Dear editors and reviewers,

Thank you very much for carefully reviewing our manuscript entitled "***Noninvasive Imaging of Hepatocellular Carcinoma: from diagnosis to prognosis***" (manuscript ID: 39036). These valuable comments are exceptionally inspiring and constructive for our work. We're horned and grateful for your decision in the letter dated April 13, considering a revised version of our manuscript, addressing all the issues brought up by editors and the reviewers.

Below, I will detail how we revised our manuscript according to each of the comment (in italic). Changes made from the previous article file were all highlighted in the manuscript.

Response to comments of reviewer # 00058381

1. *Major Comments: Figures 1-3: "Edmonson-Steinter" – the correct term is "Edmondson-Steiner" (Edmondson HA, Steiner PE: Cancer 1954; 7: 462–503).*

Author's response:

Thank you very much for this instruction. We have altered all three *"Edmonson-Steinter"* in Figures 1-3 to *"Edmondson-Steiner"* according to your comment.

2. *Please provide power of magnification and staining technique for all histopathological images.*

Author's response:

Thanks for this precious comment.

We have provided additional information of magnification powers and staining techniques for all histopathologic images, and the following sentences were revised and highlighted in the legends of Figures 1-3.

Figure 1: *The hematoxylin-eosin (H&E) staining of the mass at 200×magnification proved it to be Edmonson-Steiner grade II (D).*

Figure 2: *The mass was confirmed as Edmonson-Steiner grade II at 200×magnification with hematoxylin-eosin (H&E) staining (D).*

Figure 3: *The lesion was histopathologically proven to be Edmonson-Steiner III grade with hematoxylin-eosin (H&E) staining at 200×magnification (G). Prominent microvascular invasion was detected at 200×magnification with CD31 immunohistochemical staining (H).*

3. *Page 6, penultimate paragraph, and Table 1: "inter-and intraobserver viabilities" – did you mean "inter- and intraobserver variabilities"?*

Author's response:

Thank you for your careful review on our manuscript. We have changed *"inter-and intraobserver viabilities"* which appeared on page 6 and in Table 1 of our previous manuscript to *"inter- and intraobserver variabilities"*.

4. *Minor Comment: Language polishing is necessary (perhaps changes were made by the authors after professional editing or they did not execute all the proposed corrections); e.g., "Approximately" (page 4), "distinct hemodynamic changes occur" (page 5), "located on the sinusoidal membraned of hepatocytes" (page 5), "composed of abnormally functioning hepatocyte" (page 8), etc.*

Author's response:

Thank you for your valuable suggestion.

Standard editing by American Journal Experts have been completed and all the proposed corrections were executed before submission of our original manuscript. Another native speaker was reached to make further language polishing of the revised manuscript. The odd expressions mentioned in your comment were changed and highlighted accordingly; e.g., *"Approximately" (page 4)* was altered to *"About"*, *"distinct hemodynamic changes occur" (page 5)* was altered to *"distinct hemodynamic changes take place"*, and *"composed of abnormally functioning hepatocyte" (page 8)* to *"with abnormally functioned hepatocytes"*. Other revisions of language without changing the meanings of sentences were made and highlighted in red in the revised manuscript.

Response to comments of reviewer # 01221925

Very interesting and thorough review of an important and challenging topic. The authors present a nice overview; however, the authors may wish to refrain from statements such as "Functional MRI techniques, including diffusion-weighted imaging (DWI), MRI with hepatobiliary contrast agents, perfusion imaging and magnetic resonance elastography (MRE) can provide further important information regarding tumor biological behaviors. ", as being able to predict the biological behavior of a tumor remains a challenge.

Author's response:

Thanks for this precious comment. Indeed, although functional MRI techniques can provide important information regarding tumor histologic grade, Ki-67 labelling index, microvascular

invasion or even the transporter OATP expression level of HCC, prediction of the tumor biological behavior remains one of the most challenging areas in liver imaging.

Therefore, according to your comment, we have altered the former expression "*Functional MRI techniques, including diffusion-weighted imaging (DWI), MRI with hepatobiliary contrast agents, perfusion imaging and magnetic resonance elastography (MRE) can provide further important information regarding tumor biological behaviors*" to "*Functional MRI techniques, including diffusion-weighted imaging (DWI), MRI with hepatobiliary contrast agents, perfusion imaging and magnetic resonance elastography (MRE) show promise in providing further important information regarding tumor biological behaviors*".

Response to comments of reviewer # 03253495

Well written review although some concerns on the novelty of the manuscript were raised during the revision process.

Author's response:

Thanks for this inspiring comment and the warm words. Several reviews regarding the imaging evaluation of HCC have been published recently. Compared with their works, we think that the novelty of our manuscript predominantly lies in the following aspects:

1. First, we conducted a systematically literature searched in current databases comprising Pubmed, Web of Science, EMBASE, Cochrane Library, Springer Link, Science Direct, and Google Scholar. The most recent and influential publications were included in our review. This searching and selection strategy ensured the comprehensiveness and in the mean time quality of our included studies.
2. Second, we provided an overview of the current state-of-the-art of noninvasive imaging evaluation of HCC in this review. Important basic concepts, with most recent data, about key alterations during hepatocarcinogenesis were illustrated in our manuscript to help readers better understand the correlations between imaging features and the underlying pathophysiological and pathological characteristics of HCC. This part is not usually well explored in other reviews.
3. Third, comparisons between the most widely used current guidelines of HCC management across different geographical areas were made in this review, which to our limited knowledge, haven't been very well reported elsewhere.

4. Finally, this review also explored the potential roles of noninvasive imaging modalities for the prognosis evaluation. Special emphasis was laid on the imaging prediction of microvascular invasion, which has drawn worldwide attention as an effective risk factor for poor patient survival.

Response to comments of reviewer # 02860622

Interesting study highlighting the difficulties in the management of this type of liver cancer.

Author's response:

Thank you very much for your careful review and this encouraging comment.

We would like to express our most sincere gratitude for your extraordinary help to polish our work. We have made substantial revisions according to your comment. We hope the above response can address your questions properly. If you have any further questions, please do not hesitate to contact us.

Best regards,

Bin Song