Perelman
School of Medicine
UNIVERSITY *of* PENNSYLVANIA

Department *of* Medicine
Division *of* Gastroenterology

Nabeel Khan, MD

Assistant Professor of Clinical Medicine
Director of Gastroenterology
Philadelphia Veteran's Administration Medical Center

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Subject: Revised Manuscript Submission

Dear Editors,

We are pleased to submit our revised manuscript entitled "**Albumin as a prognostic marker for Ulcerative Colitis"** for consideration under original contribution section of *"World Journal of Gastroenterology"*. We thank you for providing us this opportunity to revise our manuscript. We have addressed the comments of each individual reviewer separately and we have also made the necessary changes in our manuscript. Also, we have addressed the comments which the editor had made in the previous version of our manuscript. We think that the addressing these valuable comments has enriched our manuscript drastically.

We are extremely grateful to you for reviewing the revised version of our manuscript.

Yours sincerely,

Nabeel Khan, M.D.

Assistant Clinical Professor of Medicine

Perelman School of Medicine at the University of Pennsylvania

Chief, Section of Gastroenterology

Philadelphia VA Medical Center

Response to Reviewers' Comments:

Reviewer 1:

There is an interesting study that evaluates the role of serum albumin values at diagnosis as a potential predictive biomarker of the outcome of inflammatory disease UC. I recommend to assess also the correlation between albumin and other known predictive parameters of the disease evolution with respect to establish a predictive model of clinical course of UC.

Our Response:

We thank the reviewer for their comment and for finding our study interesting. Our primary objective in the current study was to evaluate albumin level as a novel and independent predictor of clinical outcomes in UC. We agree that developing and externally validating a prediction model that includes albumin and other known predictor would be a logical next step for our investigation, but it would be beyond the scope of the current study. We have added the following line in the discussion section to highlight this point.

"In conjunction with other above mentioned factors albumin levels at the time of UC diagnosis could be used to develop a comprehensive prediction model to prognosticate the disease course."

Reviewer 2:

The authors demonstrated the significance of serum levels of albumin to predict outcome of patients with UC. The present study was well organized and well investigated. To improve the quality of this paper, the authors should revise it according to the following suggestion.

1) The authors should firstly investigate and determine the cut-off level of hypoalbuminemia. Because hypoalbuminemia (i.e., ≤3.5 gm/dl) would be frequently observed in active stage of UC patients, the authors should carefully determine/ define hypoalbuminemia to predict the outcome of UC.

Our Response:

We thank the reviewer for appreciating our study. We have chosen '<3.5g/dl' as that is the level that that has been used to define hypoalbuminemia in clinical practice as well as other clinical studies across different disease states. Based upon our review of the literature we chose this number. **(Reference 1, 2, 3)**

Reviewer 3:

This work looks at baseline albumin results in adults with diagnosis of UC, and the prognostic implications of low levels

Specific Comments

1. The short title is not really shorter than the full title

Our Response:

We want to thank the reviewers for this comment. We changed the short title to **"Albumin prognosticating UC"**.

2. The authors comment about disease prevalence in the INTRODUCTION, but do not qualify this with regards the region of interest. Prevalence does vary according to the region/country of interest

Our Response:

We want to thank the reviewers for this comment. We have added the following words **"in the United States"** which have been highlighted.

3. The INTRODUCTION could be enhanced with careful reformatting. The bulk of this section comprises one very long paragraph

Our Response:

We thank the reviewers for their comment. We have reformatted the introduction by reconstituting the long paragraph into two separate paragraphs.

4. There are a number of minor errors of English language or ward usage. Physician in the INTRODUCTION should be physicians, for example. Feature should be features in the METHODS

Our Response:

We thank the reviewers for their comments. We have made the highlighted changes. Physician has been changed to **"Physicians"** in the introduction as well as Feature has been changed to **"Features"** in the methods which have been highlighted. Also, this line in the outcomes, which was grammatically incorrect previously has been changed and highlighted. **"Medications dispensed for reasons other than UC and non-UC related colectomies were not included in the outcome."**

5. The authors refer to indeterminate colitis: do they actually mean IBDU? This should be used correctly

Our Response: We thank the reviewers for their observation. We have replaced the term 'indeterminate colitis' with **'IBDU'** throughout the manuscript.

6. Were patients with another known reason for hypoalbuminemia (such as renal or nutritional causes) excluded from the study cohort?

Our Response:

We thank the reviewers for their comment. Hypoalbuminemia from other causes were not excluded as it is very difficult to determine if one or the other is solely responsible for the development of hypoalbuminemia. Chronic inflammatory conditions like UC can cause hypoalbuminemia through different pathways. Malnutrition can be associated with UC. In view of this difficulty in determining causality, we did not look at excluding other conditions that may cause hypoalbuminemia.

7. The last part of the RESULTS section only refers to those with low albumin levels: there is no comparison with the other group

Our Response:

We thank the reviewers for their comments. The last part of the results was compiled to demonstrate that patients who have a poor prognosis on the basis of hypoalbuminemia were probably undertreated for their UC. We showed that among the high risk patients i.e. those who had hypoalbuminemia, only 56.3% used combination oral and rectal 5-ASA therapy. Our aim was to demonstrate that among patients with this poor prognostic factor, there is under treatment. By recognizing this group of patients with hypoalbuminemia as having poor prognosis, we hope that the number of patients   treated with combination 5-ASA therapy at the disease onset will be higher than 56.3% at the current time. As we wished to examine the treatment patterns in the poor prognosis group which we hope to impact, we did not look at the treatment patterns in the group without the poor prognostic marker i.e. hypoalbuminemia.

8. The FIGURE LEGENDS are inadequate and should be enhanced to more clearly represent the figures. The TABLE heading could also be enhanced.

Our Response:

We thank the reviewer for the valuable comment. We have changed the LEGEND for figure 1 to

"Flow chart for assembly of the study cohort" and we have also changed the TABLE heading as

"Baseline characteristics of the study cohort by absence or presence of hypoalbuminemia status at UC diagnosis".

In addition to these changes, we have also made the following changes in the manuscript:

1) We have added a signed copy of the scientific research process as a PDF file separately attached along with the revised manuscript.
2) We have added the manuscript type and the manuscript number as per the instructions at the beginning of the manuscript.
3) The specific author contributions have changed by us according to the required format as per the instruction in the comment.

4) We have also added a data sharing statement as per the instructions and also a signed PDF copy of the same has also been submitted by us along with the revised manuscript.

5) We have also added the FAX number of the corresponding author as per the instruction in the comment.

6) We have added 2 additional keywords in the manuscript as per the instructions in the comment.

7) Also we have double checked the references and removed any duplicated references according to the instructions in the comment.

8) Lastly, we have addressed all the reviewers' comments and made the above mentioned changes. We will be submitting the following things:

- Revised manuscript
- This letter responding to the reviewers comments
- PDF – Scientific Research Process
- PDF – Conflict of interest statement
- PDF – Biostatistics Statement
- PDF – Informed consent statement
- PDF – Data sharing statement
- PDF – IRB statement
- PDF – Copyright Form
- Google Scholar Images
- Audio Core Tip

Reference 1: Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: A systematic review of the epidemiological literature. Nutr J. 2010;9:69.

Reference 2: Franch-Arcas G. The meaning of hypoalbuminaemia in clinical practice. Clin Nutr. 2001;20(3):265–9.

Reference 3: Jin Y, Zhao L, Peng F. Prognostic impact of serum albumin levels on the recurrence of stage I non-small cell lung cancer. *Clinics*. 2013;68(5):686-693. doi:10.6061/clinics/2013(05)17.