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ESPS Peer-review Report
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Reviewer code: 02567564
Science editor: Qi, Yuan
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The authors review various modalities available for diagnosis of cirrhosis and portal hypertension My concerns are 1. Abbreviations: Ultrasonography instead of Utrasonography 2. Introduction 2nd line: secondary instead of 2ndary 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 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 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,.. 6. In general, histologic scoring systems?assess the grade and stage of chronic hepatitis. What is the need od II 7. 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 8. 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 9. The reference list has been provided twice 10. The authors use no tables. It may be better to list in a table the diect 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 12. 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 14. Please get the manuscript read by native speaker of English before resubmission

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		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

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 should different tests 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). - 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. - 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. - 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. - 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. - 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 unsufficiently supported by the summarized data. Please add data regarding the sensitivity and specificity of the technique. - 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. - 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. - 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. - 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

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		[ ] No records	

COMMENTS TO AUTHORS

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 "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. 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 he prognostic relevance is not a result of correlation with porto-caval gradient. Porto-caval gradient is usually used in patients with TIPS. The great values of HVPG results from his correlation with portal pressure. "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 "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. 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. - 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) - Fibrotest is one of the most validated with good results; has a validation with HVPG- Thabut 2007 - The variables of ELF score should be stated. Maybe some performance details should be provided (AUROC, Se, Sp) 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. 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 performanc