27th August 2020

Professor Lian-Sheng Ma

Editor-in-Chief

World Journal of Gastroenterology

Dear Prof Lian-Sheng Ma,

Revised Manuscript Submission – Manuscript No: 58647

Thank you very much for inviting us to submit a revised manuscript. We value the editor's and reviewer's comments and have revised the manuscript accordingly.

Please find uploaded the revised manuscript titled "Cirrhotic portal hypertension: from pathophysiology to novel therapeutics".

We have listed below the comments made by the editor and reviewer, followed by our answers.

Science Editor:

Comment: A total of 253 references are cited, including 6 references published in the last 3 years. The authors need to update the reference.

Answer: We have updated the reference list by adding a few more new references. However, we would like to mention that a majority of literature, including randomized clinical trials, which has been published more than 3 years ago and cited in this review are considered as seminal studies in the field of portal hypertension.

Comment: Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Answer: We have uploaded funding agency approval document.

Comment: 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.

Answer: We have uploaded all Figures prepared using PowerPoint.

Reviewer #1:

Major comments:

1. **Comments:** The structure should be more logical. I would suggest starting with pathophysiology, then clinical aspects. The section on HVPG should follow pathophysiology. This also applies to the section on RAS. It does not seem appropriate to separate from the main paper and clearly there is relevance.

   Answer: We agree with the first comment made by the reviewer and have therefore amended the structure of the manuscript to start with the pathophysiology, clinical diagnosis of portal hypertension followed by the clinical aspects. However, we feel that for clarity the detailed discussion of novel aspects of RAS physiology should be kept separate.

2. **Comments:** The section on RAS should be shortened as there is less clinical relevance for portal hypertension and more for hepatic fibrosis. Indeed studies have shown agents targeting RAS have variable effects on portal pressure, and should really be avoided in advanced cirrhosis I believe they should be used even more cautiously than NSBBs in this context.

   Answer: We agree with the reviewer that the literature related to the clinical aspect of the RAS in portal hypertension is scarce compared to its role in hepatic fibrosis. However, we are reluctant to make major changes to the section on the RAS. In writing this review we specifically wanted to emphasize recent findings regarding the role of the RAS in portal hypertension as we have made a number of novel findings in this field that may be of major clinical significance. Therefore, in order to get this message across to a broader audience we feel that a comprehensive background information of the RAS is necessary. This is made clear in both the abstract and introduction.

3. **Comments:** On page 4, last paragraph it is stated that NSBBs are only moderately effective in majority of patients. On page 17 it is mentioned that up to 60% fail to

achieve a reduction in HVPG with NSBB. This is in direct conflict with a later section highlighting how carvedilol can be effective in the majority and more effective than propranolol. Consistency should be maintained in this regard.

Answer: The moderate effectiveness of NSBBs in the control of variceal bleeding (on page 4 and 17) refers to the traditional NSBBs such as propranolol and nadolol. However, for consistency, as suggested by the reviewer, we have amended the sentence on page 4 (highlighted in 'introduction' section of the revised manuscript) to state that NSBBs are 'not effective in all patients' and on page 17 (highlighted in 'non-selective beta-blockers (NSBBs)' section of the revised manuscript), to state that 'traditional NSBBs' fail to achieve a reduction in up to 60% of patients.

4. **Comments:** The section in page 5 on HVPG measurements. This should mention the important of at least 3 reading and permanent tracing There should also be mention that HVPG is a measure of sinusoidal portal hypertension and does not accurately reflect pre-sinusoidal portal hypertension e.g. in early stage PBC.

   Answer: As per the reviewer's comments, we have amended the section on HVPG measurement to state the importance of permanent tracing and repeated measurement of venous pressure. We have added a reference to support the above changes made to the revised manuscript (highlighted in 'clinical diagnosis of portal hypertension' section of the revised manuscript). Moreover, in the same section, we have made the point that HVPG measurements do not accurately reflect pre-sinusoidal portal hypertension.

5. **Comments:** The discussion on hepatorenal syndrome should reference the revised definitions from the ICA: https:// www.journal-of-hepatology.eu/article/S0168-8278(16)30618-3/pdf

   Answer: We thank the reviewer for highlighting this and thus, we have amended the section on the clinical manifestation of portal hypertension (highlighted in 'clinical manifestation of portal hypertension' section of the revised manuscript). The revised definitions from ICA on hepatorenal syndrome and the suggested references were added to the revised manuscript (references #99 and #100.

6. **Comments:** Page 16: Sentence "The NSBB, carvedilol, has been shown to be more effective than propranolol in reducing first variceal bleeding" is not correct. There is not trial showing this. The only evidence is that carvedilol is more effective than propranolol in reducing portal pressure, even in propranolol non-responders.

   Answer: We have revised this sentence to state that carvedilol is effective in reducing portal pressure in cirrhotic patients compared to traditional NSBB propranolol (highlighted in 'non-selective beta-blockers (NSBBs)' section of the revised manuscript).

Minor comments:

1. **Comments:** The BSG guidelines should also be referenced: DOI: 10.1136/gutjnl-2015-309262

   Answer: The BSG guidelines have been referenced (highlighted in 'non-selective beta-blockers (NSBBs)' section of the revised manuscript).

2. **Comments:** Page 16: it would be helpful to mention 6 week mortality after a variceal bleed.

   Answer: We have discussed the average 6-week mortality rate after first variceal bleeding (highlighted in 'gastroesophageal varices' section of the revised manuscript).

3. **Comments:** Page 18, 3rd paragraph, 3rd sentence. At the end "increased intrahepatic…" should be "decrease…".

   Answer: As per reviewer's suggestion, we have now amended the above sentence to indicate that potential contribution by anti-α1 adrenergic effect of carvedilol may help reducing intrahepatic vascular tone in cirrhosis (highlighted in 'non-selective beta-blockers (NSBBs)' section of the revised manuscript).

4. **Comments:** Page 18, 1st paragraph, last sentence: "…double-blind RCT". There are large RCT's in progress in the UK which should be quoted:
   a. Tripathi D, Hayes PC, Richardson P on behalf of CALIBRE trial collaborative group, et al Study protocol for a randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE trial)BMJ Open Gastroenterology 2019;6:e000290. doi: 10.1136/bmjgast-2019-000290
   b. BOPPP trial: https://clinicaltrials.gov/ct2/show/NCT03776955

   Answer: We thank the reviewer for highlighting these important RCTs that are in progress in the UK. These RCTs have been discussed (highlighted in 'non-selective beta-blockers (NSBBs)' section of the revised manuscript).

5. **Comments:** Page 21. Discussion on statins should mention LIVERHOPE study, highlighting the risk of statins which appears to be dose related: DOI: 10.1016/S2468-1253(19)30320-6

   Answer: The discussion on statins has been improved by adding the study suggested by the reviewer, showing statins-associated risks appear to be related to the dose of the drug (highlighted in 'therapies targeting increased intrahepatic vascular tone' section of the revised manuscript).

Yours sincerely,

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