Dear Editor,

We submit a revised version of our invited minireview titled ''Associations between nonalcoholic liver disease and ischemic stroke'' for consideration for publication in the World Journal of Hepatology. We thank the Editor for deciding that our review may have the potential to be acceptable for publication. We also thank the Reviewers for their comments, which improved our paper. We modified the text according to these comments. All changes are shown in red in the revised text.

Response to Reviewers' comments

Reviewer's code: 00199807

Dear Editor, I reviewed the minireview titled "Associations between nonalcoholic fatty liver disease and ischemic stroke". I think this article can be accepted after major changes.

We thank this Reviewer for this positive comment.

- A table which contain the results of main studies should be added for clear description of the topic.

Following the suggestion of this Reviewer, we have included in our mini Review a table that summarizes all the main studies related to this topic, to help readers understand the association between NAFLD and ischemic stroke.

- A figure that includes possible mechanisms (atherosclerosis, lipid disturbances etc) between NAFLD and stroke can be added.

We added a relevant figure.

- A recently published references should be added: a. Alexander KS, Zakai NA, Lidofsky SD, Callas PW, Judd SE, Tracy RP, Cushman M. Non-alcoholic fatty liver disease, liver biomarkers and stroke risk: The Reasons for Geographic and Racial Differences in Stroke cohort. PLoS One. 2018 Mar 12;13(3):e0194153. doi: 10.1371/journal.pone.0194153. eCollection 2018. b. Kwak MS, Kim KW, Seo H, Chung GE, Yim JY, Kim D. Non-obese fatty liver disease is associated with lacunar infarct. Liver Int 2017 Dec 8. doi: 10.1111/liv.13663. [Epub ahead of print]

We now discuss these recently published interesting articles.

- More sentences are needed about the mechanistic relationship between gGT and atherosclerosis and also stroke (gGT activity in plaques etc).

We added a paragraph that analyzes further the atherogenic activity of gGT and its role in the atherosclerosis process where we mention "Importantly, gGT appears to play a role in atherogenesis. Indeed, gGT has been isolated from atheromatic plaques, macrophages and foam cells and appears to contribute to atherosclerosis by inducing oxidative stress. It was shown than gGT promotes oxidization of low-density lipoprotein and that it plays a crucial role in the catabolism of glutathione and the release of reactive oxygen species."

Reviewer's code: 02447901

In this manuscript, the authors made a brief review association between nonalcoholic fatty liver disease and ischemic stroke. The incidence and severity/outcome were items of focuses. The paragraph in the Abstract briefly described phenomena between nonalcoholic fatty liver disease and ischemic stroke. A conclusion statement is needed at the end of this paragraph.

We added a conclusion statement at the end of the abstract where we mention "Given these associations, it might be useful to evaluate patients with acute ischemic stroke for the presence of NAFLD and to manage those with NAFLD more aggressively."

- The abbreviations should be defined.

We carefully read the paper and defined all the abbreviations.

- Observations of nonalcoholic fatty liver disease and ischemic stroke prevalence and severity showed variable association. Since nonalcoholic fatty liver disease was characterized by several changes, including metabolic abnormality, steatosis, dyslipidemia, inflammation, NASH, and fibrosis, different parameters might have distinct impacts to the association study. A discussion is suggested.

We thank this Reviewer for this important comment. Regarding the role of steatosis, inflammation and fibrosis, we added "It appears that NASH is more strongly related to the risk of ischemic stroke than isolated hepatic steatosis. Indeed, in a case-control study in 295 patients with acute ischemic stroke and 1,942 subjects who underwent a

health check-up, the degree of liver fibrosis, evaluated with transient elastography, was independently associated with increased stroke risk [14]. In contrast, isolated steatosis was not related with the risk of stroke [14]." We also added that the associations reported were independent of traditional cardiovascular risk factors including dyslipidemia and metabolic abnormalities.

- The description and comparison of relevant references should be reorganized and categorized.

We reorganized the relevant references. We also added a table summarizing the findings of the most important studies in this topic.

Reviewer's code: 03730829

The manuscript is acceptable and fits into the mission of the journal. I recommend it for publication in your respectable journal. This is an interesting review article and summarizes the current knowledge regarding the relationship between NAFLD and ischemic stroke incidence, severity and outcome.

We thank this Reviewer for these positive comments.

We look forward to your decision.

Best regards,

Konstantinos Tziomalos, MD
Assistant Professor of Internal Medicine
Medical School, Aristotle University of Thessaloniki