

January 28th, 2022

Dear Editor-in-Chief, Editors and Reviewers,

Thank you all so much for your prompt review of our manuscript, we have carefully revised the manuscript per your recommendations. A revised version manuscript is attached for your review. Below please find a point-by-point response to all the comments. On behalf of all authors, thank you for your time and great job.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: the idea is good

Response: Thank you for the comments.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: It is well known that pre-operative assessment of microvascular invasion (MVI) is a relevant issue as it is closely related to recurrence in postoperative HCC and is a major topic in the HCC treatment setting. Currently, MVI is assessed primarily through pathological and immunohistochemical analysis of postoperative tissue samples being needle biopsy the only method to accurately confirm the diagnosis before surgery but it is limited by suboptimal sensitivity since biopsy may cause false negatives. In this interesting multicenter study, the authors aimed to develop and validate radiomics scores and nomogram of Gd-EOB-DTPA enhanced MRI for preoperative prediction of MVI in small HCC (sHCC). The study evaluated retrospectively 221 patients, 94 external and 100 prospective patients with postoperative pathological diagnosis of sHCC. Radiomics models of Gd-EOB-DTPA enhanced MRI and diffusion weighted images (DWI) were constructed and validated by machine learning.

A prediction model was developed using multivariable logistic regression analysis which included: radiomics scores, radiologic features and alpha-fetoprotein (AFP) level. The radiomics nomogram was analyzed based on its discrimination ability, calibration, and clinical usefulness. The radiomics nomogram was validated by external independent cohort data. Predictive capability was assessed using the areas under the receiver operating characteristic curve (AUC). They found that pathological examination confirmed MVI in 64 (28.9%), 22 (23.4%) and 16 (16.0%) of 221, 94 and 100 patients. AFP, tumor size, nonsmooth tumor margin, incomplete capsule and peritumoral hypointensity on hepatobiliary phases (HBP) had poor diagnostic value for MVI of sHCC. A total of 1409 quantitative imaging features were extracted. The classifier of Logistic regression (LR) was the best machine learning method, the radiomics scores of HBP and DWI had the great diagnostic efficiency for prediction of MVI, in the testing set and validation set the AUC of HBP was 0.979, 0.970 and 0.803, the AUC of DWI was 0.971, 0.816 and 0.801 ($P < 0.05$). The radiomics and clinic combine nomogram model exhibited good calibration and discrimination in the testing and two external validation cohorts (C-index of HBP and DWI was 0.971, 0.912, 0.808 and 0.970, 0.843, 0.869, respectively). They concluded that machine learning with LR classifier has the best radiomics score in HBP and DWI. The developed radiomics nomogram as a noninvasive preoperative prediction method shows favorable predictive accuracy for evaluate MVI in sHCC. The study is of interest and of current clinical relevance. However, in my opinion some issue deserve further details and important literature data are lacking and should be discussed to improve the clinical significance. - it is well know that imaging diagnostic features (and non-invasive diagnosis) of HCC are validated only in patient with underlying cirrhosis. **Please describe in details characteristics and etiology of underlying liver disease of study population (how many had cirrhosis and how many were non-cirrhotic?).** - As the major finding of the study is that the radiomics signatures of HBP and DWI can further improve the ability to predict MVI, **I would suggest to recall in discussion that such a approach of a combination of MR parameters has already previously reported as a useful tool for the early diagnosis of small hepatocellular carcinoma (HCC).** For example, it has previously reported that double hypointensity in the portal/venous and hepatobiliary phases can be regarded a MRI pattern, highly suggestive of hypovascular hepatocellular carcinoma (which is vey difficult to diagnose by imaging) as previously reported (Impact of gadoxetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance on the non-invasive diagnosis of small hepatocellular

carcinoma: a prospective study. *Aliment Pharmacol Ther.* 2013;37(3):355-63). - **Another topic worth mentioning is the difficult imaging characterization of recurrent HCC nodules due to the potential different imaging features of recurrent nodules.** It is well known that in cirrhosis primary and recurrent nodules (10-30 mm nodules after a previously treated hepatocellular carcinoma) may display variations in enhancement pattern, as previously reported (Characterization of primary and recurrent nodules in liver cirrhosis using contrast-enhanced ultrasound: Which vascular criteria should be adopted? *Ultraschall in der Medizin* 2013;34:280-287). The authors should discuss that, in this setting, radiomics may be useful to better characterize recurrent nodules. Thus in such a setting, the proposed radiomic approach could be of major clinical interest.

(1) Please describe in details characteristics and etiology of underlying liver disease of study population (how many had cirrhosis and how many were non-cirrhotic?)

Response: Thank you for the comment. We have added it in the Results and table 1, the number of patients with cirrhosis is 173 (78.3%), 69 (73.4%) and 70 (70%) in the hospital A, B and C, respectively.

(2) I would suggest to recall in discussion that such an approach of a combination of MR parameters has already previously reported as a useful tool for the early diagnosis of small hepatocellular carcinoma (HCC).

Response: Thank you for the comment. This is a great suggestion that the literature (Impact of gadoxetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance on the non-invasive diagnosis of small hepatocellular carcinoma: a prospective study. *Aliment Pharmacol Ther.* 2013;37(3):355-63) showed Gd-EOB-DTPA enhanced magnetic resonance may enhance the sensitivity of the noninvasive diagnosis of small hepatocellular carcinoma nodules in cirrhotic patients, and that double hypointensity in the portal/venous and hepatobiliary phases can be regarded a MRI pattern, highly suggestive of hypovascular hepatocellular carcinoma. We added the literature in the section of our discussion.

(3) Another topic worth mentioning is the difficult imaging characterization of recurrent HCC nodules due to the potential different imaging features of recurrent nodules. The authors should discuss that, in this setting, radiomics may be useful to better characterize recurrent nodules.

Response: Thank you for the comment. This is a very interesting topic and it is the difficult imaging characterization of recurrent HCC nodules due to the potential different imaging features of recurrent nodules. We well know that in cirrhosis primary and recurrent may display variations in enhancement pattern, **but in our current study** all of patients with primary hepatocellular carcinoma, because of all patients underwent hepatectomy, there was no preoperative history of primary liver tumor and any antitumor therapy had been performed. and All lesions were postoperatively confirmed as primary hepatocellular carcinoma, and microvascular invasion was assessed pathologically. Thus, we will discuss the MRI characteristics and radiomics features between of recurrent HCC and primary HCC in the following research work.

LANGUAGE

We have sent our revised manuscript to a native English-speaking expert to polish the manuscript further.

ABBREVIATIONS

We make sure our manuscript following the basic rules on abbreviations

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The study is interesting and innovative. The methodological approach is well outlined. The results need to be better shown. One of the reviewers makes an important consideration: "addition of data from the population studied". Discussion is fragile and needs to be more powerful. Figures need better resolution.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Response: Thank you for the comment. We have added the patients condition of with or without liver cirrhosis in result, and made revision for discussion.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. **The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).** Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: Thank you for the suggestions.

(1) The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words), we have changed the title of the manuscript made it meet the requirement of the journal. The current title is "Radiomics and Nomogram of Magnetic Resonance Imaging for Preoperative Prediction of Microvascular Invasion in Small Hepatocellular Carcinoma".

(2) Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file, we have made it.

(3) tables are meet the requirement of the journal.