Dear Editors and Reviewers:

Thank you very much for giving us an opportunity to revise our manuscript. We greatly appreciate the editor and reviewers for their constructive comments and suggestions on our manuscript entitled "Predictors and optimal management of tumor necrosis factor antagonist in inflammatory bowel disease: A literature review" (84666).

Those comments are very helpful for revising and improving our paper. We have studied the comments carefully and made corrections. We hope that the revision is acceptable and look forward to hearing from you soon. At the same time, we have uploaded the file of the revised manuscript.

Below, please find our responses. The main corrections are in the manuscript and the responds to the reviewers' and editor's comments are as follows.

Thank you for your consideration.

Best regards,
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Replies to the review's comments:

Reviewer #1:

Nice paper, well organized and clearly written. Good to be published.

Response: Thank you for your efforts in revising our manuscript and positive comments on our work.

Reviewer #2:

I noticed that the title lacked the indication that it is a review. The manuscript is well written, the authors have done extensive literature research, and the articles used are relevant. The flowcharts presented are important for quick consultation on conducts proposed by the consulted literature.

Response: 1) We really appreciate your efforts in revising our manuscript and positive evaluation of our work.

2) We agree with your suggestion and revise the title of the article to " Predictors and optimal management of tumor necrosis factor antagonist nonresponse in inflammatory bowel disease: A literature review "

Reviewer #3:

The authors demonstrate good analytical approach to important clinical aspects of the disease, starting from the definition of terms, however, the manuscript requires improvement.

Response: Thank you for your summary and positive evaluation of our work. We really appreciate your efforts in reviewing our manuscript.

Please include the most relevant information in the abstract avoiding generalities. The same is also true for the conclusions.

Response: Your comment is valuable and has been very helpful for improving our manuscript. We have re-wrote these two parts in the revised manuscript.

Please describe the process of literature search in details and provide a table

with the workflow.

Response: Thank you for your precious comments and advice. We agree with your suggestion and describe the process of literature search in the revised manuscript and added a flowchart in the supplemental material.

Since the authors analyzed ant-TNF treatment depending on disease phenotype, CD and UC should be assessed separately.

Response: Thank you for your precious comments and advice. We apologize for not assessing predictors of primary and secondary nonresponse to TNF antagonists separately in CD and UC patients, because some of the original studies included both CD and UC, and evaluating CD and UC separately would lead to high reproducibility of article content. To this end, in the revised manuscript, we describe the populations described in the reference more explicitly (UC, CD, or IBD). Furthermore, we listed the predictors of primary nonresponse and secondary nonresponse to TNF antagonists in patients with CD and UC, respectively.

Please consider presenting in a table the information which is in the PREDICTORS OF PRIMARY NONRESPONSE and PREDICTORS OF SECONDARY NONRESPONSE sections. In this way, the most valuable for practicians section of the manuscript shall become more prominent and the manuscript will be easier to read.

Response: Very good point. We have added the tables suggested in the revised manuscript.

Please correct typos and minor imperfections: 1) "Morita et al. found a significant significantly higher serum albumin in responders than in primary nonresponders" 2) "The key mechanism by which infliximab and adalimumab exert their anti-inflammatory effects is by the induction of apoptosis" This statement is misleading because of insufficient information. Please specify. 3)

Decipher all abbreviations: FCGR3A-158V/V , PK/PD model, ATG16L1, etc. 4)

Do not provide references to the literature in the conclusions.

Response: Thank you for your careful review.

1) We have made the suggested language changes.

2) We apologize for the misunderstanding caused by not providing detailed information and we have provided a supplementary description in the revised manuscript.

3) We have deciphered other abbreviations in the revised manuscript.

4) We have deleted the references in the discussion section.

Final remark: in order to strengthen the review itself and suggestions for treatment prognosis made by the authors I would recommend to perform a meta-analysis of the selected publications separetaly for CD and UC. In this way, this review will get more attention from readers.

Response: Thank you for your constructive comments. However, this article is a descriptive review, which aims to summarize the recent research in this field and inspire follow-up research. As for the relevant meta you mentioned, we would like to conduct related research separately in the future.