Feb 10, 2018

Editor in Chief
World Journal of Gastroenterology

Dear Editor:

Thank you for the opportunity to revise our manuscript, *Serum Autotaxin Levels Are Correlated with Hepatic Fibrosis and Ballooning in Patients with Non-alcoholic Fatty Liver Disease*. We appreciate the careful review and constructive suggestions.

Following this letter are reviewer comments with our responses.

Thank you for your consideration.
We appreciate your review of this work.

Respectfully yours,

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Response to Reviewers

Reviewer #1 (Reviewer's code: 01555255)

-Introduction section: The Author define liver biopsy as a the "gold standard" in the evaluation and assessment of NAFLD. This is correct. However, general limitations of liver biopsy are the costs, the not acceptance by patients, but also sampling error and inter- and intra-observer variability (Kobyliak Rev Recent Clin Trials. 2014).

Response

We appreciate for your constructive comment. As you suggested, we added the statement regarding liver biopsy limitations and reference in the Introduction section.

- Methods section: include the Country (Japan) were the study has been performed. I suggest also to describe briefly the serum assessment of ATX.

Response

We stated that the study has been performed in Japan. Also, we described the method for serum ATX measurement.

- Results section: Is essential to include the assessed values, as a APRI, ATX, FIB-4, and to disccuss it.

Response

We showed new data comparing diagnostic performance of severe liver fibrosis (≥F3) between ATX and conventional fibrosis indicators, such as hyaluronic acid and FIB-4 index, as Table 4. AUC values and sensitivity of ATX was inferior to those other indicators, but specificity of ATX was highest among the other conventional parameters. Therefore, ATX might be useful as a biomarker for excluding severe fibrosis. We added the corresponding statements in the Results and Discussion sections.

- Discussion section: in this section the Author can discuss the literature data on ATX, and in particular the serum values of ATX and the correlation between different NAFLD/NASH severity stage. This is necessary in the possible application of ATX in clinical practice, as a non-invasive marker of NAFLD

staging.

Response

Thank you for your comments. We added the statements regarding diagnostic significance and clinical application of ATX to the Discussion section. Additionally, we stated the relationship between ATX and NAFLD activity score, an indicator of histological severity of NAFLD/NASH, in the Discussion section.

Reviewer #2 (Reviewer's code: 01805500)

Authors should give readers a complete view of this new proposed marker of fibrosis----at least it should be the aim---- (ATX) showing its sensitivity and specificity towards any fibrosis score at histology as well as the positive and negative predictive likehood to better evaluate the reliability of ATX. A cost/benefit analysis is mandatory.

Response

We appreciate your comments. We demonstrated diagnostic performance of ATX for predicting NAFLD fibrosis stage in Table 3, including positive and negative predictive values and accuracy. Since ATX cannot be measured commercially at present, it is difficult to conduct cost benefit analysis. Thank you for your understanding.

Looking at the AUROCs of other fibrotic markers, authors should lessen of enthusiasm in their discussion because all in all ATX showed nearly always the worst performance with very few exceptions.

Response

We showed new data comparing diagnostic performance of severe liver fibrosis (≥F3) between ATX and conventional fibrosis indicators, such as hyaluronic acid and FIB-4 index, as Table 4. AUC values and sensitivity of ATX was inferior to those other indicators, but specificity of ATX was highest among those other indicators. So, ATX might be useful as a biomarker for excluding severe fibrosis.

The selected population suffering from NAFLD did not present high grade of obesity, nor dyslipidemia nor T2DM, thus it could be interesting to know the entity of abdominal adiposity, which is the main driver of hepatic steatosis, contributing also in worsening the prognosis of NAFLD, and is strongly linked to

other co-morbidities as clearly emphasised in.....Should visceral fat be reduced to increase longevity? Ageing Res Rev. 2013 Sep;12(4):996-1004. In case it is not available this datum, i.e., WC or WHR, put this point as limitation to the study, referring to the afore-mentioned article.

Response

As you pointed out, we felt the necessity to examine the relationship between serum ATX and visceral fat, but we do not have enough data in this study. Therefore, we stated this point as a limitation of the present study and future consideration in this research field.

Reviewer #3 (Reviewer's code: 03024603)

I revised the manuscript entitled "Serum Autotaxin Levels Are Correlated with Hepatic Fibrosis and Ballooning in Patients with Non-alcoholic Fatty Liver Disease" The study is interesting and well written; however I have the following comments:

The authors did not mention the sensitivity, specificity and accuracy of Autotaxin as a noninvasive marker; it should be added and described in details including the best cutoff value that gives the best accuracy.

Response

Thank you for your comments. We added Table 3 to show the performance of ATX as noninvasive liver fibrosis marker, including sensitivity, specificity, accuracy, and cut-off value and the corresponding statements to the Results and Discussion sections.

The authors should add a comparison between the performance of Autotaxin and other noninvasive markers of fibrosis as: APRI, FIB-4 score etc…

Response

We added Table 4 to compare diagnostic performance of severe fibrosis between ATX and other conventional fibrosis indicators (APRI, FIB-4, HA, and 4C7S) and the corresponding statements to the Results and Discussion sections.