Dear **Prof. Tarnawsk,**

We thank the referees for their careful reading our manuscript and for giving us many useful comments. In response to the referees' comments, we have revised the manuscript: **ID 52096**. We look forward to the publication of our manuscript in the *World Journal of Gastroenterology*.

Response to Reviewer 1:
Thank you for your detailed comments. They have helped us improve our manuscript.

Comment 1:
1.Introduction part: The last paragraph, Page 8 line 5,"The assessment for the complications of LC is especially valuable in helping to make treatment decisions" Can authors provide reference(s) to state that how valuable of assessment for the complications of LC to clinical?

We agree with the reviewer's concerns on this point. In accordance with the reviewer's comment, we have added the reference.

"11 **Ge PS**, Runyon BA. Treatment of patients with cirrhosis. *N Engl J Med* 2016; **375**: 767-777. [PMID: 27557303 DOI: 10.1056/NEJMra1504367]"

Page 8 line 6: "...Therefore, the ATX level may be... " . The word 'Therefore', I think ,does not fit here. It is just a speculation of the authors but there's no cause and effect if there are not accurate evidence from exiting studies. Please rectify.

Accordingly, we have changed this text to the next text. (p. 6, lines 31-32 and p. 7, lines 1-2).
"The ATX level may be a useful biomarker to select treatment therapy for ascites, hepatic encephalopathy, and varix ruptures. And the assessment for the complications of LC is especially valuable in helping to make treatment decisions."

Methods: "Patients" paragraph, the last sentence "Patients with poorly controlled heart failure, severe renal dysfunction, and malignancies other than HCC were excluded". So, the patients with HCC also included in this study, right? However, the situation of ATX in patients with HCC and the relationship between ATX and tumor-related index (e.g. AFP) were not reported.

The patients with HCC were included in this study. Please see Table 1. There was no correlation between AFP and ATX levels. And the ATX levels were not significantly different between patients with and those without HCC. To clarify, we have added the following text to the Results and Table 3 (p. 11, lines 1-6 and Table 3).

"***ATX for patients with and those without HCC***
The average ATX levels (mg/L) in men and women were 1.65 ± 0.40 and 2.02 ± 0.68, respectively, for patients with HCC and 1.56 ± 0.54 and 1.97 ± 0.76, respectively, for patients without HCC. However, the ATX levels were not significantly different among patients with and those without HCC in men and women (Men: P = 0.178, women P = 0.215).

Discussion: Although was a multiple center study which increased credibility of evidence, the inconsistency between experimental equipment and standardization should be one of the limitation in this study. (p.14, lines 2-4).

In accordance with the reviewer's comment, we have added the reference.
"this study was a multiple center study. Therefore, there may have been inconsistencies between the experimental equipment and standardization. "

3.Conclusion: The Conclusion is too simple. Please add 1~2 sentences to state the clinical significance of this study.((p.14 lines 8-10).

In accordance with the reviewer's comment, we have added the conclusion.
"To make treatment decisions, it is necessary to consider that patients with high ATX levels may have complications of LC.

Response to Reviewer 2:

Thank you for your detailed comments. They have helped us improve our manuscript.

Comment 1:

Minor points. Page 13, last paragraph: The last two sentences are redundant. One should be deleted.

Reply: In accordance with the reviewer's comment, we have deleted the text.

Comment 2:

Discussion, page 16: My major criticism is the following statement made by the authors: "Third, the correlation between ATX and the hepatic venous pressure gradient (HVPG) was not confirmed." No data on hepatic venous pressure gradient measurements are included in the core article. It is mandatory to show the data and to describe those data in the results. Furthermore, this observation should be discussed in context of the relevant literature that has not been highlighted, but should be acknowledged.

Reply: We agree that additional information on HVPG as the reviewer suggested would be valuable. Regrettably, however, we are unable to do the experimentation because these data were not evaluated for all the enrolled patients. Therefore, we could not show the data or describe those data in the results. To clarify, we have changed this accordingly. (p. 13, lines 29-31).

"Regrettably, however, the correlation between ATX and HVPG was unknown because these data were not evaluated for all the enrolled patients due to it being a retrospective study."

Response to Reviewer 3:

Thank you for your detailed comments. They have helped us improve our manuscript.

Main comments 1. More details are needed for experimental procedures. For example, for the measurement of serum AXT, please indicate the sample amount used and procedure of the blood collection and processing for others to repeat.

Reply: In accordance with the reviewer's comment, we have deleted the text. (p. 8, lines 1-6).

"Serum concentrations of ATX were measured using a two-site enzyme immunoassay and an automated immunoassay analyzer (Tosoh Corp., Tokyo, Japan). The assay reagent was compatible with a commercial automated immunoassay analyzer AIA System (Tosho Corp., Tokyo Japan). This system included automated 10 uL of specimen dispensation, incubation of the reaction cup, bound-free washing, 4-methylumbelliferyl phosphate substrate dispensation and fluorometric detection [8-10]."

Main comments 2.

Please include serum ATX levels from healthy control subjects or subjects without reduction of liver functions. The comparison is essential to indicate that there is an elevation of ATX levels when there is a reduction of hepatic endothelial function of ATX clearance.

Reply: We agree that additional information on ATX levels from healthy control subjects, as the reviewer suggested, would be valuable. Regrettably, however, we are unable to do the experimentation because this study is a retrospective study and only on enrolled patients with liver cirrhosis. Because ATX levels from healthy control subjects was discussed in context of the relevant literature, we have added the following (p. 13, lines 1-3).

“Pleli et al. reported serum levels of ATX levels from subjects with LC were elevated compared to healthy control subjects, and serum ATX levels correlated with the Child-Pugh score in predicting the severity of the disease [10].”

Thank you again for your comments on our manuscript. I trust that the revised manuscript is now suitable for publication in the *World Journal of Gastroenterology*.

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