Author’s response to reviews

Title: A Simple Prediction Model to Estimate Obstructive Coronary Artery Disease

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Version: 1 Date: 20 Nov 2017

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November 19, 2017,

Fabrizio D'Ascenzo

Editor-in-Chief

BMC Cardiovascular Disorders

Dear, Fabrizio D'Ascenzo

Many thanks for reviewing our manuscript titled “A Simple Prediction Model to Estimate Obstructive Coronary Artery Disease in Patients with Suspected Coronary Artery Disease”. We have made substantial changes according to the reviewers’ comments. We have also addressed their comments as below.
Reviewer reports:

Shih-Hsien Sung (Reviewer 1): Editor

Interesting paper.

DO the authors tried to relate risk factors with kind of plaque evaluated with imaging? (quote on PMID: 26508517)

Response: Thank you for your sincere comments. We acknowledged that there was lack of kind of plaque evaluated with imaging (OCTs or IVUS) and stated it in the discussion and limitation section. We have added “In addition, we would investigate the risk factors of dangerous culprit lesions with culprit plaque rupture (CPR) and thin-cap fibro-atheroma (TCFA), such as hypertension, advanced ages, diabetes mellitus or hyperlipidemia, which were evaluated by optical coherence tomography (OCT) or intravenous ultrasound (IVUS) in the futures [25].” (Paragraph 1, Page 15) in Discussion section and “Fourthly, our study only focused on the anatomical result of angiography without kind of plaque evaluated with imaging (OCTs or IVUS), such as culprit plaque rupture (CPR) and thin-cap fibro-atheroma (TCFA), which could trigger acute coronary syndrome (ACS).” (Paragraph 1, Page 16) in Limitation section in the revised manuscript.


Chen et al. have conducted an interesting study to compute a modified Framingham risks score (FRS) for the prediction of obstructive coronary artery disease (OCAD). They demonstrated additional incorporations of anemia, hs-CRP and LVEF into Framingham risk score might improve the predictive power of OCAD in a total of 1262 subjects undergoing CAG. The results are exciting, however, I have some comments.
1. The authors suggested the modified FRS outperform FRS by ROC analysis. The authors may further calculate the net reclassification improvement to show how much improvement by using modified FRS to predict OCAD.

Response: Thank for your sincere suggestions, we have added “Our simple modified Framingham risk score (FRS) might outperform FRS by ROC analysis, while we could not further calculate the net reclassification improvement to show how much improvement by using modified FRS to predict OCAD. Because FRS was to predict the 10-year risk of CAD, whose endpoint rate was lower than 15%, however, the modified FRS was to predict the OCAD with higher rate (more than 50%) for patients with suspected CAD, we could not find out ideal overlapping parts, ever after adopting all the cut-off value of endpoint rate [3].” (Paragraph 2, Page 12) in Discussion section in the revised manuscript.

2. OCAD is defined by >=50% stenosis in at least one major coronary vessel. Is it referred to diameter or lumen area?

Response: Thank you for your sincere remind. We are sorry to miss the statement of measurement method of coronary stenosis and changed the statement “The primary endpoint of our study was OCAD, which was defined as (≥50% stenosis by diameter in at least one major coronary vessel based on CAG)”in the (Paragraph 2, Page 7) in Methods section in the revised manuscript.

3. Given that LVEF is an important predictor, please describe how LVEF is measured.

Response: Good remind! Thank you very much! We have added “Left ventricular ejection fraction (LVEF) was calculated by using the biplane modified Simpson’s rule by Two-Dimensional Echocardiography” in the (Paragraph 1, Page 7) in Methods section in the revised manuscript.

4. FRS is for the prediction of the development of CHD/atherosclerosis. What is the clinical application of the modified FRS? It is to reduce the invasive procedure?
Response: Thank you for your comments, we have added “In other word, the simple MFS model will improve the precision of risk stratification for more physicians, to increase invasive procedure among high risk patients, but to reduce invasive procedure among low risk patients.” (Paragraph 2, Page 13) and stated “More expensive or limited diagnostic tests in the risk stratification in a large community population can be addressed by the MFS model.” (Paragraph 2, Page 13) in Discussion section in the revised manuscript.

Minor comments:

1. How did the authors compute model selection? How did they conduct "Backward elimination approach…"? Are all the variables in Table 1 enrolled in the multivariate analysis?

Response: Good suggestions, we did enroll all the variables in Table I in the multivariate analysis, we revised “Significant predictors from the univariate analysis and non-significant variables with potential clinical relevance, including traditional Framingham risk factors, were evaluated as candidate factors (age, sex, smoking status, diabetes, CHO, high-density lipoprotein cholesterol [HDL-C], hypertension, baseline systolic blood pressure, and diastolic blood pressure, high-sensitivity C reactive protein [hs-CRP], left ventricular ejection fraction [LVEF], anemia, weight, serum creatinine, serum albumin, uric acid, HbA1c, Lp(a), blood urea nitrogen, ) to determine their association with OCAD in a multivariable model [3]. Collinearity and interaction between variables were also evaluated. Backward elimination approach was employed to create a reduced model by successively removing non-significant covariates until all the remaining predictors (age, sex, CHO and HDL-C, hypertension, smoke, anemia, hs-CRP and LVEF) are statistically significant (P<0.1). Then, we manually investigated the contribution of the remaining predictors to find out the final predictors including age, sex, CHO and HDL-C, hypertension, anemia, hs-CRP, LVEF.” (Paragraph 3, Page 7- Paragraph 1, Page 8) in Methods section in the revised manuscript.

2. "…similarly, the modified Framingham risk factors model had a higher area under the ROC curve than the Framingham risk factors model (c-statistic, 0.719 vs. 0.693; P=0.059)…” A P value of 0.059 is not significant.

Response: Thank you for your good comments, yes, there was no significant improvement for modified Framingham risk factors mode, however, our present study focused on the modified Framingham risk score ant stated “MFS provided adequate goodness of fit (P=0.43) and showed
better performance than Framingham score (c statistic, 0.703 vs. 0.521; P<0.001) in predicting OCAD” (Paragraph 3, Page 3) in Abstract section or (Table 3) in the revised manuscript.

3. In “Figure legends”, Figure 1 is not study flow.

Response: Thank you for your sincere remind. We are sorry to mistake the statement and revised as “Figure 1. Bimodal Modified Framingham scoring (MFS) distribution and Supplementary Figure 1. Study flow” in Figure legends in the revised manuscript.

Leonid Goubergrits (Reviewer 2): The manuscript "A simple prediction model to estimate obstructive coronary artery disease in patients with suspected coronary artery disease" propose and test the modified Framingham scoring by adding of tree parameters (anemia, high-sensitivity C-reactive protein and left ventricle EF).

The new model has higher predictive power and seems to be a better predictive model.

Major Comments:

The new score model should be described in the manuscript in more details including a definition of scoring for protein and EF parameters. In general only figure 3 shows the new model.

Response: Thank you for your sincere remind! We have added “High-sensitivity C reactive protein was tested with a Beckman Coulter Immage immunobiochemistry system (USA) using nephelometry (unit: mg/L). Left ventricular ejection fraction (LVEF) was calculated by using the biplane modified Simpson’s rule by Two-Dimensional Echocardiography.” (Paragraph 1, Page 7) in Methods section in the revised manuscript.

You noted that a logistic regression model was developed. Please, include the model (equation) into the manuscript.
Response: Thank you for your good suggestions, we have added “and our model equation was
\[ F(y) = -0.0468 + 0.0204\text{(age)} + 1.0961\text{(sex)} + 0.5444\text{(hypertension)} + 0.0055\text{(CHO)} - 0.0257\text{(HDL-C)} - 0.022\text{(LVEF)} + 0.5677\text{(anemia)} + 0.0254\text{(hs-CRP)} \] (Table 2)” (Paragraph 3, Page 9) in Results section in the revised manuscript.

According to your text, I suppose that you tested a large set of parameters before the final model was elaborated. It is not clear which parameters you tested.

Response: Thank you for your comments, yes, we have revised “Significant predictors from the univariate analysis and non-significant variables with potential clinical relevance, including traditional Framingham risk factors, were evaluated as candidate factors (age, sex, smoking status, diabetes, CHO, high-density lipoprotein cholesterol [HDL-C], hypertension, baseline systolic blood pressure, and diastolic blood pressure, high-sensitivity C reactive protein [hs-CRP], left ventricular ejection fraction [LVEF], anemia, weight, serum creatinine, serum albumin, uric acid, HbA1c, Lp(a), blood urea nitrogen,) to determine their association with OCAD in a multivariable model[3]” (Paragraph 3, Page 7- Paragraph 1, Page 8) in Methods section in the revised manuscript.

Minor Comments:

I recommend to change the title of the manuscript in order to avoid a use of "coronary artery disease" term twice in the title.

Response: Good suggestion, we have revised the title as “A Simple Prediction Model to Estimate Obstructive Coronary Artery Disease”.

Described in the text figure 1 is a study flow, but the figure included in the manuscript was score distribution.

Response: Thank you for your sincere remind. We are sorry to mistake the statement and revised as “Figure 1. Bimodal Modified Framingham scoring (MFS) distribution and Supplementary Figure 1. Study flow” in Figure legends in the revised manuscript.

Please add also a definition of hypertension.
Response: Thank you for your sincere suggestions, we have added “Hypertension was definite present if the participant was under treatment with antihypertensive medication or systolic≥140 mm Hg or diastolic ≥ 90 mm Hg [3].” (Paragraph 2, Page 7) in Methods section in the revised manuscript.

I wish a better comparison between two models may be visualized by a figure.

Response: Thank you for your sincere suggestions, yes, we have revised the Figure 2 in the revised manuscript as follow:

Figure 2. Receiver operating characteristic curve