

Response to Reviewers

April 18, 2022

Dear Editor,

Thank you for your e-mail of April 11, 2022 regarding our mini-review, “Risk factors and diagnostic biomarkers for NAFLD-associated HCC: Current evidence and future perspectives”. I am sending herewith the revised manuscript and our responses to the reviewers’ comments. Revision/additions in the manuscript are highlighted in red.

Response to comments by Reviewer #1

Comment 1: *This sentence should be re-written: “NAFLD is a spectrum of chronic liver diseases characterized by excess hepatocyte fat accumulation [5].” may be “excess fat accumulation in hepatocyte.”*

Reply 1: Thank you for your kind advice. We corrected the sentence accordingly.

Changes in the text:

NAFLD is a spectrum of chronic liver diseases characterized by excess fat accumulation in hepatocytes [5]. (page 4, line 9–10)

Comment 2: *“2382289 person-years” should be “2,382,289 person-years”.*

Reply 2: We added delimiters according to your advice.

Changes in the text:

However, in a large-scale retrospective cohort study, out of 2,382,289 person-years of follow-up, only 490 patients with NAFLD were diagnosed with HCC (0.21/1000 person-years) [15]. (page 5, line 1–3).

Comment 3: *“Diabetes and other metabolic traits Several studies have demonstrated that (mostly type 2) diabetes” In first usage of Diabetes pls refer as “Diabetes mellitus”... Diabetes mellitus? Diabetes insipidus??*

Reply 3: We revised the subheading and sentence accordingly.

Changes in the text:

Diabetes mellitus and other metabolic traits

Several studies have demonstrated that (mostly type 2) diabetes mellitus is associated with an increased risk of HCC development in NAFLD patients. (page 6, line 16–18)

Comment 4: *“Therefore, the risk of HCC should be assessed, not only for the presence or absence of diabetes but also for fibrosis markers”risk for fibrosis marker???*

Reply 4: We corrected the sentence as below.

Changes in the text:

Therefore, the degree of liver fibrosis, together with presence or absence of diabetes, should be assessed to predict the risk of NAFLD-HCC. (page 6, line 22–23)

Comment 5: *“A propensity score-matched study showed that the incidence of NASH and HCC was significantly lower in patients who underwent bariatric surgery, indicating a protective role of bariatric surgery[33].” should be “A propensity score-matched study showed that the incidence of NASH and HCC was significantly lower in patients who underwent bariatric surgery, indicating a protective role sustained weight loss by bariatric surgery[33].” according to the conclusion of Ref. 33.*

Reply 5: We corrected the sentence accordingly.

Changes in the text:

A propensity score-matched study showed that the incidence of NASH and HCC was significantly lower in patients who underwent bariatric surgery, indicating a protective role of sustained weight loss by bariatric surgery [33]. (page 7, line 9–12)

Comment 6: *“Old age, male sex, and Hispanic ethnicity are also known risk factors for NAFLD-HCC[31]” Ref.31 is a review paper which should be addressed.*

Reply 6: We revised the sentence and mentioned that ref. 31 was a review article.

Changes in the text:

Old age, male sex, and Hispanic ethnicity are also known risk factors for NAFLD-HCC; the details are described in another review article [31]. (page 7, line 15–16).

Comment 7: *Several studies have shown that elevated liver enzymes in NAFLD patients are significantly associated with an increased risk of HCC (hazard ratio, 2.07–8.20)[41–43]” this paragraph should include recent studies which found normal transaminases does not exclude fibrosis.*

Reply 7: We added the following sentence according to your advice.

Changes in the text:

At the same time, however, normal transaminase levels do not exclude the possibility of advanced liver fibrosis [44]. (page 8, line 19–20)

Response to comments by Reviewer #2

Comment 1: *Metabolic associated fatty liver disease (MAFLD) is a novel concept proposed in 2020, Su Lin, et al (PMID: 32478487) gave the conclusion that MAFLD definition is more practical for identifying patients with fatty liver disease with high risk of disease progression. So, can the relevant conclusions on NAFLD risk factors and diagnostic markers obtained in this paper also be extended to the evaluation and diagnosis of mafld, or are there differences?*

Reply 1: As MAFLD is still a recent concept, there have been few studies investigating the risk factors and diagnostic biomarkers for MAFLD-HCC. However, as you pointed out, it will be better to mention this issue. Thus, we added a new paragraph in the future perspectives section.

Changes in the text:

Novel conceptional criteria for metabolic dysfunction-associated fatty liver disease (MAFLD) were proposed in 2020[81]. Although MAFLD has been reported as a more practical definition for identifying patients with fatty liver disease with high risk of disease progression [82], it remains unclear whether the evidence of risk factors and diagnostic markers for NAFLD-HCC can be extended to MAFLD-HCC. A nationwide cohort study conducted in Taiwan revealed that patients with NAFLD/MAFLD overlap had similar risk of HCC compared to those with NAFLD alone [83]. Nonetheless, further studies are warranted on this topic. (page 12, line 23–page 13, line 4)

We would be grateful if the manuscript could be re-reviewed and considered for publication in the *World Journal of Gastroenterology*.

Sincerely,

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