

Dear Editor,

September 13, 2016

RE: ESPS manuscript No: 27917: "Serum gamma-glutamyltransferase fraction patterns in patients with non-alcoholic fatty liver disease"

Dear Editor:

Thank you for your letter dated August 3, 2016 and for the reviewing process. We are enclosing a point-by-point reply to the reviewers' comments and a revised manuscript which includes every one of suggestions they made.

I believe that the revised manuscript will now be considered suitable for publication in the World Journal of Hepatology.

Sincerely yours,

Fumio Nomura, M.D., Ph.D

Point-by-point reply to Reviewer (Reviewer's code: 03648154)

1) It should be assumed that these obese patients (16) were examined for viral serology, relevant liver auto antibodies, ferritin, ceruloplasmin, alpha 1 antitrypsin and that the results were within normal. If so is the case they should mention it in the methodology.

Thank you for this comment. Subjects suspected to have autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson's disease and alpha 1

anti-trypsin deficiency were excluded from this study. This point has been described in the new text (Page 7, lines 13-16)

2) The inclusion of cases of cholelithiasis (2) in the analysis does not seem to have relevance to the theme of the study and their data should not be added to the concluded results.

I agree with the reviewer. I deleted these cases from the manuscript.

Point-by-point reply to Reviewer (Reviewer's code: 03478516)

1) Authors should discuss also the NAFLD presence without clear increase of GGT, as evident in....Circulating levels of cytochrome C, gamma-glutamyl transferase, triglycerides and unconjugated bilirubin in overweight/obese patients with non-alcoholic fatty liver disease. J Biol Regul Homeost Agents. 2011 Jan-Mar;25(1):47-56.

I agree with the reviewer.

Although we could not determine serum cytochrome C levels in the present study, we have added the reference (Ref 22) you recommended and also some discussion (Page 12, lines 6-8).

Point-by-point reply to Reviewer (Reviewer's code: 03647837)

1) Throughout the text, the authors expressed the importance of this research in relation to ALD/NAFLD differentiation. The title does not reflect the approach that authors used in these research.

I thank you for this suggestion.

I changed the title to "Fractionation of gamma-glutamyltransferase in patients with nonalcoholic fatty liver disease and alcoholic liver disease".

2) The authors used patients in different stages of ALD and non-alcoholic liver disease. This would not be a limiting factor in the research and could not justify the large variation between patients of the same group?

I agree with the reviewer. One of the limitations of this study is that the numbers of the biopsy-proven cases was small. Obviously, we will have to assess how serum GGT profiles may change with disease progression both in non-alcoholic fatty liver diseases and alcoholic liver diseases. This point has been stated in the new text (page12, lines 4-6).

3) Currently, there is strategies to differentiate NAFLD and NAFLD. Authors should explore that in the text. Further details can be found in the review "Molecular basis of alcoholic fatty liver disease: From incidence to treatment" (Hepatology Research 2016; 46: 111-123 - doi: 10.1111/hepr.12594).

Thank you for this comment. This article has been cited as ref 8.

4) Why the authors did not perform a plasma biochemistry analyses of "apparently healthy " subjects? . . . . .

Biochemical data of apparently healthy subjects are presented in the new Table 1.