Dear Subrata Ghosh and Andrzej S Tarnawski,

Editors-in-Chief of the "World Journal of Gastroenterology",

We wish to thank you for your decision letter from October 16th, 2021 regarding our review article entitled "**Non-alcoholic fatty liver disease and hepatocellular carcinoma: Clinical challenges of an intriguing link**" (Manuscript NO: 71488) and for allowing us to resubmit a revised version of our manuscript. In addition, we would like to thank the editors and the reviewers for their insightful comments and suggestions, which have helped to improve and strengthen our manuscript. We have carefully revised our manuscript, according to the comments made by the editors and reviewers. Please find attached in the online submission system the revised manuscript. The responses to the Editors' and Reviewers´ comments are appended.

Looking forward to hearing from you in due course,

Kind regards,

Evangelos Cholongitas (00761439),

MD, PhD, Associate Professor of Internal Medicine, First Department of Internal Medicine, Laiko General Hospital, Medical School of National and Kapodistrian University of Athens, Agiou Thoma 17, 11527 Athens, Greece. Email: cholongitas@yahoo.gr

RESPONSE TO THE REFEREES

We wish to thank the reviewers for their constructive comments, which helped us improve our manuscript. We have revised the manuscript, according to the Referees' comments.

Reviewer: 1

Non-alcoholic fatty liver disease (NAFLD) can develop into non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC), and HCC can also occur in NAFLD patients without cirrhosis. With the effective treatment of viral hepatitis and the global prevalence of obesity and type 2 diabetes mellitus (T2DM), NAFLD has become the most common liver disease worldwide. Therefore, NAFLD is expected to become the main cause of HCC all over the world. This review summarizes the latest data concerning the epidemiology, pathogenesis, risk factors, prognosis, surveillance and prevention of NAFLD-related HCC patients. Although other articles on similar topics(Huang et al., 2020; Margini and Dufour, 2016) have been published, the literature listed by the author is more representative, and some contents are summarized in figures and tables. This article has clear logic, excellent language ability and strong readability. Finally, from my point of view, in the section of "Pathgenetic pathways and risk factors", it's better that if the author can list some representative pathogenic molecular pathways involved in the development of NAFLD-related HCC then add details to the supplementary document. References Huang, D.Q., El-Serag, H.B., and Loomba, R. (2020). Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nature Reviews Gastroenterology &#38 Hepatology 18. Margini, C., and Dufour, J.F. (2016). The story of HCC in NAFLD: from epidemiology, across pathogenesis, to prevention and treatment. Liver International Official Journal of the International Association for the Study of the Liver 36.

Response 1

We thank the reviewer for the appreciation of our work and for this very useful comment. In our revised manuscript we have added a new section entitled "Pathogenetic pathways", (with changes underlined) in which we have described the major molecular pathways implicated in the development of NAFLD-related HCC. The remaining pathogenetic pathways are further described in the **Supplementary Material**.

Moreover, we added the two References (**Huang, D.Q., El-Serag, H.B., and Loomba, R. (2020). Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nature Reviews Gastroenterology &#38 Hepatology 18. Margini, C., and Dufour, J.F.**

(2016). The story of HCC in NAFLD: from epidemiology, across pathogenesis, to prevention and treatment.) indicated by the Reviewer, in the "Introduction" section of the main text.

Reviewer 2

This review article is about an overview of non-alcoholic fatty liver disease (NAFLD) and progressive stages of NAFLD, its impact on public health worldwide, risk factors, pathogenesis, the prevention strategies, and the healthcare policies regarding NAFLD-related hepatocellular carcinoma (HCC). The authors provided the discussion detail in each section as followings; The first section, the authors discussed the brief background knowledge focused on NALFD. Secondly, the authors described the prevalence of various disorders related to HCC, i.e., type II DM, vital hepatitis, obesity, metabolic syndrome. The third part was about the pathogenic pathway and risk factors. The authors mentioned only the possible some risk factors such as smoking, alcohol, genetic variations related to HCC. The remaining possible pathways were seen in the supplementary file. The prognosis of the disease was discussed in the fourth part. Even though the controversial findings were reported, it could be assumed that HCC with NAFLD is the most risky when compared with the others. However, these patients have received less attention than the other groups, then the higher risk of mortality while waiting for lung transplant were observed in this patient group. The recent guideline and the proposed future surveillance guideline in NAFLD patient were then discussed in this section. The diagrams were shown in Figure 2 and Figure 3, respectively. The preventive strategies were discussed under the prevention section, including the weight management, diets, alcohol limitation, and medications. Some pharmaceutical treatments including aspirin, statins, metformin were recommended to reduce the progression of HCC. In conclusion part, the authors' point of concern is regarding an inappropriate surveillance latest guideline for NAFLD related HCC patients. In order to identify an appropriate implementation, the authors further suggested the proposed guideline for HCC surveillance in NAFLD patients based on future perspectives. Overall, the title, abstract and keywords reflect the focus point of the review manuscript. The detail of literature used in the review is mentioned in the literature search section. The manuscript detail is in logical organization and provide the in-depth discussion in each section. There are some of the following points should be considered for minor editing. 1. Lots of abbreviations throughout the main manuscript (MS), the authors should provide abbreviation lists in the front page then it make the readers easy to follow. 2. The authors included the pathogenic pathway review in the supplementary file, it would be better for giving main concepts of the related pathways in either the main MS or the legend explanation in Figure 1. The remaining of the pathway can still be in the supplementary file.

Response 2

We thank the reviewer for his/her positive remarks and for raising those points.

1. Indeed, a plethora of abbreviations were used. In our revised manuscript, we have added two abbreviation lists (with changes underlined), the first one in the front page of the main manuscript, before the "Introduction" section and the second one in the front page of the **Supplementary Material**.
2. As we previously mentioned, we have incorporated a new section entitled "Pathogenetic mechanisms" (with changes describing the main molecular pathways involved in the development of NAFLD-related HCC.

Reviewer 3

A nicely written review about the HCC prevalence and pathogenic pathways in patients with NAFLD, and potential impact on disease prognosis, surveillance and prevention. One minor comments is that it would be good to update the global prevalence information in introduction with more recently references. Reference 2 is an example.

Response 3

We thank the reviewer for this insightful comment. In the "Introduction section" of our revised manuscript, we have replaced 2 References (1st and 2nd) with more recent References dealing with the same matter as well as we have added 2 additional recent References.

Science Editor

This review article is about an overview of non-alcoholic fatty liver disease (NAFLD) and progressive stages of NAFLD, its impact on public health worldwide, risk factors, pathogenesis, the prevention strategies, and the healthcare policies regarding NAFLD-related hepatocellular carcinoma (HCC). The manuscript has been well written. Some minor comments should be considered for minor editing. Lots of abbreviations throughout the main manuscript, the authors should provide abbreviation lists. Add more recently references in introduction section. And other questions asked by reviewers need to be answered.

Response to the Science Editor

We would like to thank the Science Editor for the appreciation of our work and for the insightful comments that helped us to improve our manuscript.

We provided point-by-point responses to all the issues raised by the Reviewers relevant to abbreviation list, references and pathogenetic mechanisms' section.

Company editor-in-chief

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response to company editor-in-chief

We thank the Company Editor-in-chief for his/her positive remarks and for raising those useful points.

Regarding the figures, we have created three distinct figures with no figure panels within the same figure showing the same or similar content (e.g. "**Figure 1 A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...").** Furthermore**,** in the online revision system we provided a single PowerPoint file including all the Figures, while the corresponding Figure legends and abbreviations are in the main manuscript. In that PowerPoint file, we have re-organized Figure 2 and Figure 3 as editable files. Concerning the Figure 1, since we have created that figure using the "BioRender" application, it cannot be

edited using PowerPoint. However, herein, we can provide the corresponding "BioRender" link along with the login credentials (Username and Password) for potential further manipulation of the Figure 1.

https://app.biorender.com/illustrations/5fa59f2bb4720a00a8947300

Username: lchrisaugis@gmail.com

Password: 2102795361

Regarding the Tables format, in our point of view, we have provided three-line Tables, including the top line, the column line below the headings of its column and the bottom line at the end of each Table, before the abbreviations. However, if we have misunderstood that point, we can re-format the presentation of the Tables presentation according to your instructions. In addition, we re-organized them into a single Word File uploaded in the online re-submission system following the editing specifications for the Tables.

Finally, we would like to kindly inform you that both Figures and Tables were deleted from the main manuscript and they were uploaded separately as Image File and Table File respectively, following revision's guidelines. Figure legends and abbreviations pertinent to Figures are in the end of the main manuscript.