

September 24, 2016

Ze-Mao Gong

Scientific Editor

World Journal of Gastroenterology

Re: **ESPS Manuscript NO. 29622**. Editorial: Clinical role of non-invasive assessment of portal hypertension, by Massimo Bolognesi *et al.*

Dear Editor,

Please find enclosed the manuscript (Editorial) "**Clinical role of non-invasive assessment of portal hypertension**", which I am re-submitting for publication in the *World Journal of Gastroenterology*.

All authors have reviewed the manuscript and approved the changes made therein according to the comments and questions raised by the reviewers and the Scientific Editor. We wish to thank the Editor and the reviewers for their careful consideration and hope that the manuscript is now acceptable for publication.

Please find our point-by point responses to each of the comments below. The modified portions of the original manuscript have been highlighted in **yellow** for ready identification.

My invitation ID is 00005704.

Thank you for your consideration and I look forward to hearing from you.

Sincerely,

Massimo Bolognesi, MD, PhD

Department of Medicine - University of Padua

Azienda Ospedaliera Università di Padova, Clinica Medica 5

Via Giustiniani 2. 35128 Padova - Italy

Telephone: +39 049 8212383

Fax: +39 049 8754179

Email: massimo.bolognesi@unipd.it

Reviewer #1 code: 1560862

Comment: Color Doppler ultrasonography is a useful noninvasive modality for assessing gastrointestinal varices including rectal varices. In section of estimation of portal hypertension by Doppler ultrasound techniques, please add the below references. 1. Komatsuda et al (Abdom Imaging 1998; 23:45-50) reported the usefulness of color Doppler ultrasonography for the diagnosis of gastric and duodenal varices. 2. Sato et al (J Gastroenterol 2002; 37: 604-10) reported the usefulness of color Doppler ultrasonography for the hemodynamics of gastric varices. 3. Sato et al (Am J Gastroenterol 2007; 102: 2253-8) reported the usefulness of color Doppler ultrasonography for the diagnosis of rectal varices. 4. Sato et al (J Ultrasound Med 2009; 28: 1125-31) reported the usefulness of color Doppler ultrasonography for the hemodynamics of gastric varices and for evaluation of therapeutic effects of gastric variceal treatment.

Response:

We apologize for the confusion on this topic. The section of text describing our estimation of portal hypertension by Doppler ultrasound techniques has been clarified, with a new paragraph (and appropriate references) added to explain the usefulness of this method in diagnosis of gastric, duodenal and rectal varices.

Reviewer #2 code: 53950

Comment: The authors aim to evaluate the role of non-invasive methods in assessment of portal hypertension. The level of portal hypertension correlates with complications of liver cirrhosis. However, the pressure can be accurately measured only with an invasive method. Remarks: - The authors disclose that the measurement of liver stiffness is a breakthrough in assessing the level of portal hypertension. This fact may be an overstatement as we know that transient elastography is sensitive in estimating stage 0 and stage 3-4 liver fibrosis. Thus, it is obvious that patients with moderate fibrosis and PH are more difficult to assess with TE, as well. - Several scores and indexes have been used as a marker of PH, but mostly they are too robust in use. In fact, in clinical practice parameters used in these scores are those which the clinician uses to estimate the level of liver disease and PH. Reduced thrombocyte count, collaterals, varices, the size of the

spleen, the volume and direction and the width of portal flow etc. are findings very useful in assessing PH in clinical practice. In addition, many parameters used in scores are affected by various interventions. - Nevertheless, simple non-invasive methods in screening purposes are needed. Quantitative MRI is too expensive for this and according to the Baveno VI criteria TE and platelet count may be used to discriminate patients without a need for screening varices but not assess the level of PH. - There are increasing number of studies using SWE for assessing liver and spleen stiffness especially in patients with B- and C-hepatitis. The results are encouraging. - There are no figures or tables and the language needs polishing.

Response:

The manuscript has been modified according to the reviewer's suggestions. Specifically, the inappropriate term "breakthrough" has been withdrawn and the role of TE in estimating liver fibrosis has been better defined. The role of platelet count in discriminating patients without a need for screening varices has been clarified, as has its role in a proposed algorithm for screening and evaluation of CSPH. Finally, a figure has been added and the English language presentation has been revised by a professional English language editing company, Filipodia (Certificate of Editing Service provided).

Reviewer #3 code: 34635

Comment:

The authors comprehensively reviewed different non-invasive methods for evaluating portal hypertension, including biochemical, Doppler US and transient elastography-based and in particular shear wave elastography. There some other methods such as sub-harmonic aided pressure (Eisenbrey et al Radiology 2013) that should be commented and discussed. In addition, I would suggest to incorporate an algorithm for screening and evaluation of CSPHT and selecting out what patients should be further evaluated with endoscopy and/or invasive HVGP.

Response:

We thank the reviewer for their constructive comments. Accordingly, we have added a new paragraph, with appropriate references, to clarify the SHAPE method and its potential to the section on *Estimation of portal hypertension by Doppler ultrasound techniques*. In addition, a new figure outlining a hypothetical algorithm for screening and evaluation of CSPH has been added, as suggested.

Reviewer #4 code: 68215

Comment: Assessment of portal pressure by the hepatic venous pressure gradient (HVPG) has been a useful predictor of outcomes in both stages of cirrhosis. Diagnostic endoscopy findings related to portal hypertension are esophageal varices (EV), gastric varices and portal hypertensive gastropathy PHG. Rarely, ectopic duodenal varices can be found. The risk of bleeding from EV is tightly related to their size and presence of so-called 'high-risk signs'. HVPG and endoscopy are current gold-standard techniques to assess portal hypertension. However, its use is limited by their invasiveness. Patients would benefit from noninvasive tests that are able to provide similar information. The non-invasive methods are also necessary for assessment of the hemodynamic response to pharmacological therapy for portal hypertension. The combination of different methods provides theoretical advantages over the use of a single method and complementary information may lead to more robust predictions. Please, add the combined indices/algorithms based on these non-invasive methods with their sensitivity and specificity to permit a fair clinical judgment.

Response:

We thank the reviewer for these insightful comments. According to the data published to date, the use of non-invasive methods for routine clinical assessment of the hemodynamic response to pharmacological therapy is not feasible. The measurement of spleen stiffness and/or of subharmonic-aided pressure estimation might be of use in particular clinical situations, but available data are not sufficient to support this hypothesis.

We agree with the reviewer's comments that the combination of different non-invasive methods provides theoretical advantages over the use of a single method and that complementary information may lead to more robust predictions. Indeed, we believe that

this will be the next line of research in this field. According to the reviewer's suggestion, we have added a new figure outlining a hypothetical algorithm for noninvasively screening and evaluating CSPH.

Reviewer #5 code: 159367

Comment: The review is comprehensive and the topic is very important. Evaluation of portal hypertension by means of noninvasive, reproductive methods underlined. Maybe in the conclusions of the review more clearcut indications for practical use of the noninvasive methods in the estimation of the severity of portal hypertension to be described.

Response:

Thank you for the positive review. We apologize for the lack of clarity in the conclusion and have modified the section accordingly; specifically, we have introduced a figure detailing a hypothetical algorithm for non-invasive screening and evaluating of CSPH. Therefore, more clear-cut indications for practical use of the described non-invasive method are now reported and we are appreciative for the suggestion as it has made our manuscript stronger.

Reviewer #6 code: 13649

Comment: Very nice work. It offers a concise and good balanced overview of the most important aspects related with the topic.

Response:

Thank you for the positive review. We look forward to sharing this work with the *WJG* readership audience.

Reviewer #7 code: 53451

Comment: Summary and general comments This is a review article about the study of non-invasive assessment of portal hypertension. The authors overviewed literatures, outlined the current clinical significance and discussed future perspective. Most of the knowledge is well known, and further improvement may be needed. Major comments: Unfortunately, the number of the reference paper is not enough. Please make clear the way for literature search and conduct comprehensive review. Page 6 -7 The paragraph regarding Doppler US could be shortened because of the limited utility as the authors already recognized. Instead, please add sentences about contrast US since there are many accumulated data. Please refer following paper, and you will find recent trends. Non-invasive assessment of portal hypertension and liver fibrosis using contrast-enhanced ultrasonography. Maruyama H, Shiha G, Yokosuka O, Kumar A, Sharma BC, Ibrahim A, Saraswat V, Lesmana CR, Omata M. *Hepatol Int.* 2016 Mar;10(2):267-76. Please add tables and figures to summarize the data for better understanding the knowledge.

Response:

To stay within the scope of an invited Editorial, we chose to not report the method of literature search that was used for our comprehensive review; unfortunately, a comprehensive review on the subject falls beyond the objectives stated by the publisher in the *WJG* guidelines. According to the Journal guidelines, the purpose of an Editorial is the discussion of one or several topics in the field of gastroenterology and hepatology written from the perspective of the author as an Editorial Board Member that will help guide the direction of future research. We aimed to write the manuscript so as to achieve this goal.

However, we sincerely appreciate the appropriate observations made by this reviewer regarding contrast US. To address these, we have enhanced our reference list and added a new paragraph regarding the data about contrast US and portal hypertension. A particular passage was also included on the SHAPE method and its potential, as well as a figure summarizing the data.