June 12, 2022

Dear editors and reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "A preoperative contrast-enhanced CT-based radiomics model for survival prediction in hepatocellular carcinoma" (Manuscript NO.: 77205, Retrospective Study).

Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewers' comments are described as follows.

I'm very sorry to trouble you so much.

Thank you very much again for your consideration.

Sincerely,

Weijia Liao

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Responds to the reviewer's comments:

Reviewer #1: Reviewer's comments Authors have made radiomics based model for survival prediction in HCC. It includes AFP and NLR. I have few comments. 1. Though additional file 1 has been given, but I feel it inadequate. The radiomics features have been given in a coded language, they should be explained as what these 7 features mean. 2. Is this a unique software which pertains to single MRI machine model specified to a manufacturer or the software is generalized. This should also be explained.

Comment 1: Though additional file 1 has been given, but I feel it inadequate. The radiomics features have been given in a coded language, they should be explained as what these 7 features mean.

Response: Thanks for your comments. We have improved the additional file 1 with the description of the selected radiomics features. All details were collected from Pyradiomics official website.

Comment 2: Is this a unique software which pertains to single MRI machine model specified to a manufacturer or the software is generalized. This should also be explained.

Response: It has been reported[1-3] that Pyradiomics can extract radiomic data from medical imaging (such as CT, MRI, PET). It is a generalized software for radiomics analysis.

Reviewer #2: This study has implications for predicting overall survival in patients with hepatocellular carcinoma. In general, the abstract, background, methods, results and statistical methods are described in detail and clearly. Please add the ratio between training group and verification group. There was no consistent analysis of the ROI delineated by different people. The topic of the study was survival prediction, and the follow-up mentioned progression-free survival, but the results only included the overall survival. Please describe in detail the methods used to predict patient survival based on TNM staging. Although there is no external validation, if there are prospective data results, the results of the study will be more convincing. And the proportion between the training group and the verification group The shortcoming is that the logical structure of the discussion section is a little confused. I suggest that the author briefly describe the main methods and important results of the experiment in the first paragraph. Next, the innovation of this study and the significance of this field are discussed. Then the significance of AFP.NLR and omics score for OS prediction is discussed. Finally, the value of the model established in this study was highlighted by comparing the results of OS prediction between the model established in this study and TNM and BCLC staging system.

Comment 1: Please add the ratio between training group and verification group.

Response: Thank you for your comments. The ratio between training cohort and validation cohort was added.

Comment 2: There was no consistent analysis of the ROI delineated by different people.

Response: The ROI was semi-automatically delineated and manually corrected, and reviewed independently by two blinded radiologists with 7 and 8 years of experience. In case of disagreement between the two reviewers, a third radiologist was consulted to reach a consensus. It has been reported that semi-automated approaches reduce inter-observer variability[4]. Previous studies[3,5] have critically reviewed the ROI, and the consistent analysis was omitted. Thus, although the consistent analysis wasn't

performed in our study, but the ROI was highly credible due to the rigorous review.

Comment 3: The topic of the study was survival prediction, and the follow-up mentioned progression-free survival, but the results only included the overall survival.

Response: The topic of our study was revised to "overall survival prediction".

Comment 4: Please describe in detail the methods used to predict patient survival based on TNM staging.

Response: Patients were categorized into grade I, grade II, grade III and grade IV according to TNM staging system. We have modified the corresponding part of the method section.

Comment 5: Although there is no external validation, if there are prospective data results, the results of the study will be more convincing.

Response: Our study was a single-centre retrospective study. Lacking of external data could be a major limitation of single-centre studies. Therefore, more patients from other centres are needed to further validate this prognostic model. This limitation was described in the discussion section.

Comment 6: The shortcoming is that the logical structure of the discussion section is a little confused. I suggest that the author briefly describe the main methods and important results of the experiment in the first paragraph. Next, the innovation of this study and the significance of this field are discussed. Then the significance of AFP.NLR and omics score for OS prediction is discussed.

Response: Thank you for your opinion. We have modified the discussion section according to your suggestion.

Once again, thank you very much for your comments and suggestions.

References

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