Answering Reviewers

Authors List: Amporn Atsawarungruangkit, Jirat Chenbhanich, George Dickstein.

Correspondence to: Amporn Atsawarungruangkit, Department of Medicine, MetroWest Medical Center, Framingham, MA, 01702, USA. a.atsawarungraungkit.@mwmc.com

Dear Editors and Reviewers:

Thank you very much for your comments regarding our manuscript. We have carefully revised the manuscripts per your suggestion. These changes will not influence the content and framework of the paper. The revised sections are marked in tracked changes and highlighted in turquoise in the revised paper. Below are our specific responses to reviewers:

Response to reviewer #1 (reviewer's code: 01555255)

Reviewer's comment:
- Title: I suggest to dele the acronym "NAFLD" from the text
- Introduction section: references on epidemiology of NAFLD and its relationship with metabolic feature are not updated. Recently are been published many articles on these topic. I suggest also to improve this section, and to describe all the pathogenetic link between C-peptide and NAFLD
- Results section: the description of the reported data is mandatory.
- Discussion section: previous studies reported the same data of the present paper. In particular the relationship between C-peptide and NAFLD in non-diabetic patitens. What is the novelty here described?

Our response:
- Per your suggestion, we have adjusted the title by removing NAFLD.
- To the best of our knowledge, there is only a limited evidence regarding the association between C-peptide and NAFLD. We already stated in the second paragraph of introduction section and discussion section. Most of them are in specific groups of population (i.e., obese adolescents and adults, latent autoimmune diabetes, and diabetes patients. We have already explained the pathogenesis of C-peptide and NAFLD in the second and third paragraph of introduction section.

- We have reported data in Table 1 to Table 3 by describing the important findings in the result section.
- Unlike other articles, we are the first to report C-peptide as an important risk factor for NAFLD in the general population using multivariate analysis. Based on adjusted pseudo R^2, we also demonstrated that three most important risk factors for NAFLD are waist circumference, fasting C-peptide, and ALT, respectively

Response to reviewer #2 (reviewer's code: 02741591)

Reviewer's comment:
- The title could be refined to better reflect the content and signify the importance of the studied C-peptide in NAFLD and to stratify that the study was conducted on patients.
- The introduction, methodology, results and discussion are nicely written. The references could be better wrapped up to be a maximum of 40 references rather than 51. The tables should be self descriptive and the abbreviations fully expanded at the foot note.

Our response:
- We have changed the title to "C-peptide is a key risk factor for non-alcoholic fatty liver disease in the United States population".
- We have adjusted tables by using commonly used abbreviations in the table and added the fully expanded descriptions at the bottom of table. However, we would like to keep all references remain unchanged since there is no maximum number of references in this journal.

Response to reviewer #3 (reviewer's code: 00036318)

Reviewer's comment:
- This is an interesting study reporting novel findings regarding the association between c-peptide levels and NAFLD. The study population is large and the methods are adequate. The results are clearly presented and the discussion is well organized and balanced.

Our response:
- We really appreciate your compliments.

Response to reviewer #4 (reviewer's code: 01404215)

Reviewer's comment:
- We have added a short explanation how we selected the independent variables including biochemical entities in the study population and study design part of the methods section as follows:
  "Besides demographic variables, the above variables were selected as the risk factors based on the usage in clinical practice and the supporting evidence that

demonstrated the association with NAFLD or its commonly accepted risk factors (e.g. obesity, insulin resistance, and liver fibrosis)."

- We have added a short explanation why logistic model is selected in the statistical analysis part of the methods section as follows:
  "Since the response variable is dichotomous variable (NAFLD or non-NAFLD), logistic model is an appropriate model for determining if predictors are significantly associated with the response variable."

Sincerely,
Amporn Atsawarungruangkit
Department of Internal Medicine
MetroWest Medical Center, Framingham, Massachusetts, 01702, USA
Phone: (857) 312-6114
E-mail: a.atsawarungruangkit@mwmc.com