

Thank you very much for your letter and advice on our manuscript. We have resubmitted new version of paper accordance with recommendations of science editor. We have addressed the comments raised by the peer reviewers, and the amendments are highlighted in red in the revised manuscript. We hope that the revision is acceptable and look forward to hearing from you soon.

With best wishes.

Below, please find the comments in black, followed by our responses in red. Exact changes in the manuscript are also presented in red font.

**(1) The title is too long, and it should be no more than 18 words**

Thank you for your valuable advice. Too long title will reduce reading experience. Therefore, we subtract unnecessary description and change the title to "A novel model combined contrast-enhanced ultrasound with serology predicts hepatocellular carcinoma recurrence after hepatectomy".

**(2) 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).**

Thanks for the editor's reminder. Due to our negligence, we did not upload the grand approval document. In this revision process, we will upload the grand approval document, and highlight the relevant information of the grand in the document, facilitating review. Grand approval document contains two parts, one is the description of grand information uploaded in PDF format, the other is the grand code uploaded in Excel format our grand is located in row 304, and the grand number is "2019QH1302".

**(3) 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.**

Thanks for the editor's reminder, we have uploaded the original data of all the pictures with PPT format. We found that the six pictures had different size, however the PowerPoint only allow uniform size. For showing all original pictures, the size were suitable for Fig5 and Fig6 , but it was too large for other picture, we had worked for a long time to resolve this bug, unfortunately we failed. If needed, we can upload original picture in PPT format separately. As the same time, we uploaded the original pictures in PDF format to **Supplementary Material**, that is may be helpful for editor, PDF format can be edited by Adobe Illustrator software.

**(4) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.**

We are very sorry for our negligence in ignoring such an important content and adding a burden to your work. We have added highlight to the article. Our highlight are below:

**Background**

Surgery is the main treatment for hepatocellular carcinoma (HCC). However, 30% - 50% of patients recurrence within 2 years, which is the main cause of death.

## **Motivation**

Screening patients with high recurrence risk plays an important role in making reasonable clinical decisions.

## **Objectives**

Utilizing contrast-enhanced ultrasound (CEUS) liver imaging reporting and data system (LIRADS) and serology biomarkers, construct a non-invasive prediction model predict the early recurrence of HCC, and verified the model.

## **Method**

Collecting one pilot patients' information, dividing them into early recurrence (ER) and non-early recurrence (n-ER) group, appropriate statistical methods was applied for discovering ER hazard factor. Then construct a non-invasive prediction model, named CEUS model, predict 6 months, 12 months, 24 months recurrence. Calculate every patient score, and divided them into high risk and low risk according to appropriate cut-off value, compared their Kaplan-Miere curve. Lastly, verified the model.

## **Result**

Tumor diameter, preoperative alpha-fetoprotein (AFP) level, and LIRADS are independent hazard factor, the HR was 1.123 (95%CI: 1.041-1.211), 1.547 (95%CI: 1.245-1.922), 1.428 (95%CI: 1.059-1.925) separately. A nomogram based on them was constructed, the cut-off value of 6 months, 12 months and 24 months was 100,80,50 separately, the C-index was 0.748 (95%CI: 0.683-0.813), 0.762 (95%CI: 0.704-0.820), 0.762 (95%CI: 0.706-0.819) separately. the calibration at 6 months was desirable; however, the calibration at 12 and 24 months should be improved.

## **Conclusion**

The CEUS model can screen out patients who had high recurrence risk, it's helpful for making reasonable treatment strategy.

## **Perspective**

We hope that in the future, we can conduct a multi-center study, with an expanded sample size and prospective verification.

(5) Self-cited references: There is 1 self-cited reference.

Thanks to the editor for reminding us that due to our negligence, we made a stupid mistake. The 29th reference in our original manuscript was published in WJG. Now we have replaced it with an article published in other journal.

(6) Language evaluation: Classification: Grade B and Grade A. A language editing certificate issued by KG Support Limited was provided.

We apologize for the poor language of our manuscript. We worked on the manuscript for a long time and repeated addition and removal of sentences and sections obviously led to poor readability. We have now worked on both language and readability and have also involved native English speakers for language corrections. We really hope that the flow and language level have been substantially improved and can meet the requirements of published this time.

**Below are answer for peer-review comments**

Reviewer 1: The limitations of the study and its findings as follows: Data authenticity of the cases included in the manuscript, how to avoid data errors caused by respiratory phase in quantitative analysis of CEUS.

This is a very good question. If you can ask this question, it means that you are very familiar with radiology examination methods. Enhanced CT and enhanced MRI examination need patients to have good respiratory cooperation, otherwise it is easy to cause respiratory artifacts, especially in enhanced MRI examination. There are some differences between ultrasound and them. Ultrasound can observe the lesions in real time. As long as the patient's breathing range is not very large, it will not affect the observation of the lesions. We also conduct breathing training for patients before examination, so that they can cooperate with our examination, so breathing will not lead to the misevaluation of CEUS LIRADS.

Reviewer 2:

(1) Please tell me the reason why you select AFP to monitor recurrence after surgery.

This is a very good question. From your question, we can see that you have profound knowledge in the study of serology indicator of HCC. In this study, AFP was selected as the main research target, mainly attributed to the following aspects: (1) AFP is usually used as the main tumor marker of HCC, although the specificity is not the highest, but the sensitivity is good. As the main indicator of monitoring HCC, AFP can not only be used as an important evidence for detecting HCC, but also has a close relationship with prognosis after operation. Therefore, AFP is the most familiar index in clinical work<sup>[1]</sup>. However, there are relatively few studies combined CEUS with AFP for predicting recurrence. (2) AFP is a routine inspection project in our hospital, it's convenient for us to collect data. (3) In the published articles that focused on prediction, AFP was used as routine indicator<sup>[2]</sup>, thus we chose AFP as the research indicator.

(2) Does AFP react more sensitively to post-treatment recurrence of liver cancer than other biomarkers ( DCP, AFPL3)?

This is a good question, as we know AFP, AFP-L3, DCP are widely used as tumor markers for the diagnosis of HCC. In this article, we had not compared the three markers, we search some published articles for your question. In the study of preoperative monitoring, Choi's research showed AFP has the highest accuracy<sup>[3]</sup>, but in Qi's research DCP showed the highest accuracy<sup>[4]</sup>. In terms of postoperative monitoring, Zhang's study showed that the lower the AFP-L3 level, the better the prognosis<sup>[5]</sup>. In a curative ablation research showed that AFP > 100 ng/mL and AFP-L3 > 15%, both pre- and post-ablation, were significant predictors for HCC recurrence<sup>[6]</sup>. Tomoki's research showed that both double- and triple-positive tumor markers are associated with early recurrence and poor survival in HCC patients within the Milan criteria and Child-Pugh class A<sup>[7]</sup>. Positive preoperative AFP-L3 and continuously positive or negative-turn-positive AFP-L3 results after surgery predicted a more aggressive tumor behavior, higher tumor recurrence, and poorer clinical outcomes<sup>[8]</sup>. In recent study, AFP and AFP-L3 may show high value for predicting recurrence.

- [1] Koch C, Bette T, Waidmann O, et al. AFP ratio predicts HCC recurrence after liver transplantation[J]. PLoS One, 2020, 15(7): e0235576. doi: 10.1371/journal.pone.0235576
- [2] Ji GW, Zhu FP, Xu Q, et al. Radiomic Features at Contrast-enhanced CT Predict Recurrence in Early Stage Hepatocellular Carcinoma: A Multi-Institutional Study[J]. Radiology, 2020, 294(3): 568-579. doi: 10.1148/radiol.2020191470
- [3] Choi J, Kim GA, Han S, et al. Longitudinal Assessment of Three Serum Biomarkers to Detect Very Early-Stage Hepatocellular Carcinoma[J]. Hepatology, 2019, 69(5): 1983-1994. doi: 10.1002/hep.30233
- [4] Qi F, Zhou A, Yan L, et al. The diagnostic value of PIVKA-II, AFP, AFP-L3, CEA, and their combinations in primary and metastatic hepatocellular carcinoma[J]. J Clin Lab Anal, 2020, 34(5): e23158. doi: 10.1002/jcla.23158
- [5] Zhang XF, Yin ZF, Wang K, et al. Changes of serum alpha-fetoprotein and alpha-fetoprotein-L3 after hepatectomy for hepatocellular carcinoma: prognostic significance[J]. Hepatobiliary Pancreat Dis Int, 2012, 11(6): 618-623. doi: 10.1016/s1499-3872(12)60234-3
- [6] Tateishi R, Shiina S, Yoshida H, et al. Prediction of recurrence of hepatocellular carcinoma after curative ablation using three tumor markers[J]. Hepatology, 2006, 44(6): 1518-1527. doi: 10.1002/hep.21408
- [7] Ryu T, Takami Y, Wada Y, et al. Double- and Triple-Positive Tumor Markers Predict Early Recurrence and Poor Survival in Patients with Hepatocellular Carcinoma within the Milan Criteria and Child-Pugh Class A[J]. J Gastrointest Surg, 2017, 21(6): 957-966. doi: 10.1007/s11605-017-3394-1
- [8] Zhang XF, Lai EC, Kang XY, et al. Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein as a marker of prognosis and a monitor of recurrence of hepatocellular carcinoma after curative liver resection[J]. Ann Surg Oncol, 2011, 18(8): 2218-2223. doi: 10.1245/s10434-011-1613-7