Author’s response to reviews

Title: Radiomics-based classification of hepatocellular carcinoma and hepatic haemangioma on precontrast magnetic resonance images

Authors:

Jingjun Wu (wujingjun1994@163.com)
Ailian Liu (cjr.liuailian@vip.163.com)
Jingjing Cui (cuijingjing@huiyihuiying.com)
Anliang Chen (chenliang.zi@163.com)
Qingwei Song (songqw1964@163.com)
Lizhi Xie (rokage@163.com)

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Author’s response to reviews:

Dear Editor and reviewers,

Thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “Radiomics-based classification of hepatocellular carcinoma and hepatic haemangioma on precontrast magnetic resonance images” (BMIM-D-18-00135). We have thoroughly considered all comments and substantially revised our manuscript, and the major revised portions are indicated in our revised manuscript by highlighting. We have also responded point by point to all comments as listed below, along with a clear indication of the location of the revision. We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Sincerely,

Ailian Liu

The First Affiliated Hospital of Dalian Medical University, Department of Radiology, Xigang district, Zhongshan road, No.222, Dalian, China;
E-mail: cjr.liuailian@vip.163.com
Editor Comments:

The reviewers' comments are below and attached. In addition we have the following editorial requests:

- Please use initials only in the author contribution section.

Response: We really appreciate this reminder sincerely. We have used initials in the “author contribution” section (page 18, line 36-48).

Reviewer #1:

This is an interesting study investigating the value of radiomics in differentiating between HCC and hemangioma. However, I'd like to make several comments, mainly clinical issues.

Comment 1:

If we think about our clinical practice, it is not much common to have a hard time differentiating, specifically, between HCC and hemangioma in general population. To me, distinguishing hemangioma from metastasis has been more challenging in practice. If a patient is at risk of developing HCC (i.e. cirrhosis), then this differentiation (i.e. HCC vs. hemangioma) may become more important. I suggest that the authors present the patients' status of chronic liver disease.

Response: Thank you very much for your thoughtful suggestions. In our revised manuscript, we have presented the patients' status of liver cirrhosis. The patients' status of liver cirrhosis were recorded according to MRI features of liver cirrhosis: a nodular liver margin, lobar atrophy / hypertrophy, parenchymal heterogeneity. Finally, 59 HCC lesions and 19 HH lesions were accompanied by liver cirrhosis (page 6, line 14-24).

Comment 2: In addition, in many cases it is not that difficult to differentiate between HCC and hemangioma using non-contrast MR images. I suggest showing how difficult it was by conventional qualitative analysis, by including the results of qualitative image analysis by radiologists and comparing it with the results by radiomics analysis.

Response:

Thank you very much for your comment. In our revised manuscript, we have reported the qualitative image analysis by radiologists and compared it with the results by radiomics analysis.

In the “Materials and Methods 2.7” section, we reported the “Classification by two radiologists”: The conventional qualitative analysis for classification of HCC and HH was performed by two abdominal radiologists with different experience (2 and 10 years,
respectively). They were blinded to all patients’ information, reviewed the MR images, and recorded their own diagnosis. For evaluation of the performances of the two radiologists in the task of classification, the AUC, sensitivity, and specificity were calculated and compared (page 10, line 28-46).

In the “Results” section, we reported the results of qualitative image analysis by radiologists: During the conventional qualitative analysis for classification of HCC and HH, the radiologist 1 (with 2 years of experience) achieved the diagnostic performance with AUC of 0.702 (95% CI: 0.65-0.75; sensitivity, 0.625; and specificity, 0.779). The radiologist 2 (with 10 years of experience) achieved the diagnostic performance with AUC of 0.908 (95% CI: 0.88-0.94; sensitivity, 0.915; and specificity, 0.901). The AUC value for radiologist 1 was significantly lower (AUC=0.702) than that for radiologist 2 and the optimal radiomics-based combined model (AUC=0.908, and 0.89, respectively; p<0.05). Furthermore, the AUC for radiologist 2 and the optimal radiomics-based combined model had no statistic difference (p>0.05) (page 11, line 59; page 12, line 1-21).

In the “Discussion” section, we added the relevant content:

The combination of four sequences with logistic regression showed improved diagnostic performance, and its AUC value (AUC=0.89) was significantly higher than that for the less experienced radiologist (2-years experience) (AUC=0.702). The diagnostic performances were almost equal between the radiomics-based combined model and the experienced radiologist (10-years experience) (AUC=0.89, and 0.908, respectively; p>0.05) (page 12, line 41-57).

Further, we found the radiomics-based model with logistic regression showed significantly higher diagnostic performance than that for the less experienced radiologist (2-years experience), and the diagnostic performances were almost equal between the logistic regression combined model and the experienced radiologist (10-years experience) (page 16, line 17-29).

In the “Conclusions” section, we added the relevant content:

The diagnostic performance for the radiomics-based combined model with logistic regression outperformed the less experienced radiologist (2-years experience), and was nearly equal to the experienced radiologist (10-years experience) (page 17, line 1-7).

Comment 3: In this study, in-phase and out-of-phase images were analyzed separately. Theoretically, without fat components in a tumor, these two images should not show much differences, while intralesional fat causes a signal drop in out-of-phase images, which favors the diagnosis of HCC. The results of this study show considerable differences in performance between in- and out-of-phase images. I can't help thinking that these differences mostly result from random errors (e.g. from measuring, segmentation, ROI drawing, etc.). I think that this should be discussed.

Response: Thank you very much for your comment. In our study, we found the out-phase T1WI showed the performance for classification of HCC and HH, this can be explained by the presence
of intralesional fat for HCC. Furthermore, we found the classification performance of in- and out-phase images was different, which may result from the different signal of fat tissue on in- and out-phase images (the signal of tissue containing fat is significantly attenuated on out-phase images, and is not attenuated on in-phase images), and the random errors such as measuring, segmentation, and ROI drawing may also cause differences between in- and out-phase images. We have discussed this section in our revised manuscript (page 15, line 23-45).

Comment 4: As the authors state, standardization of MRI signals is a critical issue when it comes to quantitative analysis. I didn't understand the method of standardization used in this study (Page 7 Line 12-33). Is it a legitimate method? What does scaling factor, s, means in this formula? Without the s, the formula seems just a statistical standardization.

Response: Thank you very much for your comment. We really appreciate this reminder sincerely. Yes, it is a legitimate method. This method, referred to as Z-score, is also known as zero mean unit variance. It rescales and shifts the intensities by mentioned question. The method assumes that each scan has the same intensity distribution. The rescaling and shifting is done based on this assumption. All means are rescaled to zero, but the means do not automatically correspond to the same tissue type (Reference 14: Potter M C, Goldberg J, Aboufadel E F. Advanced Engineering Mathematics[J]. Wiley, 1999, 6(3):xv–xvii.). s is an optional scaling, by default, it is set to 1, and we haven't changed it. We have added this section in our revised manuscript (page 7, line 48).

Comment 5: Some minor points Page 3 Line 20-23: HCC is the most common PRIMARY malignancy in liver (metastasis is the most common malignant lesions). Page 4 Line 36-50: This paragraph is too long for Introduction (Background); I don't think that it is necessary to list several specific papers here. If the authors think this should be included, how about moving it to Discussion? Table 2 seems not necessary. Please consider omitting this table.

Response: Thank you very much for your thoughtful suggestions.

(1) We agree that the metastasis is the most common malignant lesions in liver. We have revised this sentence: Hepatocellular carcinoma (HCC) and hepatic haemangioma (HH) are common hepatic malignant and benign tumours respectively (page 3, line 38-42).

(2) We agree that it is unnecessary to list several specific papers in “Introduction (Background)”. We have removed these sentences in our revised manuscript (page 4, line 55).

(3) We agree that “Table 2” is unnecessary, we have removed it in our revised manuscript.
OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)? Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective? Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results? Yes - experiments and analyses were performed appropriately

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated? Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Could an appropriately REVISED version of this work represent a technically sound contribution? Yes - current version is technically sound

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The paper is interesting and well written. It describes a possible new MR diagnostic tool that can help radiologists in differentiating Hepatocellular carcinoma and hepatic haemangioma, the most common hepatic malignant and benign tumours respectively. This radiomics signature is validated with an accurate statistical analysis performed by the authors and can avoid, in some cases, the intra-venous contrast media administration.

Response: Thank you very much for your recognition!