Response Letter

Dear Editors,

Thank you very much for your consideration of our manuscript (*Manuscript NO.: 82118, Retrospective Study*) entitled *"Preoperative prediction of macrotrabecular-massive hepatocellular carcinoma through dynamic contrast-enhanced MRI-based radiomics"*.

We also thank the reviewers for the positive feedback and constructive suggestions. Accordingly, we have revised the manuscript. Point-by-point responses to the comments are listed at the end of this letter.

This revised manuscript has been proofread and corrected by *American Journal Experts*.

We hope that the revision is suitable for the publication in *World Journal of Gastroenterology*.

Look forward to hearing from you soon.

With best wishes,

Yours sincerely,

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Response to Reviewer 1 Comments

Point： Thank you for having the opportunity to review the manuscript entitled "Preoperative prediction of macrotrabecular-massive hepatocellular carcinoma through dynamic contrast-enhanced MRI-based radiomics".

Response: Firstly, we would like to express our sincere gratitude to the reviewer for your insightful comments. We have revised our manuscript according to your constructive suggestions, and we hope that these revisions can meet your requirements.

Point 1: Reference 9 appears to have been cited inappropriately. There is no consensus or internationally agreed guideline recommending avoiding liver transplantation in such patients. Moreover reference 9, on which the Authors base their statement, cites a study aimed at predicting the microvascular invasion in HCC patients through deep learning but with restrictive selection criteria not adequate to draw conclusions regarding liver transplantation for HCC (e.g. Child-Pugh only A, excluded all patients with locoregional or systemic treatments, …).

Response 1: Thank you very much for your careful review and constructive suggestion. We think you are referring to the original reference 8 "Prediction of Microvascular Invasion in Hepatocellular Carcinoma via Deep Learning: A Multi-Center and Prospective Validation Study. Cancers 2021; 13(10)". In the revised manuscript, we have deleted this reference and made the following changes, hoping to meet your requirements: "Early diagnosis and appropriate treatment of MTM-HCC are beneficial to prevent early recurrence and improve prognosis. Current studies have shown that radiofrequency ablation is not recommended for patients with aggressive HCC, while performing resection with wide margins or anatomical hepatectomy and shorter follow-up intervals may be recommended for monitoring[8, 9]. MTM-HCC shows an aggressive phenotype[10]. Therefore, an accurate preoperative diagnosis of MTM-HCC can provide the best individualized treatment plan. **(Introduction-the second paragraph)"**

Point 2: Reference 12 is cited in an inappropriate and highly misleading way. The Authors state that. “MRI has gradually become the mainstream of preoperative tumour evaluation” when the AASLD guidelines cited clearly report that: “2. The AASLD recommends diagnostic evaluation for HCC with either multiphasic CT or multiphasic MRI because of similar diagnostic performance characteristics. Quality/Certainty of Evidence: Low for CT versus MRI. Strength of Recommendation: Strong”. Moreover, the 2018 AASLD Imaging for the Diagnosis of Hepatocellular Carcinoma: A Systematic Review and Meta-analysis conclude that: “CT, extracellular contrast– enhanced MRI, or gadoxetate-enhanced MRI could not be definitively preferred for HCC diagnosis in patients with cirrhosis”. Therefore, it cannot be said that MRI is the preferred imaging method, in fact in the Western World the highly majority of HCC patients undergo CT rather that MRI imaging.

Response 2: Thank you very much for your professional suggestion. We intended to describe the application value of MRI in MTM-HCC, but through careful reading, we found that the original expression was indeed prone to misunderstanding. Therefore, we have made the related corrections in the revised manuscript **(Introduction-the third paragraph)** as follows: “With the development of imaging technology, successful applications of MRI have been reported in identifying the MTM-HCC subtype[11].”

Point 3: The clinical data included appear to be very limited, not taking into account the aetiology of the liver disease, if not for the HBV status, the severity of the liver disease, BCLC stage, …

Response 3: Thank you very much for your question. Based on a review of relevant literature, two recent articles were published in *Radiology* and *European Radiology*, which analyzed the clinical features in detail, including the aetiology of liver disease, BCLC stage, platelet counts and various serum markers, and found that AFP levels and platelet counts were independent predictors of MTM-HCC. Therefore, clinical features including previously

reported independent predictors (AFP levels and platelet counts), various serum tumor markers, and liver function indicators were included in the analysis in our study. In addition, our research focuses on the value of radiomics in the preoperative prediction of MTM-HCC. Therefore, the radiomics features and machine learning algorithms are emphasized in our study. Hope to meet the requirements of the reviewer and readers.

Point 4: It appears to be no mention of satellite nodules, biliary invasion and other relevant oncologic characteristics.

Response 4: Thank you very much for your constructive suggestions. We have added the pathological features, including Edmondson-Steiner grade, microvascular invasion, satellite nodules, and biliary invasion in the revised manuscript. The results showed that there were no significant differences in any of features between the training and test sets (P>0.05). In terms of the MTM-HCC and nMTM-HCC groups, Edmondson-Steiner grade were significantly different in the test set (P=0.048). Corrections have been found in the revised manuscript **(Materials and Methods-Pathological data Part, Results-Patient characteristics Part, and Table 1).**

Point 5: What do the Authors think are the clinical applications of their model that they mention in the conclusions? Which patients would have a different therapeutic strategy (and which ones) due to their observations" Do they think their results are sufficient to change the clinical practice and preclude some patients the present consensus preferred treatment due to their radiomics predictions and do the Authors consider it ethically sound?

Response 5: Thank you very much for your professional questions. In this study, we found that AFP (OR=10.066), tumour size (OR=3.316), rad-score (OR=2.923), and so on were significant independent predictors of MTM-HCC. For HCC patients with AFP > 400μg/L, tumor size > 5 cm, and rad score > -1.663, the likelihood of MTM-HCC was higher. Our study highlights the ability of preoperative contrast-enhanced MRI-based radiomics to

identify MTM-HCC subtype. The purpose of our study was to preoperatively predict MTM-HCC, and then guide patients to individual treatment according to the treatment strategies and the current preferred treatment methods that should be adopted for patients with this subtype. Of course, this is only a preliminary exploration of the radiomics on MTM-HCC, and is not enough to change clinical practice and the current consensus on preferred treatment. Therefore, the clinical application of the model has yet to be further verified by larger multi-center samples.

Response to Reviewer 2 Comments

Point: In brief: Methods: This retrospective study enrolled 232 (training set, 162; test set, 70) hepatocellular carcinoma patients. A total of 3111 radiomics features were extracted from dynamic contrast-enhanced MRI, followed by dimension reduction of these features. Logistic regression (LR), K-nearest neighbour, Bayes, Tree, and support vector machine algorithms were used to select the best radiomics signature. Multivariable logistic regression was used to select the useful clinical and radiological features, and different predictive models were established. Finally, the predictive performances of different models were assessed by evaluating the area under the curve The authors have found that 0.739 in the training and test sets, respectively. In the multivariable analysis, age (OR=0.956, P=0.034), alpha-fetoprotein (OR=10.066, P<0.001), tumour size (OR=3.316, P=0.002), tumour-to-liver ADC ratio (OR=0.156, P=0.037), and rad-score (OR=2.923, P<0.001) were independent predictors of MTM-HCC. The nomogram performed best, with AUCs of 0.896 and 0.805 in the training and test sets, respectively. The manuscript is well written.

Response: We greatly appreciate your efforts and recognition of our manuscript. Thank you again for all your hard work.