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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 37644
Title: Quantitative and Noninvasive Assessment of Chronic Liver Diseases using 2D-SWE
Reviewer's code: 03317257
Reviewer's country: Morocco
Science editor: Ze-Mao Gong
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

good paper but it need minor revision

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 37644
Title: Quantitative and Noninvasive Assessment of Chronic Liver Diseases using 2D-SWE
Reviewer's code: 03262644
Reviewer's country: Croatia
Science editor: Ze-Mao Gong
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

GENERAL COMMENT This is an important review, as it has passed 7 years from the first paper published on the value of 2DSWE as new and technologically most advanced among the ultrasound based elastography methods for noninvasive assessment of chronic liver disease, primarily staging finrosis. In the meanwhile multiple papers have been published focused not only to fibrosis staging by the means of 2DSWE, but also risk assessment in cheonic liver disease including diagnosis of the presence of clinically significant portal hypertension and large esophageal varices, and prognostication of the clinical outcomes as well. The most recent area is the use of 2DSWE for characterization of focal liver lesions. These issues are important and should be encompassed by an review article since ultrasound maschines containing 2DSWE technology have been introduced in many clinical institutions and practice. The ptacticing doctors should have

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available information on the performance of 2DSWE in different aspects of chronic liver disease. This manuscript is well written and interesting but should be a bit more specific in a certain topics. For example, the authors should provide readers the calculated cut-off values for different stages of liver fibrosis as these are available and published by several meta-analyses…this is important for the reader to have available complete information from this article. English language should be polished a bit, so please give this manuscript to native English speaker for correction. Several important papers should be quotes as suggested later on. SPECIFIC COMMENTS Page 2 "however, there are no clear standard cut-off values for diagnosing fibrosis stage" Not entirely truth. Please see 3 meta-analyses and the multicentric study by Hermann E et al. Hepatology 2017. "whether 2D-SWE can be used to accurately guide clinical therapy and monitor prognosis has not yet been „determined. Not entirely truth. Please see the manuscript by grgurevic I et al. Croat Med Journal 2015. In this paper the authors clearly demonstrated utility of 2DSWE to prognosticate clinical outcomessin patients with compensated cirrhosis. "2D-SWE appears to be an excellent tool for the early detection of cirrhosis and may have prognostic value in this context." This is correct, and refers to the previous comment. However, these 2 sentences are contradictory, so the authors have to be more specific or rephrase one of them. Page 4 "liver biopsy is invasive, costly, and painful, and it is associated with easy bleeding" I wouldn't say easy...please omit this term "Given these limitations, liver biopsy is not an ideal method for the repeated assessment of disease progression." please add "as well" at the end of the sentence. Page 5 „2D-SWE was performed using an Aixplorer" This section is written as if the authors were presenting their original results. There this should be rephrased: "2DSWE examination of the liver is performed by using convex ultrasound probes with integrated technological solutions alowing to perform elasticity imaging and measurements." Please do not write as if you are explaining the way how did you perform 2DSWE measurements in any experimental study. Be more narrative and explain general principles of measurements for all available 2DSWE methods. There are some other manufacturers that use 2DSWE such as Philips, GE, Toshiba..the authors should mention them as well. Page 6 „Comparison of elastography methods" I would suggest to place this section before previous 3 sections, so the final order will be as follows: Comparison of elastography methods Principles of two-dimensional (2D)-SWE Examination technique Normal value of liver stiffness by 2DSWE "using different imaging modalities, such as 2D-SWE, magnetic resonance elastography (MRE), transient elastography (TE), and acoustic radiation force impulse (ARFI) elastography. Among these…" Here, the authors should present current division of the Ultrasound based elastography: 1-strain elastography 2-SWE SWE can be furtherly subdivided to: 2.1.-transient elastography 2.2.-point SWE (VTQ, ElastPQ etc.) 2.3.-2DSWE (SSI, GE,

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Philips, Toshiba etc.)...please see EFSUM guidelines for classification of elastography meth "However, this method is limited by high unreliability." It is not correct to state that unrealibility is high. I would suggest just to cite the exact % of unreliable results and to sustain from giving such a strong conclusion. The author should state here limitations to elastographic examination which are pretty common for all elastography methods, such as obesity and narrow intercostal spaces. For TE they should add that it is not applicable in patients with ascites. The limitation of the obesity has tried to be overcome by the introduction of specially designed XL probe that measures liver stiffness deeper compared to standard M probe. Since most of the discussed results in the following text refer to the studies performed by Supersonic 2DSWE the authors should specifically state this in order to avoid missunderstanding and generalisation of these results to all other 2DSWE methods. „Recent domestic and foreign studies have focused…" Please avoid "domestic and foreign" Page 6, the last 3 rows: I suggest to move this sentence at the end of this section, after the authors quote the examples such as Bavu study, Ferraioli study . Here I would suggest to include the reference Grgurevic I et al. Eur Rad 2015 in which the authors examined spleen stiffness in addition to liver stiffness in order to stage liver fibrosis, and where they showed that liver and spleen stiffness continue to increase even after the cirrhosis has been developed. In fact they noticed that spleen and liver stiffness tended to converge in more advanced stages of liver cirrhosis. This is important study to show that 2DSWE might be used to study evolution of liver disease beyond cirrhosis. Page 7 „they found that real-time SWE was more accurate than TE for assessing significant fibrosis (≥F2)" . After quoting previuos study by Hermann E et al. Hepatology 2017, the authors should quote for 3 other meta-analyses that adressed the performance of 2DSWE for staging liver fibrosis in chronic viral hepatitis: Feng J-C, Li J, Wu X-W, Peng X-Y. Diagnostic Accuracy of SuperSonic Shear Imaging for Staging of Liver Fibrosis: A Meta-analysis. J Ultrasound Med [Internet]. 2016 Feb [cited 2016 Aug 23];35(2):329–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26795041 Li C, Zhang C, Li J, Huo H, Song D. Diagnostic Accuracy of Real-Time Shear Wave Elastography for Staging of Liver Fibrosis: A Meta-Analysis. Med Sci Monit [Internet]. 2016 [cited 2016 Aug 23];22:1349–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27102449 Jiang T, Tian G, Zhao Q, Kong D, Cheng C, Zhong L, et al. Diagnostic Accuracy of 2D-Shear Wave Elastography for Liver Fibrosis Severity: A Meta-Analysis. PLoS One [Internet]. 2016 [cited 2016 Aug 23];11(6):e0157219. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27300569 "Unfortunately, some published studies have lacked accurate criteria for validating the liver fibrosis stage." I do not iunderstand, please specify "CHB and CHC, even though viral hepatitis can also lead to liver fibrosis" please omit this "resulting in differences in the diagnostic

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performance of SWE." It has been well appreciated by various authors that LSM by TE are lower for HBV as compared to HCV, and this is probably due to the different tissue patern of fibrosis development and distribution. Specifically in cirrhosis HBV tends to produce larger regenerative nodules which may lead to lower values of LSM if the ROI is placed over such an area. „Figure 4 showed 2D-SWE of the liver fibrosis" Depicts instead of showed Page 8 "differentiating NASH from SFL and assessing the severity of liver fibrosis is crucial for risk stratification management in patients with NAFLD" Even SFL may result in fibrosis development, as demonstrated by the meta-analysis by Singh et al. Clin Gastro Hepatol 2015. They demonstrated that fibrosis development may be observed in around 30% of patients with SFL as well as in patients with NASH. Liver fibrosis has been demonstrated as the single most important histological feature associated to the risk of liver-related complications and death in patients with NAFLD (Angulo Gastroenterology 2017, Ekstead M, Hepatology 2017) Therefore, the most imporimtant issue in patients with NAFLD is to recognize and stage liver fibrosis, which is possible by using US elastography. "They compared three elastography methods, 2D-SWE, TE and ARFI elastography" ARFI elastography is not completly precize term to use_ ARFI is a way how SWE works, and there are different methods that use ARFi such as VTQ (Siemens), ElastPQ (Philips), and all 2DSWE methods. In this specific study the authors used siemens technology (VTQ)-please correct. „Hence, the next question is whether SWE can differentiate NASH from SFL, especially in the early stages of fibrosis" Probably not, and this is an area of biochemical methods-please include this. Page 9 "using liver biopsy as a reference [41]." Did the authors mean reference 42 instead? "The study found that SWE was a remarkable tool for diagnosing alcoholic fibrosis" Please cite the main results of the study Page 10 "SWE has outstanding diagnostic accuracy, with a specificity and sensitivity above 80%, and is superior to TE" .Is this general comment or it refers to the previous study? "Regrettably, another study found that clinically significant portal hypertension (CSPH) could not be ruled out in more than 30% of patients because their SWE values were close to the cut-off values[53]." This is not readable, I could not understand what the authors meant by this...please be more precisze? It is important that the main results and messages of the quoted studies are presented to the reader. „Thus, while 2D-SWE has exceptional clinical value for assessing HCC patients with PH and EGVB, it still cannot replace digestive endoscopy[51]." Again, I do not understand the meaning, please rephrase to sound logical. Page 11 „A recent report has indicated that 2D-SWE can accurately assess 96% of patients with benign and malignant FLLs[63]" ...provided that the 2DSWE measurements were successfull. This study used 3 elastographic parameters, i.e. mean stiffness of the FLL, the ratio between the minimal and maximum lesion stiffness and the ratio between the stiffness of the FLL and

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surrounding liver parenchyma, to calculate so called Liver elastography malignancy prediction score (LEMP) based on the regression analysis. Otherwise, with more simple approach that uses only mean lesion stiffness in dichotomized fashion it was possible to rule-in and rule-out malignancy at cut-off values of 14 and 32.5 kPa respectively with 96% accuracy in 55% of the examined lesions. Page 12 "cross-sectional diagnosis but also in longitudinal studies considering disease progression, regression and clinical outcomes" Please quote the study by Grgurevic I et al. Croat Med Journal 2015 Page 13 "Can we use SWE to distinguish different types of liver disease, such as differentiating NASH from simple steatosis or differentiating PBC from PSC? „ This is not correct question. SWE as other elastography methods cannot differentiate among different etiologies of liver disease. Therefore, it cannot differentiate patients with PBC from PSC. SWE measures liver stiffness, and liver stiffness mainly results from accumulation of fibrous tissue. In addition, any other process that increase liver tension such as cholestasis, liver congestion or infiltration with malignant cells or inflammatory cells may lead to increased stiffness. In these cases the resultant stiffness is the sum of fibrosis + one or more of the mentioned factors. Therefore, when attempting to asses liver fibrosis stage by the means of liver elastography patients with overt cholestasis, liver congestion and pronounced inflammatory activity (as represented by ALT increased >5x ULN) should be excluded. For the remaining patients liver stiffness is representative of the amount of liver fibrosis. As such, SWE probably should not be expected to differentiate between SFL and NASH "6. In compensated cirrhosis of adult CLD, what SWE LS cut-off value allows us to accurately rule out the presence of high-risk esophageal varices and eliminate the need for gastroscopy?" This issue has already been addressed.. please see Baveno 6 conference recommendations , and the related studies. Page 14 "2D-SWE is known to be a multifactorial process" 2DSWE is not a process...please rephrase Page 16 "Large differences among the measurements provided by different instruments create obstacles to the clinical application of SWE that need be addressed in the f"ture" Please quote the reference Piscaglia F, Salvatore V, Mulazzani L, Cantisani V, Colecchia A, Di Donato R, et al. Differences in liver stiffness values obtained with new ultrasound elastography machines and Fibroscan: A comparative study. Digestive and Liver Disease. 2017. DOI: http://dx.doi.org/10.1016/j.dld.2017.03.001 „In conclusion, 2D-SWE appears to be an ideal, simple, fast, reproducible…" Please omit the word "ideal" „While it is impossible to completely eliminate the need for liver biopsy, the combination of liver biopsy and SWE can compensate for sampling error during puncture and improve the accuracy of clinical biopsy. „ There are no evidences to support this conclusion. Please omit. "for clinical applications, including accurate quantification, 3D measurements" Why 3D ? This has not been addressed anywhere in the previous text, and there are no data about

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3DSWE. Please omit. Page 35, Table 2 First column…"ARFI"- The method is Point Shear Wave Elastography- please change! Disadvantages of ARFI-ascites: Not true. Can be used even in patients with ascites Limitations of TE: TE cannot be used in patients with ascites Page 36, table 2- continued, the last column, 2DSWE disadvantages: Lack of accurate criteria to asses liver fibrosis….Not true...please see the comments in the related section of this manuscript. Page 38, Table 3 Please include reference by Grgurevic I et al. Eur Radiol 2015

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Reviewer's country: Romania
Science editor: Ze-Mao Gong
Date sent for review: 2017-12-29
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[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The review is important, but needs to be more practical informations regarding how to score better liver fibrosis for different pathologies and sometimes the stile of authors is too narrative. The review needs to be more practicle to be usefull for the reader. The English language has to be polished.