Dear editor and reviewer,

Thank you very much for your comments concerning our manuscript entitled " Radiomics Signature: A Potential Biomarker for β-Arrestin1 Phosphorylation Prediction in Hepatocellular Carcinoma " (Manuscript NO.: 73077, Retrospective Study). Your comments are all valuable and have guiding significance for revising and improving our paper. We have studied comments carefully and have made a correction which we hope to meet with approval. Revised portions are marked in red in this paper. The main corrections in the paper and the responses to the comments are as follows.

Reviewer #1

1. Feng C et al provided an interesting retrospective study on the role of radiomics as a marker of β-Arrestin1 Phosphorylation in HCC. The manuscript is well written and the reading enjoyable. I do have a concern regarding the methodology of the study and the selection of patients. The authors included only patients undergoing therapy with sorafenib as an adjuvant therapy after hepatic resection, and tested the CRR model not only for the prediction of β-Arrestin1 Phosphorylation but also for the prediction of overall survival. This is something the model was not built for (and less interesting, as the prognosis is related to the presence to β-Arrestin1 Phosphorylation that can be assessed on the specimen, making a preoperative model is useless in this setting).

Response:

Thank you very much for your advice. As you mentioned that we included patients treated with sorafenib after hepatic section, and build the CRR model for β-arrestin1 phosphorylation prediction. Then we compared the overall survival according to the CRR model prediction results by log-rank test, and found that β-arrestin1 phosphorylation positive patients predicted by the model live longer than the β-arrestin1 phosphorylation negative patients predicted by the model. Actually, we just compared the overall survival between the β-arrestin1 phosphorylation positive and the β-arrestin1 phosphorylation negative patients predicted by the CRR model. The aim of our study is to build a model for β-arrestin1 phosphorylation prediction and we also compared the outcome between the two groups predicted by the model to further testify

the prognosis value of β-arrestin1 phosphorylation in HCC patients. Thanks for the reminder which lets us notice that our description may mislead the readers, we modify the content in the first paragraph of the discussion section into a more appropriate “In addition, in patients treated with sorafenib, we found that p-β-arrestin1-positive HCC patients predicted by the CRR model were associated with better prognosis. The CRR model may serve as a noninvasive and effective tool to predict HCC patients β-arrestin1 phosphorylation status and help select patients who are suitable for sorafenib treatment.” to express the purpose of the study more clearly.

Reviewer #2

1. This is a well-written and interesting article examining the role of radiomics as a potential biomarker for β-Arrestin1 phosphorylation prediction in patients with Hepatocellular Carcinoma. Although MVI was analyzed in your study, no mention of this previous paper that created a radiomics normogram to help predict MVI. Please reference this in your paper. Could this normogram have affected your results? Ma X, Wei J, Gu D, Zhu Y, Feng B, Liang M, Wang S, Zhao X, Tian J. Preoperative radiomics nomogram for microvascular invasion prediction in hepatocellular carcinoma using contrast-enhanced CT. Eur Radiol. 2019 Jul;29(7):3595-3605. doi: 10.1007/s00330-018-5985-y. Epub 2019 Feb 15. PMID: 30770969. Another paper on Radiomics and MVI prediction also includes: Xu X, Zhang HL, Liu QP, Sun SW, Zhang J, Zhu FP, Yang G, Yan X, Zhang YD, Liu XS. Radiomic analysis of contrast-enhanced CT predicts microvascular invasion and outcome in hepatocellular carcinoma. J Hepatol. 2019 Jun;70(6):1133-1144. doi: 10.1016/j.jhep.2019.02.023. Epub 2019 Mar 13. PMID: 30876945. I see you referenced: Wang W, Gu D, Wei J, Ding Y, Yang L, Zhu K, Luo R, Rao SX, Tian J, Zeng M. A radiomics-based biomarker for cytokeratin 19 status of hepatocellular carcinoma with gadoxetic acid-enhanced MRI. Eur Radiol. 2020 May;30(5):3004-3014. doi: 10.1007/s00330-019-06585-y. Epub 2020 Jan 30. PMID: 32002645. Can you discuss how combing these 2 studies may help clinicians in the future? Please explain why you did not include this analysis in your study and how future studies combing findings from both your study and this one may help clinicians.

If the authors believe that a study of this kind would not be beneficial, please explain why.

Response:

Thank you for this reminder and suggestion. According to your advice we add the two references in the third paragraph of introduction section, referenced #21,24, to further explain the predictive value of radiomics. As you mentioned how the article about a radiomics-based biomarker for cytokeratin 19 status of HCC we referenced and our study may help clinicians, on the one hand the use of noninvasive method of radiomics can enhance the communication with patients of target molecular expression without biopsy or surgery. On the other hand, most patients recommended for systematic treatment are not candidates for surgery due to their poor condition, thus our study provides a potential way to help identify patients who are more sensitive for targeted drug and guide clinical management. As you asked why we did not include this analysis in our study, our study focus more attention on the radiomics prediction of β-arrestin1 phosphorylation and highlight the function of β-arrestin1 phosphorylation in the occurrence and development of HCC and its influence in sorafenib treatment to specify the aim of our study. We analysis its clinical significance as you can see in the final part of the conclusion section as “This finding suggests that CT radiomics may provide promising and noninvasive biomarkers for the evaluation of p-β-arrestin1 expression and may help identify the subset of HCC patients who are more sensitive to sorafenib treatment, thus potentially guiding personalized treatment strategies.”. According to your advice we add more analysis in the third paragraph of discussion section in our revised manuscript as “Our study investigates the predictive aspects of computational-assisted models for the preoperative prediction of β-arrestin1 phosphorylation status, which currently can now only be attained by invasive biopsy or surgery. This computational method can guide clinical management by identifying patients for targeted therapy, as most patients recommended for systematic treatment according to the Barcelona Clinic Liver Cancer algorithm are not candidates for surgery due to their poor condition” to better emphasis how our study may help with clinicians in future clinical practice.

Thank you again for your professional and carefully comment.

We would like to express our most sincere gratitude for the carefully, patiently, and constructive comments. They are extremely helpful for our work. We have made substantial revisions according to these comments. We sincerely hope that this revision will meet the expectations of the reviewer and the above responses can address all the questions properly. If you have any further questions, please do not hesitate to contact us.

Best regards.

Sincerely,
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China