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Answering Reviewers

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Quantitative and Noninvasive Assessment of Chronic Liver Diseases using 2D-SWE" (Manuscript NO: 37644, *World Journal of Gastroenterology*). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope it may meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Answering Reviewer #1

Name of journal: World Journal of Gastroenterology

Manuscript NO: 37644

Title: Quantitative and Noninvasive Assessment of Chronic Liver Diseases using 2D-SWE

Reviewer #1:

Reviewer's code: 03317257

Reviewer's country: Morocco

Science editor: Ze-Mao Gong

1. Response to comment: "The latest guidelines (EFSUMB) for the clinical use of liver ultrasound elastography state that it is a valid technique for the noninvasive evaluation of the degree of liver fibrosis [9]."U can cite also that according to EASL-ALEH Clinical

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Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis (2D-SWE is a promising technique that is currently under investigation. It seems to be at least equivalent to TE and pSWE/ARFI for non-invasive staging of liver fibrosis in viral hepatitis) Journal of Hepatology 2015 vol. 63 j 237–264

Response: Thank you very much for your comments and suggestions. We have read the valuable EASL-ALEH Clinical Practice Guidelines and cited it, as well as added the important information to the paper, which really help comparison with different noninvasive methods (2D-SWE, TE and pSWE/ARFI).

The revised details showed in Page 4, Paragraph 2, Line 12-20 (marked in red)

2.Response to comment: Reformulate, easy bleeding (risk of bleeding) and mention the contre indication of liver biopsy in case of ascites.

Response: We are very sorry for our incorrect writing by using the word "easy". We have turned it into "risk of bleeding", and mention the contraindications of liver biopsy, such as the cases of massive ascites.

The revised details showed in Page 4, Paragraph 2, Line 1-4 (marked in red).

3.Response to comment: "In a study of 13,369 CLD patients over a 5-year period using TE, unreliable results were obtained in 15.8% of cases [26]." Can u please give more explanations about causes of unreliability? obesity? use of XL probe?

Response: We are very sorry for our negligence of the unreliable causes. We have explained the causes of unreliability: obesity, narrow intercostal spaces, variations in operator experience, and that TE is not applicable in patients with ascites. It is a pity that this research didn't describe what kinds of probe they used. In addition，we further demonstrated the obesity issue has been partially addressed by the introduction of specially designed XL probes that measure liver stiffness deeper than standard M probes.

7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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The revised details showed in Page 5, Paragraph 1, Line 7-13 (marked in red).

4.Response to comment: Comparison of elastography methods: in there any studies comparing elastography methods to liver biopsy?

Response: Thanks for your question. There are many studies use liver biopsy as the reference standard for the diagnostic accuracy of 2D-SWE, or comparison with other elastography methods, for noninvasively assessing liver fibrosis in patients with CLDs. Here, we give some examples showed in our paper, as followings:

(1) Ferraioli et al (Page 7, Reference 20 of the revised manuscript). Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012;

(2) Cassinotto et al (Page 9, Reference 46), Liver stiffness in nonalcoholic fatty liver disease: a comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology 2016;

(3) Jie Zeng et al (Page 14, Reference 66), Non-invasive assessment of liver fibrosis using two-dimensional shear wave elastography in patients with autoimmune liver diseases. World J Gastroenterol 2017;

5.Response to comment: "Therefore, differentiating NASH from SFL and assessing the severity of liver fibrosis is crucial for risk stratification management in patients with NAFLD." I think that the goal of noninvasive methods in NAFLD is identifying patients with fibrosis and not differentiate between SFL and NASH.

Response: As reviewer suggested that the goal of noninvasive methods in NAFLD is identifying patients with fibrosis and not differentiate between SFL and NASH. SWE, as other elastography methods, cannot differentiate among different etiologies of liver disease. We have reformulated this description.

7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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The revised details showed in Page 9, Paragraph 1, Line 13-15 (marked in red).

6.Response to comment: Cassinotto et al. [40] enrolled 291 patients with NAFLD and used liver biopsy as the reference standard for assessing and staging liver fibrosis. They compared three elastography methods, 2D-SWE, TE and ARFI elastography, you cite that: especially SWE, were valuable for diagnosing liver fibrosis in patients with NAFLD.Can u give details about its sensitivity and specificity)

Response: Thanks for your considerable reminding, we are sorry for our negligence of important details: the sensitivity and specificity of the diagnostic performances of 2D-SWE for assessing liver fibrosis. We have added the relevant sensitivity, specificity and AUROC of significant fibrosis (≥F2), severe fibrosis (≥F3), and cirrhosis (F4), respectively.

The revised details showed in Page 9, Paragraph 2, Line 6-11 (marked in red).

7.Response to comment: When 2D ultrasound and Doppler ultrasound suggest that lesions are benign tumors, but elastography suggests malignancy, can a final diagnosis of malignancy be made? Please reformulate this without question

Response: As Reviewer suggested, we have reformulated this sentence without question." the lesion cannot therefore be diagnosed as malignant."

The revised details showed in Page 13, Paragraph 3, Line 2-4 (marked in red).

8.Response to comment: The basic problem 1. Shear wave Young's modulus vs shear wave velocity: which is more representative? 2. Are multiple measurements in one location necessary when satisfactory measures of stiffness are obtained? Or, are measurements in more than one location needed? 3. Does a simple semi-quantitative fibrosis score adequately reflect the complexity of the pathophysiological process?; u can

7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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summarize as stipulated in above mentioned EASL guidelines that Although alternative techniques, such as pSWE/ARFI or 2D-SWE seem to overcome limitations of TE, their quality criteria for correct interpretation are not yet well defined (A1)

Response: We have re-written this part according to your crucial suggestion. We summarized the basic problem and added a new problem of 2D-SWE. Details were as following:

The basic problem

1. Although alternative techniques, such as pSWE/ARFI or 2D-SWE seem to overcome the limitations of TE, their quality criteria for the staging of liver fibrosis are not yet well defined.

a. It remains unclear whether the shear wave Young's modulus or shear wave velocity is more representative.

b. Are multiple measurements in one location necessary when satisfactory measures of stiffness are obtained? Or, are measurements in more than one location needed?

c. There is currently no agreement on objective quality criteria regarding what constitutes a valid measurement and what is an invalid measurement.

2. Does a simple semi-quantitative fibrosis score adequately reflect the complexity of the pathophysiological process?

The revised details showed in Page 15, The basic problem (marked in red).

9.Response to comment: The clinical problems 1" In the era of the promotion of precision medicine, can 2D-SWE accurately guide clinical work to design a reasonable treatment strategy?" It is not true for in hepatitis c, the only goal of noninvasive methods is to rule out liver cirrhosis, distinguishing between intermediate liver fibrosis stages is not crucial any more. According to EASL guidelines (Liver disease severity should be assessed prior to therapy. Identifying patients with cirrhosis is of particular importance, as their

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Fax: +1-925-223-8243
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treatment regimen and post-treatment surveillance must be adapted)

Response: We are very sorry for our incorrect writing. We have make correction and stressed it is aim at hepatitis B patients. Besides, we make a further explanation in the next page of answering the first clinical problem

The revised details showed in Page 15, The clinical problem 1 (marked in red) and Page 16, Paragraph 3, Line 5-7 (marked in red).

10.Response to comment: "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? "U can refer to baveno 6 in response to this question Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. The most important for SWE is to correlate with te –ls but in baveno 6 guidelines only TE is mentioned

Response: Thanks for your suggestion. We have read the Baveno VI criteria, "Patients with a liver stiffness <20 kPa (measured by TE) and with a platelet count >150,000 have a very low risk of having varices requiring treatment, and can avoid screening endoscopy; These patients can be followed up by yearly repetition of TE and platelet count", which does help us to increase our knowledge. As you suggested in baveno VI guidelines only TE is mentioned, we thought it was also significant to 2D-SWE. We read more related studies about the cut-off value to rule out the high-risk esophageal varices in patients with compensated cirrhosis of CLDs and found this issue has already been addressed. But the cut-off value to avoid screening endoscopy of 2D-SWE is still an unresolved issue. Therefore, we put forward the latter question.

The details showed in Page 16, The clinical problems 6 (marked in red).

11.Response to comment: shrunken liver, what that mean?

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Response: We are sorry for our incorrect description of "shrunken", we want to describe the liver size is become smaller in patients with cirrhosis than the healthy people. We have make correction and changed the "shrunken" into "shrinking".
The revised details showed in Page 17, the last 1 line (marked in red).

12.Response to comment: We cannot perform a liver biopsy every year, but we can use SWE to monitor liver fibrosis after treatment: please reformulate.
Response: Thanks for your advice, we have re-written this part. "As liver biopsies cannot be performed frequently, SWE can be used to regularly monitor liver fibrosis over the long term".
The details showed in Page 18-19, the last 1 line (marked in red).

Special thanks to you for your good comments.

Answering Reviewer #2

Name of journal: World Journal of Gastroenterology

Manuscript NO: 37644

Title: Quantitative and Noninvasive Assessment of Chronic Liver Diseases using 2D-SWE

Reviewer #2:

Reviewer's code: 03262644

Reviewer's country: Croatia

Science editor: Ze-Mao Gong

1.Response to comment: Page 2 "however, there are no clear standard cut-off values for

7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
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diagnosing fibrosis stage". Not entirely truth. Please see 3 meta-analyses and the metacentric 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 2D-SWE to prognosticate clinical outcomes in 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.

Response: Special thanks to you for your good comments. We are very sorry for our incorrect writing and have studied several meta-analyses about the 2D-SWE diagnosing liver fibrosis. We have made correction: "However, the quality criteria for the staging of liver fibrosis are not yet well defined." We also read the valuable manuscript written by grgurevic I et al (Real-time two-dimensional shear wave ultrasound elastography of the liver is a reliable predictor of clinical outcomes and the presence of esophageal varices in patients with compensated liver cirrhosis), and delete the previous incorrect writing: "whether 2D-SWE can be used to accurately guide clinical therapy and monitor prognosis has not yet been determined". Thanks for your correction and improve our knowledge.

The revised details showed in Page 2, Paragraph 1, Line 7-8 (marked in red).

2.Response to comment: 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.

Response: We are so sorry for our incorrect writing by using the word "easy". We have

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Fax: +1-925-223-8243
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turned it into "risk of bleeding" and have added the "as well".

The revised details showed in Page 4, Paragraph 2, Line 3 (marked in red) and Page 4, Paragraph 2, Line 8 (marked in red)

3.Response to comment: 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 allowing 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.

Response: Thanks for your crucial suggestion. We have made correction according to your great comment. In addition, according to the suggestion, there are some other manufacturers that use 2D-SWE such as Philips, GE, Toshiba et al, so we add detailed manufacturers in Table 1.

The revised details showed in Page 6, Paragraph 2, Line 1-3 (marked in red) and Page 32-34, Table 1.

4.Response to comment: 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.

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Fax: +1-925-223-8243
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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, Philips, Toshiba etc.)...please see EFSUM guidelines for classification of elastography method

Response: Special thanks to you for your comment. We have change the section order according to your suggestion, and re-write this part after reading the EFSUM guidelines for classification of elastography method.

The revised details showed in Page 5, Paragraph 1, Line 1-4 (marked in red).

5.Response to comment: "However, this method is limited by high unreliability. "It is not correct to state that unreliability 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 misunderstanding and generalization of these results to all other 2DSWE methods. "Recent domestic and foreign studies have focused…" Please avoid "domestic and foreign"

Response: According to your important suggestion, we have turned the "unreliability is high" into "the exact % of unreliable results" and explained the limitations of unreliability: obesity, narrow intercostal spaces, variations in operator experience, and that TE is not applicable in patients with ascites. It is a pity that this research didn't

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Telephone: +1-925-223-8242
Fax: +1-925-223-8243
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describe what kinds of probe they used. In addition，we further demonstrated the obesity issue has been partially addressed by the introduction of specially designed XL probes. We are very sorry for our wrong writing and have deleted the "domestic and foreign"

The revised details showed in Page 5, Paragraph 1, Line 7-13 (marked in red) and in Page 7, Paragraph 2, Line 1 (marked in red)

6.Response to comment: 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.

Response: Thanks for your suggestion, we have made the relevant correction. We have changed the section order and cited the significant reference, besides, we read the important study earnestly, which really further improve our cognition.

The revised details showed in Page 7, Paragraph 2, the last 3 Line (marked in red) and in Page 8, Paragraph 1(marked in red)

7.Response to comment: (1)Page 7 "they found that real-time SWE was more accurate than TE for assessing significant fibrosis (≥F2)" . After quoting previous study by Hermann E et al. Hepatology 2017, the authors should quote for 3 other meta-analyses that addressed the performance of 2DSWE for staging liver fibrosis in chronic viral

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hepatitis: Feng J-C, et al. J Ultrasound Med, 2016; Li C, Zhang C, et al. Med Sci Monit, 2016; Jiang T, et al. PLoS One, 2016.

(2)"Unfortunately, some published studies have lacked accurate criteria for validating the liver fibrosis stage." I do not understand, please specify

(3)"CHB and CHC, even though viral hepatitis can also lead to liver fibrosis", please omit this.

Response: (1) As reviewer suggested that we have cited the three meta-analyses to address the performance of 2DSWE for staging liver fibrosis in chronic viral hepatitis.

The revised details showed in Page 7, Paragraph 2, the last 3-5 Line (marked in red)

(2) We are sorry for our incorrect description and have made correction:" However, the quality criteria for the staging of liver fibrosis are not yet well defined."

The revised details showed in Page 8, Paragraph 2, Line 5-6 (marked in red)

(3) we have omitted the wrong writing.

8.Response to comment: (1) "resulting in differences in the diagnostic 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 pattern 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.

(2) "Figure 4 showed 2D-SWE of the liver fibrosis ". Depicts instead of showed

Response: (1) Thanks for your important suggestion, we re-write this part. We have read relevant research of pathology about regenerative nodules of cirrhosis HBV and HCV, which do help us to improve our knowledge why 2D-SWE has different diagnostic accuracies for liver fibrosis in patients with CHB and CHC.

The revised details showed in Page 8, Paragraph 2, Line 6-12 (marked in red).

7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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Fax: +1-925-223-8243
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(2) We have shown detailed depicts in the figure legend

The revised details showed in Page 8, the last 3 Line (marked in red) and more details in the legend of Page 31, Figure 3.

9.Response to comment: 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 important issue in patients with NAFLD is to recognize and stage liver fibrosis, which is possible by using US elastography.

Response: According to the reviewer suggestion, we re-write this part and read the crucial researches, which increase our cognition. Details:" A meta-analysis[44] demonstrated that even SFL may result in fibrosis development, and fibrosis development was observed in approximately 30% of patients with SFL as well as in patients with NASH. Liver fibrosis, but no other histological features, has been demonstrated as the single most crucial histological feature associated with the risk of liver-related complications and death in patients with NAFLD [45]".

The revised details showed in Page 9, Paragraph 1, Line 7-15 (marked in red).

10.Response to comment: (1)"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

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Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
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(Siemens), ElastPQ (Philips), and all 2DSWE methods. In this specific study the authors used siemens technology (VTQ)-please correct.

(2)"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.

Response: (1) We are very sorry for our incorrect writing and have changed it into "Virtual Touch Quantification (VTQ)"

The revised details showed in Page 9, Paragraph 2, Line 2 (marked in red).

(2) We have added this sentence.

The revised details showed in Page 10, Paragraph 1, Line 4 (marked in red).

11.Response to comment: 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

Response: Thanks for your reminding, we are sorry for our careless, we have corrected it. And we have cited the main results of the prospective study of 199 alcohol-overusing individuals with varying degrees of alcoholic liver fibrosis evaluated two elastography methods.

The revised details showed in Page 11, Paragraph 1, Line 1-6 (marked in red).

12.Response to comment: (1) 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?

(2)"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

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Pleasanton, CA 94588, USA
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the authors meant by this...please be more precise? It is important that the main results and messages of the quoted studies are presented to the reader.

(3) "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.

Response: (1) This general comment did not refer to the previous study. We are sorry for our unclear writing and have made a clear description about this part.

The revised details showed in Page 11, Paragraph 2, Line 9-12 (marked in red).

(2) (3) We are sorry again, we have re-write this part with precise description.

The revised details showed in Page 11, Paragraph 2, Line 12-18 (marked in red).

13.Response to comment: 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 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.

Response: Thanks for your detailed introduction of the valuable research, which do help to improve our understanding. We have read the important study and made a detailed analysis, which also help the reader to understand the meaningful research.

The revised details showed in Page 13, Paragraph 2, Line 1-10 (marked in red).

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Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
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14.Response to comment: (1) 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

(2) Response to comment: 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.

Response: (1) We have quoted the significant research, which really showed many great information. Most importantly, it helps readers to understand the value of 2D-SWE to predict the presence of esophageal varices in patients with compensated liver cirrhosis.

(2) Thanks for your detailed introduction again. Your comments are always full of details and encouraged, we do learn a lot from your suggestions. We have deleted the incorrect problem.

15.Response to comment: "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

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Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
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varices and eliminate the need for gastroscopy? "This issue has already been addressed. please see Baveno 6 conference recommendations, and the related studies.

Response: We have read the Baveno VI conference. In baveno VI guidelines, only TE is mentioned. In another study, an important manuscript you suggested (written by grgurevic I et al, Croat Med Journal 2015, Real-time two-dimensional shear wave ultrasound elastography of the liver is a reliable predictor of clinical outcomes and the presence of esophageal varices in patients with compensated liver cirrhosis), this issue has already been addressed. And the cut-off value to avoid screening endoscopy of 2D-SWE is still an unresolved issue. Therefore, we put forward the latter question.

The details showed in Page 16, Paragraph 1, Line 1-2 (marked in red).

17.Response to comment: (1) Page 14 "2D-SWE is known to be a multifactorial process" 2DSWE is not a process...please rephrase

(2) 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 future" Please quote the reference. Piscaglia F, et al. Digestive and Liver Disease. 2017.

(3) "In conclusion, 2D-SWE appears to be an ideal, simple, fast, reproducible…" Please omit the word "ideal".

Response: Thanks for your suggestion. We have changed the "process" into "technique"; we have read the crucial reference and quoted it; we have omitted the word "ideal".

18.Response to comment: "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

7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
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accurate quantification, 3D measurements" Why 3D ? This has not been addressed anywhere in the previous text, and there are no data about 3DSWE. Please omit.

Response: we have omitted the no evidences information.

19.Response to comment: (1) 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.

(2) Page 38, Table 3 Please include reference by Grgurevic I et al. Eur Radiol 2015

Response: (1) We have made a big change in the table of comparison of currently available non-invasive methods in patients with chronic liver disease.

The details showed in Page 32-43 (marked in red).

(2) We have cited the important reference.

Special thanks to you for your good comments.

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Fax: +1-925-223-8243
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Answering Reviewer #3

Name of journal: World Journal of Gastroenterology

Manuscript NO: 37644

Title: Quantitative and Noninvasive Assessment of Chronic Liver Diseases using 2D-SWE

Reviewer #3:

Reviewer's code: 00159367

Reviewer's country: Romania

Science editor: Ze-Mao Gong

Response to comment: The review is important, but needs to be more practical information regarding how to score better liver fibrosis for different pathologies and sometimes the style of authors is too narrative. The review needs to be more practice to be useful for the reader. The English language has to be polished.

Response: Thanks for your valuable comments, which are very helpful for revising and improving our paper. We have added more practical information, such as the new table about the detailed precautions and techniques of 2D-SWE (Table3, Page 35-36). Besides, We analyzed the reference with more accurate results, and showed more details about the cut-off values, which can help us and readers to understand, such as,

The revised details showed in Page 5, Paragraph 1, Line 7-13 (marked in red);

The revised details showed in Page 7, Paragraph 2, the last 3-5 Line (marked in red);

The revised details showed in Page 9, Paragraph 1, Line 7-15 (marked in red);

The revised details showed in Page 9, Paragraph 2, Line 6-11 (marked in red);

The revised details showed in Page 11, Paragraph 1, Line 1-6 (marked in red);

The revised details showed in Page 11, Paragraph 2, Line 9-18 (marked in red);

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Fax: +1-925-223-8243
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The revised details showed in Page 13, Paragraph 2, Line 1-10 (marked in red).

We tried our best to improve the manuscript and made some changes, we hope the correction will meet your approval. We appreciate for your earnest comment.

Special thanks to you for your good comments.

Other changes (marked in red):

1. Page 3, added all the authors abbreviation names and manuscript title;
2. Page 4, the part of "THE BASICS OF TWO-DIMENSION SHEAR WAVE ELASTOGRAPHY" was added, the last Line 5.
3. Page 17, the part of anatomy of the liver, Line 3-6 was added.
4. Page 18, the part of the operator experience and differences in manufacturer equipment were revised.
5. Page 18-19, the part of the conclusion Line 3-10 was revised.
6. Page 29-32, we have made a big change in the legend of the figures (figure 1,2 ,3 5), and change figure 3A, 3B, 3C, 3D, 5A and 5B into more representative figures.
7. Page 32-36, we have made a big change in table 1, and added a new table (table3) about the detailed precautions and techniques of 2D-SWE.

Dear Editors and Reviewers:

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we marked in red in revised paper.

We appreciate for Editors' and Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Yours sincerely

Baishideng Publishing Group

7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
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Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Li-Ting Xie