PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Simple risk score based on the China Acute Myocardial Infarction registry for predicting in-hospital mortality among patients with non-ST-segment elevation myocardial infarction: results of a prospective observational cohort study
AUTHORS	Song, Chenxi; Fu, Rui; Li, Sidong; Yang, Jingang; Wang, Yan; Xu, Haiyan; Gao, Xiaojin; Liu, Jia; Liu, Qianqian; Wang, Chunyue; Dou, Kefei; Yang, Yuejin

VERSION 1 - REVIEW

REVIEWER	Hedley Knejwen Quintana Department of Research and Health Technology Assessment Gorgas Memorial Institute for Health Studies Panama City, Panama
REVIEW RETURNED	09-Apr-2019

GENERAL COMMENTS	First of all, I consider the methods suggested by the authors can help clinicians to perform their daily activities. In my humble view, this manuscript should be broadcast to a wider audience. However, I have several concerns regarding some them as shown below. 1-Please define any acromyn before using it. "CAMI" was used first time on line 38 of the manuscript without defining it first. "CAMI" was also used in the abstract without defining it: remember that some reader will only the abstract! 2-Please allow the reader to easily distinguish between the old CAMI-NSTEMI score from the paper the authors published last year and the one presented in the manuscript. I recommend using acronym SCAMI every time you use it for the new score to clearly distinguish it from the old one. 3-I understand how the CAMI-STEMI points are awarded to the patients,However, I don't understand how the SCAMI-STEMI points led to different scores if you used the same methods as the one to develop the CAMI-STEMI score 4-WBC count is more than white blood cells, hemoglobin and PLT: it also includes the red bloood cell counts, RDW, and the WBC cell lines counts. Could you clarify why such parameters, readly

	available in any automated WBC report was excluded from scores? 5-Regarding smoking, I have several queries: a-Do the data allow to describe which tobacco products are the patients using? b-Do the data allow to quantify the amount of tobacco products used by the patients? c-Can you better explain why do non-smoking patients have better in-hospital prognosis as compared to current smoker? d-What happened to former smokers? Do they were excluded from the study or do they have the same risk as the reference category (as far i understand "current smokers"). 6-"ST depression" can represent a transmural MI of a heart side not shown in standard ECG setup, ergo an ST elevation of a posterior MI. Non-standard ECG setups including V7-V9 might discard such miss diagnosis. Data on non-standard setups can be or not included in the data. If such information exists, please reconsider using it in both scores, if not, I consider it a limitation of the study and authors should state that. 7-The results of the study should be put in the broader context: there are 10 references in this paper, but I think there should be more written about this interesting topic, Is it possible to broaden the literature review in order to argue for the need of the study, as well as, to discuss its results, its implications and their external validity.

REVIEWER	Ana Teresa Timóteo Santa Marta Hospital, Lisbon, Portugal
REVIEW RETURNED	15-Apr-2019

GENERAL COMMENTS	The authors present a manuscript with the development of a risk score for in-hospital death for patients with NSTEMI, to facilitate rapid risk assessment. They included 5775 patients included in the CAMI registry between 2013 and 2014. Patients were divided in a development cohort with 4332 patients and an internal valiation cohort with 1443 patients. There were 5.9% of in-hospital deaths in this sample. Laboratorial variables were not included in the present score. They obtained a good discrimination with this score (c-satistic of 0.777), even better in the validation cohort (0.861) and higher than the original CAMI risk score and GRACE risk score (0.782). There was also good calibration, as assessed by Hosmer-Lemeshow test, and a significant NRI of 38.9%. The methods used are appropriate. There are however some remarks: 1 – The authors categorized continuous variables. There is no indication about the linearity of those variables regarding prognosis. Linearity of continuous variables should have been checked. 2 – I believe there is an error in the main text. In page 8, it is stated “SCAMI-NSTEMI is higher than SCAMI-NSTEMI” (??) 3 – The prevalence of hyperlipidemia in this population of patients with acute coronary syndrome is only 6% - very low! What is the explanation?

	4 – In the tables, we can observe that 40% of the patients had a MI 1-7 days before. This is not an early assessment. In this case, it does not seem to be useful to use the risk score. Only patients with symptoms with < 24-48 hours should have been included. 5 – What is the real impact of this score? In NSTEMI, high risk patients that require intervention in < 2 hours are usually identified by clinical signs (severe arrhythmias, hemodinamic instability,…). They do not require this risk score. All other cases should undergo coronary angiography in less than 24 hours ou 72 hours according to ischemic risk. Laboratory results can be available well below the 24 hours limit and thus, the present score does not seem to have a significant impact. 6 – The authors state that this is ”the first risk score to predict in-hospital mortality risk”. This is not the case. In a literature review, we can find other simple and early risk scores: C-ACS, ProACS, and others. Having said that, this is not original. However, the main importance is that it concerns Asian patients. For that reason, and as several other authors recognize, it would be more useful to externally validate existing risk scores instead of developing more scores that will probably never be used in clinical practice. For that reason, the authors should present a comparison with other existing risk score (for the same objective) and compare it’s discrimination and calibration.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Hedley Knejwen Quintana

Institution and Country: Department of Research and Health Technology Assessment

Gorgas Memorial Institute for Health Studies

Panama City, Panama

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

First of all, I consider the methods suggested by the authors can help clinicians to perform their daily activities. In my humble view, this manuscript should be broadcast to a wider audience. However, I have several concerns regarding some them as shown below.

1-Please define any acromyn before using it. "CAMI" was used first time on line 38 of the manuscript without defining it first. "CAMI" was also used in the abstract without defining it: remember that some reader will only the abstract!

Re: Thank you for your comments. We have revised the abstract and manuscript, and defined the acromyn before using it.

2-Please allow the reader to easily distinguish between the old CAMI-NSTEMI score from the paper the authors published last year and the one presented in the manuscript. I recommend using acronym SCAMI every time you use it for the new score to clearly distinguish it from the old one.

Re: Thank you for your comments. We revised the manuscript and used SCAMI each time for the new score.

3-I understand how the CAMI-STEMI points are awarded to the patients, However, I don't understand how the SCAMI-STEMI points led to different scores if you used the same methods as the one to develop the CAMI-STEMI score

Re:

Thank you for your comments. We used the following methods to develop the CAMI-STEMI score: First, univarite analysis was performed to show the unadjusted association between each individual baseline character with in-hospital mortality. Those with $P<0.25$ were selected to enter the multivariable model, which was constructed using stepwise variable selection with entry and exit criteria $P<0.05$. The score was then derived by attributing integer numbers to the variables retained in the multivariable model. The variable with the smallest estimated coefficient was attributed 1 point and was considered as the reference variable. The scores of the other variables were determined by dividing their estimated coefficients by the coefficient of the reference variable.

Regarding SCAMI-NSTEMI score, lab test results (WBC count and creatinine level) were not eligible to enter the multivariable model. Therefore, the variables retained in the multivariable model, and the corresponding coefficient for each variable were different from those in the original CAMI-NSTEMI score. This led to different scores between CAMI and SCAMI scores.

4-WBC count is more than white blood cells, hemoglobin and PLT: it also includes the red bloood cell counts, RDW, and the WBC cell lines counts. Could you clarify why such parameters, readly available in any automated WBC report was excluded from scores?

Re: Thank you for your comments. CAMI registry collected white blood cells, hemoglobin and PLT, but did not collect red blood cell counts, RDW, and the WBC cell lines counts. When we developed CAMI-NSTEMI score, only WBC cell count achieved statistical significance in multiple analysis and were retained in the score 7. When we developed the SCAMI-NSTEMI score, all lab test variables were excluded to allow for rapid risk stratification at the time of first medical contact, before lab test results.

5-Regarding smoking, I have several queries:

a-Do the data allow to describe which tobacco products are the patients using?

b-Do the data allow to quantify the amount of tobacco products used by the patients?

c-Can you better explain why do non-smoking patients have better in-hospital prognosis as compared to current smoker?

d-What happened to former smokers? Do they were excluded from the study or do they have the same risk as the reference category (as far i understand "current smokers").

Re: Thank you for your comments. The data do not allow to describe the specific tobacco products the patients used and the amount of tobacco products. We also acknowledge this in limitation subsection as follows:

“Third, CAMI registry did not collect data on the specific type of tobacco products the patients used and the amount of tobacco products.”

Regarding c and d, as shown in table 2, odds ratio of in-hospital morality for non-smokers relative to current smokers was 1.90 (95% CI: 1.338-2.698, $p<0.001$). That is, non-smokers have worse outcome than current smoker, a phenomenon also referred to as “smoker’s paradox”. Explanations for smoker’s paradox were added in discussion subsection.

We added the odds ratio for ex-smokers in table 2. Ex-smokers had a tendency towards higher risk than non-smokers. But the difference didn’t achieve statistical significance.

6-"ST depression" can represent a transmural MI of a heart side not shown in standard ECG setup, ergo an ST elevation of a posterior MI. Non-standard ECG setups including V7-V9 might discard such miss diagnosis. Data on non-standard setups can be or not included in the data. If such information exists, please reconsider using it in both scores, if not, I consider it a limitation of the study and authors should state that.

Re: Thank you for your comments. CAMI registry collected data on 18-lead ECG including standard 12 leads, V7-V9 and V3R-V4R. Patients with ST-segment elevation in two contiguous leads on ECG were considered as STEMI and excluded from our analysis.

7-The results of the study should be put in the broader context: there are 10 references in this paper, but I think there should be more written about this interesting topic, Is it possible to broaden the literature review in order to argue for the need of the study, as well as, to discuss its results, its implications and their external validity.

Re：Thank you for your comments. We broadened the literature review and expanded the introduction section to argue for the need of the study. We expanded the discussion subsection to discuss about our results regarding the association between BMI, and smoking status with in-hospital mortality. We also expanded our “clinical implications” subsection regarding the importance of early risk stratification and the potential use of SCAMI-CAMI score for better identification of high-risk patients. We discussed about external validity in limitation subsection as follows:

Introduction:

“Many risk scores have been developed to estimate mortality risk of patients with ACS, including GRACE risk score3, ACTION risk score4, C-ACS risk score5, and ProACS risk score6 et al. However, these scores included only a small number of Chinese patients. Additionally, to our knowledge no risk scores focused on patients with NSTEMI. To fill in knowledge gap, our team previously developed and validated a novel risk score—the CAMI-NSTEMI score to predict in-hospital mortality risk among non-ST segment elevation myocardial infarction (NSTEMI) patients based on China Myocardial Infarction (CAMI) registry 7.

A large scale meta-analysis including 5324 patients from 8 trials showed that among high risk subgroups, early invasive strategy was associated with lower in-hospital mortality8. However, our CAMI-NSTEMI score included white blood cell (WBC) count and creatinine level, which limits its application at the time of first medical contact, before lab test resuls. The objective of our study is to revise the CAMI-NSTEMI risk score, to develop and validate a simplified risk score, which can save time in score calculation and allows for early risk assessment. ”

Obesity and smoker’s paradox:

Although obesity and smoking are well-established risk factors of coronary artery disease, our study found that patients with higher BMI had lower in-hospital mortality than those with normal BMI, and smokers current smokers had lower in-hospital mortality than those with non-smokers. These phenomenon are referred to as “obesity paradox”9 and “smoker’s paradox”10 respectively. Possible explanations for obesity paradox include: obese patients are younger than normal weight patients and more likely to receive aggressive treatment11. In addition, when patients suffer from AMI, metabolic demands increases sharply and body fat may serve as nutritional reserves12.

Regarding smoker’s paradox, the observed association may be subject to selection bias. On the one hand, the distribution of risk factors was significantly different between smokers and non-smokers. It’s likely that we did not adjust for some unmeasured variables, which lead to selection bias. On the other hand, CAMI registry did not collect data on patients who died before hospitalization. Failing to account for pre-hospital deaths may also lead to selection bias13. In addition to selection bias, smoker’s paradox may be explained by the biological effect of smoking. Smoking could lead to a chronic ischemic state (ischemic preconditioning)14; therefore, smokers may have better tolerance for an acute ischemic event, such as acute myocardial infarction.

Clinical implications

“A large-scale meta analysis included 5324 patients from 8 trials, and found that early invasive strategy was associated with lower mortality among high-risk patients, including those with elevated cardiac biomarkers at baseline, diabetes, a GRACE risk score more than 140, and aged 75 years older8. …

Second, SCAMI-NSTEMI score may help better identification of high risk patients. Current guidelines recommended prompt revascularization in very high-risk patients with one the following characteristics including cardiogenic shock, severe left ventricular dysfunction, hemodynamic instability, etc15. However, many other baseline characters affect mortality risk, and comprehensive risk assessment is of clinical importance. Our study firstly identified independent risk factors on the basis of variables that can be easily obtained in clinical practice, and then integrated these risk factors

to establish a risk score system. Therefore, our score may help better identify patients at high risk of in-hospital mortality with the absence of severe clinical presentation."

Limitations:

"First, external validation of the CAMI-NSTEMI score in a larger independent cohort from China and other countries is required in future studies."

Reviewer: 2

Reviewer Name: Ana Teresa Timóteo

Institution and Country: Santa Marta Hospital, Lisbon, Portugal

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The authors present a manuscript with the development of a risk score for in-hospital death for patients with NSTEMI, to facilitate rapid risk assessment. They included 5775 patients included in the CAMI registry between 2013 and 2014. Patients were divided in a development cohort with 4332 patients and an internal valiation cohort with 1443 patients. There were 5.9% of in-hospital deaths in this sample. Laboratorial variables were not included in the present score. They obtained a good discrimination with this score (c-satistic of 0.777), even better in the validation cohort (0.861) and higher than the original CAMI risk score and GRACE risk score (0.782). There was also good calibration, as assessed by Hosmer-Lemeshow test, and a significant NRI of 38.9%.

The methods used are appropriate. There are however some remarks:

1 – The authors categorized continuous variables. There is no indication about the linearity of those variables regarding prognosis. Linearity of continuous variables should have been checked.

Re: Thank you for your comments. We first investigated the association between each variable (as continuous variable) with prognosis by using multiple logistic model. The continuous variables with a $P<0.05$ were selected to build the risk score (table 2). Therefore, for the continuous variables retained in the risk score, the linearity of these variables regarding prognosis was indicated. We categorized continuous variables in the risk score for easier clinical application.

2 – I believe there is an error in the main text. In page 8, it is stated "SCAMI-NSTEMI is higher than SCAMI-NSTEMI" (??)

Re: Thank you for your comments. We would love to compare the diagnostic performance between SCAMI-NSTEMI model and SCAMI- NSTEMI score. We firstly developed the SCAMI- NSTEMI model by fitting independent risk factors into a multivariate logistic regression model. However, such a regression model did not allow easy calculation. So we simplified the risk model and developed the SCAMI-CAMI score by attributing integer number to each variable according to their coefficients. Such transformation may reduce the diagnostic performance of the original SCAMI- NSTEMI model. So we compared the AUC value between risk model and risk score to see if there's a significant difference.

3 – The prevalence of hyperlipidemia in this population of patients with acute coronary syndrome is only 6% - very low! What is the explanation?

Re: Thank you for your comments. "Heperlipidemia" in table 1 refers to past medical history and was obtained by asking questions of the patient or his family. In China, the awareness rate of dyslipidemia was low and was reported to be 31.0%16, which may explain the low prevalence of hyperlipidemia in our population.

4 – In the tables, we can observe that 40% of the patients had a MI 1-7 days before. This is not an early assessment. In this case, it does not seem to be useful to use the risk score. Only patients with symptoms with < 24-48 hours should have been included.

Re: Thank you for your comments. We agreed with your comments that pre-hospital patient delay is a significant barrier for effective management of AMI in China. Previous study also reported that time to hospital presentation was longer in China than that in other countries17. However, the objective of our study is to develop a risk score which can reduce time in risk assessment at first medical contact, a time of the first contact of the patient with the physician, rather than to reduce time in pre-hospital patient delay. We also clarify this point in "clinical implications" as follows.

"First, the simplified score can help save time in risk estimation at first medical contact, (time of the first contact of the patient with the physician) before lab test results."

5 – What is the real impact of this score? In NSTEMI, high risk patients that require intervention in < 2 hours are usually identified by clinical signs (severe arrhythmias, hemodinamic instability,…). They do not require this risk score. All other cases should undergo coronary angiography in less than 24 hours ou 72 hours according to ischemic risk. Laboratory results can be available well below the 24 hours limit and thus, the present score does not seem to have a significant impact.

Re: Thank you for your comments. One of the clinical implications of this study is better identification of high risk patients. In addition to severe clinical signs, many other risk factors may affect mortality risk, so comprehensive risk assessment is of clinical importance. Our score integrated 9 nine variables which can be obtained easily in clinical practice. Therefore our score may help better

identify patients at high risk of in-hospital mortality with the absence of severe clinical presentation. We also clarified this point in “clinical implication” subsection as follows:

“Second, SCAMI-NSTEMI score may help better identification of high risk patients. Current guidelines recommended prompt revascularization in very high-risk patients with one the following characteristics including cardiogenic shock, severe left ventricular dysfunction, hemodynamic instability, etc15. However, many other baseline characters affect mortality risk, and comprehensive risk assessment is of clinical importance. Our study firstly identified independent risk factors on the basis of variables that can be easily obtained in clinical practice, and then integrated these risk factors to establish a risk score system. Therefore, our score may help better identify patients at high risk of in-hospital mortality with the absence of severe clinical presentation.”

6 – The authors state that this is ”the first risk score to predict in-hospital mortality risk”. This is not the case. In a literature review, we can find other simple and early risk scores: C-ACS, ProACS, and others. Having said that, this is not original. However, the main importance is that it concerns Asian patients. For that reason, and as several other authors recognize, it would be more useful to externally validate existing risk scores instead of developing more scores that will probably never be used in clinical practice. For that reason, the authors should present a comparison with other existing risk score (for the same objective) and compare it’s discrimination and calibration.

Re: Thank you for your comments. We deleted the sentence “the first risk score to predict in-hospital mortality risk”. We broadened our literature review and found that one review published in 2018 discussed the most important risk factors and risk models to predict mortality18. The review indicated that GRACE risk score was the most validated and commonly used risk prediction model. In addition, previous study found that GRACE risk score performed better than TIMI risk score in Chinese patients with NSTEMI 19. Therefore, in the present study, we compared the diagnostic performance between our risk score and GRACE risk score. However, we agreed very much with your opinion that external validation and comparison between existing risk scores in Chinese population. This will be an important direction of our future research.

We also clarified this point in discussion subsection as follows:

“Many risk scores have been developed to predict short- and long-term outcome among AMI patients, and GRACE risk score is the most validated and commonly used risk prediction tool by clinicians 3, 20. In addition, GRACE risk score performed better than TIMI risk score in Chinese patients with NSTEMI19. Therefore, we compared SCAMI-CAMI risk score with GRACE risk score.”

Reference:

1. Reed GW, Rossi JE and Cannon CP. Acute myocardial infarction. Lancet (London, England). 2017;389:197-210.

2. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ and Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of

the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013;61:e78-e140.

3. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD and Fox KA. Predictors of hospital mortality in the global registry of acute coronary events. Archives of internal medicine. 2003;163:2345-53.

4. McNamara RL, Kennedy KF, Cohen DJ, Diercks DB, Moscucci M, Ramee S, Wang TY, Connolly T and Spertus JA. Predicting In-Hospital Mortality in Patients With Acute Myocardial Infarction. Journal of the American College of Cardiology. 2016;68:626-635.

5. Huynh T, Kouz S, Yan AT, Danchin N, O'Loughlin J, Schampaert E, Yan RT, Rinfret S, Tardif JC, Eisenberg MJ, Afilalo M, Chong A, Dery JP, Nguyen M, Lauzon C, Mansour S, Ko DT, Tu JV and Goodman S. Canada Acute Coronary Syndrome Risk Score: a new risk score for early prognostication in acute coronary syndromes. American heart journal. 2013;166:58-63.

6. Timoteo AT, Aguiar Rosa S, Afonso Nogueira M, Belo A and Cruz Ferreira R. ProACS risk score: An early and simple score for risk stratification of patients with acute coronary syndromes. Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of Cardiology. 2017;36:77-83.

7. Fu R, Song C, Yang J, Wang Y, Li B, Xu H, Gao X, Li W, Liu J, Dou K and Yang Y. CAMI-NSTEMI Score- China Acute Myocardial Infarction Registry-Derived Novel Tool to Predict In-Hospital Death in Non-ST Segment Elevation Myocardial Infarction Patients. Circulation journal : official journal of the Japanese Circulation Society. 2018;82:1884-1891.

8. Jobs A, Mehta SR, Montalescot G, Vicaut E, Van't Hof AWJ, Badings EA, Neumann FJ, Kastrati A, Sciahbasi A, Reuter PG, Lapostolle F, Milosevic A, Stankovic G, Milasinovic D, Vonthein R, Desch S and Thiele H. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. Lancet (London, England). 2017;390:737-746.

9. Elagizi A, Kachur S, Lavie CJ, Carbone S, Pandey A, Ortega FB and Milani RV. An Overview and Update on Obesity and the Obesity Paradox in Cardiovascular Diseases. Progress in cardiovascular diseases. 2018;61:142-150.

10. Aune E, Roislien J, Mathisen M, Thelle DS and Otterstad JE. The "smoker's paradox" in patients with acute coronary syndrome: a systematic review. BMC medicine. 2011;9:97.

11. Niedziela J, Hudzik B, Niedziela N, Gasior M, Gierlotka M, Wasilewski J, Myrda K, Lekston A, Polonski L and Rozentryt P. The obesity paradox in acute coronary syndrome: a meta-analysis. European journal of epidemiology. 2014;29:801-12.

12. Bucholz EM, Beckman AL, Krumholz HA and Krumholz HM. Excess weight and life expectancy after acute myocardial infarction: The obesity paradox reexamined. American heart journal. 2016;172:173-81.

13. Banack HR, Harper S and Kaufman JS. Accounting for Selection Bias in Studies of Acute Cardiac Events. The Canadian journal of cardiology. 2018;34:709-716.

14. Miyazaki T, Ashikaga T, Ohigashi H, Komura M, Kobayashi K and Isobe M. Impact of smoking on coronary microcirculatory resistance in patients with coronary artery disease. International heart journal. 2015;56:29-36.

15. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF and Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European heart journal. 2016;37:267-315.

16. Pan L, Yang Z, Wu Y, Yin RX, Liao Y, Wang J, Gao B and Zhang L. The prevalence, awareness, treatment and control of dyslipidemia among adults in China. Atherosclerosis. 2016;248:2-9.

17. Guan W, Venkatesh AK, Bai X, Xuan S, Li J, Li X, Zhang H, Zheng X, Masoudi FA, Spertus JA, Krumholz HM and Jiang L. Time to hospital arrival among patients with acute myocardial infarction in China: a report from China PEACE prospective study. European heart journal Quality of care & clinical outcomes. 2019;5:63-71.

18. Castro-Dominguez Y, Dharmarajan K and McNamara RL. Predicting death after acute myocardial infarction. Trends in cardiovascular medicine. 2018;28:102-109.

19. Wu C, Gao XJ, Zhao YY, Yang JG, Yang YJ, Xu HY, Yan RH, Wu Y, Qiao SB, Wang Y, Li W, Sun Y, Jin C and Chun YS. [Prognostic value of TIMI and GRACE risk scores for in-hospital mortality in Chinese patients with non-ST-segment elevation myocardial infarction]. Zhonghua xin xue guan bing za zhi. 2019;47:297-304.

20. D'Ascenzo F, Biondi-Zoccai G, Moretti C, Bollati M, Omede P, Sciuto F, Presutti DG, Modena MG, Gasparini M, Reed MJ, Sheiban I and Gaita F. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes: a meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. Contemporary clinical trials. 2012;33:507-14.

VERSION 2 – REVIEW

REVIEWER	Hedley Quintana Gorgas Memorial Institute for Health Studies
REVIEW RETURNED	25-Jun-2019

GENERAL COMMENTS	1- Regarding my earlier comment: "3-I understand how the CAMI-STEMI points are awarded to the patients, However, I don't understand how the SCAMI-STEMI points led to different scores if you used the same methods as the one to develop the CAMI-STEMI score" The authors' response wasn't still so clear enough for me. I still cannot understand a clear difference between CAMI and SCAMI methods! As far as I read between lines, I think the authors deliberately drop lab data to "simplify" the old CAMI score towards the novel SCAMI one. If so, you must spell it out as objective! Furthermore, please compare the CAMI and SCAMI performances side by side: this is quite important, for example using ROC curves with their respective AUC! I understand that such data is present in the old paper, but I need to see that in the current manuscript! 2-Following along, with this train of thought, saying that there is a "delay" in order to get lab data seems very difficult to understand!

	As an international reader. I am not convinced about this argument, because cardiac enzymes are also lab data needed to diagnose NSTEMI. I am puzzled about how cardiac enzymes are more readily to be interpreted by a physician taking a decision regarding NSTEMI patients as compared to more "basic" lab data such as WBC, kidney function and other ones. The fact that such "basic" labs are hard to read can explain why reviewer #2 is as surprised as me that patients are extremely delayed in the stratification and subsequent treatment: but it doesn't solve the issue that such physician can bypass the NSTEMI diagnosis with a very "complicated" lab test such as cardiac enzymes, skipping other more "basic" blood tests,

REVIEWER	Ana Teresa Timoteo Santa Marta Hospital, Portugal
REVIEW RETURNED	27-Jun-2019

GENERAL COMMENTS	The authors answered properly to my comments.

VERSION 2 – AUTHOR RESPONSE

1- Regarding my earlier comment: "3-I understand how the CAMI-STEMI points are awarded to the patients, However, I don't understand how the SCAMI-STEMI points led to different scores if you used the same methods as the one to develop the CAMI-STEMI score"

The authors' response wasn't still so clear enough for me. I still cannot understand a clear difference between CAMI and SCAMI methods! As far as I read between lines, I think the authors deliberately drop lab data to "simplify" the old CAMI score towards the novel SCAMI one. If so, you must spell it out as objective! Furthermore, please compare the CAMI and SCAMI performances side by side: this is quite important, for example using ROC curves with their respective AUC! I understand that such data is present in the old paper, but I need to see that in the current manuscript!

Re：Thank you for your comments. We apologize that our previous response were not clear enough. First, we spell out our objective as follows in abstract and manuscript as follows:

Abstract:

“Objective: To simplify our previous risk score for predicting in-hospital mortality risk in patients with non-ST segment elevation myocardial infarction (NSTEMI) by dropping lab data.”

Manuscript:

“The objective of our study is to drop lab data from the previous CAMI-NSTEMI risk score”.

In addition, we also compared the diagnostic performance between SCAMI-NSTEMI score and the original CAMI-NSTEMI score. Although difference achieved statistical significance, the absolute

difference was small (0.2) given that SCAMI-NSTEMI score contains fewer variables and more simple. We added this part in the manuscript as follows:

“We first compared the diagnostic performance between SCAMI-NSTEMI score and the original CAMI-NSTEMI score. AUC value for CAMI-NSTEMI score was greater than that for SCAMI-NSTEMI score within the entire cohort (0.8080 vs. 0.7819, p<0.0001 for comparison, Supplemental Figure 1).”

2-Following along, with this train of thought, saying that there is a "delay" in order to get lab data seems very difficult to understand! As an international reader. I am not convinced about this argument, because cardiac enzymes are also lab data needed to diagnose NSTEMI. I am puzzled about how cardiac enzymes are more readily to be interpreted by a physician taking a decision regarding NSTEMI patients as compared to more "basic" lab data such as WBC, kidney function and other ones. The fact that such "basic" labs are hard to read can explain why reviewer #2 is as surprised as me that patients are extremely delayed in the stratification and subsequent treatment: but it doesn't solve the issue that such physician can bypass the NSTEMI diagnosis with a very "complicated" lab test such as cardiac enzymes, skipping other more "basic" blood tests,

First, we apologize that we don’t quite get your point and we really appreciate it if you can specify how we should revise this part. As far as we understand, you want to ask why basic lab data were included in the original risk score, but cardiac enzymes (which was necessary for NSTEMI diagnosis) wasn’t included. This is because CAMI registry was a multicenter registry including 108 participating hospitals. Type of cardiac enzymes and the corresponding normal range of cTn differs across hospitals. Therefore, we included basic lab data rather than cTn. In addition, approximately one out of six hospitals doesn’t have the capability to examine troponin level. To allow for broad application of CAMI-NSTEMI score, we didn’t include cardiac enzyme but included basic lab data. Regarding the current study, the objective is to further simplify CAMI-NSTEMI score by dropping lab data and to allow for early risk stratification at first medical contact.

Reviewer: 2

Reviewer Name: Ana Teresa Timoteo

Institution and Country: Santa Marta Hospital, Portugal

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The authors answered properly to my comments.

Re: Thank you for your comments.

VERSION 3 - REVIEW

REVIEWER	Hedley Quintana Gorgas Memorial Institute for Health Studies
REVIEW RETURNED	25-Jul-2019

GENERAL COMMENTS	Let me quote the authors first: "...you want to ask why basic lab data were included in the original risk score, but cardiac enzymes (which was necessary for NSTEMI diagnosis) wasn't included...." Reviewer: I understand that cardiac biomarkers are not relevant in the simplified score, and I am deeply sorry the authors about this misunderstanding! My queries can be summarized as follows: 1-Are the results of cardiac biomarkers needed for non-ST elevation MI diagnosis more readily available than white blood cell counts and creatinine which are now omitted in the new score? 2-If the answer to the previous question were "yes", please state so in the manuscript and you'd solved my query. If it were "no", you have to justify which benefits of not ordering these labs. For example, reduced costs for the hospital or health system, or you can give another strong convincing argument.

VERSION 3 – AUTHOR RESPONSE

Re: Thank you for your comments and we appreciated your explanation. Regarding the first query, our answer was "yes", since cardiac biomarker is necessary for NSTEMI diagnosis. We have also stated this in "methods"-"CAMI-NSTEMI score" subsection as follows:

"Although cardiac biomarkers are more available than serum creatinine level and white blood cell count, CAMI-NSTEMI risk score didn't include cardiac biomarkers because CAMI registry was a multicenter registry including 108 participating hospitals. The type of cardiac enzymes and the corresponding normal range differed across hospitals. Including cardiac biomarkers may reduce the diagnostic performance of the risk score."