

Journal title: World Journal of Gastroenterology

Manuscript No: 48524

Title: The value of controlled attenuation parameter in fibrosis prediction in nonalcoholic steatohepatitis

Dear Editor,

We are very grateful for the kind and considerate comments by the reviewers on our work.

We tried our best to make the appropriate changes according to the reviewers' advices as the followings. The parts that are revised are marked as underlined words in blue in the manuscript.

Comments from the editor

1. Language certificate: For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies.

The revised version went through English editing service and the link to the certificate of the English editing service has been included at the end of the manuscript, after the "Reference" section, as follow:

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see:

<http://www.textcheck.com/certificate/Iq0YYo>

2. You need to provide the grant application form(s) or certificate of funding agency for every grant.

The grant was from the National Research Foundation (NRF) of Korea, and the application process was done online. I captured the homepage of NRF where my grant number could be seen (2016R1A2B4015192), and uploaded the file.

3. Please offer the audio core tip, the requirement are as follows.

[We made the audio file and uploaded it as directed.](#)

4. Please write “Article Highlights” section.

[We added this section as the recommendations.](#)

5. Please check and confirm that there are no repeated references.

[We checked the references.](#)

6. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

[We provided figures in a PowerPoint file, and uploaded separately. We left the figure legends without abbreviations in the titles as the recommendation.](#)

7. Please don't include abbreviations in the title of the figure/table.

[We revised the tables and legends as the recommendations.](#)

Reviewer: 1

The paper is well written. The study is informative in drawing a conclusion that LSM in NASH may overestimate stages of liver fibrosis especially in patients with high CAP values. Interpretation of LSM considering simultaneously measured CAP scores may provide more helpful information sparing unnecessary liver biopsy in NAFLD patients

Reviewer: 2

The Manuscript No 48524, titled the value of control attenuation parameter in fibrosis prediction in nonalcoholic steatohepatitis is an interesting article that compares in a population with NASH the degree of fibrosis by two methodologies: a) liver biopsy and b) the use of transient elastography (TE) fibroscan to measure LIVER stiffness measurement (LSM) with a software controlled attenuation parameter (CAP) to measure liver fibrosis. The authors found a good correlation between the grade of fibrosis using the Kleiner fibrosis stage (F0-1). The authors

also compared the fibrosis after the treatment between pioglitazone and ursodeoxycholic acid (UDCA). They found that patients treated with pioglitazone demonstrated decrease in fibrosis after a year of treatment when that in UDCA treated patients did not show significant changes. The authors conclude in NASH patients the combination of LSM with CAP scores may provide helpful information about the grade of fibrosis. I consider that is an interesting study with good results using the LSM with CAP software. It is important to have diagnostic tools alternative to liver biopsy and ET is one of them.

Reviewer: 3

1. Grammatical errors are few but present.

We underwent English correction and the link to the certificate of the English editing service has been included at the end of the manuscript, after the "Reference" section.

2. The exclusion criteria for NAFLD designation should have also included Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency.

We made amendment in exclusion criteria.

3. Because of the subjective nature of histologic assessment, two pathologists would have been better one.

In our hospital, a single pathologist, who is specialized in liver pathology, is designated as an evaluator for liver pathology only. When there were any unclear matters in giving out the final report, the liver pathologist would send out the specimen to other liver pathologists to get the second opinion. Although readings from two pathologists might be ideal, we are quite confident that the histological assessment in this study is reliable.

4. The rationale or explanation used for calculating the cutoff values for fibrosis with respect to CAP tertiles is not clear. The calculation could potentially be used to reduce the effect of hepatic steatosis that are presented as CAP scores when LSM is used to predict fibrosis. It might also be arbitrary to apply these cutoff values to estimate the effect of pioglitazone and UDCA use on follow up LSM values performed 1 year after the treatment with the two drugs.

Actually we assessed association of biopsy proven liver steatosis and CAP scores. Although CAP scores were could significantly different between steatosis grade (S) 1 from S2 and S3, no reliable cutoff was demonstrated to detect S3 from S2 when S2 and S3 resulted in 76.1% (140/184) of our study patients. Furthermore, according

to multivariate analysis, CAP values but not pathologically detected steatosis grades were associated with LSM. Therefore, variations of LSM within the same stage of liver fibrosis was evaluated according to the arbitrary CAP tertiles. We described the result of assessment of steatosis using CAP in the “Result” section, and laid out the explanation for arbitrary use of CAP tertiles in the “Discussion” section. All the patients with either pioglitazone or UDCA treatment were included in the assessment of LSM cutoffs with respect to CAP values, and CAP values did not show significant changes. These are described in the “Result” and “Discussion” sections.

5. Matches were not made in the baseline demographic findings between pioglitazone and UDCA-treated groups.

Since this study was a retrospective, observational study, the baseline demographic findings between the two groups were not matched as the reviewer pointed out. We do realize that this is a limitation of our study and stated this in the “Discussion” section.

6. Discussion section, the possible effect of other treatment drugs on LSM-CAP estimations of fibrosis and steatosis has not been mentioned even though for this study, it would suffice to use these two drugs.

Medical treatment for NASH still needs to be investigated, and it been reported that pioglitazone or 800 IU/day use of vitamin E are the two agents that show some effects on liver fibrosis in NASH patients. We described this in the “Discussion” section.

7. There was no mention of the current tools used to assess both steatosis and fibrosis and how they would compare with the LSM and CAP applications.

We added discussions on MRE and MRI-PDFF in the “Discussion” section.

Once again, thank you very much for the recommendations. We hope that the amendments we made would satisfy the reviewers and the editor.

Sincerely,

Jung Il Lee, MD, PhD.