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Ling-Ling Wen, Science Editor, Editorial Office
Baishideng Publishing Group Co., Limited

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3828-revised.doc).

Name of Journal: World Journal of Gastrointestinal Oncology
ESPS Manuscript No: 3828
Title: Primary Hepatocellular Carcinoma and Metabolic Syndrome: An Update
Authors: Rubayat Rahman, MD, MPH; Ghassan Hammoud, MD; Ashraf Almashhrawi, MD; Khulood Ahmed, MD; and Jamal A. Ibdah, MD, PhD.

The manuscript has been updated.

(1) Format has been updated as per revision policies for reviews.

(2) Revision has been made according to the suggestions of the reviewers as follows:

Reviewer 01439739:

This is an invited review on the link between the metabolic syndrome and HCC. I have only a few observations. The review is timely, although the reader would like to see a more comprehensive summary of all recent efforts in the field, e.g., data on preventing

HCC by weight management, use of statins, FXR agonists, etc. The manuscript feels at times a little repetitive. For instance, instead of writing the same sentence with different RR values for each condition (...The Metabolic Syndrome and Cancer Project (Me-Can) from Norway, Sweden and Austria examining 578,700 subjects showed RR of...), it would be more elegant to create a table with all the relevant relative risks and odds ratios to summarize this part of the work. Moreover, RR is less than 1.0 for hyperlipidemia in the Me-Can study, suggesting a protective effect from developing HCC - this finding would deserve at least a brief comment. Also, there is something missing in the bottom line on page 10 from the sentence; it is not clear which parameter the RR=0.85 belongs to.

Author's Response: We appreciate the reviewer comments and interest in our manuscript. We have modified the manuscript to address the reviewer comments. A new Table (Table 4) was added to the revised manuscript to summarize the relative risk (RR) or odd ratio (OR) of developing HCC in the background of MetS as the reviewer suggested. The reviewer is correct regarding the 0.85 RR of developing HCC with hyperlipidemia In the Me-Can study. It should be noted that this finding in the Me-Can study contrasts the finding in another study (Welzel et al, reference 42) with a hyperlipidemia OR of 1.35 for developing of HCC. Although not well understood, this discrepancy could be secondary to the short follow up period in the Me-Can study. A sentence was added to the revised manuscript to address this discrepancy.

Reviewer 01489938:

The topic of this review is interesting, but there are some points that must be revised. The title of the manuscript would be better like this "Association of Primary Hepatocellular Cancer to Metabolic Syndrome: An Update". The abstract is too short: some important conclusion of the main body text should be mentioned in it. The discussion of Metabolic syndrome is rough-and-ready. There are main clinical conditions/symptoms and minor symptoms/conditions that may be in association with MetS. It would be necessary to expand the discussion of MetS, and of course,

summarizing the association between HCC an the minor symptoms. Not all the NAFLD/NASH patients have MetS. This must be also discussed. The role of rosuvastatin and ursodeoxycholic acid in the treatment of NASH and in prevention of NASH-associated HCC must be also discussed. A schematic figure summarizing the potential pathways in MetS leading to HCC would enhance the strength of the review. The reference list is up-to-date. Minor English language revision is necessary. After major revision I suggest to consider the manuscript for publication in WJGO.

Author's Response: We thank the reviewer for finding our review topic interesting. We expanded the Abstract as the reviewer suggested. Also, we have added a figure to the revised manuscript summarizing the potential pathways in MetS leading to HCC in response to the reviewer suggestion (Figure 1). We modified the manuscript to address the reviewers concerns and suggestions (ref # 80, 81). Minor conditions for MetS are not part of the diagnostic criteria and often very difficult to quantify the contribution of these minor conditions to the development of MetS related complications.

Reviewer 00012265:

Major comments:

1. The authors described that the association between HCC and metabolic syndrome. Unfortunately the paper can give little and wrong information and not interesting.

There were a lot of inappropriate descriptions throughout the text. For example, the mortality of HCC become decreasing in Japan. You cited ref #1 published in 1999. It's too old. The pathophysiology of NASH is also pretty old and nothing new. You should cite more recent original papers. Do you know PNPLA3?

Authors' Response: Mortality from HCC in Japan is indeed decreasing (please see ref # 67 published in 2011), although reference # 1 was published in 1999, it is a seminal article in a high impact journal that deserves to be included in our review, and it reflects that time frame of in depth studies in this field. Our review contains updated

information on the pathophysiology (ref # 53-68, all published in the past 5 years and the vast majority over the past 2 years). The PNPLA3, although reported to confer susceptibility to NAFLD in humans, is not directly relevant to this review which is focused on the pathophysiology of HCC in the background of MetS.

2. *As I mentioned, the citation paper is pretty old. If the authors insist on "an update" you should use at least less than 5 years. There are lots of work about NASH and HCC. This paper did not give the readers useful information at the current format.*

Authors' Response: We used both current and recent information. Most of the citations are in the past 5 years. Original studies in the field deserve to be acknowledged. It should be noted that the epidemiological studies on MetS were done mostly from 2001 to 2005.

3. *Surveillance for HCC and Summary are poor. The authors should show concrete action for surveillance. What is the recommendation of surveillance? Your recommendations are based on what? Otherwise the readers will not be satisfied with the paper and feel novelty. We are not making any recommendation at this time*.

Author's Response: Currently there are no guidelines exist for surveillance. This study discusses the link between MetS and HCC. Ultimately, with the identification of the high risk groups for the development of HCC with MetS, it is imperative to develop surveillance strategies. Future studies in the field should address this question.

Minor comments:

1. *Title should be changed. We usually use "hepatocellular carcinoma" not " hepatocellular cancer".*

Author's Response: We have made the change in the title as the reviewer suggested.

2. *“Acknowledgements" should be uniformed in font style.*

Author’s Response: Corrected

3. *If the authors abbreviate“Hepatocellular carcinoma" as HCC. The abbreviation should be used later the first appearance. The same is true in metabolic syndrome.*

Author’s Response: No change, we searched the documents and abbreviations appropriately used after the first appearance.

Reviewer 02446317:

The review manuscript entitled “Primary Hepatocellular Cancer and Metabolic Syndrome: An Update” by Rahman et al is a good addition to its field, and brings a necessary update regarding the relationship between HCC and metabolic syndrome. In order to be considered for publication, several comments detailed below should be addressed, as this would provide a more complete picture.

Author’s Response: We thank the reviewer for acknowledging the importance of this review.

Major comments:

The review should be completed with information regarding MetS that has emerged within last years, such as: the epidemiological data regarding the role of maternal metabolism/nutrition status as a risk factor for MetS at younger ages (see Epidemiology of MetS. This is an important aspects to be revealed when it comes to discussing potentially preventive interventions against MetS and, therefore, against HCC occurrence. Maternal metabolism may be a risk factor for MetS at younger age but its relation and pathogenesis to the development of HCC is not well understood. In this context, the paragraph discussing the epidemiology of MetS is too brief, and should be

enhanced according to other data available for the epidemiology of MetS.

Author's Response: The text was modified and improved as suggested by the reviewer. The epidemiology of MetS section was expanded in the revised manuscript to address the potential role for maternal factors and appropriate references were added.

Minor comments:

1) *In many places references should be indicated. Example: page 10 "Hyperlipidemia is closely related with the central mechanism of insulin resistance in MetS". While true, it cannot be inferred that all cases of insulin resistance associate with hyperlipidemia. Therefore, references should be given, and the sentence be nuanced more.*

Author's Response: The text was modified as suggested by the reviewer.

2) *In several other places, assertions of certainty are made, but the reality is more nuanced. Example: page 15, lines 4-7. It is considered that antidiabetic medication has no association with HCC risk, but in the same phrase it is indicated that there is heterogeneity between many studies. Therefore, space for controversy should be left in the text.*

Author's Response: The text was modified and improved as suggested by the reviewer.

3) *In several places, the term "etiology" is improperly used. This refers to considering MetS as the "etiology for either CVD manifestations and diabetes (e.g. page 3 and other places). At best, MetS is a group of signs that were lumped together in the absence of a clear, unique, etiology. To say that a group of sign (clinical and metabolic) are the etiology of a disease is improper. The text should be modified accordingly.*

Author's Response: The text was modified, whenever applicable, as suggested by the

reviewer.

4) *Table 3, first column header: Risk Factors should be replaced by Diagnostic Criterion or other similar term. Those are not risk factors for MetS, but the very signs that DEFINE the MetS.*

Author's Response: We agree and have modified the text accordingly.

5) *Page 15, Summary. The authors declare that the NAFLD is the hepatic manifestation of MetS. This is not true in all cases (again, more nuance). For instance, micronutrient deficiencies such as Choline deficiency can lead to NAFLD, but in the absence of MetS (see PMID 23292069, PMID 21129376, etc.).*

Authors Response: We agree and have modified the text accordingly.

Reviewer 02441391:

Metabolic syndrome is growing epidemics associated with an increased risk for many type of cancer. In the liver, change in hepatic inflammation and angiogenesis due to insulin resistance are associated with an increased incidence of hepatocellular carcinoma (HCC). Regardless of underlying liver disease, cirrhosis remains the most important risk factor for HCC although some cases of HCC arise without cirrhosis in the background of metabolic syndrome. This raises the possibility of a direct carcinogenesis secondary to underlying insulin resistance that is well documented major role in the development of non-alcoholic fatty liver disease. In addition, the other components of metabolic syndrome including obesity, diabetes, hyperlipidemia and hypertension may also increase the risk of HCC in the setting of chronic liver diseases of other causes such as viral hepatitis or alcohol abuse. Taking into account all these data, it is necessary to better determine the risk of developing HCC in patients with metabolic syndrome to provide appropriate surveillance strategies in this setting. This comprehensive review

summarizes the current literature of HCC and metabolic syndrome epidemiology, as well as pathophysiology and clinical course of HCC in the background of metabolic syndrome.

Author's Response: We thank the Editor for acknowledging our comprehensive review.

Editor's Comments to the Author:

1) *Please provide a figure demonstrating factors that are associated with the development of HCC in the background of metabolic syndrome to better understand tumorigenesis in metabolic syndrome.*

Author's Response: Diagrammatic figure is provided in the revised manuscript (Figure 1) for the pathogenesis of HCC in the background of MetS.

2) *Page 3, first paragraph, please provide full sentence with abbreviation of HBV and HCV.*

Author's Response: Corrected as the Editor suggested.

3) *Page 7, first paragraph, 5th line: "The overall prevalence rate" should be changed to "The overall prevalence".*

Author's Response: Corrected as the Editor suggested.

4) *Page 8, 2nd paragraph, First line: "Hepatocellular Risk factors" should be changed to "Hepatocellular Carcinoma Risk Factors".*

Author's Response: Corrected as the Editor Suggested.

(3) References and typesetting were corrected

We believe that the comments made by the reviewers have greatly improved this mini-review. We have made all necessary changes as suggested.

Thank you again for publishing our mini-review in the *World Journal of Gastrointestinal Oncology*.

Sincerely yours,

Jamal A. Ibdah, MD, PhD