Peer Review File

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Reviewer A

Comment 1: The use of the term “machine learning”
Reply 1: Thank you for pointing this out. In the process of constructing the radiomics model, we used the method of machine learning, such as maximum relevance minimum redundancy algorithm (mRMR). As recommended, we have added it in methods of abstract (page2, lines 35-36)
“The minimum redundancy maximum relevance algorithm (mRMR) and Recursive feature elimination (RFE) were used for feature selection.”

Comment 2: The necessity for predicting RRM2 expression by using CT radiomics.
Reply 2: We appreciate the reviewer’s careful review of our manuscript. Radiomics is a field of study that aims to extract quantitative imaging features from radiological images for use in disease characterization. Radiomic features capture high-dimensional quantitative phenotypes in imaging data that are beyond what a radiologist can normally perceive via visual assessment. Radiomics were reported to predict molecular classification of many disease outcomes. Quantitative radiomics has shown the potential to be used as non-invasive imaging biomarkers to characterize tumor-s diagnosis, progression/prognosis, and treatment response [Sun R, Limkin EJ, Vakalopoulou M, Dercle L, Champiat S, Han SR, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. Lancet Oncol. 2018;19(9):1180–91. https:// doi.org/10.1016/S1470-2045(18)30413-3.]

Comment 3: My third major concern is the “can be predicted accurately through radiomics features” in the conclusion, as reported by the authors the ROC for 5-year survival is only 0.729.
Reply 3: We appreciate the reviewer's encouragement and helpful comment. This study is an exploratory study of imaging omics, and the constructed model has a good prediction effect: as shown in the ROC curve, the AUC value of the ROC curve of the whole tumor model is 0.776; The AUC value of 50% cross verification is 0.763; The AUC of ROC curve of whole tumor and peritumor model was 0.803. The AUC value of 50% cross verification is 0.773; Calibration curve and Hosmer-Lemeshow goodness of fit test showed that the prediction probability of high expression of RRM2 was consistent with the true value ($P>0.05$). The DCA display model has clinical practicability.
In the previous published literature, it is common to find a model with an AUC value of less than 0.75 for the prediction model ([1].An C, Kim DW, Park YN, Chung YE, Rhee H, Kim MJ. Single Hepatocellular Carcinoma: Preoperative MR Imaging to

Predict Early Recurrence after Curative Resection. Radiology. 2015. 276(2): 433-43; [2]. Liao H, Zhang Z, Chen J, et al. Preoperative Radiomic Approach to Evaluate Tumor-Infiltrating CD8+ T Cells in Hepatocellular Carcinoma Patients Using Contrast-Enhanced Computed Tomography. Ann Surg Oncol. 2019. 26(13): 4537-4547; [3]. He M, Zhang P, Ma X, He B, Fang C, Jia F. Radiomic Feature-Based Predictive Model for Microvascular Invasion in Patients With Hepatocellular Carcinoma. Front Oncol. 2020. 10: 574228). These studies all point out the direction for further exploration.

Comment 4: The fourth major concern is no external validation sample to validate the nomogram.
Reply 4: This study is an exploratory study of imaging omics, and we will add validation in future studies.

Comment 5: The abstract needs further revisions.
Reply 5: We have modified our text as advised.
Changes in the text: Page 1-2, line 25-51
"Radiomics can be used to noninvasively predict molecular markers to address the clinical dilemma that some patients cannot accept invasive procedures."
", which were utilized for prognosis analysis, radiomic feature extraction and model construction, respectively. The minimum redundancy maximum relevance algorithm (mRMR) and Recursive feature elimination (RFE) were used for feature selection."
"Receiver operating characteristic (ROC) curve analysis was employed to assess the model performance. Clinical utility was determined by decision curve analysis (DCA)."

Comment 6: The introduction needs further revisions.
Reply 6: We have modified our text as advised.
Changes in the text: Page 3-4, line 60-100
"Overexpression of *RRM2* enhances the proliferation and migration ability of Hep3B and Huh7 cells(8)."
"Radiomics is an emerging field of research aimed at extracting quantitative imaging features from radiological images for expression of disease signatures. These radiological features may not be detectable by the radiologist through visual assessment. It has been reported that radiomics can predict the molecular classification of many disease outcomes. Quantitative radiomics has shown potential as a non-invasive imaging biomarker to characterize tumor diagnosis, progression/prognosis, and treatment response."

Comment 7: Use a flowchart to briefly describe the research procedures of this study.
Reply7: We have modified our text as advised.
Changes in the text: Page 19, Figure 1

Reviewer B

Comment 1: The radiomics model was the crucial topic in the study. Please make a brief introduction.

Reply 1:We appreciate the reviewer's encouragement and helpful comment. We have modified our text as advised.

Changes in the text:Page 4, line 92-98

“Radiomics is an emerging field of research aimed at extracting quantitative imaging features from radiological images for expression of disease signatures. These radiological features may not be detectable by the radiologist through visual assessment. It has been reported that radiomics can predict the molecular classification of many disease outcomes. Quantitative radiomics has shown potential as a non-invasive imaging biomarker to characterize tumor diagnosis, progression/prognosis, and treatment response.”

Comment 2: In the introduction, it was better to add related reference (DOI: 10.21037/atm-22-6089) about RRM2.

Reply 2: We have modified our text as advised.

Changes in the text: Page 12, line 368

“It has been confirmed that *RRM2* is a potential biomarker in a variety of tumors (12-15).”

Comment 3: What were the roles of RRM2 in the process of HCC? Please state in the introduction.

Reply 3: We have modified our text as advised.

Changes in the text: Page 3, line 81-86

Comment 4: Why to choose whole tumor and whole tumor & peritumoral models? Please state in the part of results.

Reply 4: We have modified our text as advised.

Changes in the text: Page 10, line 296-301

“Marasco et al. studied the effect of excision margins on the recurrence rate of patients undergoing hepatectomy and found that a wide margin (> 1cm) had a better prognosis than a narrow margin (< 1cm), because micrometastases may exist around the 1cm tumor (11). Therefore, we believe that the establishment of whole-tumor and whole-tumor plus peritumoral models can better predict the prognosis of patients and the expression of some molecular markers.”

Comment 5: In constructing nomogram, how to determine the risk factors? Please state in the discussion.

Reply 5: We have modified our text as advised.

Changes in the text: Page 14, line 429-431

“Variables were obtained by the minimal Akaike information criterion (AIC)-based stepwise selection method.”

Comment 6: Missing experimental data was the biggest short board in the study. It was better to at least validate the expressions of RRM2 by experiments.
Reply 6: This study is an exploratory study of imaging omics, and we will add validation in future studies.

Comment 7: How about the mechanism of RRM2 on immune cell infiltration? Please supplement in the discussion.
Reply 7: We have modified our text as advised.
Changes in the text: Page 12, line 368-372
"expression of *RRM2* is strongly positively linked to infiltration of immune cells and immune checkpoint expression, the upregulation of *RRM2* mediated by *ncRNAs* correlates with poor prognosis and tumor immune infiltration of HCC (17)."

Comment 8: Compared to other predictive models, what were the advantaged of the constructed model in the study? Please state in the discussion.
Reply 8: We have modified our text as advised.
Changes in the text: Page 10, line 296-301; Page 13, line 396-400
"In this research, four features were screened out from 107 imaging features to construct a whole-tumor model, and a whole-tumor and peritumoral model was constructed using the same method considering micrometastasis and microinfiltration of immune-associated cells of the surrounding area of HCC，which was used less frequently in previous studies (21,22)."