Author’s response to reviews

Title: Combined value of left ventricular ejection fraction and the Model for End-Stage Liver Disease (MELD) score for predicting mortality in patients with acute coronary syndrome who were undergoing percutaneous coronary intervention

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Author’s response to reviews:

February 17, 2018

Dear Editor

We thank for your decision about our manuscript. We resubmit the revised manuscript (ID BCAR-D-18-00037R1) entitled with “Combined value of left ventricular ejection fraction and the Model for End-Stage Liver Disease (MELD) score for predicting mortality in patients with acute coronary syndrome who were undergoing percutaneous coronary intervention ”. Corrections suggested by reviewers were written in red color. Our response to reviewers were provided on separate pages.

Thank you for your time in considering our submission.

Sincerely Yours.

Eyüp Avci MD on behalf of authors

Comment 1: I would like to say the percentage of diabetics patients admitted for STEMI, and for NSTEMI. As second, I would like to know the percentage of incretin users vs. never incretin users in STEMI diabetics, and in NSTEMI diabetics. In fact, incretin therapy may
reduce major adverse cardiac events (MACE) in diabetics admitted for STEMI events (Effects of incretin treatment on cardiovascular outcomes in diabetic STEMI-patients with culprit obstructive and multivessel non obstructive-coronary-stenosis. Diabetol Metab Syndr. 2018 Jan 3;10:1), and for NSTEMI events (Non-ST-elevation myocardial infarction outcomes in patients with type 2 diabetes with non-obstructive coronary artery stenosis: Effects of incretin treatment. Diabetes Obes Metab. 2017 Sep 26). This is relevant, and it may impact your study outcomes. Please respond to this question looking these references. The incretin effect may be explained at molecular level by interaction with complex inflammatory and apoptotic pathways (Sirtuin 6 expression and inflammatory activity in diabetic atherosclerotic plaques: effects of incretin treatment. Diabetes. 2015 Apr;64(4):1395-406), leading to a unique protective and modulative effect on atherosclerotic plaque function, and stability. Please discuss this point and this reference. Can you report the serum level of injury biomarkers as Troponine I and CK-MB, and stress biomarkers as BNP common used in the acute coronary syndromes and heart failure? In fact cardiac biomarkers may predict mortality in subjects with normal left ventricle ejection fraction (Cardiac Biomarkers Predict 1-Year Mortality in Elderly Patients Undergoing Hip Fracture Surgery. Orthopedics. 2017 May 1;40(3):e417-e424), and in patients affected by heart failure (NT-proBNP, IGF-I and survival in patients with chronic heart failure. Growth Horm IGF Res. 2007 Aug;17(4):288-96). Please discuss these two points, and introduce these biomarkers in your article, in your tables and in multivariate analysis. Do BNP serum levels predict clinical outcomes in your study? Please respond to this question. Please include a more detailed description about stenosis length, diameter, lesion extension.

Reply: Thank you these suggestions.

- 250 patients had a history of DM in our study. Data regarding incretin usage in the present study, 45 patients with DM were using this agent. There were 32 patients in survivor group, and 13 patients in non-survivors group,(5% vs 7%, p = 0.224). Therefore, as the use of this agent in our study was very low compared with above-mentioned studies, its effect on mortality in present study could not be assessed. This situation was added to limitation in discussion.

- Serum peak level of troponine –I was measured in both patients with STEMI and NSTEMI. Troponine –I levels were comparable between groups. [30 (18-51) vs 28 (19-44), p = 0.444] for STEMI patient; [2.3 (0.5-12.4) vs 1.8 (0.6-4.2), p = 0.853] for NSTEMI. This result has been presented in revised Table 2. However, as there was not difference between groups, this parameter was not included in multivariate analysis.

- BNP level was not measured in present study. Therefore, we could not evaluate effect of BNP on mortality. This situation was added to limitation in discussion.
- In our study, coronary artery narrowing was visually assessed and reported as percentage luminal diameter stenosis, and also culprit lesion was evaluated by visual estimation. Lesion size and length of infarct related artery or culprit lesion were parallel to both the size and length the used stents. Also, the extent of CAD burden in culprit lesion was defined as the total length in millimeters of culprit lesion in a major epicardial vessel. An important imitation of this study was that syntax score indicating complexity of coronary artery lesions was not used in present study.

- Multivessel disease was defined as at least 50% diameter stenosis of two or more epicardial coronary arteries, or left main by visual estimation

Reviewer 1:

Comment 1: Evaluation of Syntax score should be added, or if not added in limit.

Reply 1: Thank you these considerations. In our study, we did not evaluate Syntax score. This limitation was added in last paragraph of discussing section in main text.

Comment 2: In patients with liver disease related to depressed, also right ventricle function should be evaluated. If not it should be put in limitation.

Reply 2: Thank you these considerations.

In our study, patients with right ventricle dysfunction or right ventricular dilatation were excluded from this study. Therefore, association hepatic dysfunction with right ventricle was not evaluated. Also, we did not evaluated the association between depressed EF and hepatic dysfunction in this study. These topics were added to limitations in last paragraph of discussion section in main text.

Comment 3: Kind of stent along with length of dapt have been linked to events

(quote on PMID: 29020300)

Reply 3: Thank you this criticism. Both aspirin (100 mg/day) and clopidogrel (75 mg /day) or prasugrel (10 mg /day) or tigacrelor (90 mg twice daily) were maintained for at least 12 months, followed by indefinite single antiplatelet therapy in our study. The above-mentioned sentence which was written red color has been added to treatment section of main text.

Comment 4: Subgroup analysis for age and gender should be added
Reply 4: Subgroup analysis according to both gender and age was performed. For age, age was categorized as < 65, and ≥ 65 years. Also, this analysis was presented as supplement tables 6, 7, 8 (for gender), and 9, 10, 11 (for age).

- The above-mentioned sentence has been added to results section of main text.

Reviewer 2:

Comment 1: Patients with ACS did not specify whether they had Tricuspid stenosis, insufficiency, or right heart failure while the patient population was selected in the "Method" section. Is this patient group (patients with ACS with Tricuspid stenosis, insufficiency or right heart failure) excluded from the study?

Reply 1: In fact, at the beginning of our study these patients were not included in this study in the beginning so it was not mentioned in part of excluded patient. In our study, at the beginning 910 patients were included in this study. 29 patients with moderate to severe tricuspid regurgitation and right ventricular dilatation/failure were excluded from the our study at the beginning.

- The sentence in method section “We retrospectively evaluated 871 consecutive patients with ACS treated with PCI from April 2008 and July 2015. To be enrolled in the study, patients had to have angiographically proven ACS and baseline INR, sCr, and TB measurements. Nine patients with incomplete data, two with a history of liver cirrhosis, and fourteen who had received anticoagulant therapy (vitamin-K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors, or enoxaparin) were excluded from the analysis.” was changed as “We retrospectively evaluated 910 consecutive patients with ACS treated with PCI from April 2008 and July 2015. To be enrolled in the study, patients had to have angiographically proven ACS and baseline INR, sCr, and TB measurements. Nine patients with incomplete data, two with a history of liver cirrhosis, fourteen who had received anticoagulant therapy (vitamin-K antagonists, direct thrombin inhibitors, direct factor Xa inhibitors, or enoxaparin), twenty nine patients with right ventricular dilatation/failure and moderate to severe tricuspid regurgitation were excluded from the analysis.”

Comment 2: Parameters for right ventricular EF, tricuspid valve insufficiency, stenosis or pulmonary hypertension have not been specified in the section "Echocardiographic analysis".

Reply 2: We agree with the reviewer. We performed all measurements according to standard American Society of Echocardiography guidelines. Tricuspid regurgitation severity was quantified and classified on an ordinal scale as absent, mild, moderate, and severe. To estimate of right atrial (RA) pressure during echocardiography, we used 2-dimensional and Doppler imaging characteristics of the inferior vena cava and hepatic veins and graded as 5, 10, 15, and
20 mm Hg. Right ventricle (RV) systolic pressure was calculated as 4 times the square of the peak trans–tricuspid valve systolic regurgitant velocity (according to the simplified Bernoulli equation) plus the estimated RA pressure.

RA and RV enlargement and RV systolic function were semiquantitatively described as normal, mild, moderate, or severe enlargement or dysfunction in accordance with an ordinal qualitative scale based on visual assessment.

--- The above-mentioned sentence which was written red color has been added to Echocardiographic analysis in the main tex. Also, we performed rearrangement in reference of this sentence.

Comment 3: There is a sentence beginning with 'All of them are associated with' on the second page of the "Discussion" section. This sentence (associated with) is repeated twice. Please correct that.

Reply 3: Thank you this suggestion. We corrected this sentence in discussion of main text.

Comment 4: On the third page of the "Discussion" section there is a paragraph starting with "MELD score was firstly developed to predict mortality in patients ". This paragraph is unnecessary. It would be more appropriate if you exclude this paragraph.

Reply 4: We agree with the reviewer. The paragraph starting with "MELD score was firstly developed to predict mortality...... " was removed from discussion section. Therefore, references belonging to the paragraph (references 47,49) was deleted, and references were reorganized.

Comment 5: The number of references is too much. Please re-arrange the 'BMC Cardiovascular Disorders Journal's according to the "Reference Writing Rules".

Reply 5: We agree with the reviewer. We tried to decrease the number of reference. However, we had to add new references to refer to the topics recommended by the reviewers and to be corrected.

To decrease the number of reference the following sentence and references were removed from main text.

--- Another study found that greater bilirubin levels were related to favorable coronary collateral flow in patients with chronic total occlusion [23].

---- Sutton et al. showed that lower EF was associated with mortality and hospital readmission in older patients after MI [43].
LVEF was more predictive than GRACE score for mortality in Korea Acute Myocardial Infarction Registry Score (46).

References 5, 13, 23, 41, 46, 47, and 49.

References 12-13, 44-47 as new references were added to references section in main text, and these references were written red color.

Additional corrections

--The sentence “……serum albumin (SA) levels were lower in non-survivors than survivors.----SA levels (r = -0.24, p < 0.001) ….” was removed from laboratory finding of results section in main text, because the level of SA was only present in 346 patients.

-----Stent sizes and lengths were mistakenly expressed as [ 3.4 ± 0.6 vs 3.5 ± 0.6, 23 (16-49) vs 27 (19-53), respectively ]. These values were corrected. Analysis was performed again in all groups. The corrected parameters were provided in revised Table 3.

- In result section of abstract, a p value which was compare MELD with MELD plus LVEF was mistakenly expressed as < 0.001. This value was corrected as < 0.05.

Comparison

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