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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 58647

Title: Cirrhotic portal hypertension: From pathophysiology to novel therapeutics

Reviewer's code: 03252237
Position: Peer Reviewer
Academic degree: MD
Professional title: PhD
Reviewer's Country/Territory: England
Author's Country/Territory: Australia

Manuscript submission date: 2020-07-31
Reviewer chosen by: AI Technique
Reviewer accepted review: 2020-08-01 13:40
Reviewer performed review: 2020-08-08 14:44
Review time: 7 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

This is a well written and comprehensive review of the pathophysiology of portal hypertension, with some focus on novel mechanisms and therapies. I have some comments to improve the structure and impact.

Major

1. 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.
2. 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.
3. 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.
4. The section in page 5 on HVPG measurements. This should mention the important of at least 3 readings 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.
5. 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
6. 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.

Minor:

1. The BSG guidelines should also be referenced: DOI: 10.1136/gutjnl-2015-309262
2. Page 16: it would be helpful to mention 6 week mortality after a variceal bleed.
3. Page 18, 3rd paragraph, 3rd sentence. At the end "increased intrahepatic…" should be "decrease…".

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4. 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
5. 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