March 3, 2023

Dear Editor-in-Chief,

Thank you very much for giving us the opportunity to address the reviewers' comments by submitting a revised version of our manuscript (NO: 81639, Minireviews) entitled "Radiomic advances in the Transarterial chemoembolization (TACE)-related therapy for hepatocellular carcinoma" for your favorable consideration for publication in the **World Journal of Radiology**.

Following the extensive and insightful comments and suggestions made by the reviewers and Editorial Board, now we have revised the manuscript and provided clarifications/suggestions as suggested by the reviewers. The point wise answers to comments are also provided below for your consideration. The manuscript has been revised accordingly and I hope the revised manuscript would be acceptable for publication in your esteemed journal.

We are looking forward to hearing from you.

Yours Sincerely,

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Responses to Reviewer's Comments:

Reviewer #1

1. Page 4. The authors documented the results reported by Kuang Y, et al [8]. The nomogram combined with radiomics and clinical model showed predictive potential for postoperative response to TACE. The authors should describe what responses were shown to be predictive by the nomogram.

Answer: Thanks for the reviewer's comments. We have added to this paragraph a description of the predictors that influence response to TACE treatment. The authors evaluated TACE response in patients with liver cancer by using the the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Images (enhanced CT/MR) were analyzed 3/4 months after the first TACE treatment in all patients. All patients were divided into good response group (CR+PR) and poor response group (SD+PD). Radiomics selected the image features using the minimum absolute contraction and least absolute shrinkage and selection operator (LASSO) regression and the maximum correlation-minimum redundancy (mRMR) algorithm, and then selected 11 of the best subsets of features based on the arterial phase to calculate the radiation score. The clinical model based on T2WI was ultimately developed by combining platelet count (PLT), pseudocapsule, border, and peritumoral augmentation, and well-response was suggested by a normal PLT value, pseudocapsule, and obvious border on the T2WI sequence. Another clinical model based on DCE-MRI arterial phase (AP) was developed by combining Child-Pugh class, border, and peritumoral augmentation. Low Child–Pugh class (class A), clear border, and no peritumoral enhancement on AP all point to well-response. Clinics models and Radiomics were obtained which could predict the postoperative response of TACE, and the maximum AUC value were 0.76, 0.78 respectively. When combining Clinics

models with Radiomics models, predictive power peaked at 0.84. The T2WI-Nomogram and AP-Nomogram were the models with the highest clinical decision effectiveness, according to a comparison of each model's clinical decision effectiveness. (Page 6 line 3-Page 7 line 10).

2. Page 5. The authors described about the report by Meng XP, et al [16]. The present article seems important. Therefore, the authors should describe their results very easily to understand. How was the Radiomics important as a prognosticator?

Answer: Thanks for the reviewer's comments. We agree to amend this paragraph of the article and describe it in detail. By comparing the CRC model with the existing 7-medium survival prediction model, the author found that the CRC model showed better prediction performance. A radiomics signature (Rad-signature) for survival was constructed using the least absolute shrinkage and selection operator method in the training cohort. The author used univariate and multivariate Cox regressions to identify associations between the Rad- signature and clinical factors of survival. From these, a CRC model was developed, validated, and further compared with previously published prognostic models, including four-and-seven criteria, six-and-twelve score, hepatoma arterial-embolization prognostic scores, and albumin-bilirubin grade. The CRC model incorporated two variables: The Rad-signature (composed of features extracted from intra- and peritumoral regions on the arterial phase and portal venous phase) and tumor number. The authors created customized risk scores by linearly combining the rad score and the number of tumors (<4 vs.≥4), weighted by their respective coefficients in the multivariate Cox regression model, in order to aid clinical practice. Patients were separated into two groups based on their median risk scores for the training cohort (0.0214): stratum 1, with a risk score of <-0.0214, and stratum 2, with a risk score of >-0.0214. In the training cohort, stratum 1 patients had a considerably longer median survival (31.3 months) than

stratum 2 patients (12.5 months), with a hazard ratio of 3.63 (95% CI 2.36-5.60, log-rank test P<0.0001). For the test cohort Applying the same cutoff to the testing cohort: the hazard ratio was 2.43 (95% CI 1.91-4.98, P=0.0014), and the median survival for the two groups was 30.9 and 17.0 months, respectively. The CRC model showed improved survival predictive performance, and researchers believe that the CT radiomics signature represents an independent biomarker of survival in patients with HCC undergoing TACE. (page7 line27-page8 line6, page8 line 15-page 8 line 30)

3. Page 6. The authors discussed about the report by Kong C, et al [19]. The authors summary of the manuscript also seemed difficult to understand the results. The authors should show the results easily understandable.

Answer: Thanks for the reviewer's comments. We agree to amend this paragraph of the article and describe it in detail. The authors aim to evaluate the effectiveness of radiomics features based on preoperative contrast-enhanced computed tomography (CECT) in predicting response to transarterial chemotherapy (TACE), categorized 111 patients with intermediate HCC who received CECT in the arterial phase and venous phase before and following TACE into objective response group (n = 38) and non-response group (n = 73) groups. Radiomics feature extraction from CECT pictures. The best monophasic radiomics features of AP and VP in the training set were discovered using two feature ranking methods and three classifiers. In parallel, decision level fusion and feature level fusion were used to combine the pictures of the two CECT phases and establish the multiphase radiomics properties. For AP signature, the combination of MRMR and SVM showed the best performance (AUC=0.814). For VP signatures, the best performance was obtained by MRMR and LASSO (AUC=0.861). For the performance of multiphase radiomics signatures, DLF signatures had the highest AUC value of 0.883 among all radiomics signatures by using the features selected by MRMR and SVM classifiers. Eventually, a

nomogram was constructed by combining two common features (tumor size and tumor number) and radiomics signature, using multivariate logistic regression, and its predictive ability was assessed by AUC on the test dataset. To determine the accuracy, sensitivity, and specificity values, the cut-off point closest to the upper left corner of the training ROC was used. Scores below or above the cutoff were considered either objective-response or non-response. It was discovered that multiphase radiomics features (AUC = 0.883) outperformed the best single-phase radiomics signature (AUC = 0.861) in predicting response to TACE treatment. The nomogram in test dataset and training dataset showed better performance than any radiomics signatures. The authors conclude that the radiomic model will be helpful in assessing the therapeutic advantages of TACE treatment. (page9 line12-page10 line10)

Reviewer #2

1. This topic is considered new and has many nomenclatures that have been mentioned without explanation or hint about it.

Answer: Thanks for the reviewer's comments. This part of the content has been corrected, many nomenclature mentioned in the article have explained accordingly.

2. In order for anyone who is going to read such review article to understand this new topic, it should be written in simplified and illustrated manner. Although this topic about radiomics, there is no single figure, image or illustration to show how it looks like, how it is designed.

Answer: Thanks for the reviewer's comments. An illustration is added to explain the basic process of imagomics.

3. The introduction was mainly about HCC and TACE and very short regarding radiomics. There should be a section to explain the basics of radiomics and the words used in this issue.

Answer: The article has been added to explain the fundamentals of imagomics and the terminology used in this issue (Page 4, line 9-Page 5, line 20).

4. Page 5: HAP score, mHAP score, mHAP-II score, mHAP-III score and ALBI grade for arterial embolization of liver cancer. These abbreviations should be written complete first.

Answer: These abbreviations have been supplemented with full names. Hepatoma arterial-embolisation prognostic (HAP score), modified hepatoma arterial embolization prognostic (mHAP score), modified hepatoma arterial embolization prognostic II (mHAP-II score), modified hepatoma arterial embolization prognostic III (mHAP-III score) and albumin-bilirubin (ALBI) grade (Page 7, line 22-page 7, line 26).

5. Page 6: The modified solid tumor response assessment criteria (mRECIST) Should be the modified Response Evaluation Criteria in Solid Tumors

Answer: Modified solid Tumor response Evaluation Criteria (mRECIST) has been revised to modified Response Evaluation Criteria in Solid Tumors (Page 6, line 8). Where mRECIST appears in the rest of the text, the abbreviation is used instead.