

RESPONSE TO THE REVIEWERS (Manuscript ID: 85318)

Dear Editors and Reviewers,

Thank you for your valuable comments and suggestions about our manuscript entitled **“Compensated liver cirrhosis: Natural course and disease modifying strategies**” (manuscript no 85318; review). These are very helpful for revising and improving our manuscript.

In the revised manuscript we have incorporated all the changes as suggested by the reviewers. Revised portion are marked underlined in the paper. Moreover, the revised manuscript has been edited for proper English language by a profession body (certificate included). Our point-by-point responses to the issues raised in the peer review report are as follows:

1. Response to reviewers' comments

Reviewer #1:

1. The major problem is that author misleads the progression of compensated liver cirrhosis corresponding to its consequence of decompensated liver cirrhosis. The length of this manuscript was extremely spent for the transition between compensated and decompensated liver cirrhosis as well as several factors to interrupt or induce these different stages of liver cirrhosis. Hence, these demonstrations are not consistent with the title and abstract of this manuscript. In addition, the structure of this manuscript is not proper. For example, the definition of CLC and cACLD can not be the independent section. Their definitions should be provided in the introduction concisely.

Authors' response: Thank you for your valuable comments. The development of decompensation is the most important event in the natural history of compensated cirrhosis. However, we concur with the reviewer's observation that a sizable portion of this

manuscript was devoted to outlining the transition between compensated and decompensated liver cirrhosis. Taking this into consideration, we drastically condensed the aforementioned parts while maintaining the main idea and applicability of the variables that are crucial to the advancement of cirrhosis naturally. Additionally, the definitions have been condensed and placed to the introductory section per the reviewer's suggestion. (Changes highlighted as underlined)

2. PHT is now thought to be the symptom of compensated liver cirrhosis and PHT can not be the factor associated with decompensation of compensated liver cirrhosis directly. Other factors should be reduced and integrated into the following section about disease modifying treatment strategies.

Authors' response: Thank you for your valuable comments. We agree that PHT is an integral part of compensated liver cirrhosis. The mounting evidence now strongly indicates that reducing portal pressure by non-selective beta blockers prevents decompensation of compensated liver cirrhosis, suggesting that PHT is an important driver of decompensation [PREDESCI trial, Lancet.2019;393(10181):1597-1608, Meta-analysis J Hepatol.2022;77(4):1014-1025]. Many other studies have also found that PHT measured by HVPG significantly influences the risk of decompensation (reference no 10, 15,21, in the current manuscript). Other factors relevant to modifying treatment strategies have been reduced and integrated in accordance with the suggestion.

3. The section of regression of LC (liver cirrhosis) should be deleted because it exceeds the range of this manuscript.

Authors' response: We have deleted this section as per the suggestion

4. Figure 1 seems not exact because the total percentages are above 100% in the bottom.

Authors' response: I appreciate your thoughtful observations and remarks. Suitable corrections have been made in the revised figure. For clinical relevance, the five-year

mortality rates of CLC with or without varices and decompensated LC with decompensation have been have been illustrated.

5. Table 4 should be removed because it is not coincided with the whole manuscript.

Authors' response: Thank you for your valuable comments. We have removed table 4 from the revised manuscript.

Reviewer #2:

1. This review is comprehensive. It should not be attributed to a minireview alone.

Authors' response: Thank you for your valuable comment. The manuscript's category has already been changed from minireviews to the review article.

2. In the Keywords section, the authors should provide the full names of cACLD and ACLF. The use of "et al" in the article should be unified. For example, in the INTRODUCTION section, the authors said "Wanless et al were the first to describe the reversal of ... in numerous series of LC patients with diverse etiologies". However, in the REGRESSION OF LC section, the authors said "Wanless et al. recognised a number of histologic characteristics of LC as ... aberrant parenchymal veins".

Authors' response: Thank you for your valuable comments. The revised manuscript includes the full names of cACLD and ACLFT. It has been thoroughly been edited by the authors keeping in mind the aforementioned suggestions. As suggested by another reviewer, some of the text has also been removed. Finally, a professional body edited the revised manuscript to ensure proper English language.

3. In the NATURAL HISTORY OF CLC section, the authors said “The first decompensation of CLC does not always indicate a point of no return in the natural course of LC cirrhosis”. “LC cirrhosis” should be modified as “LC”.

Authors’ response: Thank you for your valuable comment. We have made the said correction.

4. In the a. PHT section of the FACTORS ASSOCIATED WITH DECOMPENSATION OF CLC, the authors said “In a study, patients with an HVPg <10 mm Hg have a 90% probability of not developing clinical decompensation over 4 years”. “HVPg <10 mm Hg” should be modified as “HVPg <10 mmHg”.

Authors’ response: Thank you for your valuable comment. We have made the said correction.

5. And the authors said “As the HVPg rises above 10 mmHg, which signify CSpH, risk of decompensation begins to rise [11]”, where “[11]” should be superscripted.

Authors’ response: In the revised manuscript, this reference (now reference no 10) has been superscripted.

6. Moreover, check format (such as font, size and italic) of titles of the article carefully. For example, the font sizes of the “CLC” and the “Compensated advanced chronic liver disease (cACLD)” should be consistent. And the font sizes of the “INTRODUCTION” and the “DEFINITION” should be consistent.

Authors’ response: Thank you for your valuable comments. The revised manuscript has been thoroughly been edited by the authors keeping in mind the aforementioned suggestions.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Authors' response: The revised manuscript has been edited for proper English language by a profession body and a high quality has been achieved (certificate included).

5 ABBREVIATIONS

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

Authors' response: The revised manuscript has been thoroughly been edited keeping in mind the aforementioned suggestions.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Authors' response: Thank you for your valuable opinion.

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Methodology. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

Authors' response: Thank you for recommending acceptance of our paper for the esteemed journal – World Journal of Methodology. We have revised the manuscript thoroughly as per the revisers' suggestions and the journal's guidelines.

Best regards,

Ramesh Kumar,

MD, DM, Additional Professor, Head,

Department of Gastroenterology, 4th floor, IPD Block-C,

All India Institute of Medical Sciences, Patna-801507, India.,

Email: docrameshkr@gmail.com