PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between smoking and in-hospital mortality in patients with acute myocardial infarction: results from a prospective, multicenter, observational study in China
AUTHORS	Song, Chenxi; Fu, Rui; Dou, Kefei; Yang, Jingang; Xu, Haiyan; Gao, Xiaojin; Wang, Hao; Liu, Shuai; Fan, Xiaoxue; Yang, Yuejin

VERSION 1 – REVIEW

REVIEWER	Dragana Radovanovic AMIS Plus Data Center University of Zurich Switzerland
REVIEW RETURNED	09-Apr-2019

GENERAL COMMENTS	This paper by Song C. et al. reports lower in-hospital mortality among AMI patients who smoke compared to non-smokers even after adjustment for several confounders. The paper addresses an interesting topic and has the strength that 37,614 patients from a broad geographic region in China could be included. However, I have some comments and questions which should be addressed. The paper should also be checked by a native English speaker. General comments: - From the baseline characteristics, before and after matching, it is not clear whether there are differences between the smoking groups regarding immediate treatment such as PCI and the use of P2Y12 inhibitors which could have a great impact on mortality. Although PCI is included in the multivariable analysis please show the differences between the three groups. - Systolic blood pressure, heart rate, creatinine, haemoglobin and the GRACEe risk score are also not shown in the baseline characteristics. How were these variables used for matching? As binary variables? If yes, what were the cut offs? Minor comments: - Page 2, line 58: Cox regression should be logistic regression. - Page 4, line 29: Please list the comorbidities and risk factors separately.

	- On page 5, line 18: Please define here which “two groups” were compared and not first in the following paragraph. - The same abbreviation (SD) is used for standard deviation and standardized difference. Please correct. - For the categorical variables, only the percentages are presented in the baseline characteristics table although you write in the methods that you present counts and frequencies. What is the proportion of missing data for the single variables? I would suggest presenting the data as counts vs. total number of available data and frequencies for better transparency unless there are no missing data for all variables. - Page 5, line 57: for better readability, instead of repeating the variables included in the model you could simply write that you used the same variables as for the matching. - Page 7: I would suggest switching the paragraphs “Propensity score matching” and “in-hospital mortality” as it is more logical to start with the description of unadjusted results. - Table 2: Please indicate the number of patients included in the adjusted model. - The sentence on page 9, lines 23-28 is redundant. Please delete.

REVIEWER	Mark Rutherford University of Leicester, UK
REVIEW RETURNED	29-Apr-2019

GENERAL COMMENTS	Introduction Why did you hypothesise initially that smokers have lower in hospital mortality? What was the a-priori justification for it? The introduction needs more details to evidence this hypothesis. As an aside, I’m not sure I also fully follow the clinical utility of knowing this either even if there is evidence of a true effect - again some motivation here would be of interest in the introduction. Hardly a good public health approach to promote smoking to prevent in-hospital mortality following an MI, is it? when it could well be smoking and other lifestyle factors that caused the MI in the first place. Methods I encourage the authors to look further into the literature on Index event bias. https://www.onlinecjc.ca/article/S0828-282X(18)30244-7/pdf and then reflect on this in how the study is conducted and interpreted. There are broad categorisations used in the paper: Current smokers –very broad, ex-smokers - very broad. Did you further categorise to check if results still held? All-cause death – have you further compared the rates of varying causes of mortality?

	More details are needed on how things were modelled – my guess is that a poor model or the index event bias highlighted above are the reasons for the persisting association. The authors mention "appropriate missing data methods" in the last line of the methods. Such as? What was actually done in this regard? Discussion - Interpretation of our results: section. Precision has a specific statistical meaning – be careful with wording, not sure you are referring here to precision as such here. Throughout - there needs to be some changes in the English for further clarity.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dragana Radovanovic
Institution and Country: AMIS Plus Data Center - University of Zurich - Switzerland
Please state any competing interests or state 'None declared': Non declared

Please leave your comments for the authors below
This paper by Song C. et al. reports lower in-hospital mortality among AMI patients who smoke compared to non-smokers even after adjustment for several confounders. The paper addresses an interesting topic and has the strength that 37,614 patients from a broad geographic region in China could be included.

However, I have some comments and questions which should be addressed. The paper should also be checked by a native English speaker.

General comments:

- From the baseline characteristics, before and after matching, it is not clear whether there are differences between the smoking groups regarding immediate treatment such as PCI and the use of P2Y12 inhibitors which could have a great impact on mortality. Although PCI is included in the multivariable analysis please show the differences between the three groups.

Re: Thank you for your comments. We have compared the use of PCI and P2Y12 inhibitors across smoking groups as follows, we also added this part in the revised tables.

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
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
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
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
GRACE risk score	151.43 ±33.02	171.34 ±35.63	169.61 ±35.89	<0.0001

SBP: systolic blood pressure; Hb: hemoglobin

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
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
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
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
GRACE risk score	161.33 ±34.18	161.31 ±34.22	0.9460	0.0008

SBP: systolic blood pressure; Hb: hemoglobin

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
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
SBP(mmHg)	129.62 ±25.19	129.58 ±25.12	0.9422	0.0016
Heart rate (bpm)	79.66 ±19.73	79.65 ±18.75	0.9679	0.0009
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
GRACE risk score	170.68 ±35.39	169.90 ±36.56	0.2587	0.0215

SBP: systolic blood pressure; Hb: hemoglobin

- Systolic blood pressure, heart rate, creatinine, haemoglobin and the GRACEe risk score are also not shown in the baseline characteristics. How were these variables used for matching? As binary variables? If yes, what were the cut offs?

Re: Thank you for your comments. We have added systolic blood pressure, heart rate, creatinine, haemoglobin and the GRACE risk score in the tables above and also the revised tables. In addition, these variables were used as continuous variables for PS matching.

Minor comments:

- Page 2, line 58: Cox regression should be logistic regression.
Re: Thank you for your comments. We have replaced “cox regression” with “logistic regression”.

- Page 4, line 29: Please list the comorbidities and risk factors separately.
Re: Thank you for your comments. We have separated comorbidities and risk factors separately as follows:

“risk factors (hypertension, hyperlipidemia, diabetes), comorbidities (heart failure, peripheral vascular disease, stroke, chronic kidney disease, and chronic obstructive pulmonary disease [COPD]),”

- On page 5, line 18: Please define here which “two groups” were compared and not first in the following paragraph.

Re: Thank you for your comments. We defined here the “two groups” and removed the corresponding description in the following paragraph.

“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.”

- The same abbreviation (SD) is used for standard deviation and standardized difference. Please correct.

Re: Thank you for your comments. We spelled out the abbreviation for standardized difference in subsection “Statistical analysis”, and Supplementary Table 1 and Supplementary Table 2.

- For the categorical variables, only the percentages are presented in the baseline characteristics table although you write in the methods that you present counts and frequencies. What is the proportion of missing data for the single variables? I would suggest presenting the data as counts vs. total number of available data and frequencies for better transparency unless there are no missing data for all variables.

Re: Thank you for your comments. We have revised table 1, supplementary table 1 and supplementary table 2, and presented the data as “counts/total numbers available (frequencies) ” for categorical variables.

- Page 5, line 57: for better readability, instead of repeating the variables included in the model you could simply write that you used the same variables as for the matching.
Re: Thank you for your comments. We have revised this part as follows:

“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.”

- Page 7: I would suggest switching the paragraphs “Propensity score matching” and “in-hospital mortality” as it is more logical to start with the description of unadjusted results.

Re: Thank you for your comments. We have switched the two paragraphs.

- Table 2: Please indicate the number of patients included in the adjusted model.

Re: Thank you for your comments. The number of patients included in the adjusted model was 37614 and we have indicated the number as footnotes for table 2.
- The sentence on page 9, lines 23-28 is redundant. Please delete.
Re: Thank you for your comments. We have deleted lines 23-28.

Reviewer: 2
Reviewer Name: Mark Rutherford
Institution and Country: University of Leicester, UK
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
Introduction
Why did you hypothesise initially that smokers have lower in hospital mortality? What was the a-priori justification for it? The introduction needs more details to evidence this hypothesis.
Re: Thank you for your comments. We removed the hypothesis because we didn't have much robust evidence to support this hypothesis. In addition, we provided more details regarding the background and purpose of your study as follows:

"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."

As an aside, I'm not sure I also fully follow the clinical utility of knowing this either even if there is evidence of a true effect - again some motivation here would be of interest in the introduction. Hardly a good public health approach to promote smoking to prevent in-hospital mortality following an MI, is it? when it could well be smoking and other lifestyle factors that caused the MI in the first place.

Re: Thank you for your comments. Our results should never be interpreted as encouraging patients to smoke. As described above and in the revised introduction, our motivation is to
examine the true association between smoking and mortality. This is of clinical significance in terms of not only public health, but also implications for future studies.
The revised manuscript ia as follows:

"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."

Methods

I encourage the authors to look further into the literature on Index event bias. https://www.onlinecjc.ca/article/S0828-282X(18)30244-7/pdf and then reflect on this in how the study is conducted and interpreted.

Re: Thank you for your comments. We have read the editorial by Dr Christopher, which gave comments on the study conducted by Banack. In this study, Banack and colleagues used the method of inverse probability censoring weights (IPCWs) to correct for selection bias[19]. After reading this paper, we reflected on this regarding our study design and interpretation.

Study design:

Although we adjusted for known and measured confounders, our study may still subject to selection bias. First, we acknowledged our limitation that CAMI registry didn't collect data regarding patients died before hospitalization. So we were unable to use IPCWs to account for such selection bias. On the other hand, smoking is a well-known risk factor for first myocardial infarction (MI). Similarly, there are many other risk factors contributing to MI. Thus, if we select patients who already suffered AMI, those who never smoked may have a tendency towards more risk factors. Therefore, when we compared in-hospital mortality risk among smokers vs. non-smokers, we literally compared those with few vs. many risk factors, leading to the "smoker's paradox".

We added this part in "limitation section" as follows:

"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."

Study interpretation:

Our results should be interpreted with caution. On the one hand, although we adjust many common confounders, our study was still subject to selection bias as discussed above. On the other hand, our results shouldn't be interpreted as encouraging patients to smoke. Instead, the results indicated potential mechanisms underlying the protective effect of smoking, and future studies may explore novel therapies to protect myocardium by targeting the relevant pathways.

We also revised the corresponding "interpretation of our results" part.

There are broad categorisations used in the paper: Current smokers –very broad, ex-smokers - very broad. Did you further categorise to check if results still held?

Re：Thank you for your comments. CAMI registry didn't collect data regarding details of smoking status. We acknowledged this in "limitation" section. However, our definition was in accordance with most literatures regarding "smoker's paradox"[20-22]. The corresponding revised manuscript are as follows:

"accuracy of data still depends greatly on the expertise of local investigators. The CAMI registry didn't collect detailed data regarding smoking status. Smoking status might"

All-cause death – have you further compared the rates of varying causes of mortality?

Re：Thank you for your comments. We have further compared the rates of varying causes of mortality. In general, the rate of any cause of mortality was lowest in smokers, following ex-smokers and non-smokers. The difference achieved significance in "sudden cardiac death". We have also added this part in supplementary table 3 as follows.

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

More details are needed on how things were modelled – my guess is that a poor model or the index event bias highlighted above are the reasons for the persisting association.

Re: Thank you for your comments. We have added methods building the multivariable model as follows:

“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.”

The authors mention "appropriate missing data methods" in the last line of the methods. Such as? What was actually done in this regard?
Re: Thank you for your comments. For most variables, less than 2.0% of the data were missing. We used simple imputation methods to deal with missing data[23] and missing data were imputed with median, or mode value of the available cases. According to the comments of the first reviewer, we revised our tables and presented our data as “counts/total numbers available (frequencies) ” for better transparency.
In the process of revising our manuscript, we found that for variables regarding drinking history (drinking history, drinking duration, drinking frequency, and drinking preference), more than 10% of the data were missing. So we removed these variables from table 1. We also described the methods used for dealing with missing data in subsection “statistical methods” as follows:

“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[23] . Patients with missing data were excluded from analysis. We presented data as “counts/total numbers available (frequencies) ” for categorical variables. “

Discussion - Interpretation of our results: section.

Precision has a specific statistical meaning – be careful with wording, not sure you are referring here to precision as such here.

Re: Thank you for your comments. We have removed “precision” and revised this part as follows:

“Although we adjusted for many common confounders, our study was still subject to selection bias as discussed below in the Limitations subsection.”

Throughout - there needs to be some changes in the English for further clarity.

Re: Thank you for your comments. We have enlisted the help of Liwen Bianji, Edanz Group China. We appreciate the kind help of Ellen Knapp, PhD for editing our English text and added this acknowledgement in the subsection of “Acknowledgments” as follows:

“We thank Ellen Knapp, PhD, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.”

理文编辑

Certificate of Editing

Edited provisional title
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While this certificate confirms the authors have used Edanz's editing services, we cannot guarantee that additional changes have not been made after our edits.

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VERSION 2 – REVIEW

REVIEWER	Radovanovic Dragana AMIS Plus Data Center, University of Zurich, Switzerland
REVIEW RETURNED	19-Jun-2019

GENERAL COMMENTS	One remark: 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. - This sentence is somehow confusing. We have to recommend to EVERY patient to quit smoking, independent of existing of the smoking paradox.

VERSION 2 – AUTHOR RESPONSE

One remark:

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.

- This sentence is somehow confusing. We have to recommend to EVERY patient to quit smoking, independent of existing of the smoking paradox.

Re: Thank you for your comments. We have clarify this point and revise the manuscript as follows:

"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."