July 17, 2021

Dear Dr. Ma

We would like to thank you and your reviewers for your helpful and thorough review of our manuscript entitled "**Noninvasive imaging of hepatic dysfunction: the state-of-the-art review**", **No. 65938**, and for potentially accepting the manuscript for publication.

We have revised the manuscript and have made every effort to carefully address all the editor's and reviewers' comments. In the following pages, you will find a detailed, point-by-point list to explain our changes based on your and the reviewers' comments.

- **Editor's Comments:**

(1) Science editor:

1. Scientific quality: The manuscript describes a minireview of the noninvasive imaging of hepatic dysfunction. The topic is within the scope of the WJG.

(1) Classification: Two Grades C;

(2) Summary of the Peer-Review Report: The review gives us a good overview of summary of noninvasive imaging modalities for assessing hepatic dysfunction along the pathophysiological track, and the challenges and goal in hepatic dysfunction imaging. However, there are several similar review articles regarding noninvasive diagnostics of liver diseases. The questions raised by the reviewers should be answered;

(3) Format: There is 1 table and 6 figures;

(4) References: A total of 85 references are cited, including 41 references published in the last 3 years;

(5) Self-cited references: There is 1 self-cited reference. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the

manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and

Thanks for your kind reminder, we confirm that the self-referencing rates is less than 10%, and the cited references are closely related to the subject.

(6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

2 Language evaluation: Classification: Two Grades B. A language editing certificate issued by AJESCI was provided.

3 Academic norms and rules: No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. The study was supported by Science and Technology Support Program of Sichuan Province. The topic has not previously been published in the WJG.

5 Issues raised:

(1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Thank you for your kind reminder. We will upload the funding application forms.

(2) The authors did not provide original pictures. Please provide the

original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and

Thanks for reminding. We're very sorry for this oversight. We will provide all the original documents and arrange them using PowerPoint.

(3) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Thank you for your kind reminder. There is no figure which is re-used.

6 Re-Review: Required.

7 Recommendation: Conditional acceptance.

(2) Company editor-in-chief: I have reviewed the Peer-Review Report, full

text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

- **Comments from Reviewer 1:**

The review article submitted by Duan et al. gives us a good overview of summary of noninvasive imaging modalities for assessing hepatic dysfunction along the pathophysiological track, and the challenges and goal in hepatic dysfunction imaging. However, there are several similar review articles regarding noninvasive diagnostics of liver diseases. I think you should describe the characteristics of your article, which is different from other articles.

Thank for your kind review and constructive comments. We made some revision in the review.

1. We added a new chapter called progress of diffuse liver disease, including liver fibrosis and portal hypertension. In the review, we first discuss the various etiology of hepatic dysfunction and imaging evaluation methods, and then summarize evaluation of the common pathway of a variety of progressive diffuse liver diseases.

2. For each cause of hepatic dysfunction, we have summarized the recommended imaging modalities in the end of each section. Including the first line imaging equipment and further examination methods. It can also be seen from the changed Figure 6.

Compared with other reviews evaluating liver function, our review has the following characteristics.

Firstly, we pay more attention on clinical scenes. We did not organize this

review from the perspective of modalities, such as what progress CT has made in the field of hepatic dysfunction, and what progress MRI has made. We organize this review from the clinical application. In other words, we summarize the recommended imaging modalities and the latest research progress in hepatic dysfunction caused by various reasons.

Secondly, in each category, we combine pathophysiological changes with imaging findings. For example， Acute hepatitis results of increased lymph inflow and blocked lymph backflow， so "halo-ring sign" or "track sign" appears around the portal vein. This combination may deepen clinicians' understanding of the choice of image modalities.

In summary. this review focuses on helping clinicians choosing non-invasive imaging methods in assessing liver function.

I have some comments.

1. Reference 15 and reference 17 are the same? Please check other references.

Thanks for reminding. We're very sorry for this mistake. We have checked them and reorder the references.

2. The naming of authors in the publication is very variable. Some are given first with the family name and then the first name, others the other way around. This should be consistent in the work.

Thanks for your kind suggestion. We have checked all the publication, then all the publication is given the family name.

3. The abbreviations appear in many places, I think it's a bit redundant.

Thank you for your kind advice. We have deleted some abbreviations that

appear less frequently.

4. The “c” in Figure 3 should be uppercase letter “C”.

Thank you for your careful review. We’re sorry for this negligence. We have corrected it.

5. The “a “and “b” in figure 4 Legend inconsistent with figure 4. The “a “and “b” in figure 4 Legend should be uppercase letter.

We appreciate your thorough review. We’re sorry for this negligence. Corrections have been made accordingly.

6. “Iron storage disorder is characterized by unregulated iron increase or decrease in the liver[65].” The “Iron storage disorder” in this sentence maybe “Iron storage disorders”, it need to be check.

Thank you for this input. Revisions have been made in compliance with your comment.

- **Comments from Reviewer 2:**

Major comments:

1， The authors mentioned that the study aim was to identify affected individuals at early stages to enable targeted intervention strategies, which can improve prognosis. Although the authors correlated the pathological changes with the radiological findings, they need to be more focused on the clinical situations and case scenarios in which these modalities help early diagnosis and allow intervention and how these can affect the outcome compared to the conventional invasive methods.

Thank you very much for your valuable comment. Based on your comment, we have made modification on the review.
In the introduction， we stated the limitation of liver biopsy as the gold standard. In the following chapters, we also added the necessity of early assessment through imaging. For example, in the content of portal hypertension, we mentioned the evaluation of esophageal and gastric varices by imaging equipment, which can screen out patients at risk and reduce unnecessary esophageal endoscopy.

2, The authors need to clarify which invasive modalities that can be substituted by these recent non-invasive methods and pros and cons of each modality. For example, the role of liver biopsy as a gold standard for detection of hepatic fibrosis, steatosis and inflammation and its potential risks that justify the need to study other methods for diagnosis.

I am very grateful to your comments. According with your advice, we added a variety of imaging methods for the diagnosis of liver fibrosis, steatosis and so on. For each cause of hepatic dysfunction, we have summarized the recommended imaging modalities in the end of each section, including the first line imaging equipment and further examination methods. It can also be seen from the changed Figure 6. Using these methods to replace liver biopsy can avoid the risks bleeding and sampling error.

3, In figure 1, the authors mentioned all imaging modalities that can be used in each type of hepatic disease like acute or chronic hepatitis, cholestasis, NAFLD and others. Are all these imaging techniques needed at once? Taking into consideration that most of these procedures are costly, some of them have hazards as radiological exposure or renal compromise of the contrast. So the authors need to do a step up algorithm to clarify the clinical indication of each approach in a comprehensive

manner.

Thank you so much for your careful review. We are wondering if it is figure 6 needed modified. According with your advice, we added a summary about image modality choice in each chapter. Besides, we redraw the Figure 6, in which the bold modalities represent the first line and preferred methods.

4, The authors did not mention the role of non-invasive radiological methods for screening for portal hypertension and esophageal varices to stratify which patient has an increased risk of bleeding and indicated for an endoscopy. I recommend to add a separate section for portal hypertension with description of different findings in ultrasound, Doppler, elastography, phase-contrast MRI, 2D PC MRI, 4D flow MRI, DCE-MRI and relaxometry. In addition, to mention the role of these methods to detect treatment response.

We are really appreciated for this point. We added a new chapter called progress of diffuse liver disease and adjust the framework.
In the review， we first discuss the various etiology of hepatic dysfunction and imaging evaluation methods, and then summarize evaluation of the common pathway of a variety of progressive diffuse liver diseases. Various imaging findings about liver fibrosis and portal hypertension were reviewed, in various practice scenarios, including ruling out significant fibrosis or portal hypertension in low risk patients, diagnosing and Staging, longitudinal monitoring.

5, The authors mentioned ‘’biliary atresia’’ among the causes of acute cholestasis. I suggest deleting it for several reasons. First, it is not a form of acute cholestasis; it is a chronic progressive fibro-inflammatory disorder in neonates and infants. So, it is out of the scope of this manuscript, as you did not mention the ultrasound findings of biliary

atresia or radiological findings in other chronic cholestatic or metabolic diseases of infancy and childhood. Moreover, MRCP is not the best tool to diagnose biliary atresia as you mentioned and still liver biopsy has the upper hand in diagnosis and sintigraphy in selected cases. Accordingly, it is better to skip biliary atresia from the manuscript and keep focusing on adulthood conditions.

Thank you for this comment. We have deleted the section on “biliary atresia” accordingly.

Minor comments:

1, In the second line of the introduction, ‘’systematic’’ should be corrected to ‘’systemic’’

Thank you for your careful advice. I'm very sorry for this negligence. We have corrected it.

2, You mentioned reference number 61 in the last paragraph of NAFLD although this study is investigating the prediction of portal hypertension in children and young adults with autoimmune liver disease. Please delete or replace this reference with a relevant one.

Thank you so much for your careful review. We have replaced it with a new reference numbered 47.

Sincerely,

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