Author’s response to reviews

Title: The Predictive Value of the Prognostic Nutritional Index for Postoperative Acute Kidney Injury in Patients Undergoing On-Pump Coronary Bypass Surgery

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Version: 1 Date: 07 Mar 2019

Author’s response to reviews:

March 7, 2019

Dear Editor

We thank for your suggestions. We are sending the corrected manuscript JCST--D-19-00017 entitled "The Predictive Value of the Prognostic Nutritional Index for Postoperative Acute Kidney Injury in Patients Undergoing On-Pump Coronary Bypass Surgery”. Corrections suggested by you were written in red color. Our response to you was provided on separate pages.

Thank you for your time in considering our submission.

Sincerely Yours.

Ahmet Dolapoglu MD on behalf of authors

COMMENTS

Reviewer #1:

The paper for review is a single institutional retrospective observational study comprised of 336 consecutive patients with normal serum creatinine levels elective undergoing on-pump CABG. The purpose of the study was to identify postoperatively patients who developed AKI by Acute Kidney Injury Network (AKIN) criteria based on the occurrence of creatinine changes within the
first 48 h after CABG surgery. The authors used common pre and postoperative variables as well as prenutritional index scores calculated using the following formula: PNI = serum albumin levels (g/dl)

\[ \text{PNI} = 10 + \text{total lymphocyte count (per mm}^3) \times 0.005. \]

The authors preoperative bias was that decreased immunonutritional status as indicated by PNI might influence postoperative outcome which in this study was the incidence of AKI.

AKI developed in 82 (24.4%) of all patients. In univariate analysis, the PNI was independently predictive of AKI (OR: 0.829, 95% CI: 0.783-0.877, p < 0.001). Moreover, C-reactive protein (CRP), a history of diabetes mellitus, and positive inotropic usage were independent risk factors for AKI. Using multivariate analysis adding PNI to the process improved greatly the discrimination of the predictive occurrence of AKI.

The authors concluded that decreased PNI could be associated with AKI.

The authors are to be congratulated on recognizing (as others have reported) a preoperative factor which can be a surrogate for poorer postoperative outcomes. Unfortunately the study has a binary conclusion, that is either a patient does or doesn't have AKI. Further, although PNI can be considered a marker of nutritional status the relative arbitrary limits of what is considered normal and abnormal leaves some area of gray. My questions for the authors are as follows:

1. There is a marked difference in mortality between AKI and non-AKI patients, as well as double the rate of inotropic usage, and use of IABCP. This would indicate the AKI group had worse hemodynamics intra and postoperatively setting them up for AKI. How do the authors differentiate these factors from those related to PNI.

Reply 1: Thank you this criticism.

We performed separate analysis in patients with worse hemodynamics. We found difference between patients with positive inotrope usage and without these treatment regarding PNI values (47.21 ± 7.46 vs 49.35 ± 5.76, p = 0.008). However, there was no difference between two groups in terms of PNI values ( patients with use of IABCP vs without use of IABCP, 45.89 ± 7.57 vs 48.95 ± 6.19, p = 0.127). As shown in Table 3, these parameters were included in multivariate analysis.

2. In patients with low PNI as a separate analysis what were the results of subset analysis?

Reply 2: Thank you this suggestion.

We divided to the patients two groups according to PNI values for subgroup analysis; low PNI or high PNI.
Low PNI (n = 110) and high PNI (n = 226) groups were defined as patients having values in the third tertile (˂ 46.50) and higher 2 tertiles (≥ 46.50), respectively. This sentence was added to last paragraph in methods section of definition of the PNI in main text.

The rate of AKI was higher in low PNI group compared with high PNI group (54% vs 13%, p < 0.001). Also, low PNI group had higher mortality rate than high PNI group (10% vs 3%, p = 0.001).

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The last paragraph in the results section of main text was rearranged as...

“In sub-group analysis, the rate of AKI was higher in low PNI group compared with high PNI group (54% vs 13%, p < 0.001). Also, low PNI group had higher mortality rate than high PNI group (10% vs 3%, p = 0.001).”

3. Unfortunately the authors did not include frailty indices as another indicator of preoperative status. Do they believe that low PNI and frailty are similar in their effects on outcome?

Reply 3: We agree with the reviewer.

In our study AKI was seemed more common in older population. We know that chronological age is not only factor for assessment of frailty. Frailty index for older patients undergoing cardiac surgery includes physical, cognitive, and psychosocial criteria. This index was measured through the patients physical and cognitive test, nutritional status and functional deterioration. Therefore, this index can have similar effect with PNI on the development of AKI. Unfortunately, we did not measure frailty index of patients in our study. As you expressed this index is another marker of preoperative status. Thus, a high frailty score may be associated with the development of AKI.

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The following sentence was added in limitations paragraph of discussion section in main text.

“Also, frailty status which is associated with PNI is an another indicator of preoperative status. Moreover, the overall frailty status of a patient may be correlated renal functional reserve, and therefore it may constitute an independent risk factor for AKI in patients underwent CABG. However, frailty status was not measured in our study..”

4. Believe there is an error in Table 1 as the incidence of IABCP usage in the nonAKI group was 5/254 or 1.9% not 6%

Reply 4: Thank you this criticism.

Unfortunately, we mistakenly expressed the AKI(+) and AKI (-) patients number in both tables 1 and 2. The number of AKI(+) patients was 88, and AKI (-) patients number was 248. All
results were performed according to these numbers. Therefore, the presented percentage and values are correct. [IABP usage, 88/5 (6%) vs 248/5 (2%), p = 0.082]

We corrected the numbers in both tables 1 and 2. Also, table 1 as revised table, and table 2 as revised table 2 were saved.

5. Given the authors conclusion about predictive value of PNI what chances have they made in their preoperative nutritional or physical rehab for patients to improve outcomes?

Reply 5: Thank you this criticism.

Proper assessments of nutritional status of coronary artery patients elective undergoing on-pump CABG can help to minimize (if not prevent) the development of AKI.

I would ask the statistical editor for the predictive power of the 84 patients in the AKI group as well as the selection of variables which have been well described in the past. I would reserve my acceptance of the paper for both this review and answers to the above questions.

Reply: I hope we understand the question correctly.

The mortality also was higher in patients with AKI group that was 17.6 times higher (95% CI, 3.8–81.0) than those without AKI.

Reviewer #2:

I appreciate the opportunity to review this work. briefly, the authors used a single center, retrospective data analysis to evaluate whether the Prognostic Nutritional Index is associated with post CPB CABG outcomes. Unfortunately, I have major concerns with the data interpretation. Indeed, the statistical calculations revealed "significant" differences between the AKI and non-AKI groups, however, review of the actual laboratory values of albumin, lymphocyte count, and CRP reveals no actual clinically significant difference. Even more important: the levels of albumin concentration, lymphocyte count, and CRP are actually either normal or close to the normal range. Hence, any assumption based on normal or close to normal levels would be inaccurate. Other concern is with the clinical significance of the difference in creatinine levels between the subgroups. I find it very hard to make any assumptions based on the almost similar creatinine levels cited by the authors. Finally, I would like to caution the authors that their abstract conclusion is not similar to that they reached in the actual manuscript and is impossible to make based on the data they provided.

Reply: Thank you this criticism.
We reported statistical results in our study. Although the presented values were close to normal range, there were differences between groups regarding the predictors of the development of AKI.

Reviewer #3:

The Authors investigate the predictive value of the Prognostic Nutritional Index (PNI) for the occurrence of Acute Kidney Injury in patients undergoing On-Pump CABG. The PNI level was determined according the following formula: $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count per mm}^3$ proposed by Onodera et Al.

Preoperative PNI is a simple and useful marker to predict clinicopathological features and long-term survival outcome in patients with cancer.

It has been demonstrated that a low PNI affected surgical outcomes in hemodialysis-dependent patients undergoing cardiac surgery and was the most influential factor on length of stay for infants after cardiac surgery.

AKI is the most common clinically important complication in adult patients undergoing open heart surgery, and is associated with increased mortality and morbidity. The identification of risk factors for AKI is an important issue with the aim to prevent and treat this severe complication.

EuroScore, STS score, ACEF score have been studied with this purpose.

The Authors demonstrate that PNI might be a further easy tool for predicting postoperative AKI.

The hypothesis of the present study is original and striking.

Methods and Results are clearly and correctly described

Discussion and Conclusion are congruent with the data reported.

Suggestions

- The Limitations are correctly listed, but the first one ("information on intra- and postoperative hemodynamic conditions") is too important to be left without further clarification. It seems mandatory to complete these data.

- In the Literature, usually, a PNI cutoff value is reported. Did you try to find a cutoff value in your analysis?

Reply 1: Thank you this criticism.
The limitation section of discussion in main text as “The present study had several limitations. We lacked detailed information about the patients’ postoperative hemodynamic conditions, which are known to affect the incidence of AKI development. ……” was rearranged.

Reply 2: Thank you this criticism.

As you expressed, the various cutoff values of PNI were reported. However, these values are different according to the clinical situation (A PNI of 40 was identified in ureter cancer patients, A PNI OF 34 …hemodialysis-dependent undergoing CABG, A PNI of 44 acute coronary syndromes patients treated with percutaneous coronary intervention).

In another study, Keskin et al.(reference 39 in main text) divided in to patients quartiles in their study included coronary artery disease undergoing. CABG. Similarly, we grouped patients as high PNI and low PNI according to the tertiles.