 (1.8%)	1.0000	0.0000
Chronic kidney disease	92 /8552 (1.1%)	89/8552 (1.0%)	0.8206	0.0034
Hb (g/L)	137.32 ±18.04	137.46 ±18.20	0.5606	0.0076
Creatinine (mg/L)	37.40 ±0.59	37.40 ±1.13	0.9837	0.0003
Primary PCI	3778 /8552 (44.2%)	3858/8552 (42.3%)	0.1966	0.0188
P2Y12 inhibitors	7880/8552 (92.1%)	7912/8552 (92.5%)	0.3576	0.0141
GRACE risk score	161.33±34.18	161.31 ±34.22	0.9460	0.0008
In-hospital mortality	438/8552 (5.1%)	522/8552 (6.1%)	0.0045	

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events
PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

Supplementary Table 3 Baseline characteristics between ex-smokers vs. non-smokers (After matching)

Variable	Ex-smokers (N=4142)	Non-smokers (N=4142)	p value	Standardized difference
Age	66.28±11.49	66.02±12.19	0.2242	0.0222
Male	3887/4142 (93.8%)	3886 /4142(93.8%)	0.3173	0.0010
BMI (Kg/m^2)	23.96±2.83	24.02 ±2.79	0.2900	0.0226
ST-elevation on ECG	2740 /4142 (66.2%)	2753 /4142 (66.5%)	0.4054	0.0175
SBP(mmHg)	129.62±25.19	129.58±25.12	0.9422	0.0016
HR (bpm)	79.66±19.73	79.65±18.75	0.9679	0.0009
Heart failure on admission	763 /4142 (18.4%)	775 /4142 (18.7%)	0.7158	0.0075
Cardiac shock	171/4142 (4.1%)	147/4142 (3.5%)	0.1701	0.0302
Killip classification			0.4505	0.0157
I	2868/4142 (69.2%)	2898/4142 (70.0%)		
II	767/4142(18.5%)	764 /4142(18.4%)		
III	301/4142(7.3%)	270/4142(6.5%)		
IV	206/4142(5.0%)	210 /4142(5.1%)		
Comorbidities				
Hypertension	2255/4142 (54.4%)	2223/4142 (53.7%)	0.4668	0.0155
Hyperlipidemia	339 /4142(8.2%)	309/4142 (7.5%)	0.2057	0.0270
Diabetes	892/4142 (21.5%)	881/4142 (21.3%)	0.7664	0.0065
PVD	46 /4142 (1.1%)	23/4142 (0.6%)	0.0050	0.0611
Heart failure	170 /4142 (4.1%)	147/4142 (3.5%)	0.1466	0.0289
Stroke	532 /4142 (12.8%)	532/4142 (12.8%)	1.0000	0.0000
COPD	143/4142 (3.5%)	124 /4142 (3.0%)	0.1294	0.0260
Chronic kidney disease	92 /4142 (2.2%)	89/4142 (2.1%)	0.8108	0.0050
Hb (g/L)	135.50 ±19.39	135.48 ±19.08	0.9618	0.0010
Creatinine (mg/L)	37.40 ±0.47	37.40 ±1.14	0.8868	0.0031
Primary PCI	1541/4142 (37.2%)	1575/4142 (38.0%)	0.4060	0.0169
P2Y12 inhibitors	3813/4142 (92.1%)	3842/4142 (92.8%)	0.2345	0.0264
GRACE risk score	170.68 ±35.39	169.90 ±36.56	0.2587	0.0215
In-hospital mortality	292/4142 (7.0%)	307 /4142 (7.4%)	0.5198	

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events
PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Association between smoking and in-hospital mortality in patients with acute myocardial infarction: results from a prospective, multicenter, observational study in China

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Secondary Subject Heading:	Cardiovascular medicine
Keywords:	smoking, in-hospital mortality, acute myocardial infarction

Association between smoking and in-hospital mortality in patients with acute myocardial infarction: results from a prospective, multicenter, observational study in China

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Abstract

Introduction: Smoking is a well-established risk factor for cardiovascular disease. However, the effect of smoking on in-hospital mortality in patients with acute myocardial infarction (AMI) who are managed by contemporary treatment is still unclear.

Methods: A cohort study was conducted using data from the China AMI registry between 2013 and 2016. Eligible patients were diagnosed with AMI in accordance with the third Universal Definition of Myocardial Infarction. Propensity score matching and multivariable logistic regression were used to control for confounders. Subgroup analysis was performed to examine whether the association between smoking and in-hospital mortality varies according to baseline characteristics.

Results: A total of 37,614 patients were included. Smokers were younger and more frequently men with fewer comorbidities than non-smokers. After propensity score matching and multivariable log regression analysis was performed, the difference in in-hospital mortality between current smokers versus non-smokers was reduced, but it was still significant (5.1% vs.6.1%, p=0.0045; adjusted odds ratio: 0.78; 95% confidence interval: 0.69–0.88, p<0.001). Among all subgroups, there was a trend toward lower in-hospital mortality in current smokers or ex-smokers compared with non-smokers.

Conclusions: Smoking is associated with lower in-hospital mortality in patients with AMI, even after multiple analyses to control for potential confounders. This "smoker's paradox" cannot be fully explained by confounding alone.

Keywords:

smoking; in-hospital mortality; acute myocardial infarction

Strengths and limitations of the study

This study used data from a large-scale multicenter registry in a contemporary era of PCI.

We used propensity score matching and the multivariable logistic regression model to adjust for confounders, which ensured the robustness of our conclusion.

The current study did not include data on patients who died before hospitalization, which may have caused index event bias (type of selection bias).

The current study did not adjust for unmeasured confounders.

INTRODUCTION

Smoking is a well-established risk factor of cardiovascular disease[1,2]. However, some previous studies have shown that smokers have a better outcome than do non-smokers following AMI. This phenomenon is referred to as "smoker's paradox". This phenomenon was first introduced in the 1970s, when Helmers found that smokers had a lower risk of mortality than did nonsmokers[3]. Some subsequent studies also showed smoker's paradox in patients with acute coronary syndrome [4]. This paradox may be explained by differences in baseline characteristics between smokers and non-smokers[5]. Additionally, the anti-platelet response may differ according to smoking status because of the effect of smoking on pharmacodynamics of clopidogrel therapy[6]. Notably, most studies regarding smoker's paradox were conducted in the era of thrombolysis, while the association between smoking and in-hospital mortality in patients who are treated with percutaneous intervention (PCI) remains controversial. Some studies have reported that the difference in in-hospital mortality was not significant between smokers and non-smokers after accounting for age and other baseline characteristics[7-13]. Other studies reported that smokers had a lower in-hospital mortality rate compared with non-smokers, even after adjustment for potential confounders (smoker's paradox)[14-18].

Examining the true effect of smoking on outcome among contemporary patients with AMI is important. One the one hand, the phenomenon of "smoking paradox" has a negative effect on quitting smoking in a public health perspective. On the other hand, if smoker's paradox still exists in the contemporary era of PCI, the biochemical basis for this phenomenon should be investigated. This investigation may promote development of novel therapy for myocardial protection.

This study aimed to assess how smoking affects in-hospital mortality of patients receiving contemporary management of AMI.

METHODS

Data source

A cohort study was conducted by using data from the China AMI (CAMI) registry between January 1, 2013 and January 31, 2016. A detailed description of the registry design was published previously[19]. Briefly, the CAMI registry was a prospective, multicenter, observational registry. The project included Chinese patients with AMI and data were collected on patients' characteristics, treatments, and outcomes. A total of 108 hospitals covering a broad geographic region participated in the project. This assured a good representation of all of the patients with AMI in China and reduced selection bias[19]. Our study was approved by the institutional review board central committee at Fuwai Hospital, NCCD of China (approval ID: 2012-431). Written informed consent was obtained from each patient who was included in the study. If the patient was not able to communicate, informed consent was obtained from a family member. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The CAMI registry was registered at www.clinicaltrials.gov (registration number: NCT01874691).

Study population

We included the study population from the CAMI registry. Eligible patients were diagnosed with AMI and within 7 days of ischemic symptoms. Diagnostic criteria of AMI were in accordance with the third Universal Definition of Myocardial Infarction[20]. We excluded patients who were aged <18 or >100 years, and those with missing or invalid data on sex, admission diagnosis, and smoking status.

Data were extracted by trained researchers using standard definitions to reduce measurement and reporting bias. These data included age, sex, height, weight, clinical presentation (symptoms, ST-segment elevation, anterior wall myocardial infarction [MI], blood pressure, heart rate, heart failure, cardiac shock, fatal arrhythmia, cardiac

arrest, and Killip classification), risk factors (hypertension, hyperlipidemia, diabetes), comorbidities (heart failure, peripheral vascular disease, stroke, chronic kidney disease, and chronic obstructive pulmonary disease [COPD]), medical history (family history of premature coronary artery disease [CAD], prior angina or MI, prior coronary intervention, prior coronary artery bypass grafting [CABG]), initial reperfusion strategy (primary PCI, thrombolysis, and conservative therapy), laboratory results (creatinine, hemoglobin, and left ventricular ejection fraction [LVEF]) and in-hospital outcome.

Patient and public involvement

We did not involve patients or the public in our work

Definition of variables

All patients were divided into three groups according to smoking status. Current smokers were defined as those who smoked within 1 month before registration. Ex-smokers were defined as those who quitted smoking for at least 1 month. Non-smokers were defined as those who never smoked. Standard definitions of the medical history and physical examination elements were well described in the ACC/AHA Task Force on clinical Data Standards and the NCDR-ACTION-GWTG element dictionary[21-23]. Electrocardiograms and echocardiograms were interpreted locally.

The primary endpoint was all-cause in-hospital mortality, which was defined as all-cause death during hospitalization.

Statistical analysis

Baseline continuous data are presented as mean±SD or median (25th–75th percentiles) and were compared using one-way ANOVA. This was followed by the Bonferroni t test with a corrected p value of 0.05/3. Categorical data are presented as counts and frequencies and were compared using the χ^2 test. Propensity score (PS) matching was used to control for baseline differences. We performed PS matching between current smokers and non-smokers, and between ex-smokers and non-smokers. We used a multivariable logistic regression model to estimate propensity scores, with smoking as the dependent variable and the following factors as covariates: age, sex, body mass

index (BMI), systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, Killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure, renal failure, and COPD), medical history (previous angina, PCI, and CABG), creatinine levels, hemoglobin levels, Global Registry of Acute Coronary Events (GRACE) risk score, and primary PCI. These variables were chosen as covariates because the difference in these baseline characteristics reached statistical significance or these variables were previously reported to be associated with patients' outcome.

Matching was performed using the greedy nearest matching algorithm and a 1:1 fashion. The caliper width was equal to 0.01 of the standardized difference of the score. McNemar's and paired t-tests were used to compare continuous and categorical variables between the two groups after matching. For each variable in the PS model, we computed the standardized difference between the two groups, with a standardized difference less than 0.1 indicating good balance.

The stepwise selection method was used to compare in-hospital mortality across the different groups. Baseline characteristics that significantly differed across the groups and those of clinical importance were included in the model. These variables were the same as those used for propensity matching. A p value <0.1 was used as the entry criterion and a p value <0.05 was used as the removal criterion. To determine whether the association between smoking and in-hospital mortality varied according to baseline patients' characteristics, we performed the same multivariable logistic analysis in subgroups that were stratified by age, sex, BMI, presence or absence of hypertension, diabetes, hyperlipidemia, heart failure, prior angina, MI or coronary intervention, and admission diagnosis. A two-sided p value <0.05 was considered significant. For the interaction test, a p value <0.1 was considered significant. For all variables included in our study, less than 2% of the data were missing. We used complete case analysis to deal with missing data[24] . Patients with missing data were excluded from analysis. We presented data as "counts/total numbers available (frequencies) " for categorical variables.

RESULTS

Baseline characteristics

From January 1, 2013 to January 31, 2016, a total of 41,590 continuous patients were registered in the CAMI registry. We excluded 118 patients aged <18 or >100 years, and those with missing or invalid data on sex (n=18), admission diagnosis (n=1237), and detailed smoking status (n=1543). The final cohort included 37,614 patients (Figure 1).

Baseline characteristics before matching are shown in Table 1. A total of 16,664 (44.3%) patients were current smokers, 843 (2.2%) quit smoking before or at 1 year, 3410 (9.1%) quit smoking after 1 year, and 16,697 (44.4%) were non-smokers. Current smokers were younger (57.99±11.81 vs. 66.59±11.82 years) and had a higher BMI (24.39±2.87 vs. 23.98±2.95 kg/m^2) compared with non-smokers. The proportion of men (93.7% vs.49.8%) and Killip class I (80.5% vs. 72.1%) was higher in current smokers compared with non-smokers. Compared with non-smokers, current smokers were less likely to have hypertension, diabetes, heart failure, stroke, or chronic kidney disease, but more likely to have hyperlipidemia. Among ex-smokers, the proportions of male sex, hyperlipidemia, heart failure, peripheral vascular disease (PVD), and stroke were higher than those of current smokers. Ex-smokers also showed a trend towards old age and a low proportion of hypertension and diabetes than did current smokers, but these differences were less significant compared with the differences between current and non-smokers.

In-hospital outcomes

Overall, 2370 patients died before discharge. There were 614 (3.7%) deaths in the current smoker group, 306 (7.2%) deaths in the ex-smoker group, and 1450 (8.7%) deaths in the non-smoker group. Causes of mortality are shown in supplementary table 1. The unadjusted odds ratio (OR) for in-hospital mortality was 0.4 (95% confidence interval [CI]: 0.37–0.44, p<0.0001) in current smokers and 0.82 (95% CI:

0.72–0.93, p=0.0018) in ex-smokers relative to non-smokers (Table 2). After adjustment for potential confounders, current smoking status was significantly associated with lower in-hospital mortality relative to non-smokers (adjusted OR: 0.78, 95% CI: 0.69–0.88, p<0.001) (Table 2). No difference in in-hospital mortality was detected between ex- and non-smokers (OR: 0.89, 95% CI: 0.77–1.04, p=0.1443).

Propensity score matching

Before PS matching, there were differences in almost all baseline variables among the different groups (Table 1). To control for potential confounding, we matched 8552 current smokers with 8552 non-smokers, as well as 4142 ex-smokers and 4142 non-smokers (Supplementary Table 2). The standardized differences were less than 10.0% for all variables after matching, which indicated a good match between two groups. After PS matching, current smokers still had lower in-hospital mortality than did non-smokers (5.1% vs. 6.1%, p=0.0045), but the difference in in-hospital mortality was not significant between ex-smokers and non-smokers (7.0% vs. 7.4%, p=0.5198) (Supplementary Table 3).

Subgroup analysis

Subgroup analysis indicated significant interactions between smoking status and age ($p_{interaction}$: 0.0986), sex ($p_{interaction}$: 0.0163), LVEF ($p_{interaction}$: 0.0149), previous MI ($p_{interaction}$: 0.0557), and previous heart failure ($p_{interaction}$: 0.0086) for in-hospital mortality (Table 3). However, there was a trend toward lower in-hospital mortality in the current smoker or ex-smoker group compared with the non-smoker group.

DISCUSSION

Our study used data from the CAMI registry, which is the largest contemporary registry of patients with AMI in East Asia. Our major finding was that in patients with AMI, current-smokers had lower in-hospital mortality than did non-smokers in the whole population and in almost all subgroups, after adjusting for potential confounders by using PS matching.

Comparison with previous studies

Most previous studies were conducted in the thrombolytic era and we only identified four studies that enrolled patients in the current primary PCI era[13,18,25,26]. Of these four studies, three studies used multivariate regression analysis to control for confounders. Our study results are consistent with those from another large-scale study[18]. This previous study also showed that among patients with ST elevation myocardial infarction (STEMI) who received primary PCI, smokers (including current and ex-smokers) had a lower adjusted in-hospital mortality risk than did non-smokers. In our study, we further separated current and ex-smokers, and used PS matching to comprehensively control for potential confounders. Several mechanisms have been proposed to explain this paradox phenomenon.

First, some studies showed that a suppressive effect of clopidogrel on platelets was greater in smokers than in non-smokers[27-29]. A potential explanation for this finding is that smoking can enhance *in vivo* bioactivation of clopidogrel via increasing induction of cytochrome P450 (CYP1A2 and CYP2B6) and increased active metabolite concentrations of clopidogrel [30,31]. Therefore, smokers may respond better to clopidogrel therapy and consequently have a lower in-hospital mortality rate than non-smokers. Second, smoking was unexpectedly associated with a lower risk of adverse left ventricular remodeling post-infarction. Rolf Symons et al performed cardiac magnetic resonance imaging at 4 days and 4 months after MI. They found that smokers had an improved LVEF, which was attributable to a decrease in the end-diastolic volume index, but not an increase in the systolic volume index[32]. However, our results are not consistent with two studies, which found an absence of the smoker paradox after baseline risk adjustment[13,26]. This difference may be related to selection of the study population and sample size. One previous study enrolled patients with symptomatic CAD, including those who presented with stable or unstable angina[9], while we included patients with AMI. Patients with stable angina represent a relatively lower risk group. Therefore, enrollment of this patient subset may affect the association between smoking and mortality. The other study had a small sample size (n=382), and it may not have had sufficient statistical power to detect a difference in mortality between smokers and non-smokers.

Interpretation of our results

Our results should be interpreted with caution. Although we adjusted for many common confounders, our study was still subject to selection bias as discussed below in the Limitations subsection. Our results should not be interpreted as encouraging patients to smoke. Smoking is well established as an independent risk factor for mortality and recurrent MI[33], as well as for subacute stent thrombosis [34] in the long-term, and patients with coronary heart disease can benefit from cessation of smoking[35]. Therefore, we still recommend that patients stop smoking. Our results indicated potential mechanisms underlying the protective effect of smoking. Future studies should investigate novel therapies to protect the myocardium by targeting the relevant pathways. Smoking might lead to a chronic ischemic state (ischemic preconditioning)[36]; therefore, smokers might have better tolerance for an acute ischemic event, such as a heart attack. The phenomenon could be investigated by examining whether pre-conditioning therapy or a brief period of reversible ischemia can protect the myocardium and improve outcome.

Our subgroup analysis showed a significant interaction between smoking status and age, sex, LVEF, previous MI, and previous heart failure. However, currently, we cannot reach the conclusion that these baseline characteristics had a significant effect on the relationship between smoking and in-hospital mortality. This is because there was a similar trend among all subgroups that current smokers and ex-smokers had a lower in-hospital mortality risk compared with non-smokers. A significant p value may be attributed to a different OR value between subgroups of smokers and non-smokers, as well as a large sample size of some of the subgroups.

Limitations

Our study may have been subject to selection bias. The CAMI registry did not collect data on patients who died before hospitalization. Failing to account for pre-hospital deaths may have led to selection bias. The distribution of risk factors was significantly different between smokers and non-smokers. Although we adjusted for known and measured variables, there are likely to be other unmeasured variables leading to selection bias. The CAMI registry was a multicenter, large-scale study that involved

more than 100 hospitals. Although a standardized data collection procedure was emphasized, the accuracy of data still greatly depends on the expertise of local investigators. The CAMI registry did not collect detailed data regarding smoking status. Smoking status might be modified after onset of MI. However, we asked the patients about their smoking status before onset of AMI and all patients were enrolled within 7 days of symptom onset. We only assessed the association between smoking and short-term outcome. Future studies are required to investigate this association in the long-term.

Conclusions:

Our study showed that the in-hospital mortality rate was lower in smokers compared with non-smokers in a large-scale, contemporary cohort representing patients with AMI in China. Our findings indicate that future studies should be performed to further explore the potential biological mechanisms that may explain this phenomenon.

Declaration of interests:

We confirm that there are no known conflicts of interest associated with this publication.

Author contributions:

Chenxi Song and Rui fu were major contributors in writing the manuscript. Kefei Dou and Yuejin Yang contributed substantially to the conception and design of the study. Jingang Yang, Haiyan Xu, Xiaojin Gao, Hao Wang, Shuai Liu revised it critically for important intellectual content. Xiaoxue Fan made contribution to analysis and interpretation of data.

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Data availability statement

Data are available from corresponding author on reasonable request.

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Figure and table legends:

Table 1 Baseline characteristics according to smoking status (Before matching)

Table 2 Association between Smoking and In-hospital Mortality

Table 3 Association between smoking and in-hospital mortality according to baseline characteristics

Figure legend: Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age＜18 or ＞100 years old (n=1178), with missing or invalid data on gender (n=18) , admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

Table 1 Baseline characteristics according to smoking status (Before matching)

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Age	57.99±11.81	66.49±11.50	66.59 ±11.82	<0.0001
Male	15616/16664 (93.7%)	3997/4253 (94.0%)	8317/16697 (49.8%)	<0.0001
BMI (Kg/m²)	24.39±2.87	23.95±2.84	23.98±2.95	<0.0001
ST-elevation on ECG	12044/16330 (74.3%)	2725/4185 (65.7%)	10822/16374 (66.7%)	0.2338
SBP(mmHg)	127.82 ±24.69	129.71 ±25.17	130.58 ±25.97	<0.0001
Heart rate (bpm)	76.74 ±17.40	79.85 ±19.82	79.47 ±18.89	<0.0001
Heart failure on admission	1851/16608 (11.1%)	817 /4227 (19.2%)	3016/16620 (18.1%)	0.0781
Cardiac shock	512/16597 (3.1%)	175/4227 (4.1%)	658/16614 (3.9%)	0.5962
Killip classification				<0.0001
I	13332/16577 (80.4%)	2877 /4215 (68.3%)	11906 /16568 (71.9%)	
II	2272 /16577 (13.7%)	799/4215 (19.0%)	2892 /16568 (17.5%)	
III	472/16577 (2.8%)	324 /4215 (7.7%)	951/16568 (5.7%)	
IV	501/16577 (3.0%)	215 /4215 (5.1%)	819 /16568 (4.9%)	
Comorbidities				
Hypertension	7288/16653 (43.8%)	2328/4251(54.8%)	9434/16693 (56.5%)	0.0401
Hyperlipidemia	1329/16640 (8.0%)	367 /4247 (8.6%)	1020 /16679 (6.1%)	<0.0001

Diabetes	2451/ 16635 (14.7%)	924 /4242 (21.8%)	3893 /16672 (23.4%)	0.0295
PVD	100 /16611 (0.6%)	49 / 4234 (1.2%)	115 /16642 (0.7%)	0.0035
Heart failure	177 /16628 (1.1%)	199 /4235 (4.7%)	528 /16638 (3.2%)	<0.0001
Stroke	1176 /16616 (7.1%)	570 /4237 (13.5%)	1666 /16648 (10.0%)	<0.0001
COPD	277 /16664 (1.7%)	191 /4253 (4.5%)	277/16697 (1.7%)	<0.0001
Chronic kidney disease	121 /16588 (0.7%)	103 /4222 (2.4%)	257 /16612 (1.5%)	0.0001
Smoking duration (year)	30.38±11.89	26.86 ±11.99	NA	<0.0001
Number of cigarettes/ day	21.23 ±11.10	19.13 ±10.93	NA	<0.0001
Hb (g/L)	142.15 ±17.42	135.38 ±19.39	130.18 ±19.43	<0.0001
Creatinine (mg/L)	37.40 ±0.69	37.40 ±0.46	37.42 ±2.04	0.1842
Primary PCI	8499/16544 (51.4%)	1566/4224 (37.1%)	6369/16579 (38.4%)	0.1084
P2Y12 inhibitors	16086/16458 (97.7%)	4030/4186 (96.3%)	15837/16446 (96.3%)	0.9423
GRACE risk score	151.43 ±33.02	171.34 ±35.63	169.61 ±35.89	<0.0001
In-hospital mortality	614/16664 (3.7%)	306/4325 (7.2%)	1450/16679 (8.7%)	0.0015

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events

Table 2 Association between Smoking and In-hospital Mortality

Smoking status	OR (95% CI)			*p* value[b]
	Unadjusted	Adjusted[a]	PS matching	
Current smokers vs non-smokers	0.40 (0.37, 0.44)	0.78 (0.69, 0.88)	0.80 (0.69, 0.92)	<.0001
Ex- smokers vs non-smokers	0.82 (0.72, 0.93)	0.89 (0.77, 1.04)	1.03 (1.02, 1.04)	0.1443

a: adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI. The number of patients included in the adjusted model was 37614.

b: adjusted p value

Table 3 Association between smoking and in-hospital mortality according to baseline characteristics

Baseline characteristics	Current smoker	Ex-smoker	Non-smoker	$P_{interaction}$
Age≥55 years	0.78 (0.69, 0.89)	0.90 (0.77, 1.05)	reference	0.0986
Age＜55 years	0.72 (0.53, 0.99)	0.85 (0.48, 1.49)	reference	
Male	0.78 (0.68, 0.89)	0.94 (0.80, 1.10)	reference	0.0163
Female	0.75 (0.58, 0.98)	0.45 (0.26, 0.77)	reference	
BMI≥24 kg/m^2	0.80 (0.67, 0.94)	0.89 (0.71, 1.12)	reference	0.2063
BMI＜24 kg/m^2	0.74 (0.63, 0.88)	0.89 (0.73, 1.10)	reference	
LVEF≥50%	0.77 (0.67, 0.88)	0.98 (0.82, 1.16)	reference	0.0149
LVEF＜50%	0.87 (0.68, 1.11)	0.74 (0.54, 1.01)	reference	
Hypertension-Yes	0.85 (0.72, 1.00)	0.96 (0.78, 1.17)	reference	0.4556

Hypertension-No	0.70 (0.59, 0.83)	0.80 (0.64, 1.01)	reference	
Previous angina-Yes	0.84 (0.65, 1.07)	0.83 (0.62, 1.12)	reference	0.1833
Previous angina-No	0.76 (0.66, 0.87)	0.92 (0.78, 1.10)	reference	
Previous MI-Yes	0.67 (0.47, 0.97)	0.67 (0.45, 1.00)	reference	0.0557
Previous MI-No	0.77 (0.68, 0.87)	0.91 (0.78, 1.07)	reference	
Previous PCI-Yes	0.95 (0.44, 2.04)	1.23 (0.56, 2.72)	reference	0.7975
Previous PCI-No	0.78 (0.69, 0.88)	0.89 (0.76, 1.04)	reference	
Previous HF-Yes	0.96 (0.57, 1.60)	0.85 (0.53, 1.37)	reference	0.0086
Previous HF-No	0.77 (0.68, 0.87)	0.88 (0.76, 1.03)	reference	
Diabetes-Yes	0.78 (0.60, 1.02)	0.86 (0.63, 1.18)	reference	0.4065
Diabetes-No	0.77 (0.67, 0.88)	0.90 (0.76, 1.07)	reference	
Hyperlipidemia -Yes	0.75 (0.45, 1.24)	1.16 (0.66, 2.03)	reference	0.1239
Hyperlipidemia -No	0.77 (0.68, 0.87)	0.87 (0.74, 1.02)	reference	
Diagnosis of STEMI	0.81 (0.71, 0.93)	0.93 (0.78, 1.11)	reference	0.9700
Diagnosis of NSTEMI	0.61 (0.48, 0.78)	0.71 (0.54, 0.92)	reference	

adjusted for age, gender, BMI, systolic blood pressure, heart rate, admission diagnosis, cardiac arrest, chest pain, ST elevation, anterior wall MI, killip classification, risk factor (medical history of diabetes, hypertension, hyperlipidemia, premature family CAD history, heart failure ,renal failure, COPD), medical history (previous angina, PCI, CABG), creatinine level, hemoglobin level, grace risk score, primary PCI.

BMI: body mass index; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; HF: heart failure;

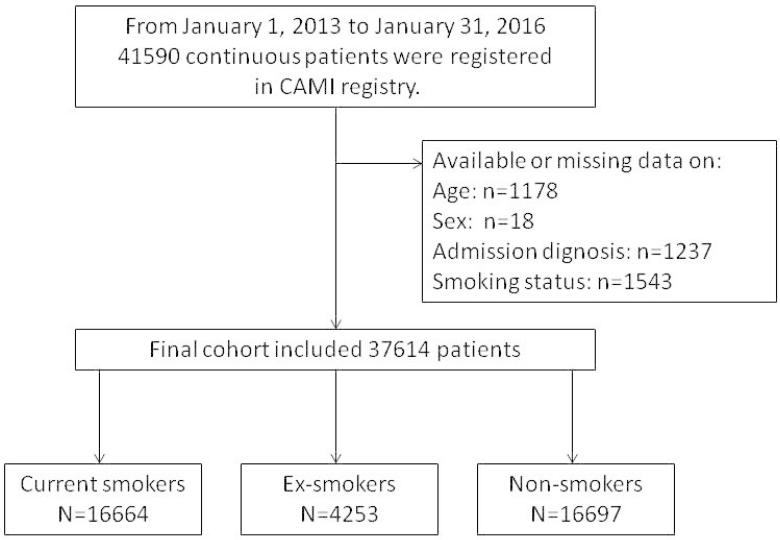

Figure 1 Study flow chart. From January, 2013 to January, 2016, 41590 continuous patients were registered in CAMI registry. Those with age＜18 or＞100 years old (n=1178), with missing or invalid data on gender (n=18) , admission diagnosis (n=1237) and detailed smoking status (n=1543) were excluded. The final cohort included 37614 patients

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Supplementary Table 1 Causes of mortality according to smoking status

Variable	Current Smokers (N=16664)	Ex-smokers (N=4253)	Non-smokers (N=16697)	p value
Sudden cardiac death	202/16664 (1.2%)	107/4253 (2.5%)	519/16697 (3.1%)	0.0387
Cardiac shock	157/16664 (0.9%)	85/4253 (2.0%)	375/16697 (2.2%)	0.3203
Heart failure	121/16664 (0.7%)	65/4253 (1.5%)	291/16697 (1.7%)	0.3277
Intracerebral hemorrhage	4/16664 (0.0%)	1/4253 (0%)	3/16697 (0%)	0.8199
Lung infection	15/16664 (0.1%)	10/4253 (0.2%)	26/16697 (0.2%)	0.2833
Ischemic stroke	3/16664 (0.0%)	2/4253 (0%)	7/16697 (0.0%)	0.8873
Major bleeding	3/16664 (0.0%)	0/4253 (0%)	6/16697 (0.0%)	0.0989
Others	25/16664 (0.2%)	9/4253 (0.2%)	47/16697 (0.3%)	0.4176

Supplementary Table 2 Baseline characteristics between current smokers vs. non-smokers (After matching)

Variable	Current Smokers (N=8552)	Non-smokers (N=8552)	p value	Standardized difference
Age	62.80±11.53	62.84±12.04	0.6983	0.0035
Male	1048/8552 (87.7%)	7485/8552 (87.5%)	0.0995	0.0067
BMI (Kg/m^2)	24.18±2.88	24.17`±2.79	0.7580	0.0047
ST-elevation on ECG	71.1%	71.5%	0.5830	0.0083
SBP(mmHg)	129.01±25.75	128.90±24.68	0.7767	0.0043
Heart rate(bpm)	77.88±18.55	77.61±17.40	0.3279	0.0147
Heart failure on admission	1208 (14.1%)	1144 (13.4%)	0.1448	0.0217
Cardiac shock	297 (3.5%)	285 (3.3%)	0.6165	0.0077
Killip classification			0.6823	0.0080
I	6564/8552 (76.8%)	6593/8552 (77.1%)		
II	1312/8552 (15.3%)	1301 /8552 (15.2%)		
III	341 /8552 (4.0%)	330/8552 (3.9%)		
IV	335 /8552 (3.9%)	328 /8552 (3.8%)		
Comorbidities				
Hypertension	4309/8552 (50.4%)	4256 /8552 (49.8%)	0.4066	0.0124
Hyperlipidemia	582/8552 (6.8%)	550 /8552 (6.4%)	0.3293	0.0151
Diabetes	1629 /8552 (19.0%)	1575/8552 (18.4%)	0.2747	0.0162
PVD	67 /8552 (0.8%)	45/8552 (0.5%)	0.0376	0.0319
Heart failure	146 /8552 (1.7%)	143 //8552 (1.7%)	0.8570	0.0027
Stroke	762/8552 (8.9%)	751 /8552 (8.8%)	0.7671	0.0045
COPD	150/8552 (1.8%)	150 /8552 (1.8%)	1.0000	0.0000
Chronic kidney disease	92 /8552 (1.1%)	89/8552 (1.0%)	0.8206	0.0034
Hb (g/L)	137.32 ±18.04	137.46 ±18.20	0.5606	0.0076
Creatinine (mg/L)	37.40 ±0.59	37.40 ±1.13	0.9837	0.0003
Primary PCI	3778 /8552 (44.2%)	3858/8552 (42.3%)	0.1966	0.0188
P2Y12 inhibitors	7880/8552 (92.1%)	7912/8552 (92.5%)	0.3576	0.0141
GRACE risk score	161.33±34.18	161.31 ±34.22	0.9460	0.0008
In-hospital mortality	438/8552 (5.1%)	522/8552 (6.1%)	0.0045	

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events
PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

Supplementary Table 3 Baseline characteristics between ex-smokers vs. non-smokers (After matching)

Variable	Ex-smokers (N=4142)	Non-smokers (N=4142)	p value	Standardized difference
Age	66.28±11.49	66.02±12.19	0.2242	0.0222
Male	3887/4142 (93.8%)	3886 /4142(93.8%)	0.3173	0.0010
BMI (Kg/m^2)	23.96±2.83	24.02 ±2.79	0.2900	0.0226
ST-elevation on ECG	2740 /4142 (66.2%)	2753 /4142 (66.5%)	0.4054	0.0175
SBP(mmHg)	129.62±25.19	129.58±25.12	0.9422	0.0016
HR (bpm)	79.66±19.73	79.65±18.75	0.9679	0.0009
Heart failure on admission	763 /4142 (18.4%)	775 /4142 (18.7%)	0.7158	0.0075
Cardiac shock	171/4142 (4.1%)	147/4142 (3.5%)	0.1701	0.0302
Killip classification			0.4505	0.0157
I	2868/4142 (69.2%)	2898/4142 (70.0%)		
II	767/4142(18.5%)	764 /4142(18.4%)		
III	301/4142(7.3%)	270/4142(6.5%)		
IV	206/4142(5.0%)	210 /4142(5.1%)		
Comorbidities				
Hypertension	2255/4142 (54.4%)	2223/4142 (53.7%)	0.4668	0.0155
Hyperlipidemia	339 /4142(8.2%)	309/4142 (7.5%)	0.2057	0.0270
Diabetes	892/4142 (21.5%)	881/4142 (21.3%)	0.7664	0.0065
PVD	46 /4142 (1.1%)	23/4142 (0.6%)	0.0050	0.0611
Heart failure	170 /4142 (4.1%)	147/4142 (3.5%)	0.1466	0.0289
Stroke	532 /4142 (12.8%)	532/4142 (12.8%)	1.0000	0.0000
COPD	143/4142 (3.5%)	124 /4142 (3.0%)	0.1294	0.0260
Chronic kidney disease	92 /4142 (2.2%)	89/4142 (2.1%)	0.8108	0.0050
Hb (g/L)	135.50 ±19.39	135.48 ±19.08	0.9618	0.0010
Creatinine (mg/L)	37.40 ±0.47	37.40 ±1.14	0.8868	0.0031
Primary PCI	1541/4142 (37.2%)	1575/4142 (38.0%)	0.4060	0.0169
P2Y12 inhibitors	3813/4142 (92.1%)	3842/4142 (92.8%)	0.2345	0.0264
GRACE risk score	170.68 ±35.39	169.90 ±36.56	0.2587	0.0215
In-hospital mortality	292/4142 (7.0%)	307 /4142 (7.4%)	0.5198	

Data are presented as mean±SD or frequencies; BMI: body mass index; ECG: electrocardiogram; SBP: systolic blood pressure; PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease; Hb: hemoglobin; GRACE: the global registry of acute coronary events
PVD: peripheral vascular disease; COPD: chronic obstructive pulmonary disease;

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	3-4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.