Author response letter to reviewers' comments

Manuscript title: **Correlation of serum albumin and prognostic nutritional index with outcomes following pancreaticoduodenectomy**

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Dear Editor,

Thank you very much for your and the reviewers' thoughtful evaluations and positive review about our manuscript entitled "Correlation of serum albumin and prognostic nutritional index with outcomes following pancreaticoduodenectomy"

In the revision of our manuscript, comments and issues raised by thereviewers have been carefully considered and appropriate changes (highlighted in yellow) have been made. Please find a point-by point response to the reviewers' comments (below).

We appreciated the time and efforts by the editor and reviewers in reviewing this manuscript. We hope that the revised manuscript will now be suitable for publication in your journal

Sincerely yours,

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Response to comments from reviewer,

Reviewer #1 (02438768)

1. This is a well written manuscript reporting interest cases. I would suggest that the authors make an appropriate explanation for Figure 1.
    Response:
    Thank you for your valuable time in reviewing our manuscript. Thank you for the suggestion. Figure 1 demonstrate the ROC curves analysis of the POD 3 PNI. The sensitivity, specificity, PPV and NPV are described in the main text. We have made an explanation for Figure 1.

Reviewer #2 (00058696)

1. Core Tip: a. Sentence 2 starting with "Only serious complications" makes no sense and needs to be rewritten. Sentence 3 starting with "Studies have reported an" needs an ending such as "after abdominal surgeries". Sentence starting with "The independent factors associated with" requires an "of" between "day 3" and "<".
    Response:
    Thank you for your valuable time in reviewing our manuscript. Thank you for the suggestion. We have corrected the sentence.

2. Introduction
    a. when describing references 15, 16, and 20 the authors need to tell us what these abdominal operations are
        Response:
        Thank you for the suggestion. We have added the kind of operation of the references in the sentence.

    b. The reader does not otherwise know whether other authors have examined pancreaticoduodenectomy. The authors should state their

hypothesis in the Introduction prior to their sentences starting with "Thus, the aim of our study

Response:

Thank you for the suggestion. We already stated our hypothesis of the early postoperative PNI in our introduction part "…There have been no studies of the use of early postoperative PNI for predicting serious complications following PD. Thus, the aim of our study was to analyze the risk factors and early postoperative PNI for predicting severe complications following PD."

3. Material and methods:

   a. paragraph 2: "a positive bowel movement"; this is slang language; what appears to be intended is "the occurrence of a".

   Response:

   Thank you for suggestion. We have corrected the sentence.

   b. Paragraph 3: in the sentence beginning with "Delayed gastric emptying was defined", the authors either need to provide a reference for their definition or consider the term "Delayed solid food tolerance"

   Response:

   Thank you for suggestion. Delay gastric emptying (DGE), as defined by the ISGPS, within 30 days after the index operation. DGE was assessed as present if either nasogastric tube insertion after POD 3 or as the inability to tolerate solid food intake by POD 7. We have stated this reference.

   Reference

   Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Buchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic

Surgery (ISGPS). *Surgery* 2007; **142**(5): 761-768 [PMID: 17981197 DOI: 10.1016/j.surg.2007.05.005]

4. Results:

   a. Paragraph 1: in the sentence "The postoperative mortality rate was", when (early or within what time period)?

      Response:

      Thank you for suggestion. The postoperative mortality definition was described in the material and methods section. Postoperative mortality was recorded as the 90-day mortality and in-hospital mortality. The patients who the cause of death did not associated with the postoperative complication were excluded from the study.

   b. In the paragraph for Patient characteristics and operative outcomes in patients, the authors need to insert a p value in the sentence that starts "The patients in the grade III-V complications group".

      Response:

      Thank you for suggestion. We have added the p value.

   c. In the paragraph for Comparison of PNI between grade 0-II and III-V complications, the authors suggest the importance of PNI 40.5. The authors however do not provide us with any of the usual validations factors: sensitivity, specificity, negative predictive value or positive predictive value

      Response:

      Thank you for the suggestion. We have added all these value in the paragraph.

   d. In the paragraph for Analysis of the risk factors for grade III-V complications, the authors list a 95% CI 0.99-1.01 and then state P = 0.03.

Since this confidence interval crosses 1.00 this cannot be statistically significant. Please correct

Response:

Thank you for the suggestion. According to this data, we considered that parameter are not statistically significant.

5. Discussion:

    a. Sentence 2 starting "Serum albumin is a commonly used indicator for evaluation of nutritional status"; well not by nutritionists and so the authors either need to provide strong references for this claim or consider "a common indicator for ongoing inflammatory processes".

    Response:

    Thank you for suggestion. The serum albumin is use in various guidelines for the evaluation of the nutritional status. We have updated the references for this statement.

    b. In paragraph 2 the authors describe the risks of "Hypoalbuminemia"; but is this finding present (mean albumin is 34.1)? If there is no hypoalbuminemia, then this speculative paragraph needs to be altered or removed

    Response:

    Thank you for suggestion. The common cut-off value for hypoalbumin is 3.5 mg/dl and correlated with our finding that the serious complication group have lower serum albumin <3.5 mg/dl. However, the difference value is modest. We have rewrote this paragraph.

    Ref.

    - **Lyu HG,** Sharma G, Brovman E, Ejiofor J, Repaka A, Urman RD, Gold JS, Whang EE. Risk factors of reoperation after pancreatic resection. *Dig Dis Sci* 2017; **62**: 1666-1675 [PMID: 28341868 DOI: 10.1007/s10620-017-4546-6]

- **Augustin T,** Burstein MD, Schneider EB, Morris-Stiff G, Wey J, Chalikonda S, Walsh RM. Frailty predicts risk of life-threatening complications and mortality after pancreatic resections. *Surgery* 2016; **160**: 987-996 [PMID: 27545992 DOI: 10.1016/j.surg.2016.07.010]

c. For the reference by Lyu et al, the authors state that there was preoperative low serum albumin, but do not tell us how low. Please insert this information

Response:

Thank you for suggestion. The low serum albumin level is Lyu et al, study is < 3.5 mg/dl. We have added in the sentence.

d. In the paragraph starting with "C-reactive protein and procalcitonin are", the authors describe the importance of low albumin at postoperative day 3. Why is it low? What is the ½ life of serum albumin? Is it not more likely that a decline in serum albumin is a reflection of protein catabolism and is unlikely due to blockade of albumin biosynthesis?

Response:

Thank you for reviewing. The pathophysiology of the low serum albumin would be resulted from stress response to injury mechanism. The half-life of serum albumin is about 20 days. We have agreed with the decline in serum albumin is a reflection of protein catabolism.

Reference

- Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. Seminars in dialysis 2004; 17(6): 432-437 [PMID: 15660573 DOI: 10.1111/j.0894-0959.2004.17603.x]
- Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. Journal of the American Dietetic Association 2004; 104(8): 1258-1264 [PMID: 15281044 DOI: 10.1016/j.jada.2004.05.213]
- Boldt J. Use of albumin: an update. British journal of anaesthesia 2010; 104(3): 276-284 [PMID: 20100698 DOI: 10.1093/bja/aep393]

e. In the paragraph starting with "Postoperative PNI might be associated with" the authors raise the idea of serum albumin as a "stress marker"; don't the authors mean that serum albumin is a marker of inflammatory processes?

Response:

Thank you for reviewing. The serum albumin could be reflected the degree of the inflammatory process. The inflammatory process correlated with the postoperative outcome. The low postoperative serum albumin be affected by the stress response to injury mechanism and this study demonstrated the correlation of the level of the serum albumin and the another factors in the PNI is associated with post-operative outcome

f. Is there evidence that biochemical stress, which is generally defined by increased free radical production or "oxidative stress", does lead to low serum albumin?

Response:

Thank you for reviewing. There are some study demonstrated the correlation of the human serum albumin and other forms of serum albumin with oxidative stress in some condition for example, chronic liver disease, chronic kidney disease, coronary artery disease and in pregnancy. For the best of our knowledge, there is no the study of the oxidative stress in correlated with post-operation. The further studies are needed.

Reference

- Oran I, Oran B. Ischemia-Modified Albumin as a Marker of Acute Coronary Syndrome: The Case for Revising the Concept of "N-Terminal Modification" to "Fatty Acid Occupation" of Albumin. Disease markers 2017; 2017: 5692583 [PMID: 28356609 PMCID: PMC5357514 DOI: 10.1155/2017/5692583]

- Bahinipati J, Mohapatra PC. Ischemia Modified Albumin as a Marker of Oxidative Stress in Normal Pregnancy. Journal of clinical and diagnostic

research : JCDR 2016; 10(9): Bc15-bc17 [PMID: 27790423 PMCID: PMC5071923 DOI: 10.7860/jcdr/2016/21609.8454]

- Seshadri Reddy V, Sethi S, Gupta N, Agrawal P, Chander Siwach R. SIGNIFICANCE OF ISCHEMIA-MODIFIED ALBUMIN AS A SIMPLE MEASURE OF OXIDATIVE STRESS AND ITS DISCRIMINATORY ABILITY IN DIABETIC RETINOPATHY: Literature Review and Meta-Analysis. Retina (Philadelphia, Pa) 2016; 36(6): 1049-1057 [PMID: 27105326 DOI: 10.1097/iae.0000000000001042]

g. In the paragraph beginning with "There is evidence that low postoperative serum albumin", the authors suggest obtaining computed tomography. Don't their results need to be confirmed in a prospective study prior to this suggestion? In the final paragraph with limitations, the authors need to consider stating that the lower serum albumin (34.1 versus 35.0) is a modest difference. The authors also need to consider stating that results in their present study and the choice of POD3 PNI of 40.5 needs to be confirmed by a prospective study.

Response:

Thank you for suggestion. We have agreed. We have added the statement of further investigation to confirm our hypothesis and the difference between 34.1 vs 35.0 is a modest difference.

6. Table:

a. Table 2: BMI for Grade III-V, the authors don't provide the range of BMIs for their patients.

Response:

Thank you for suggestion. We have added the range of BMI of grade III-V in the table.

b. Table 2: for Albumin, for Grade 0-II and for Grade III-V, the authors need to tell us what percentage of patients had Albumin less than 35 g/L

Response:

Thank you for suggestion. The percentage of patients who have serum albumin < 35 g/L was added in the Table 2.

Reviewer #3 (02454185)

1. It is unknown of the follow up period for the postoperative complication.
   Response:
   Thank you for your valuable time in reviewing our manuscript. The median follow up period is 24 month.

2. Mortality is a competing risk for the postoperative complication. that is, the occurrence of death will preclude the occurrence of complication. how did you account for this informative censoring? I suggest the use of survival analysis in the presence of competing risks or at least this should be acknowledged as a limitation for current analysis. cite a reference would be helpful for this issue (Survival analysis in the presence of competing risks.Ann Transl Med. 2017 Feb;5(3):47. doi: 10.21037/atm.2016.08.62.)
   Response:
   Thank you for suggestion. The postoperative mortality defined in our study is the 90-day mortality and in-hospital mortality. The patients who the cause of death did not associate with the postoperative complication were excluded from the study. The main objective of our study is the postoperative complication. Therefore, the survival analysis would be out of our scope.

3. In the multivariable regression model, how did you choose the covariates? there are several commonly use methods such as purposeful selection (Model building strategy for logistic regression: purposeful selection. Ann Transl Med. 2016 Mar;4(6):111. doi: 10.21037/atm.2016.02.15.), stepwise and best subset (Variable selection with stepwise and best subset approaches. Ann Transl Med. 2016 Apr;4(7):136. doi: 10.21037/atm.2016.03.35.); the authors provide no information on this point.

Response:

Thank you for suggestion. The step of model selection was applied stepwise method for multivariate logistic regression.

4. In table 3, how many variables did you included in the model? it appears that only two variables were included

   Response:

   Thank you for suggestion. The variables included in the multivariable analysis by the variable selection with stepwise approaches. Thus, the only two most significant variables were included in our study.

5. for ROC analysis, pls also provide cnofidence interval for the area under ROC

   Response:

   Thank you for suggestion. The 95% CI 0.63-0.81.

Reviewer #4 (01438831)

1. How does the lymphocyte counts influence to the outcome after PD?

   Response:

   Thank you for your valuable time in reviewing our manuscript. The preoperative lymphocyte count was not the significant factor for postoperative grade III-V complications (OR 0.97, 95% CI 0.72-1.31, p=0.84). We did not analyzed the postoperative lymphocyte count because of this parameter is one of the parameter in the PNI.

2. In the table, median Albumin was 34.9 and median preoperative PNI was 98.9. This means median lymphocyte counts was around 13000. Is that correct?

   Response:

   Thank you for suggestion. The median lymphocyte count is 1981.7 (498-7638.4)