

ROUND 1

Response to the reviewers

Dear Editor and Reviewers:

Thank you for taking time out of your busy schedule to review this manuscript. These comments are valuable and very helpful. We have read through comments carefully and have tried our best to make corrections. Now we have carefully correct and re-edit the manuscript for this version.

Revisions in the text are shown using different labels.

We would love to thank you for allowing us to resubmit a revised copy of the manuscript and we highly appreciate your time and consideration.

Sincerely yours.

Qiong Chen

The instructions are as follows:

Reviewer 1#:

1. Abstract has several sentences that may be unclear or hard to follow. I cannot understand the “****” hospital.

Response: Thank you for these suggestions and examples, and we indeed apologize for these confusion made by the former version. We have re-wrote these sentences. For example, “Conventional ultrasonography combined with CEUS was adopted to analyze the echo, size, location, and enhancement characteristics of benign and malignant nodules, as well as the enhancement methods for HCC with different diameters.” in Abstract line 6-9. We also add the hospital’s name as “Xuhui Dahua Hospital”.

2. Unfortunately, the whole manuscript needs to be revised for the English language.

Response: We apologize for the poor language in this manuscript. We have re-written this manuscript and corrected hundreds of grammar mistakes, as you can see in all the manuscript.

3. Please be more precise in the provided classification in the diagnostic criteria session. For example, the CEUS findings were classified into four different categories: 1. the lesion area was slower wash-in, and the portal and delayed phases showed isoechoic enhancement, and washed out isochronously as with the liver parenchyma, namely the "slow-in and isochronous-out" type, this suggested a dysplasia nodule. 2.....etc. You must, also, provide the reference data for this classification.

Response: We agree. Thanks for this kind suggestion. We added the diagnostic criteria session "According to American College of Radiology (ACR) CEUS Liver Imaging Reporting and Data System (CEUS LI-RADS)", and we also cited two references here (Ref. 13 and 14). In clinic, actually, physicians usually judge the enhancement degree and the wash-in and wash-out time in different lesion area according to the comparison with the surrounding liver tissue. So this judgement and classification is, to some extent, subjective. We tried to add citations here.

4. Crucial information is missing in Table 1, like the.....etc.

Response: We thank the reviewer for the kind advice. Indeed, we ignored many risk factors here. So in Table 1, we added several risk factors including BMI, HBV, HCV, Alcohol, and so on, and also list the percentage and corresponding *P* value, seen in Table 1.

5. In Table 2, the variables were supposed to be presented as "n (%)". The percentage is missing. Statistically, non-significant p-values should be presented as "NS," not as ">0.005".

Response: In Table 2, We add the percentage and presented data as "n(%)". Also, in Table 1 and Table 2, we use "NS" instead of ">0.005" in groups with no significant difference.

6. Figure 3 is missing? Authors conclude that the smaller the HCC nodule, the later the contrast agent began to wash out. They further indicate that the HCC nodule size

was negatively correlated with the duration of enhancement of the contrast agent. However, as shown in Table 4, small size HCCs ($\leq 1\text{cm}$) had a more “typical” pattern than those of 1-2 cm [Fast-in and fast-out pattern: 5 (76.92%) vs. 33 (63.46%)]. Is there any explanation for this?

Response: Thank the reviewer for reminding us this information. We add figure 3 and figure 4 information in the text (page7: **Comparison of CEUS in different-sized HCC**). Also, in Table 4, there are some calculation mistakes. We have corrected these mistakes, *i.e.* 5 (38.46%) and 8 (61.54%).

Reviewer 2#:

1. The English language needs extensive revision. There are a lot of grammatical and spelling mistakes in the manuscript.

Response: We apologize for the poor language. We have thoroughly revised this manuscript and ask an English-native editor correct these grammar mistakes. As we have labeled all the revisions through this version..

2. The presentation of the methodology and results is sometimes confusing, I recommend adding a flow chart for their presentation and adding the outcome of the patients.

Response: Agreed. This suggestion is very informative and useful and we have added a new **figure.1, Study population flowchart**.

3. Could you elaborate more on the current HCC guidelines and their limitations, and the CEUS studies performed in this area? Materials and methods: • The authors didn't mention how they diagnosed the dysplastic transformation and the HCC transformation? By biopsy or by CT triphasic, etc.?,

Response: Now, the diagnosis of HCC still depend on conventional imaging method such as enhanced CT or MRI, combined with AFP. These small liver nodules rarely display the radiological hallmarks of HCC. Delaying diagnosis until the development

of <2 cm nodules results in increased treatment failure or recurrence. The use of CEUS to monitor and diagnose small HCC may improve patient outcomes. So we intend to explore some potential imaging features and clinical value of CEUS in diagnose liver nodules less than 2cm.

4. could explain the effect of this on the diagnostic yield? and AFP level? • Ref: Diagnostic Accuracy of CEUS LI-RADS for the Characterization of Liver Nodules 20 mm or Smaller in Patients at Risk for Hepatocellular Carcinoma. Jia-Yan Huang, Jia-Wu Li, Qiang Lu, Yan Luo, Ling Lin, Yu-Jun Shi, Tao Li, Ji-Bin Liu, and Andrej Lyshchik. Radiology 2020 294:2, 329-339.

Response: Thank the reviewer for the kind suggestion. We have added this citation here and cited this criteria, seen in page 5 bottom.

5. In the inclusion criteria the authors mentioned “increase in one of combined indicators of HCC (AFP or a new HCC marker Glypican-3), but imaging examination showed no space-occupying lesions”>> but if there is no space occupying lesions how did you include for hypoechoic nodules in the first place? This statement means that the AFP was high with no ultrasound findings, then why did you include? Kindly explain

Response: Thank the reviewer for this kind advice. For the patients with high AFP, we think this is a high-risk factor. In the long-term follow-up, if liver nodules are found, these cases would be included in the further study. There were also individuals who had never found with liver nodules, and their AFP also fell back to normal. These patients are not included in the further study.

6. In the results section the authors mentioned “Of the 93 patients who underwent surgery and needle biopsy”>> why a cirrhotic patient with nodular lesion of <2 cm undergo a liver biopsy?? Could you explain the reason for biopsy and why did a surgical team do it? Not radiology or gastroenterology? And if that mean excision not just biopsy (as figure two shows a specimen of 5 cm)?

Response: We agree. Indeed, we are sorry for the vague statement. Actually, we suggest that patients with high suspicion of HCC, such as some LR-3, LR-4 and LR-5 according to CEUS LI-RADS, were treated with puncture and then surgery. Regarding to the figure 3 and figure 4, they are pictures of clinical specimen after surgical resection. In order to reduce the possibility of tumor implantation and recurrence, the resection margin should be obviously larger than the diameter of the nodule. Generally, the biopsy was performed by physicians in Ultrasound & Intervention Department. Once HCC was confirmed by pathology, the patients should underwent surgery.

7. Most parts of the discussion could be added to the introduction. • Please focus in the discussion on the explanation of your results, and the comparison with other studies done in the same area and their diagnostic accuracy yield versus yours.

Response: Thank the reviewer for this kind suggestion. We have revised although the manuscript and re-wrote a lot of paragraphs. We tried our best to make the discussion clear and incisive. We are very glad and to receive all the comments of the reviewers, and we are also willing to make further changes to improve the quality of this manuscript.

Response to Editor-in-chief and Science Editor:

In this new version, we have corrected a lot and tried our best to improve the quality. Also, we ask English-native editor polish this manuscript. So we are confirmed that this version should be much much better than the last one, no matter in grammar mistakes, or accuracy of expression.

We have added the statement and documents in this new version according to the requirements in the journal's Guidelines for manuscript type and related ethics. We have checked this manuscript and changed the form of Table 1 into a three-line table.

Very much appreciated for these kind suggestions. If there are some new problems, please let me know with no hesitation.

With regards,

Qiong Chen

ROUND 2

Reviewer 1#: Please add explanations mentioned in the answers to reviewer 2 in questions (5 and 6) to your discussion. Also, kindly modify (mo) to months in your manuscript

Response: Dear Editor, Hope you are doing well. We authors are very glad to receive the messages from editorial board. In this version, we have checked thoroughly and revised some errors in the manuscript according to reviewer's comment. We have added the Figure 2 information in the part of Results (Comparison of CEUS in different-sized HCC). Also, we have modified (mo) to months in this manuscript and added the answers to reviewer 2 in questions (5 and 6) to the Discussion part (Para 4). We are looking forward to hearing from you again. If there are some new problems, please take no hesitation to contact me. Very much appreciated for your kind help. With regards. Qiong Chen