

## Peer Review File

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### Reviewer A:

**Comment1:** This study is not a prospective study. It is a retrospective study in patients with STEMI and a control group without CAD on coronary angiography. The indication for angiography in the control group is not well described. This should be mentioned in more detail and also the final diagnosis of these control patients as this could also have some impact of the interpretation of the data.

**Reply1:** Thanks for your suggestion. A total of 129 patients who received coronary angiography to exclude coronary heart disease (that is, stenosis of each branch of coronary artery cavity < 50%) were selected as the control group in the above hospitals during the same period. These include coronary atherosclerosis, coronary muscle Bridges, coronary slow flow, and complete coronary normality.

**Changes in the text:** we added some data. (see Page 6, line 122-125)

**Comment2:** The additional value of cIMT, carotid plaque and Hcy compared with traditional risk factors is well described and analyzed for independent predictive value. However, it seems not clear if these markers have also additional value to predict STEMI compared with established cardiovascular risk score (e.g. Framingham, SCORE). The additional value in the C-statistic should be demonstrated of these markers compared to such a score.

**Reply2:** Thanks for your suggestion. Since this study is retrospective and the sample size is limited, the scheme we designed is only to add relatively new risk factors and parameters reflecting vascular status on the basis of traditional risk factors in an attempt to explore the added value of these new factors, and explore the clinical feasibility through the nomogram model. But we are relatively cautious in making direct comparisons with established cardiovascular risk score. In fact, thank you very much for your guidance and suggestions, which provide valuable suggestions for us to make the next research direction. If we can do a multicenter, large sample prospective study, we are excited and look forward to comparing such a model with established cardiovascular risk score.

**Changes in the text:-**

**Comment3:** It is well known that carotid plaque predicts cardiovascular events better than cIMT alone. It is not clear, if this is also so in this presented study. Furthermore, not only the present of plaque but also the plaque burden and plaque morphology can predict future events. Is there any information on plaque burden (e.g. plaque area) or plaque morphology (echogenicity) that could be included in these analysis?

**Reply3:** Thanks for your suggestion. Based on the OR value and the area under the curve, it seems that carotid intima-media thickness is more sensitive than carotid plaque in our study. And this result may be attributed to the bias referred to in the limitations. At present, we only include the detection rate of plaque. In the later

research and clinical work, we will pay attention to and collect data such as plaque burden and plaque morphology.

**Changes in the text:-**

**Reviewer B:**

**Comment1:** Many of the statements in this section need to be supported by quotes (all the risk scores, scoring systems accuracy still controversial, prior studies on homocysteine and carotid intimal media thickness, etc.)

**Reply1:** Thanks for your suggestion. We added some reference to support the statements.

1. Dong Zhao, Jing Liu, Wuxiang Xie, et al. Cardiovascular risk assessment: a global perspective. *Nat Rev Cardiol* 2015;12(5):301-11.

2. Anna Kabłak-Ziembicka, Tadeusz Przewłocki. Clinical Significance of Carotid Intima-Media Complex and Carotid Plaque Assessment by Ultrasound for the Prediction of Adverse Cardiovascular Events in Primary and Secondary Care Patients. *J Clin Med* 2021;10(20):4628.

3. Mainak Biswas<sup>1</sup>, Luca Saba<sup>2</sup>, Tomáš Omerzu, et al. A Review on Joint Carotid Intima-Media Thickness and Plaque Area Measurement in Ultrasound for Cardiovascular/Stroke Risk Monitoring: Artificial Intelligence Framework. *J Digit Imaging* 2021;34(3):581-604.

**Changes in the text:** We added some reference to support the statements. (see Page 3, line 63) The order of subsequent references is adjusted in turn.

**Comment2:** “exploring more scientific risk scoring systems”. Those score systems were obtained with appropriate statistical and scientific approach. They are outdated because they do not use the new risk factors, but still generated from a good scientific work. I would suggest using the term “scientific” to more “predictive” or “sensitive” ...

**Reply2:** Thanks for your suggestion. We have modified our text as advised.

**Changes in the text:** Thanks for your suggestion. (see Page 2, line 26; Page 3, line 67; Page 4, line 88)

**Comment3:** Please move the definition of absence of coronary artery disease where the authors wrote the other definitions.

**Reply3:** Thanks for your suggestion. We have modified our text as advised.

**Changes in the text:** We have modified our text as advised (see Page 5-6, line 120-125).

**Comment4:** In the exclusion criteria: “previous use of lipid-regulating drugs”. None of the patients in this study were on statins?

**Reply4:** Yes. Because the independent variable we included was lipid levels rather than the presence or absence of hyperlipidemia, so we excluded patients who were using statins in the past, considering the effect of statins on lipid levels.

**Changes in the text:** see Page 5, line 102

**Comment5:** “according to ASE”; please spell out.

**Reply5:** Thanks for your suggestion. We have modified our text as advised.

ASE: **American Society of Echocardiography**

**Changes in the text:** We have modified our text as advised (see Page 7, line 147).

**Comment6:** Nomogram is a quite “malleable” or “flexible” statistical model that can be “guided” towards the preferred direction based on the weight the statistician gives to each variable. Basically, the statistician has the possibility to manipulate the direction of the results. However, the authors showed interesting results.

**Reply6:** Nomogram is used to predict the onset, progression, and outcome of diseases with multiple variables in clinical studies. The basic principle is to build a multi-factor regression model (such as Logistic regression, Cox regression, etc.), assign a value to each value level of each influence factor according to the contribution degree of each influence factor in the model to the outcome variable (the size of the regression coefficient), and then add each score to get the total score. Finally, the predicted value of the outcome event is calculated by the function transformation relationship between the total score and the probability of the outcome event. So it's a further visualization of the results of the regression model.

**Changes in the text:** We listed the instructions(see Page 14-15, line 336-343).

**Comment7:** Please reduce the length of the biochemical explanation of homocysteine. This should be accomplished with 2-3 lines.

**Reply7:** Thanks for your suggestion. We have modified our text as advised.

**Changes in the text:** We have modified our text as advised (see Page 12, line 273-275).

**Comment8:** The sample size is quite small for this type of study. The control group of patients with chest pain cannot represent the general population. The authors can say that Hhcy and increased CIMT/carotid plaque could be independent risk factors or predictors of STEMI in patients seen for chest pain. The authors cannot generalize the results to the general population.

**Reply7:** Thanks for your suggestion. We have modified our text as advised.

**Changes in the text:** We have modified our text as advised (see page3,line52; Page 15, line 365-366).

**Reviewer C:**

**Comment1:** Previous studies (such as the one you cited Am J Transl Res 2021;13:2724-2730) have shown that also C-reactive protein (CRP) and cystatin C (Cys-C) levels have been associated to worse prognosis in patients with acute myocardial infarction. Why did you choose to include only CIMT and homocysteine levels in your analysis and not these other risk factors as well?

**Reply1:** Thanks for your suggestion. We are sorry that we did not include C-reactive protein and cystatin c and other indicators in this study. Because this study was a

retrospective study, and there were many missing data in these two indicators during collecting data, so we did not include them in the study. However, in the follow-up research and clinical work, we will strengthen the attention and management of these data.

**Comment2:** Page 3, Line 94: The control group seems to include patients with mild to moderate coronary artery disease. As such, I would turn the sentence into “A total of 129 patients who received coronary angiography to exclude significant coronary artery disease ...” Page 8, Line 324 should be modified as well. In addition, patients with nonobstructive CAD may have a different risk profile than patients without CAD, and this may have contributed to the bias you refer to in the limitations. Please discuss.

**Reply2:** Thanks for your suggestion. We have modified our text as advised.

**Changes in the text:** We have modified our text as advised (see Page 2, line 32-33; Page 13, line 312-313).

**Comment3:** The discussion section is too long (for example when discussing metabolic pathways of homocysteine) and at times repetitive (Page 7, Line 297-305; Page 8, Line 342-353). Please shorten. Also, please remove the numerical results already reported in the Results section (Line 255-260; 328-331).

**Reply3:** Thanks for your suggestion. We have modified our text as advised.

**Changes in the text:** We have modified our text as advised (see Page 12, line 273-275; Page 11, line 262; Page 14, line 318-319; Page 14, line 331).

**Comment4:** In addition, I would ask the authors to focus the discussion more on comparing their model with current scoring systems for cardiovascular disease risk: what risk scores are currently available for STEMI? Are the C-indexes of these predictive models known? Does your model appear to be better than other scores in predicting STEMI risk?

**Reply4:** There is currently no specific risk score for the occurrence of acute ST elevation myocardial infarction, and there are only established cardiovascular risk score (e.g. Framingham, SCORE). Because our study was retrospective and had a limited sample size, we are relatively cautious in making direct comparisons to established cardiovascular risk score.

**Comment5:** Table 1: one box contains the term “blood”: are you referring to blood platelet count? There seems to be a line missing.

**Reply5:** Thanks for your suggestion. We have revised "blood" to "PLT," which is an abbreviation of "blood platelet".

**Changes in the text:** We have modified our text as advised (see Table 1).

**Comment6:** Please spell acronyms below the tables.

**Reply6:** Thanks for your suggestion. We spell acronyms below the tables.

**Changes in the text:** we added some data (see Table 1 and Table 2).

**Comment7:** Page 5, Line 190-192: please rephrase, I would suggest “variables found to be significant at univariate analysis (...) were included in the multivariate logistics regression analysis. In general, the manuscript would benefit from a thorough proofread by someone with full professional proficiency in English to improve grammar.

**Reply7:** Thanks for your suggestion. We have modified our text as advised.

**Changes in the text:** We have modified our text as advised (see Page 9, line 196-198).