Peer Review File

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Reviewer A

The study examined the relationship between apparent diffusion coefficient (ADC) values derived from diffusion-weighted imaging (DWI) and Collagen IV expression in different liver tumors. The main findings indicate that there is no significant association between ADC values and Collagen IV expression across the patient sample, suggesting that the complex extracellular matrix in liver tumors is not reflected by DWI signals, which may be more influenced by tumor cellularity. A major limitation of the study is the small sample sizes of certain subgroups, such as liver metastasis derived from pancreatic cancer and colorectal cancer, limiting the generalizability of the findings. In addition, the study could not account for histological subtypes of primary tumors, which may affect tumor microstructure and extracellular matrix composition.

Dear reviewer, thank you for this good summary of our work.

In the title, I suggest the authors to indicate that this is a cross-sectional study.

We have changed it accordingly. Our new title is "**Association between diffusion-weighted imaging and tumor matrix in liver cancer. A cross-sectional study "**

In the abstract, the authors need to describe the potential clinical contribution of this research focus in the background, inclusion criteria and how the pathological and MRI characteristics were measured in the methods, the patient sample characteristics in the results, and comments on the potential clinical implications of the findings in the conclusion.

Dear reviewer, thank you for this important suggestion. We have revised the abstract accordingly
In the background part we have added the clinical contribution
"Imaging modalities can reflect the underlying histopathology of tumors. However, the exact interactions between the histopathology microstructure and the resulting imaging phenotype remain elusive. It could enhance clinical care for liver tumors to predict histopathology features including the extracellular matrix in a non-invasive way. The present study used cross-sectional guided biopsy specimen to employ the exact spatial biopsy localization to correlate the apparent diffusion coefficient (ADC) values derived from magnetic resonance imaging (MRI) with Collagen IV expression in different liver cancers."
We have added the inclusion criteria into the abstract "The inclusion criteria were defined with available cross-sectional biopsy, available biopsy specimens and a preinterventional MRI with DWI sequence."
We have added the MRI measurement into the abstract part "The ADC values were measured in a co-registered way with the cross-sectional biopsy imaging to ensure the spatial agreement of imaging and histopathology."
We have added a sentence into the conclusion "There is more research needed for clinical care to investigate the complex interactions of histopathology and the resulting imaging phenotype of the MRI."

In the introduction, the authors did not adequately analyze the clinical needs for the current research focus and what the potential clinical significance of this research focus is.

Dear reviewer, thank you for this important concern. We have expanded the introduction to better provide the relevance and clinical need for our research rationale to predict histopathology features by imaging. “There is definite clinical need to predict the underlying microstructure of tumors by imaging modalities. It could better need personalized treatment forms in a longitudinal way, whereas histopathology needs an invasive biopsy specimen, which cannot be performed multiple times. In addition, only imaging can provide information regarding the whole tumor, whereas biopsy can only analyze a small part of the tumor. The acquired specimen for example could be from a less aggressive tumor part and not be representative for the whole tumor.”

In the methodology of the main text, please accurately describe the clinical research methodology, sample size estimation, and the assessment of the clinical characteristics of the sample. In statistics, please describe the test of normality of the variables and how the spearman or pearson correlation was selected. It is necessary to describe the threshold AUC values for an acceptable diagnostic model based on MRI parameters. Also, please ensure $P<0.05$ is two-sided.

Dear reviewer, thank you very much for this important statistical concern.
-We have added two-sided p-values into the paragraph. Indeed, we used two sided p-values in all instances.
-we have added the test for normal distribution. Indeed, due to the small sample size, the distribution was not normally distributed. “after testing for normality distribution with Kolmogorow-Smirnow test.”
-we believe that there is no accurate possibility for sample size estimation due to the exploratory character of the present study. In addition, a correlation analysis can be performed in an exploratory study design. We have added a short paragraph into the methods part. “Due to the exploratory study design, no sample size estimation was possible.”
- we deleted the sentence with the AUC values, as no further subgroup analysis was possible with ROC and AUC analyses. We are deeply sorry for this mistake.

Reviewer B

1. Please provide the full name of DWI, ANOVA in the Abstract.
We have added it into the abstract.

2. Main text
1) The Main text should be structured with Introduction, Methods, Results, Discussion, and Conclusions. Please modify your article to it.
We have added introduction into the manuscript.

2) Please check all abbreviations in the main text, such as CT, TR, TE, PACS, etc. All abbreviated terms should be full when they first appear.
We have included them into the manuscript.

3) Please unify the following full name.

patients (20.5%) with intrahepatic cholangiocarcinoma (CCC), 22 patients (17.3%) with liver metastasis of colorectal cancer (CRC), 20 patients (15.7%) with liver metastasis of breast cancer (BC), with 14 (11.0%) liver metastases of pancreatic adenocarcinoma (PDAC) (10.0%).

CCC cholangiocellular carcinoma

PDAC pancreatic ductal adenocarcinoma

We have unified it.

4) K.E. is not the author of this article. Please provide the reason for it.

The biopsies of the tumors were obtained before any form of treatment. Histopathology was evaluated by two experienced investigators (D.J., K.E.) in consensus without knowledge of the patients or imaging data.

It is K.I.S. she married in the meantime and changed her name. It was not a different author.

3. Figures

1) Please list Figure legends on a separate manuscript page after the references list.

We have placed it after the references.

2) Please provide Figure 1 in higher resolution.

3) The citation of Figure 1 is missing in the text. Please check and revise.

We have provided it into the materials and methods part.

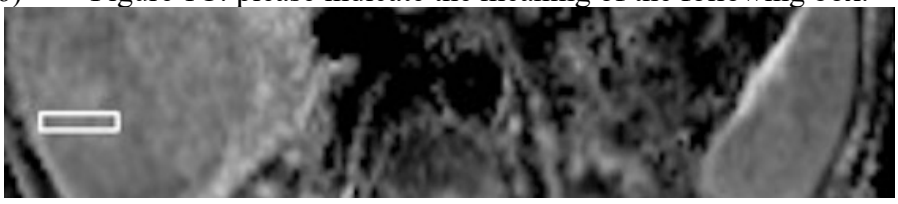
4) Figure 1: please use uppercase letter, e.g., A.

liver lobe. (a) portal-venous T1-weighted image with hypointense signal intensity of the tumor in the right liver lobe. B) Axial slice of the CT-guided biopsy with display of

We have used uppercase letters.

5) Figure 1: If there is input text (figure numbers or letters, markers) on your Images, please provide both text and no text versions to us.

6) Figure 1C: please indicate the meaning of the following box.



7) Figure 1D: please provide the scale bar or magnification.

It is not possible.

8) Figure 1: please define CT, ADC in the legend.

We have added it.

9) Figure 2: please define HCC, CCC, CRC, BC, PDAC in the legend.

We have added it.

10) Figure 3: please define HCC, ADC in the legend.

We have added it.

4. Tables

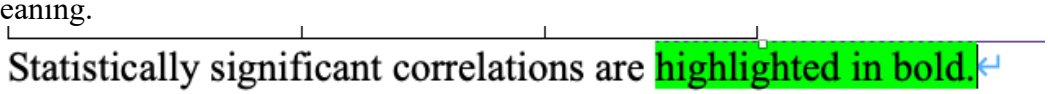
1) All Tables: please define all abbreviations in the table footnote.

We have defined all abbreviations.

2) Table 2: there is no use of 2a, 2b, 1b. please revise the table as “Table 2, 3, 4, 5, 6”.

We have changed it accordingly.

3) Table 2: Please change the expression of Bold values. According to the journal's publication norm, the data format cannot be bold. You can use other symbols to indicate the meaning.



We changed it accordingly.