

RESPONSE TO THE REVIEWERS

Dear Editors and Reviewers,

Thank you for your valuable comments and suggestions about our manuscript entitled “Lymphatic Dysfunction in Advanced Cirrhosis: Contextual Perspective and Clinical Implications” (ID: 61760). 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 portions are marked in red in the paper. Moreover, the revised manuscript has been edited for proper English language by a professional body (certificate included). Our point-by-point responses to the issues raised in the peer review report are as follows:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: -There are numerous small English language/punctuation errors that need to be corrected by an English editing service or a native speaker -LECs is a conventional abbreviation for lymphatic endothelial cells (use LECs instead of LyECs) -Table 2 “Promote lymphangiogenesis” spelling -page 12 “CLINICAL IMPLICATIONS OF LYMPHATIC DYSFUNCTION” (add “OF”) -page 5, lines 4-7 “Initial lymphatics are highly permeable for transport of interstitial fluid macromolecules and immune cells. LECs have anchoring filaments that contract and relax to allow LECs to “flap” open to allow interstitial fluid uptake [10,11].”

Authors’ response: Thank for your valuable comments and accepting our manuscript. The revised manuscript has been edited by a competent agency (of native English-speaking editors) for English language and a high quality has now been reached. All suggested changes

have been made in the revised manuscript. The term 'LyECs' has been replaced by 'LECs', as per the suggestion.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Manuscript NO: 61760 Lymphatic Dysfunction in Advanced Cirrhosis: Contextual Perspective and Clinical Implications Manuscript Type: Review
Corresponding Author: Ramesh Kumar, MD This is an educational and historical overview in lymphatic dysfunction in advanced cirrhosis. I was a little disappointed with loss of introduction of new approaches in this area. If possible, the below approaches were considered to be added in the review. 1. How about the effect of new diuretics in lymphatic dysfunction, for examples tolvaptan; vasopressin type-2 receptor antagonist? 2. High dose administration of albumin. 3. Splenectomy

Authors' response:

Thank you for your opinion and valuable inputs . The manuscript has been revised in light of your suggestions and comments.

1. Role of new diuretics: As per the suggestion, we have now added, in the revised manuscript, a brief discussion on newer molecules with diuretic effects (Vaptans, SGLT2 inhibitors) in the light of their potential to work in cirrhosis patients with lymphatic dysfunction. Data in this regard, however, is not yet available. (Section: therapeutic perspective, highlighted in red).

2. High dose administration of albumin : No literature evidence could be found with respect to the effectiveness of high-dose albumin in cirrhosis patients with lymphatic dysfunction. The possible effects of albumin in cirrhosis patients with lymphatic dysfunction has already been discussed. In the revised manuscript, we have broadened the debate a little further.

In patients with liver cirrhosis, trans-capillary escape rate of albumin is increased. To recirculate the escaped albumin back to plasma, proper lymphatic functions are needed.

However, the escaped albumin is less likely to be recirculated back into the plasma if lymphatic functions are deficient, which will not only fail to correct circulating hypovolemia, but accumulation of albumin in the interstitium could promote worsening of edema and ascites. However, it would be interesting to investigate the non-oncotic properties of albumin (anti-inflammatory, immunomodulatory, and anti-oxidant) on lymphatic functions, as chronic inflammation and neurohormonal alterations play a significant role in lymphatic dysfunction of cirrhosis. (Section: therapeutic perspective, highlighted in red).

3. Splenectomy: We have also highlighted the need to explore the role of splenectomy in cirrhosis patients with lymphatic dysfunctions. (Section: therapeutic perspective, highlighted in red).

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Authors' response: Thank for your valuable opinion. The revised manuscript has been edited by a competent agency (of native English-speaking editors) for English language and a high quality has now been reached.

EDITORIAL OFFICE'S COMMENTS

Science editor: 1 Scientific quality: The manuscript describes a review of the lymphatic dysfunction in advanced cirrhosis: contextual perspective and clinical implications. The topic is within the scope of the WJH. (1) Classification: Grade B and Grade B; (2) Summary of the Peer-Review Report: This is an educational and historical overview in lymphatic dysfunction in advanced cirrhosis. However, numerous small English language/punctuation errors should be corrected. The questions raised by the reviewers should be answered; and (3) Format:

There are 2 tables and 4 figures. A total of 81 references are cited, including 6 references published in the last 3 years. There is 1 self-citation. 2 Language evaluation: Classification: Grade B and Grade A. 3 Academic norms and rules: The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The topic has not previously been published in the WJH. 5 Issues raised: (1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (2) Authors should always cite references that are relevant to their study. Please check and remove any references that not relevant to this study. Authors should not cite their own unrelated published articles. Please check and remove any references not relevant to this study. The authors self-referencing number should be no more than 3. 6 Re-Review: Not required. 7 Recommendation: Conditional acceptance.

Authors' response: Thank you for your opinions and comments. Language editing certificate is now being provided. We are providing the images on PowerPoint slide which can be reprocessed by the editors. The references have been revised; only relevant references have been included and self-reference is only one. All other required documents are being provided.

(2) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Authors' response: Thank you for your valuable opinion and suggestions. The manuscript has been thoroughly revised in the light of peer-review Report, editorial office's comments and the criteria for manuscript revision. In the revised manuscript, we have incorporated all the changes as suggested by the reviewers. Revised portion are marked in red in the paper. We have also got the revised manuscript edited for English language by a trustworthy body, and a high quality has now been reached.

Best regards,

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