25th August 2018

President and Company Editor-in-Chief
World Journal of Gastroenterology

Dear Editor-in-Chief

Please find our revision letter on the following manuscript

Name of Journal: World Journal of Gastroenterology

Manuscript NO: 39018
Manuscript Type: MINIREVIEW

Title: Carcinogenesis on the background of liver fibrosis: implications for managing Hepatocellular Cancer.

Authors: O'Rourke JM, Sagar VM, Shah T, Shetty S.

We thank the reviewers for taking the time to read our manuscript and we appreciated the constructive feedback. We have amended the manuscript following reviewers comments and have outlined the changes below.

Reviewer #1:

A detailed analysis of the carcinogenic processes occurring in the liver in response to necroinflammation and fibrosis. The problem is expected to become of paramount importance, given the increase in the prevalence of NAFLD in the general population. The importance of microenvironment in the carcinogenic pathway is probably pivotal, as is the immune-response of the host. 1. I have no major reservations. In order to make the review more easily understandable, one or two pictures summarizing the whole process would be definitely important. 2. Not clear how the ALBI score may be calculated (in the same way as the Child-Pugh classification?). 3. The paragraph on sarcopenia must be better defined. A low muscle mass is definitely a risk factor for complications in cirrhosis, but its relation

with cancer goes well beyond the scope of this review. As a matter of fact, there is no evidence that sarcopenia may be involved in creating the microenvironment for HCC, but simply remains a risk factor mortality.

Reply to reviewer 1: Many thanks for your comments, your feedback is most appreciated. In response we have included a diagram to summarise the recognised key contributors to the process. We have also included information on how the ALBI score is calculated. We have amended the paragraph on sarcopenia so it is clear to the reader we are not suggesting it influences HCC progression but that there is evidence it impacts on outcomes.

Reviewer #2:
1 Primary liver cancer is not identical to hepatocellular carcinoma. 2 In the section of "Core tip", the phrase "development of cancer" should be specified as HCC or not. 3 HCC is resulted from various causes, not only cirrhosis. The authors are suggested to provide a table showing these causes and emphasizing the impact of cirrhosis. 4 Fibrosis is only an outside condition for carcinogenesis, genetic mutation must be stated. 5 The title is lack of sense, the word "challenge" is not clearly standed for. 6 Typo- and grammatical errors are found, including misuse of verb tense and sentence structure.

Reply to reviewer 2: We appreciate and thank you for your constructive feedback. In response we have replaced the term primary liver cancer and we have emphasised the fact that the majority of HCC cases occur in the setting of fibrosis. We thank you for your suggestion to include a table to summarise associations in the non-cirrhotic setting which we have done. In the text there is now reference to genetic mutation and the following references are included: 1) Marquardt JU. Functional and genetic deconstruction of the cellular origin in liver cancer. Nat Rev Cancer 2015. 2) Tummala KS. Hepatocellular Carcinomas Originate Predominantly from Hepatocytes and Benign Lesions from Hepatic Progenitor Cells. Cell Rep 2017; 19(3): 584-600.

We have replaced the word challenge in the title and reviewed typos and sentence structure in the manuscript.

Reviewer 3#:
This is a well-written review manuscript dealing with the issue of carcinogenesis of hepatocellular carcinoma on the background of fibrosis of liver. The following point is suggested. 1. The title of the subsection 'Discussion' is better to be modified as 'Conclusion'.

Response to reviewer 3: Thank you for your positive feedback. We have changed the subsection ‘Discussion’ to ‘Conclusion’.

Reviewer 4#:
The submitted study summarizes the state of the art of hepatocarcinogenesis under an inflammatory and fibrotic environment, emphasizing on the management of immunosuppression as a therapeutic option. The manuscript is clearly explained and the most relevant items have been comprehensively highlighted. To further detail the hepatocarcinogenic process some additional references might be of use: Sia d et al, Gastroenterology 2017; Loved JM et al Nat Rev Dis Primers, 2016; Marquardt Ju et al Nat Rev Cancer, 2015. Moreover, some references to illustrate the role of microbiota in liver cancer progression would be of interest (see, for instance, Yu LX and Schwabe RF, Nat Rev Gastroenterol Hepatol, 2017). Finally, a graphical schema to summarize the most relevant factors involved in the development of liver cancer, as described in the text, would be of great help to have an integrative view of such a complex process.

Response to reviewer 4: We thank you for your feedback and suggested improvements are appreciated. We have included reference to the following as suggested ‘Sia d et al, Gastroenterology 2017; Loved JM et al Nat Rev Dis Primers, 2016; Marquardt Ju et al Nat Rev Cancer, 2015’. We have also expanded the evidence for the role of the microbiome incorporating ‘Yu LX and Schwabe RF, Nat Rev

Gastroenterol Hepatol, 2017'. There is now also a figure outlining key players in the process of fibrosis induction and the creation of the tumour microenvironment which we hope provides an overview of a very complex process for this minireview.

Reviewer #5:
This is an update on the interplay between fibrosis and HCC, with specific comments on secured mechanisms and outcomes. The title is appropriate for the content of the minireview, with an appropriate update of therapeutics, clinical trials and issues and mechanisms. This is also covered in the abstract. I only suggest two improvements: 1. An in-depth critical analysis of the current therapeutic interventions in preventing fibrosis and HCC (based on clinical trials). This is only marginally covered. 2. To provide a positive note on the WHO on the Global health sector strategy on viral hepatitis 2016-2021 (http://www.who.int/hepatitis/strategy2016-2001/ghss-hep/en/), that is aiming a global effort on a significant reduction of HCC in the future.

Response to reviewer 5: Many thanks for taking the time to appraise this minireview, we appreciate your feedback. The prevention of fibrosis is a hot topic and there are many different avenues to explore from antiviral therapies, therapies aimed at mechanisms involved in the metabolic syndrome and agents specifically targeting fibrosis mechanisms within the liver. We decided to focus on the trials which are looking at agents which have been designed/promoted specifically as anti-fibrotic therapies, which is likely to be one of the next major therapeutic milestones in the management of patients with/at risk of cirrhosis. To make it easy for the reader we have summarised these agents in a table outlining the mechanism of action and the status of the clinical trials. We thank you for the suggestion and highlighting such an important area. We have also included reference to the WHO strategy on viral hepatitis.