Dear Reviewers

Thank you for your letter and comments concerning our manuscript entitled as "The association of GGT and the QRISK2 score: estimating 10-year cardiovascular risk in liver biopsy-proven NAFLD patients; the GO-ASIA initiative".

1.Please, provide more background data on the relationship between NAFLD and CVD, as well as on the potential association between GGT level and CVD.

Relationship between NAFLD and CVD was added in introduction part (2nd paragraph).

Potential association between GGT level and CVD was explained more in introduction part (4th paragraph).

2.Please, be more specific regarding the persistent elevated serum aminotransferase levels as the main indication for liver biopsy.

We added more detail regarding the persistent elevated serum aminotransferase levels were the main indication for liver biopsy in order to rule out other possible etiologies. Only patients with biopsy confirmed NAFLD were included in participating centers and cases section (3rd paragraph).

3.Please, add a flow chart showing the recruitment of the subjects, and also explain in more details the selection of the healthy individuals for the control group.

We added flow diagram showed number of cases included in this study in supplementary figure1.

Absolute 10-year cardiovascular risk was calculated and compared to the healthy controls with the same age, sex, and ethnicity using QRISK2 calculator which was well validated from QRESEARCH database [10-12], added this explanation in cardiovascular risk assessment section.

4.Please, discuss in more details the fact that ALT is significantly lower in high CVD risk group than in low CVD risk group,

We have discussed more details related to ALT in discussion part (7th paragraph).

We found that ALT level was significantly lower in the high-CVD-risk group, but this effect was attenuated in multivariable analysis. Previous meta-analysis in general population showed no association between ALT and overall CVD risks [34]. However, lower ALT level in NAFLD patients is associated with advanced fibrosis stage [35] and ALT level is included in fibrosis prediction scores such as NAFLD Fibrosis Score, and Fibrosis-4 Index [36]. This may confound the univariable analysis of ALT in our study.

and also comment on the highest median CVD risk in the second quartile of a baseline GGT level.

We performed further analysis and the data showed below and was added into results, correlation between baseline GGT level and 10-year CVD risk by QRISK2 section, page 10:

When divided baseline GGT into 4 quartiles (Q), median (IQR) 10-year CVD risk by QRISK2 were Q1=6.1 (2.7-11.2), Q2=6.6 (2.9-11.9), Q3=4.7 (2.4-9.1) and Q4=6.4 (2.6-12.9), with statistical significant difference ($p<0.001$)(table 3). Post hoc analysis found that the differences were between Q3 and Q1($p=0.02$), Q3 and Q2 ($p=0.009$), Q3 and Q4 ($p=0.003$).

Please, discuss in more details the fact that total and LDL cholesterol are significantly lower in high CVD risk group than in low CVD risk group.

In our finding, lower TC and LDL had higher CVD risk in univariable analysis but not in multiple variable analysis. However, this could be explained by patients included in the study may had currently on medication related to dyslipidemia and masked the level of TC and LDL. When we focused on presence of dyslipidemia that defined in earlier section, we found that dyslipidemia was a risk factor of high-risk CVD (discussion part, 3rd paragraph).

Please, correct the numerous typographical errors throughout the manuscript.

We send the manuscript for English editing service.

Second reviewer

This manuscript reported a cross-sectional study to identify the association of GGT and the QRISK2 score in liver biopsy-proven NAFLD patients. The following comments might be helpful to make the manuscript more intelligible:

1.A flow chart demonstrating the recruitment of the subjects may be drawn to make it easy for the readers to understand.

We added flow chart in Supplemental figure1.

2.Persistent elevated serum aminotransferase levels were the main indication for liver biopsy, so the patients may have comparatively severe condition in NAFLD, which may cause bias about high GGT level in patient recruitment, please explain it in the discussion part.

We added discussion related to NAFLD and GGT in discussion part (5th paragraph).

3. The references would be better in the latest 5 years, some of the references may be updated.

We updated and added new references (references no.5-9,16,19, 25-26,31,34).

4. How to apply the result in our clinical practice, wonder if you add the clinical implications part in the discussion.

We added clinical implication on our finding in discussion part (second paragraph) and summary in last paragraph.

Dear editors,

Thank you for your comment and suggestion.

We added more information related to each comment below:

1. We added “Running title”.
2. We added “ARTICLE HIGHLIGHTS”.
3. We created decomposable figure into power point format.

Sincerely yours

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