July 27, 2016

Jing Yu
Science Editor, Editorial Office, *World Journal of Gastroenterology*
Baishideng Publishing Group Inc.
8226 Regency Drive
Pleasanton, CA 94588

Re: Manuscript No. 26929: Hepatocellular Carcinoma in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD)

Dear Dr. Yu:

Thank you for considering our manuscript for publication in *World Journal of Gastroenterology*. We appreciate the reviewers' constructive comments and the opportunity for resubmission.

Included in this letter is our point-by-point response to the reviewers' comments. Also enclosed is the revised version of our manuscript with highlighted edits based on the reviewers' feedback.

We hope our revisions are appropriate and suitable for *World Journal of Gastroenterology*. We greatly appreciate your time and consideration of our work for publication.

Sincerely,

Joseph K. Lim, M.D.

Point-by-point response to reviewers' comments

Reviewer #1 (Reviewer code 03478516)
Comments to authors:

- "To give readers a wider perspective about the topic, mainly to those ones outside this specific interest, authors should emphasize the link between MS and HCC via NAFLD, referring to… Could metabolic syndrome lead to hepatocarcinoma via non-alcoholic fatty liver disease. World J Gastroenterol. 2014 Jul 28;20(28):9217-28."

Response:

- We appreciate the reviewer's point to emphasize the association of metabolic syndrome, NAFLD, and HCC. Highlighting the link between metabolic syndrome and HCC via NAFLD is a suitable opportunity to introduce the proposed mechanisms discussed in our Pathophysiology section. Notably, subsections including "Tumor Growth," "Inflammatory Cascade," "JNK1," and "Adiponectin" are functions of the metabolic syndrome, manifestations of NAFLD, and associations with hepatocarcinogenesis. We appreciate the provided reference and have included it as reference #29 in our manuscript.

  In the Pathophysiology section, we created a new subsection called "Hyperinsulinemia" and included the link between metabolic syndrome and HCC via NAFLD in highlighted text in the revised manuscript and below as follows:

  "Carcinogenic features of the metabolic syndrome including uninhibited tumor growth, chronic inflammation, increased production of proinflammatory cytokines like c-Jun amino-terminal kinase 1 (JNK1), and reduction of anti-inflammatory proteins like adiponectin are mechanisms seen in NAFLD. NAFLD is a hepatic manifestation of the metabolic syndrome and considered a mechanism through which metabolic syndrome could lead to HCC[29]."

Reviewer #2 (Reviewer code 02860874)
Comments to authors:

- "An interesting review article about the mechanisms involved in the development of HCC in NAFLD, it explores clearly the genetic, immunological and pathophysiological mechanisms related to NAFLD and HCC."

Response:

- We appreciate the reviewer's concise summary of our highlighted mechanisms of NAFLD-HCC.

Reviewer #3 (Reviewer code 01490291)
Comments to authors:

- "Wong et al present review on the hot topic of HCC complication in patients suffering from NAFLD. Before publication I would recommend just few suggestions. 1 section. "Curative treatment and outcomes" suggest also to bring the Italian experience reported by Piscaglia et al, experience already mentioned in the previous section (ref 27)."
- "2-also in the finals section entitled by authors as "future directions" it lacks a reference to the problem of the need of surveillance programs for HCC in populations at risk. Today is a good bet that cannot be neglected as an open problem."
- "3- On this field I suggest to add a comment (see also Sasdelli AM and Marchesini G; Curr Hepatology Rep DOI 10.1007/ s11901-016-0297."

Response:

- We appreciate the reviewer's comments. Under the "Curative Treatment and Outcomes" section, second paragraph, patients with NAFLD are described as less likely recipients of curative treatment. Mentioning the Piscaglia study to highlight the aforementioned argument would be appropriate evidence to support the main point of the paragraph. The Piscaglia study has been included in the second paragraph of the "Curative Treatment and Outcomes" section in yellow highlighted text and below as follows:

  "An Italian study showed that fewer patients with NAFLD-HCC received resection as compared with patients with HCV-HCC (19% vs. 11%, p=0.002)[28]."

- We appreciate the need to emphasize the void in current HCC surveillance strategies for NAFLD-HCC. In the last paragraph of the "Future Directions" section, we reference a need of HCC surveillance in high-risk groups for NAFLD-HCC (e.g. sentence 2 and 3):

  "More robust epidemiological studies to identify high-risk groups for NAFLD-HCC incidence and NAFLD-related mortality *may help inform future surveillance* and treatment strategies. Additional investigation into mechanisms and determinants of HCC development in non-cirrhotic NAFLD versus NASH *may provide critical insight to support evidence-based guidelines on HCC surveillance*."

  We also added surveillance to our closing sentence as highlighted in yellow text and below as follows:

  "Significant opportunity exists to address key deficits in knowledge regarding epidemiology, pathogenesis, *surveillance*, treatment, and surgical outcomes of NAFLD-associated HCC, which remains a rapidly growing global public health problem."

- Thank you for the additional reference. We have added Sasdelli's paper as reference #27 to highlight the prevalence of patients with NAFLD-HCC without cirrhosis.

Reviewer #4 (Reviewer code 00006258)
Comments to authors:

- "The manuscript constitutes a review of the pathophysiology and treatment of HCC in the context of NAFLD. Whilst other reviews of a similar nature exist, it is likely to be of interest to the readership of WJG. It is reasonably comprehensive, but written in a rather list like style that would maybe benefit from some contextualizing to make it more readable for a wider hepatology audience. In particular the review would be improved by addition of schematic diagrams to summarize pathogenic mechanisms and to make clear distinction between those which operate on a background of cirrhosis vs. the non-cirrhotic cases. At present the mechanism section is lacking depth as evidenced by the limited discussion of roles of the immune system in development. Similarly the contribution of hepatic progenitor cell populations should be discussed."
- "Minor comments Some typos eg 'vital' hepatitis pg1 last paragraph"
- "Editing comments still visible on submitted version."

Response:

- We appreciate the reviewer's constructive feedback. The addition of a schematic diagram to summarize the proposed mechanisms of NAFLD-HCC pathogenesis is a very helpful idea. We included Figure 1 to demonstrate the three main categories of NAFLD-HCC carcinogenesis (genetic, cellular, and metabolic). In the figure, mechanisms that have been clearly described in non-cirrhotic cases of NAFLD-HCC are noted with an asterisk. Additional discussion about roles of adaptive immune responses and hepatic progenitor cell populations has been included under a new subsection called "Cellular Mechanisms" in the Pathophysiology section as highlighted in yellow in the revised manuscript.

- Thank you for noting the typo "vital." We have corrected the word to "viral" as highlighted in yellow in the revised manuscript.

- Editing comments have been removed.