ANSWERING REVIEWERS

January 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6853-review.doc).

Title: Invasive and non-invasive diagnosis of cirrhosis and portal hypertension

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Review 1
In this article the authors review the diagnostic methods of cirrhosis and portal hypertension (PHT). Firstly they discuss the invasive methods: liver biopsy (LB) and HVPG measure, as the standard methods and, that they review the data on the non-invasive alternatives.
Here are my comments for every subtitle:

Introduction:
"Hepatic fibrosis and its 2ndary result" – 2ndary should be replace by secondary
Answer> We have revised it.

"HVPG is one of the best surrogate markers in chronic liver disease, and this parameter reflects the disease severity and has a strong prognostic value with regard to survival and decompensation in patients with compensated cirrhosis or acute bleeding and before liver resection surgery."
- Maybe a reference with a review of the clinical use of HVPG could be appropriate for this phrase.
Answer> We have revised it.

Hepatic venous pressure gradient measurement for portal hypertension:
"The measurement of the HVPG is the gold standard technique for the evaluation of PHT in liver disease, and it closely correlates with the portacaval pressure gradient"
- We cannot see the relevance of this phrase. The great utility of HVPG measuring and especially the prognostic relevance is not a result of correlation with porto-caval gradient. Porto-caval gradient is usually used in patients with TIPS. The great value of HVPG results from his correlation with portal pressure.
Answer> We have revised and omitted the underlined sentence.

"Clinically significant portal hypertension (CSPH) is necessary for the formation of esophageal varices, bleeding"
- The definition of CSPHT as HVPG ≥ 10 mmHg should be offered here
Answer> We have inserted it in the middle of sentence.

"However, no noninvasive alternatives to the HVPG measurement are currently available."
- This is a too optimistic affirmation; we believe that till now there is no non-invasive technique that can replace HVPG. LS measurement has good performances in diagnosis of PHT and, has even prognostic relevance, but at higher values of HVPG the correlation is very weak. Moreover, LS cannot be used for identification of hemodynamic responder to PHT treatment.
Answer> We absolutely agree with your comments and our description also had same meaning. We revised the sentence.

Laboratory tests
"Because of the advantages over liver biopsy, such as offering a sampling that reflects the whole liver, allowing repeated testing, reducing invasiveness, and increasing simplicity, many hematological and biochemical serum markers of fibrosis have been studied."
- We cannot agree with this statement of advantages of serum markers over LB. For the diagnosis of fibrosis stage all serum test were validated with LB as the standard method. Therefore, the sample error of LB cannot be overcome by serum test because the performance of serum test is decreased by this error. Maybe the authors referred to attractiveness of serum markers over the LB.
Answer> We absolutely agree with your comments and have revised it.

It would be interesting an analysis of the existing data on the serum scores regarding their capacity of diagnosis cirrhosis together with PHT. There are only few scores that were validated in the PHT diagnosis (especially in comparison with HVPG). To date:
APRI score beneficiated from a lot of studies but the results are very heterogeneous (AUROC from 0.56 to 0.93); no studies for PHT except for EV were the results were inadequate (AUROC-0.62 Castera2009, 0.62 Sebastiani2010)
Answer> We agree with your comments and have revised it.

Fibrotest is one of the most validated with good results; has a validation with HVPG- Thabut 2007
Answer> We have added the data of Thabut's study and others.

The variables of ELF score should be stated. Maybe some performance details should be provided (AUROC, Se, Sp)
Answer> We have revised it.

Ultrasonography-based approaches
- One of the interesting applications of CEUS is in evaluation of regional hepatic perfusion (RHP) for diagnosis of PHT. Maybe it should be added in the discussion of CEUS application in PHT.
Answer> We have added the data and revised the manuscript.

Transient elastography, acoustic radiation force impulse, supersonic shear-wave elastography, and real-time elastography:
- We believe that a more detailed discussion about LS measurement in PHT diagnosis will be appropriate. Till now: LSM by TE was maybe the most validated non-invasive technique: for diagnosis of cirrhosis many study that confirms good performances (AUROC constantly > 0.90); these findings were confirmed by 2 metanalysis; in PHT diagnosis LS measurement has good results and the problem of different cut-offs is more related to sensitivity and specificity (which one is favored); LS has prognostic relevance for complication (HCC included).
Answer> We have widely revised this part.

- ARFI it looks like it repeats the same results as Fibroscan and probably SSWE could due the same (more studies are needed)
- From this part are not resulting very well the good results of elastography.

Answer> We have added the data and revised manuscript.

CT- and MRI-based approaches: Hemodynamic changes:
"The sensitivity and specificity of CT were found to be 96% and 55%, respectively, to detect esophageal varices and 93% and 80%, respectively, to detect high-risk esophageal varices[80]."
- The reference 80 is not corresponding to the topic
Answer> There was a mistake in using reference management software and we have revised it.

MR elastography:
- Maybe more details about the performance could be more appropriate (AUROC, Se, Sp) instead of to many technical details.
Answer> We have added the data and revised the manuscript.

References:
- There is a duplicate of references section, but only the second one is corresponding to the text
Answer> There was a mistake in using reference management software and we have revised it.

Review 2
This article reviews the current evidence regarding invasive and non-invasive diagnostic methods for cirrhosis and portal hypertension. As a general comment, the review is structured according to the techniques and reads well. However, it lacks insight to support clinical decision making (e.g. when different tests should be used? Accuracy should be summarized for all main tests). Furthermore, some points need to be corrected and clarified:
- The introduction contains several information on HVPG that are also explained in the paragraph regarding HVPG measurement. Please shorten the introduction to avoid duplication. In addition a citation is required at the end of the paragraph regarding the clinical use of HVPG (I suggest to use Bosch et al. Nature Reviews Gastroenterol Hepatol 2009).
Answer> We have revised it as your comments.

- In addition, at the end of the first paragraph of the introduction it is stated that "Hepatic fibrosis and its 2ndary result, portal hypertension (PHT) are currently viewed as a dynamic process that often regresses after the successful treatment of chronic liver disease". This is only partially true. While some cases of regression of cirrhosis have been published, the overall rate of regression, and in particular the rate of regression of PHT after resolution of liver disease is unknown, especially after HCV SVR. Please, mitigate this point and add adequate references to the sentence.
Answer> We agree with your comment and we have revised it.

- Page 6, line 24: "In addition, from the clinical point of view, an important distinction is made between compensated and decompensated cirrhosis as they have distinctive prognoses. However, such a subdivision cannot be made by the current method used for the histologic examination of liver biopsies." This sentence makes no sense, since the distinction between compensated and decompensated cirrhosis is always made on a clinical ground. Hence, this sentence should be deleted.
Answer> We have revised it according to your advice.

- In the entire text it should be made emphasis on which methods allow discriminating cirrhosis and PHT in patients in the compensated phase, since in the decompensated phase the diagnosis of cirrhosis is obvious and PHT is present in 100% of cases.
Answer> We agree your comments and the main issue of this manuscript is how to discriminate clinically significant fibrosis or portal hypertension non-invasively in compensated disease. So, we have selected and referred the data that are useful for this issue.

- Laboratory tests: lines 4 to 22 are very much like a paragraph contained in the review by Berzigotti et

al. published in Disease Markers in 2011. Please cite this source of information.
Answer> We have revised it according to your advice.

- Ultrasound: the sentence "Taken together, grayscale and Doppler US are safe, inexpensive and simple to use at the bedside or for outpatients, and combining multiple US indices can improve the diagnostic accuracy of cirrhosis under some conditions" is insufficiently supported by the summarized data. Please add data regarding the sensitivity and specificity of the technique.
Answer> The data for grey scale and Doppler US is very old, huge and heterogeneous to summarize briefly. In addition, recently the clinical usefulness and significance of US have been decreased according to the development of new and more reproducible diagnostic method such as transient elastography. So, in this manuscript, we just briefly introduced this old method.

- Transient elastography: page 12, lines 21-22 "TE is useful as a screening test for cirrhosis, but is not recommended for diagnosing stages other than cirrhosis because the optimal cut-offs of LS have not been validated for individual stages of fibrosis". This is not true: see for example Castera L. Gastroenterology 2012. The second part of the sentence should be deleted.
Answer> We have revised it.

- Page 13, lines 1-2 "In non-invasive prediction of CSPH (HVPG ≥ 10 mmHg), the cut-off value of TE is diverse according to the etiology and status of chronic liver disease". It has been already noticed that the choice of a given cut-off depends on the choice of the threshold of sensitivity and specificity. Indeed, if well re-analysed, all data up to now strongly suggest that values <13 kPa exclude reliably CSPH, while values > 21 kPa reliably diagnose CSPH. I suggest modify the sentence to include this data.
Answer> We have revised it.

- Page 13, lines 17-18: "In addition, the data for their predictive values to estimate the hemodynamic response to ?-blockers is rare yet". Please cite the paper by Reiberger T et al. J Gastroenterol. 2012.
Answer> We have revised it.

- Page 15. "Because CT and MRI are not functional imaging modalities, they are not appropriate for evaluating the hemodynamic changes in the liver". This is true for standard CT and MRI. On the other h…
Answer> We have revised it.

Review 3
The authors review various modalities available for diagnosis of cirrhosis and portal hypertension My concerns are
1. Abbreviations: Ultrasonography instead of Utrasonography
Answer> We have revised it.

2. Introduction 2nd line: secondary instead of 2ndary
Answer> We have revised it.

3. Introduction: the meaning of "In addition, with the introduction of anti-viral treatments for viral hepatitis patients, the diagnosis of the heterogeneity of cirrhosis and PHT has become even more important for effective treatment." is not clear. Please modify/clarify the statement
Answer> We have revised it.

4. The definition of decompensated cirrhosis is said to include colopathy, enteropathy, variceal formation which is incorrect. Only bleeding varices, ascites, encephalopathy etc qualify to be labelled decompensation

Answer> We have revised it.

5. Modify The ideal noninvasive test for diagnosing fibrosis and PHT is one that is simple and reproducible, readily available, less expensive than a biopsy, to The ideal noninvasive test for diagnosing fibrosis and PHT should be simple and reproducible, readily available, less expensive than a biopsy,..
Answer> We have revised it.

6. In the discussion of HVPG it is important to discuss its role in EHPVO and NCPF as it can not be used to diagnose all cases of portal hypertension. Similarly since the authors are reviewing diagnosis of portal hypertension, it is important to comment briefly on role of fibroscan in diagnosis of NCPF/EHPVO and comparison with cirrhosis
Answer> We have added data and revised it.

7. Please modify the statement However, TE values correlate closely with HVPG values, but up to 10 ~ 12 mmHg and the correlation gets weak above that value[95] as the meaning is not clear
Answer> We have revised it.

8. The reference list has been provided twice
Answer> We have revised it.

9. The authors use no tables. It may be better to list in a table the direct and indirect markers of fibrosis,
11. A table may be used to clarify about various panels which are now commercially available mention the benefits and pitfalls of each
Answer> We have added a tables for noninvasive diagnosis of fibrosis.

10. The list of biomarkers is not exhaustive. The authors may consult this review and add further details
http://www.gastroenterologyandhepatology.net/index.php/archives/october-2012/noninvasive-diagnosis-of-nash-and-liver-fibrosis-within-the-spectrum-of-nafld/ Or at http://www.gastroenterologyandhepatology.net/files/2013/08/gh1012_mccullough1.pdf
Answer> We have added and revised it.

11. Please get the manuscript read by native speaker of English before resubmission
Answer> We have revised it by professional English language editing company.

3 References and typesetting were corrected

Thank you.

Sincerely yours,

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