

Dear Editor,

Please find attached our revised manuscript entitled: “Lipidomics in non-alcoholic fatty liver disease”.

We have now carefully revised the manuscript in view of the constructive and helpful reviewer comments as outlined in detail below and the paper is now ready to resubmit.

On behalf of all authors,

Kind Regards,

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Number ID: 03478442

Reviewer: 1

Comments to the Authors

Manuscript titled "Lipidomics in non-alcoholic fatty liver disease" deal an important issue of NAFLD. The purpose of this study was to summarize the findings of main human lipidomics studies in NAFLD and delineate the currently available information on pathogenetic role of each lipid class in lipotoxicity and disease progression. Based on the current literature this paper present new data to differentiate this study to others already present in the literature. The contents are very interesting and well written. Minor concerns should be solved before to accept it for publication. Please improve the introduction section. Please add a sentence regarding Fatty liver disease, nutrition and lifestyle: Please quote adequate reference as follow or other similar: Fatty liver disease and lifestyle in youngsters: diet, food intake frequency, exercise, sleep shortage and fashion. *Liver Int.* 2016 Mar;36(3):427-33. Nonalcoholic fatty liver disease (NAFLD) prevention: role of Mediterranean diet and physical activity. *Hepatobiliary Surg Nutr.* 2019 Apr;8(2):167-169. doi: 10.21037/hbsn.2018.12.05. Early effects of high-fat diet, extra-virgin olive oil and vitamin D in a sedentary rat model of non-alcoholic fatty liver disease. *Histol Histopathol.* 2018 Nov;33(11):1201-1213. 4Ps medicine of the fatty liver: the research model of predictive, preventive, personalized and participatory medicine-recommendations for facing obesity, fatty liver and fibrosis epidemics. *EPMA J.* 2014 Dec 7;5(1):21. In the conclusion section please add the scientific/clinical relevance of your work.

We thank the reviewer for the kind consideration of our work. The introduction section has been changed and the role of nutrition and lifestyle in development of NAFLD has been also presented with the noted references in the introduction and pathogenesis section. According to the reviewer suggestion, the scientific relevance and the clinical interpretation of the presented findings of lipidomic studies were included in the conclusion of the manuscript.

Reviewer: 2

Comments to the Author

This is an interesting review article on an issue that is gaining attention in the translational research on NAFLD/NASH. The authors comprehensively revised the literature dealing with the role of lipids in the disorder and, most important, on the role of lipid quantity and moiety in determining the clinical course of fatty liver. Unfortunately, the different and conflicting data are described without critical interpretation making the article poorly perspective. I suggest substantially reduce the rather acritical description of what published (a good example is the section of glycerophospholipids) and expand the discordant observations among different series and most important, the lack of concordance with lipidomic in liver and plasma. This should be the main message of the review. The possible role of lipidomic as a diagnostic tool to discriminate different stages of fatty liver (NAFLD or NASH with different grading) must be expanded.

We would like to thank the reviewer for valuable and constructive comments and suggestions. The description of what published has been rather moderately reduced, in an effort to avoid omitting important findings and also with the aim of presenting adequately the discrepancies observed in plasma lipidomics studies. Additionally, in order to emphasize the inconsistency between liver and plasma findings, a section about the limitations of plasma lipidomics studies has been added and propositions regarding this issue have been presented. The section regarding the utility of lipidomics studies in noninvasive diagnosis of NASH has been extended based on published literature.