

Peer Review File

Article information: <https://dx.doi.org/10.21037/atm-21-3142>

Reviewer A

This study investigated post-ant-viral treatment 2D-SWE a powerful predictor of LREs Liver-related events in relatively large cohort of 149 consecutive treatment-naive CHB patients with decompensated cirrhosis. This is an interesting study and overall well presented.

Reply: We thank the reviewer for the very positive feedback.

Some comments:

1. How LSM monitoring can help to adjust treatment regimen is unknown, this should be discussed as an important study limitation.

Reply1 : Thanks for the enlightening suggestion. The current study demonstrated that 2D-SWE as a more accurate noninvasive tool than the serum fibrosis markers for monitoring patients with decompensated cirrhosis and chronic hepatitis B during the antiviral treatment. It may facilitate identify patients at high risk after initiating antiviral treatment for a more closely follow-up as well as intensive therapy and patients at low risk for regular management. And we have added How LSM of 2D-SWE monitoring can help to adjust treatment regimen is unknown as an important limitation in the discussion part.

Changes in the text: See page 19, line 17-22, page 20, line 1.

2. You said: < 2D-SWE was measured using a Supersonic Imagine system (Aix-en-Provence, France) by two ‘fixed ‘sonographers with over 3 years’ experience of 2D-SWE who were unaware of the aim of the study. > pls explain how they worked together, what was each sonographer’s role?

Reply2 : Thank you for your kind reminding. In 50 cases the liver of patients with decompensated cirrhosis with chronic hepatitis B were measured by the same sonographer twice and also by a second sonographer twice for calculating intra- and interobserver agreement before the study. In this study, they perform 2D-SWE measurement independently.

Changes in the text: See page 8, line 3-9.

3. You said < Two-dimensional shear wave elastography (2D-SWE) can be used to accurately stage liver fibrosis in chronic hepatitis B (CHB). > this statement is wrong. This technique is not very accurate. It cannot reliably diagnose early-stage liver fibrosis.

Reply3-1 : We thank the reviewer for the very excellent amendment. We have rectified the statement as Two-dimensional shear wave elastography (2D-SWE) can be used to accurately assess significant liver fibrosis in chronic hepatitis B (CHB).

Changes in the text: See page 3, line 2-3.

The by 2D-SWE measurement stability (scan-rescan reproducibility) should be discussed, do you have such data?

Reply3-2 : Thanks for the constructive suggestion. Before this study, a preliminary study for 50 chronic hepatitis B patients with decompensated cirrhosis in our center showed that the kappa statistic of interobserver between the two sonographers and scan-rescan reproducibility for the same sonographer were 0.92 and 0.94, respectively.

Changes in the text: See page 8, line 17-22.

4. English expression should be much improved. In some place, it was not clearly state whether some measures were baseline measures or follow-up measures.

(1) $\Delta\% \text{ 2D-SWE LSM pre-viral control} = (\text{LSM at baseline} - \text{LSM at the time of HBV virus control}) / \text{LSM at baseline} * 100\%$; pls better explain < LSM at the time of HBV virus control > for readers' easier understanding

Reply4 : We are sorry that we did not make us clearly understood. LSM at the time of HBV virus control represented the next follow-up measures of LSM after the HBV DNA decrease to lower than 20 IU/mL.

Changes in the text: See page 10, line 12-13.

5. You said < For all patients, there were 1–5 (median: 3) measurements for LSMs of 2D-SWE in the study period>, do you want to exclude those who had only one 2D-SWE measure?

Reply5 : Thank you for your kind reminding. We are sorry that we made this mistake. For all patients, there were 1–5 (median: 3) measurements for LSMs of 2D-SWE in the study period. Those who had only one 2D-SWE measure would not be excluded,

because their data would be utilized to analyze the associations between the baseline LSM and the outcomes.

Changes in the text: See page 13, line 22, and page 14, line 1-2.

Reviewer B

The title is the opposite of the conclusion of the study which states that post-treatment value of

LSM is the best predictor. A lot of the conclusion revolves around what is the post-treatment value but it is not defined. If the post-treatment is at the end of the 48 months, then it would only seem natural that those declared in the no-LRE group have the lowest LSM values.

Reply1 : We feel very sorry that we did not make us clearly understood. The post-treatment value referred to the last follow-up LSM measurements during the yearly regular LSM follow-up after initiating antiviral therapy. It should be noted that the title of Dynamic monitoring with shear wave elastography did not mean the dynamic changes of 2D-SWE, because the value of post-treatment 2D-SWE (here we referred to the last follow-up LSM measurements during the yearly regular LSM follow-up after initiating antiviral therapy and we have modified it as the last follow-up LSM in the revised version.) would need a regular dynamic monitoring of 2D-SWE to acquire. The post-treatment was not defined as LSM at the end of the 48 months, we have added this important explanation in the methods part.

Changes in the text: See page 10, line 17-19.

A lot of data. Why is it that those having Liver Related Event dropped out of the SWE protocol? Having their LSM measurements would have been interesting.

Reply2 : Thanks very much for your interest in this point. We pretty agreed that the LSM measurements when LRE occurred was important results to support our conclusion. However, when the LREs such as esophageal varices bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatopulmonary syndrome, hepatorenal syndrome and liver failure occurred, the patients were advised to receive emergency rescue nearby instead of returning to our center for 2D-SWE measurements due to the ethnicity. The Liver Related Event included gastric or esophageal varices bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatopulmonary syndrome, hepatorenal syndrome and liver failure, hepatocellular carcinoma, or liver-related death. Some of those having Liver Related Event have received liver transplantation, Trans

jugular intrahepatic portosystemic shunt (TIPS) therapy, liver tumor resection or radiofrequency ablation, which would cause significant change of LSM that might not be associated with our topic about SWE monitoring for predicting LRE occurrence. As the complicated situation for these patients, the current SWE monitoring protocol should be further adjusted and estimated. And we have added this point as an important limitation in our article.

Changes in the text: See page 19, line 2-22.

And what about the 20/32/21/17 patients that did not reach follow-up? For what reason did they not reach follow-up?

Reply3 : This was a prospective observational study enrolling consecutive CHB patients from a clinical trial (registered in the Chinese Clinical Trial Register: ChiCTR-DCCD-15006000) in our center between February 2015 and December 2018. And these patients received yearly regular 2D-SWE follow-up until 2020 December. When the time reached to 2020 February, the covid-19 outbreaks in China and part of the cities was lock down for a long time, which limit most of those patients from coming back to receive SWE follow-up. So this observational study have to be discontinued and we analysis these data. For those recruited in 2016, it would be until 2021 that they can reach the fifth-year follow-up, and by analogy those recruited in 2018, it would be until 2023 that they can reach the fifth year follow-up, however they would miss the SWE follow-up in 2020. Therefore, 20/32/21/17 patients did not reach follow-up that was due to their entering time to this study and the last follow-up time of 2020 December.

Changes in the text: We have added the last follow-up time of 2020 December. See page 10, line 2-3.

There seems to be a mismatch between figures 1 and 2(A and B). Figure 1 mentions 10 patients reaching month 48 with LRE afterwards but figure 2A seems to report only 5 patients (the same can be said of figure 2B regarding non-LRE patients which according to figure 1 were only 6)

Reply4 : Thank you for your important reminding. We have checked the original data and found that when we imported the data the to the Prism software, some independent data points were classified into a group that was represented as a mean data point in the figure 2A and 2B because of the mis-operation. Therefore, there was a mismatch between figures 1 and 2. And we have corrected these mistakes, thanks again for the rigorous review.

Changes in the text: See figures 2A and 2B.

The overall readability of the article is quite low due to:

- languages issues and odd choices of terms. To cite a few:

Reply5 : We appreciate the rigorous academic acumen of the reviewers again, and our paper has been corrected by the American Journal Experts (AJE) language polishing (the corresponding Certificate was also uploaded as supplementary material). The following issues was also corrected as your suggestions.

Changes in the text: See the supplementary material.

◦ pg 3 lines 12-13: The liver stiffness measurements (LSM) levels persistently reduced after antiviral therapy in patients without developing liver-related events should be written as The liver stiffness measurements (LSM) levels persistently reduced after antiviral therapy in patients who did not develop liver-related events.

Reply6 : We thank the reviewer for the very excellent amendment. We have revised the sentence.

Changes in the text: See page 3, line 12.

- Pg3 line 15: $\Delta\%$ 2D-SWE LSM is not defined in page 9.

Reply7 : We thank the reviewer for the very excellent amendment. We have added the definition of $\Delta\%$ 2D-SWE LSM as $\Delta\%$ 2D-SWE LSM pre-post treatment.

Changes in the text: See page 3, line 15 and page 10, line 16-17.

◦ pg6 line 3: As a more recent elastography compared to transient elastography. Although it can be understood, it should read As a more recent elastography technique compared to transient elastography.

Reply8 : We have revised the sentence as your advice.

Changes in the text: See page 6, line 5-6.

◦ Pg 6 line 6, the following phrase needs to be reworded: minimizes the interruptions from operator movement, ascites or obesity [6]. Moreover ref. [6] does not mention operator movements.

Reply9 : We have revised the sentence as your suggestion.

Changes in the text: See page 6, line 9.

- Pg6 line 8: Area under receiver operating curves

Reply10 : We are sorry for this mistake and have revised it.

Changes in the text: See page 6, line 11-12.

- Pg6 line 9: increasing by 0.003-0.034

Reply11 : Thank you very much and we have rectified it.

Changes in the text: See page 6, line 12.

Please have a proper correction of the article so that readers may understand the article more easily.

- Pg 7, line 5: the authors should restate these in the current article.

Reply12 : We fully agree with the reviewer and have restated that the study protocol was approved by the institutional ethics committee and all patients provided signed informed consent.

Changes in the text: See page 7 line 10-14.

- Pg 7 line 15: 2D-SWE is a technique which measures Liver stiffness (LSM) so it should read : 2D-SWE was carried out using a Supersonic Imagine system

Reply13 : Thanks for the kind reminding. We have carefully read this suggestion and revised it.

Changes in the text: See page 8 line 3.

- Pg 7 line 17: missing reference

Reply14 : Thanks for the kind reminding. We have added the relevant reference as [9].

Changes in the text: See page 8 line 10.

- Pg7 line 20: how can an ultrasound image have a ROI of 4×3×3 cm ? (see also caption of supplementary figure 1)

Reply15 : We are so sorry for this mistake.

Changes in the text: See page 8 line 13 and the figure legend of supplementary figure 1.

- Pg7 line 22: how is the circular ROI chosen? The images in the supplementary

figure 1 shows an inhomogeneous elastogram so the choice of the ROI is of importance since it could alter significantly the mean value.

Reply16 : Rectangular elasticity box (4 cm *3 cm) was placed 1–2 cm under liver capsule in parenchyma area free of large vessels. Circular region of interest was 2 cm in diameter and was positioned in center of 2D-SWE elasticity box possibly. The operators aimed to achieve homogeneous color filling of the SWE ROI placed on the most homogeneous, stable elastogram area.

Changes in the text: See page 8 line 17-22.

- Pg8 line 1: Give details about the five consecutive 2D-SWE images, why is the median value used for analysis and not the mean?

Reply17 : We are so sorry for this spelling mistake and actually in our previous published article (Ref [9] in the manuscript) about the same trial, the average values were used for analysis.

Changes in the text: See page 8 line 22.

- Pg9 line 2, please correct: and the others chosen to enofovir

Reply18 : Thanks for the point and we have revised it.

Changes in the text: See page 10 line 4.

- Pg9: it is not mentioned **when** was viral control carried out.

Reply19 : Thanks for the kind reminding. We have added this important definition.

LSM at the time of HBV virus control represented the next follow-up measures of LSM after the HBV DNA decrease to lower than 20 IU/ml.

Changes in the text: See page 10 line 12-13.

- Pg 9: the choice of the 4 dynamic indicators could be explained. $\Delta\%$ 2D-SWE LSM viral control-post is not clear for me since it would imply that LSM was carried out at viral control but the study mentions 5 measurement time points only.

Reply20 : We are so sorry for our not clear expression. The choice of the 4 dynamic indicators was based on the CHB related inflammation and stiffness could be improved by the antiviral treatment and therefore the response of LSMs of 2D-SWE at the time of viral control after antiviral treatment would be considered. And the parameter of $\Delta\%$

2D-SWE LSM viral control-post was calculated from the differences of LSM was carried out at viral control and at the last follow-up.

Changes in the text: See page 10 line 20-22.

- Pg 10 line 4: is it means \pm standard deviations? Please clarify

Reply21 : We are so sorry for our missing information again.

Changes in the text: See page 11 line 15.

- Pg10 line 18: Supplementary figure 2 doesn't seem to give the same value.

Reply22 : We are so sorry for our not clear expression, a median follow-up was not of median survival time, therefor it would be not easy to be visualized in the figure.

Changes in the text: See supplementary Figure 2.

- Pg10 line 19 : why were the 4 patients lost to follow included in the LRE group?

Reply23 : Thanks for the constructive suggestion. The right censor data were all ascribed to the LRE group would lessen the overestimation of changing trend of SWE in those without LRE. And at the same time we could utilize their follow-up information.

Changes in the text: See page 12 line 16-18.

- Pg11 line 5: patients with LRE at baseline is mentioned but this doesn't appear in figure 1.

Reply24 : We are so sorry for our not clear expression, the phrase of "at baseline" represents to the LN and LSMs of 2D-SWE instead of the patients. We have adjusted it.

Changes in the text: See page 13 line 2-3.

- Pg11 line6: what are the criteria for declaring measurement failure?

Reply25 : Measurement failure was defined as obtaining no color-coded elasticity images after five trials.

Changes in the text: See page 13 line 5-6.

- Pg11 lines 7-12, given the beginning of the sentence, we would expect that the events be stated from the most common to the least common which is not the case.

Reply26 : Thanks for the point and we have rearranged the sentence.

Changes in the text: See page 13 line 7-12.

- Pg11 line 8: followed by

Reply27 : Thanks for the nice reminding and we have checked it.

Changes in the text: See page 13 line 8.

- Pg11 line 16: biochemical

Reply28 : We are so sorry for our mistakes.

Changes in the text: See page 13 line 17.

- Pg 11 line 20: please choose a single acronym when mentioning Liver Stiffness Measurement, I would choose LSMs by 2D-SWE.

Reply29 : Thank you for the enlightening suggestions, and we have replaced it as you suggested.

Changes in the text: See page 13 line 21 and page 19, 2; page 14 line 7; page 17, line 19-20; Figure legend of figure 2 and 3.

- Pg12, 6 time points are mentioned but only 5 measurements are given and figure 1 points to
only 5 time points, please correct.

Reply30 : Thanks for the important advice and we have changed it.

Changes in the text: See page 14 line 4-5.

- Pg12, the decreases in LSM in patients with respectively without LRE do not correspond to the values stated a few lines earlier. For patients with LRE, it would be 20.3% at month 24 and not 12 and for patients without LRE it would be 45.8% at month 48.

Reply31 : We appreciate the rigorous academic acumen again, and rectified the mentioned errors.

Changes in the text: See page 14 line 8-9.

- Pg12 line 6: should read LSM and not LRE

Reply32 : We are so sorry for our errors.

Changes in the text: See page 14 line 10.

- Pg12 line 13: post-treatment is **not defined** in the manuscript.

Reply33 : The post-treated 2D-SWE LSM referred to the last follow-up LSM measurements during the yearly regular LSM follow-up after initiating antiviral therapy. We have added the relevant explanation in the revised version.

Changes in the text: See page 10 line17-19.

- Pg14 line 15: a sluggish slow-down

Reply34 : We have modified it.

Changes in the text: See page 17 line 10.

- Pg14 line 17: may be attributed to the several reasons

Reply35 : We have modified it.

Changes in the text: See page 17 line 12-13.

- Pg16 line 6: this parameter is a more accurate approach

Reply36 : We have rectified it.

Changes in the text: See page 20 line 6.

- Pg31: What do the 2 dashed lines represent? Correct the caption: the cumulative rates

Reply37 : Thank you for your suggestion. The two dashed lines represent the 95% confident interval of the survival curves. And we have corrected the caption as suggested.

Changes in the text: See Supplementary Figure 2.

Reviewer C

The manuscript titled “Dynamic monitoring with shear wave elastography predicts outcomes of chronic hepatitis B patients with decompensated cirrhosis“ presents some promising results on the prognostic value of 2DSWE in identifying liver-related outcomes in patients with decompensated cirrhosis undergoing hepatitis B antiviral treatment.

The manuscript is well-structured, it presents a sound methodology, and the results are relevant in the more general context of moving away from biopsies and trying to replace them with non-invasive tests. The authors have clearly put in lots of effort in this paper,

however, there are still a few points that need to be addressed before publication of this work.

1) Can the authors specify when was follow-up counted from? Baseline or the start of antiviral therapy? I assume it was from baseline, but please make it clear near the place where the treatment of multiple LREs is defined on page 9.

Reply1 :Thank you for your recommendation. We have added the important supporting information.

Changes in the text: See page 10 line 6-7.

2) Why were the 4 patients lost to follow-up considered to be in the LRE group? These patients should have been considered as censored data point during survival analysis. It is also unclear to me what happened to patients who “did not reach to next follow-up” after each 2DSWE stage, as stated on Figure 1. Did they develop non-liver-related events? Were they lost to follow-up? Did they stop taking the antiviral drug?

Reply2 : As per the suggestion, for the reason of the 4 patients lost to follow-up considered to be in the LRE group, it was because the right censor data were all ascribed to the LRE group would lessen the overestimation of changing trend of SWE in those without LRE and at the same time we could utilize their follow-up information.

For what happened to patients who “did not reach to next follow-up” after each 2DSWE stage, as stated on Figure 1, this was a prospective observational study enrolling consecutive CHB patients from a clinical trial (registered in the Chinese Clinical Trial Register: ChiCTR-DCD-15006000) in our center between February 2015 and December 2018. And these patients received yearly regular 2D-SWE follow-up until 2020 December. When the time reached to 2020 February, the covid-19 outbreaks in China and part of the cities was lock down for a long time, which limit most of those patients from coming back to receive SWE follow-up. So this observational study have to be discontinued and we analysis these data. For those recruited in 2016, it would be until 2021 that they can reach the fifth-year follow-up, and by analogy those recruited in 2018, it would be until 2023 that they can reach the fifth year follow-up, however they would miss the SWE follow-up in 2020. Therefore, 20/32/21/17 patients did not reach follow-up that was due to their entering time to this study and the last follow-up time of 2020 December.

Changes in the text: See page 12, line 16-18 and page 10, line 7.

3) I believe the manuscript would benefit from professional English language editing to eliminate grammar errors.

Reply3 : We appreciate the rigorous academic acumen of the reviewers again, and our

paper has been corrected by the American Journal Experts (AJE) language polishing (the corresponding Certificate was also uploaded as supplementary material) . The following issues was also corrected as your suggestions.

Changes in the text: See the supplementary material.

Minor comments:

P7L16: Please specify whether the sonographers were blinded to other clinical information.

Reply5 : Thank you for your important suggestions. The sonographers were blinded to other clinical information. We have added these important descriptions in the text.

Changes in the text: See page 8, line 5.

P8L6: Would it be possible to include the questionnaire in the supporting information section?

Reply6 : Thank you for your enlightening suggestions. We have submitted our questionnaire to the supporting information section.

Changes in the text: See supplementary material of questionnaire.

P10L10: Define VIF

Reply7 : We have added the definition of VIF as variance inflation factor

Changes in the text: See page 12, line 2.

P12L6: Monotonicity could be assessed with Spearman's correlation coefficient. Have the authors considered this?

Reply8 : Thank you for your enlightening suggestions. We have tried the two-way Repeated Measures Anova to investigated the changing trends differences between patients with and without LREs. And we found that there were statistically significant differences in LSMs between the two groups ($F= 3.36, p < .001$) and across timepoints ($F = -0.15, p < .001$), with a significant interaction between group and time ($F = 0.081, p=0.0075$).

Changes in the text: See page 14, line 12-15.

P12L3-5: Please revise this sentence. Looking at figure 2D it does seem to me that the non-LRE group had the larger change after 12 months.

Reply9 : We feel sorry for this mistake. We have revised it as the largest decrease of

LSM by 2D-SWE was observed in patients with LRE at month 24 (20.2%).

Changes in the text: See page 14, line 8.

P13L18: How was the 14.3 kPa threshold determined for LSM?

Reply10 : Thank you for your important reminding. Optimal threshold of LSMs predicting LREs were determined to obtain a maximum sum of sensitivity and specificity.

Changes in the text: See page 12, line 5-6.

Table 2: $\Delta\%$ 2DSWE LSM virus control-post wasn't significant on univariable analysis, yet it was included in the multivariable analysis. Can the authors comment why was this choice made?

Reply11 : We are so sorry for our not clear description in the statistic section of the method part. As an important SWE related parameters, although $\Delta\%$ 2DSWE LSM virus control-post wasn't significant on univariable analysis, we would like to include it into the multivariate model to further adjust it to see the effect of those significant factor. And we have added the explanation as "A multivariate model was constructed with Cox regression to analyze the prognostic factors that had $P < 0.05$ or 2D-SWE related parameters in univariate analysis and collinearity diagnostics (variance inflation factor < 1.8)." in the corresponding part.

Changes in the text: See page 12, line 1.