

Dr. Lian-Sheng Ma
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Jan 22, 2017

Dear Dr. Lian-Sheng Ma;

Re: Manuscript reference No. 31393

Please find attached a revised version of our manuscript "Portal Hypertension: Imaging of Portosystemic Collateral Pathways and Associated Image-Guided Therapy.", which we would like to resubmit for publication in the World Journal of Gastroenterology.

We thank you and the reviewers for the highly insightful comments, which enabled us to improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in WJG.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Point-By-Point Responses To Reviewer 1 Comments

1. REVIEWER COMMENT: “Pathophysiology of portal hypertension”

AUTHORS’ RESPONSE: We acknowledge the recent updates in portal hypertension physiology and have updated the “Introduction” section as follows: Recent updates in pathophysiologic understanding of portal hypertension have also focused on contribution of hepatic sinusoidal endothelial dysfunction to elevated portal pressure (Cite this: Bosch J, Groszmann RJ, Shah VH. Evolution in the understanding of the pathophysiological basis of portal hypertension: How changes in paradigm are leading to successful new treatments. J Hepatol. 2015;62(1 Suppl):S121-30.)

2. REVIEWER COMMENT: “A portal pressure of 10 mmHg is not in the normal range, but complications of portal pressure arise with this portal pressure. What is portal pressure, as the authors mention? Pressure in the portal vein or HVPG (hepatovenous pressure gradient)? In the section “Imaging modalities.”: “Catheter-based based venography”: Here the authors must describe the technique of determination of FHVP and WHVP and HVPG. Normally, a portal vein imaging is not obtained using this technique. The term HWVP is not correct. Therapy of portal pressure is guided according to level of HVPG.”

AUTHORS’ RESPONSE: Thank you for pointing out the inconsistencies. We have clarified the difference between absolute portal pressure and the HVPG which is the

best surrogate available to determine portal hypertension. We have revised the “imaging modalities” section, as follows:

“Catheter-based hepatic venography allows for measurement of HVPG i.e., the difference between the wedge and the free hepatic venous pressures. Measurement of HVPG is currently the best available method to evaluate the presence and severity of portal hypertension...”

3. REVIEWER COMMENT: “The authors describe ultrasonography as: “first-line modality choice for the diagnosis and follow-up of portal hypertension”. In this context some remarks concerning the controversial correlation between US parameters and HVPG should be included. Detection of esophageal varices: This section is correct.”

AUTHORS’ RESPONSE: As requested, although US evaluation has several promising applications in portal hypertension diagnosis and followup, we acknowledge its limitations and have stated that its clinical usefulness in portal hypertension remains unsettled because of being plagued by lack of reproducibility and accuracy characterized by intra- and interobserver variation.

4. REVIEWER COMMENT: “Detection of esophageal varices: This section is correct. However, as a gastroenterologist I want to read some remarks about reliability of varices detection by CT or MRT in comparison with endoscopy. Endoscopy is and remains the standard procedure for diagnosis of esophageal varices. The same is true for gastric varices. The possibility to detect gastric varices by transhepatic portography is very theoretical. Endoscopy is much better and has much less risk for the patients.”

AUTHORS' RESPONSE: Within the second last paragraph of "Imaging modalities", we have added a short comment on CT detection of varices, "Although endoscopy is the gold standard, CT can also be useful in detection of esophageal/gastric varices. In a prospective evaluation, Perri et al demonstrated that CT had a 90% sensitivity in the identification of esophageal varices determined to be large on endoscopy, but only about 50% specificity. The sensitivity of CT in detecting gastric varices was 87%."

5. REVIEWER COMMENT: "The possibility to detect gastric varices by transhepatic portography is very theoretical. Endoscopy is much better and has much less risk for the patients."

AUTHORS' RESPONSE: Thank you. We acknowledge your comment and have reworded the sentence accordingly: "Gastric varices, along with esophageal varices, are by far the most common portosystemic pathways seen in portal hypertension"

6. REVIEWER COMMENT: "In the section "Paraumbilical and abdominal wall collaterals" the authors correctly state that the (reopened!) paraumbilical vein arises from the left portal vein (better: left main branch of portal vein!). However, in Figure 2 the arrow of PUVar aims to the right main branch. This must be corrected. What is AWVar? This abbreviation is not explained. In the caption of Figure 2: hepatopedal, not hepatopetal."

AUTHORS' RESPONSE: Thank you for pointing out the errors. We have fixed the graphic to reflect the true origin of paraumbilical vein. We have also explained the AWVar abbreviation (Abdominal wall varices). "Hepatopedal" has been corrected to "hepatopetal" in caption of Figure 2.

7. REVIEWER COMMENT: “The term “impedances to portal venous flow” is not common in the context of portal pressure. Instead “resistance to portal flow”, as the authors themselves use, is much more usual.”

AUTHORS’ RESPONSE: We have corrected this and the more widely accepted phraseology is constant throughout the paper. Thank you.

Point-By-Point Responses To Reviewer 2 Comments

1. REVIEWER COMMENT: “It is not appropriate to explain the role of CT in detecting and grading of esophageal varices with table 1, because table 1 is an endoscopic grading method, not radiographic”

AUTHORS’ RESPONSE: Thank you for pointing out the error. We have removed this table.

2. REVIEWER COMMENT: “Table 2 is about endoscopic classification of gastric varices, however, it is quoted in the part of manuscript describing blood supply of varices.”

AUTHORS’ RESPONSE: We have added a new sentence to better refer to the former table 2 (now table 1): “Esophageal and gastric varices frequently coexist, as noted in the widely used Sarin endoscopic grading classification for gastric varices (Table 1).”

3. REVIEWER COMMENT: “There are many typing mistakes in the manuscript”

AUTHORS’ RESPONSE: The manuscript has been reviewed and typographical errors have been corrected. Thank you.