July 21, 2015

To:

Editorial Board of World Journal of Hepatology

RE: Manuscript ID: 18576

Highlights Title:
Advances in Hepatocellular Carcinoma: Nonalcoholic Steatohepatitis-Related Hepatocellular Carcinoma

We would like to express our appreciation to the reviewers and editor for spending time and effort to improve our manuscript. Your suggestions were valuable to help us strengthen our work.

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to authors: Although the manuscript "Advances in Hepatocellular Carcinoma: Nonalcoholic Steatohepatitis-Related Hepatocellular Carcinoma" is an interesting review on the epidemiological evidence linking obesity, diabetes mellitus and NAFLD with cirrhosis and hepatocellular carcinoma, I suggest to add a paragraph and a figure on the possible molecular mechanisms involved in this association.
Minor point:
I suggest an English revision of the manuscript.

> **RESPONSE**: We agree with the reviewer that it is important to include additional information on the molecular mechanisms involved in the association between NAFLD and HCC. Based on the reviewer's suggestion, we have added an additional paragraph and diagram as noted below. We have also completed an English revision of the entire manuscript.

"Mechanisms underlying Nonalcoholic Steatohepatitis-related Hepatocellular Carcinoma

Numerous unique mechanisms underlie the pathogenesis of NASH-related HCC (Figure 3). Insulin resistance, associated with NAFLD, predisposes to the production of free fatty acids and several pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[25] TNF-α promotes pro-oncogenic pathways, which specifically involve NF-kB, c-Jun amino acid-

terminal kinase (JNK), and mammalian target of rapamycin complex (mTOR).[26, 27] Obesity is associated with increased IL-6 levels, while weight loss reduces levels of TNF-α and IL-6, resulting in a decreased inflammatory and potentially carcinogenic response.[28] Prolonged upregulation of the IL-6/STAT3 axis results in an increased probability that hepatocytes that have already acquired oncogenic mutations from exposure to carcinogens will continue malignant transformation.[29] Insulin resistance upregulates the production of insulin-like growth factor-1 (IGF-1). IGF-1 promotes processes linked to HCC development, such as expression of proto-oncogenes c-fos and c-jun in vitro and activating mitogen activated protein kinases (MAPK).[30] JNK, a MAPK, is activated by IR and downregulated by weight loss.[31] Histopathological analysis reveals that 70% of HCC tissue specimens stain positive for phosphorylated JNK, suggesting its role in the development of HCC.[32] Overall, several mechanisms underlying NASH-related HCC have been elucidated and pave the way for new therapeutic targets."

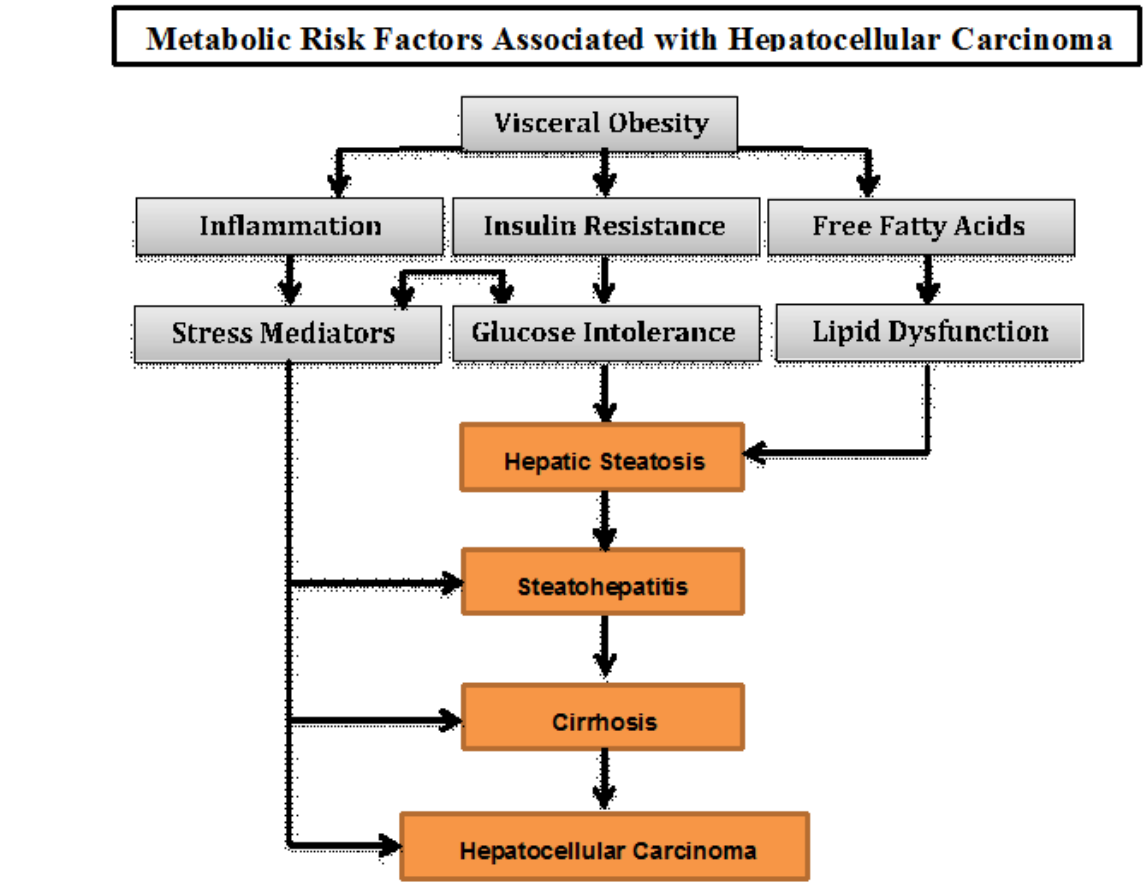

Figure 3. Metabolic Pathogenetic Pathways to Hepatocellular Carcinoma

Reviewer: 2

This is timely, well written mini-review, on interesting topic relating to risk factors contributing to the development of nonalcoholic steatohepatitis (NASH) and its progression to hepatocellular carcinoma (HCC).

RESPONSE: We appreciate the reviewer's positive feedback.

Reviewer: 3

This revision is well-written. The authors have clearly established a comprehensive explanation of the association of NASH and hepatocellular carcinoma, similar to what is known with HCV and HBV. As in HBV, they mention that cellular hepatocarcinoma may be at early stages of fibrosis, before the onset of cirrhosis. The review also covers different risk factors for HCC, they are common among obese patients, such as metabolic syndrome, insulin resistance or diabetes insulina o DM2. It is an interesting updated review that will motivate to further investigate the relationship between NASH and HCC, particularly to have a better manangement of obesity, NAFLD and NASH in risk patients. I suggest a diagram or figure to explain the relationship among the different risk factors.

RESPONSE: We appreciate the reviewer's suggestion regarding the addition of a diagram to explain the relationship among the different factors involved in the mechanism of NASH-related HCC. We have added a new figure as displayed above to address this area.

Once again, we appreciate the time that the reviewer and the editor have spent in bringing these points to our attention. We believe that the manuscript is now much improved, and we hope that the response has been adequate. We again appreciate your consideration for publishing this manuscript in *World Journal of Hepatology*.

Sincerely,

Aijaz Ahmed, MD