POINT-BY-POINT RESPONSES TO THE REVIEWERS

Dear Editor-in-Chief, dear Reviewers,

Thank you very much for considering our paper entitled **Portal hypertension in patients with Nonalcoholic fatty liver disease: current knowledge and challenges,** and for having conducted a thorough review and provided usefull comments and suggestions. We have revised our paper accordingly, and by doing so we believe it will meet high academic standards of World Journal of Gastroenterology. Below please find our point-by-point responses to all issues raised in the peer-review report. Our responses are written in red typeset to make easier to follow-up.

REVIEWER #1:

Specific Comments to Authors:

This review discussed portal hypertension in patients with nonalcoholic fatty liver disease: current knowledge and challenges. Some comments should be addressed as following :

1. A detailed explanation of the HVPG was not found in the abstract, but appears in the main text, and it is suggested that additional clarification be provided. It is also not reflected in the abbreviations.

We thank the reviewer for this important comment. We have provided detailed explanation of the HVPG abbrevitatation at the place it first appears in the abstract. It has been also included among the list of abbrevitations.

2.In the part of Impact of lipid accumulation on PH development in early NAFLD, the description is slightly lengthy and not hierarchical.Things like lipid accumulation and neutrophil chemotaxis, and related clinical trials could be addressed in segments, and shouldn't this section focus on the effects of lipid accumulation on PH?

We thank the reviewer for this meaningful comment. We have re-arranged the text of this chapter accordingly, and divided it into three (3) separate paragraphs:

(1) Impact of lipid accumulation on PH development in early NAFLD (page 5)
(2) Impact of neutrophils activation on PH development (page 6), and
(3) Animal models supporting the role of liver steatosis in the development of PH (page 6)

We have tried to follow hierarchical structure of the scientific content, and to narrow the content of each of these paragraphs to only the issue that is highlighted by the respective title.

3.Similarly,in the part of Development of fibrosis and impact of fibrosis on PH, it can be elaborated in two parts: vascular dysregulation and endothelial dysfunction.

We thank the reviewer for this suggestion. However, the suggested paragraphs about the role of endothelial dysfunction already exists as the separate paragraph (page 7), and we have written a new paragraph about vascular dysregulation (pages 8-10). In fact, the text from the previous version has been re-arranged in a way already mentioned under the previous point, i.e. we tried to narrow the content of each paragraph to the topic highlighted by the respective subititle. Therefore, the paragraph about the Development of fibrosis and impact of fibrosis on PH (page 12-13) underwent changes as well, in a way that it is focused only to mechanisms of ECM accumulation, including the

cellular and molecular mediators to this process, whereas other content including vascular and endothelial changes have been tranfered to the new paragraphs.

4. Lack of innovation, similar reviews have been reported on the relationship between portal hypertension and NAFLD and discussions can be added in targeting PH for NAFLD treatment.

We thank the reviewer for the suggestion to add the paragraph about the options of therapeutic targeting of PH in NAFLD, as this is the topic about we, the authors, discussed before submitting the first version of the manuscript to WJG. However, because no efficient therapies are approved for this indication, we decided not to include this paragraph in the first version of the manuscript. Yet, we agree thet it might be interesting for the readers to present the current data about the treatment approaches to PH in NAFLD (included in the page 22-23), even if most of them failed to show reliable effects. On the other hand, we disagree with the comment pertaining the lack of innovation of this manuscript, as the knowledge in the field is under ongoing development, and the fact that several review papers have been published over the time does not preclude new reviews to appear as they (including our review) deal with the issue of PH in NAFLD from different perspectives and they do not include the same original paperes and all the results available in the field. At the end of review process the editorial board of WJG would make the final judgement, based on the reports of the reviewers, if our paper contains sufficient scientific information that would be atractive and usefull for the readers.

REVIEWER #2:

Specific Comments to Authors:

This is a very interesting topic. In traditional understanding, portal hypertension (PH) in advanced liver fibrosis or cirrhosis is an important complication and the main cause of ascites, splenomegaly, and upper gastrointestinal bleeding. However, few studies have focused on the presence of PH in different stages of non-alcoholic fatty liver disease (NAFLD), which is actually quite astonishing. Recently, some research has started to pay attention to this phenomenon, and studying the combination of NAFLD and PH may help in early diagnosis and the design of early intervention drugs, which could be beneficial in slowing down or alleviating the progression of liver pathology. However, before publication, the authors still need to clarify some issues.

1.Epidemiological evidence for the presence of PH in NAFLD, especially in non-cirrhotic or non-fibrotic stages, needs further supplementation. In fact, splenomegaly can be observed in different stages of NAFLD, which may be an early "alarm symptom" of PH.

We thank the reviewer for this important comment. However, upon the thorough search of the scientific literature we are not aware of any large-scale study that would adress the problem of PH in NAFLD from the epidemiological standpoint. In fact, the results on the prevalence of PH in NAFLD come from small to medium-sized clinical studies with heterogeneous design, and these studies have been mentioned and discussed in our review (Mendes FD et al. Clinical Gastroenterology and Hepatology 2012; Francque S, et al. Int J Obes 2011; 35: 270–278, Vonghia L, et al. PLoS One 2015; 10: e0143380, Rodrigues SG, et al. Clinical Gastroenterology and Hepatology 2019; 17: 2101-2109, Moga L, et al. J Hepatol. 2021; 74: 1269–1270.). We have especially adressed the issue of PH prevalence in non-cirrhotic stages of NAFLD in the paragraph entitled **Portal hypertension in relation to the stage of liver fibrosis and grade of steatosis: clinical data** (pages 13-15).

Upon suggestion of this reviewer we have added the paragraph about the splenomegaly as the potential indicator of PH in NAFLD, at the end of the chapted entitled Portal hypertension in relation to the stage of liver fibrosis and grade of steatosis: clinical data (page 15).

2.Transient elastography is the main technique for assessing PH, but its invasiveness affects its clinical application, and hepatic venous pressure gradient (HVPG) often underestimates the pressure threshold. How to improve the diagnostic accuracy by utilizing emerging imaging techniques or seeking early highly specific sensitive markers needs to be further considered.

We believe that the first part of the comment is related to the features of HVPG as a invasive technique for obtaining the estimates of portal pressure, and this has been mentioned at several locations throughout the manuscript.

As for the imaging techniques we have extensivelly discussed elastography (mostly transient elastography and other ultrasound based elastography methods, but we also mentioned MR elastography,and classical imaging methods) that is currently best validated method in this regard. However, we have also dedicated the entire paragraph to the emerging techniques represented by EUS-PPG measurement, including its clinical applicability, preliminary results, strenghts and limitations of the method (pages 17-18). At the end of the chapter about the non-invasive diagnostic methods for PH we have now added a paragraph about the metabolomic approach to finding the reliable marker(s) of early PH in NAFLD (which is (are) not available, and further research is needed) (page 20).

3.The occurrence of PH in different stages of NAFLD suggests that vascular dynamics factors such as fibrosis may not be the only contributing factors, and the roles of metabolism and inflammation in the formation of PH need to be further evaluated.

We thank the reviewer for this comment. However, we believe that the problem of fibrogenesis, impact of immune system activation in NAFLD, with endothelial dysfunction and vascular dysregulation have been extensivelly discussed under the respective chapters. Following the re-arrangement of the text in the revised version of the manuscript we believe that now the content is more clearly presented.

4.The heterogeneity of NAFLD supports the focus on elevated postprandial glucose (PPG) throughout the disease process, which may occur prior to fibrosis in NAFLD, indicating a bidirectional relationship between these pathological processes. A better understanding of the hepatic biomechanics of NAFLD may contribute to the development of new drug targets for the prevention and management of this disease.

We thank the reviewer for thies meaningful comment. We have included the data about the interrelationship of PPG and fibrosis progression in NAFLD, including the potential to use PPG as the early biomarker of this process, at the end of chapter about non-invasive diagnosis of portal hypertension in NAFLD (page 20)