

Dear reviewer:

Thank you for your comments concerning our manuscript entitled “Intravoxel incoherent motion diffusion-weighted MR imaging for predicting the histological grade of hepatocellular carcinomas: Comparison with conventional DWI” (Manuscript NO: 37358). These comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made revision which we hope meet with approval. The main corrections in the paper and the responds to the reviewer’ s comments are as following:

Question1: The study objectives written in the abstract section with that in the end of the introduction did not match.

Response: The study objectives are to compare IVIM-derived parameters with conventional DWI-derived ADC values for determining the histologic grades of HCCs and evaluated the correlation between the parameters and the histological grades. The measurement reproducibility between the two observers shows the reliability of parameters, and it makes sure that the results for the study objectives are more persuasive. The diagnostic performance of the parameters in differentiating grades is one part of the determining the histologic grades. So I revise the objectives in the end of the introduction to match the study objectives in the abstract.

Question2: Authors did not provided any clinical, etiological and functional classification of all patients.

Response: We are very sorry for our negligence of the clinical, etiological and functional classification of all patients. 62 patients diagnosed with HCC for analysis. The patients comprised 50 men and 12 women (mean age,  $54.31 \pm 9.36$  years; range, 30-76 years). 49 patients tested positive for the hepatitis B surface antigen and 6 for the hepatitis C virus antibody. The remaining 7 patients tested negative for both antigens. According to Child-Pugh class, the population of the liver stages were 54 patients in A5, 6 patients in A6 , 2 patients in B , and nobody in Child-Pugh C. All the tumors were histologically classified according to the major Edmondson-Steiner

grade on the final pathologic reports as follows: grade 1 (n=14), grade 2 (n=24), grade 3 (n=24), and grade 4 (n=0).

Question3: Interesting 40 (40%) patients were excluded for different reasons.

Response: In China, The incidence of hepatocellular carcinoma is very high. clinical symptoms was not obvious, when a patient has clinical symptoms, it usually has been high-grade hepatocellular carcinoma, And the clinical treatment will take measures of radiofrequency ablation, transarterial chemoembolization, particle implantation, So, because of the history of preoperative treatment before MRI examination. Moreover, the poor image quality, the small size of the tumor, the pathological result showing not be HCC, and so on. Therefore, nearly 40% of the patients were excluded.

Question4: The first paragraph of the discussion section is very similar to the last paragraph of the introduction section.

Response: We have made correction according to the Reviewer' s comments. The first paragraph of the discussion section has similarity with the last paragraph of the introduction section. We revise the first paragraph of the discussion carefully, which makes the discussion focus on the results, avoids the repetition with the last paragraph of the introduction, and makes the article more concise, simultaneously. "Moreover, DWI parameters are used in the pathological grading of hepatocellular carcinomas. Therefore, the present study investigated the correlation between DWI parameters and different histopathological grades of HCCs and compared the conventional DWI and IVIM-DWI parameters." is replaced by "Thus, an effective method is needed to evaluate the tumor cell differentiation grade and predict the tumor's prognosis."

Question5: I suggest to authors rewrite the discussion section. It looks redundant compare with the results section. They need focus on their main results.

Response: We have rewritten the discussion according to the reviewer' s suggestions, We modified the discussion part earnestly, and carried out that the discussion section focuses on the main results, which showing the reason of the results, Unrealized objective, the limitations of the study, avoiding dispensable discussions.

1. Revise the first paragraph of the discussion carefully, avoiding the repetition with the last paragraph of the introduction.
2. In the second paragraph of the discussion. The sentences that “we quantified the ADC and IVIM-derived parameters in different histological grades, and ”, “IVIM parameters could reflect the intrinsic characteristics of carcinomas.”, “and have been shown to be helpful in evaluating the pathological differentiation grades of the carcinomas. Conversely,”, “with a correlation coefficient of 0.737, ” were deleted. “the results may be related to the location of the lesion and the feeding artery. ” was changed as “So the results of the  $D^*$  and  $f$  values may be related to the location of the lesion and the feeding artery.”
3. In the third paragraph of the discussion. “In this study” revised as “In the present study”; The sentences “In addition, both the  $ADC_{slow}$  and ADC values were significantly correlated with the histologic grade of the HCCs, as well as with the  $ADC_{slow}$  ( $r = -0.628$ ,  $P < 0.001$ , measured by radiologist 1;  $r = -0.633$ ,  $P < 0.001$ , measured by radiologist 2) and ADC ( $r = -0.619$ ,  $P < 0.001$ , measured by radiologist 1;  $r = -0.622$ ,  $P < 0.001$ , measured by radiologist 2) values.” were placed in the last of the paragraph. And behind the sentences, added “Which demonstrate a moderate to good correlation between  $D$  and grading, between ADC and grading.”.

Question 6 and 7: Some abbreviations were written in an irregular form? A list of abbreviations is mandatory.

Response: We are very sorry for our application of abbreviations in irregular format and a list of abbreviations is mandatory. So we made correction some abbreviations which we hope meet with approval. 1. “US (ultrasonic) -biopsy” in the introduction was corrected as “Ultrasonic (US) -biopsy”; 2. “slow ADC ( $ADC_{slow}$ )” was revised as “pure diffusion coefficient ( $D$ )”; 3. “fast ADC ( $ADC_{fast}$ )” was changed as “pseudo-diffusion coefficient ( $D^*$ )”; 4. “grade1, grade2, grade3” were equal to G1, G2, G3, respectively.

We tried our best to improve the manuscript and made some changes in the

manuscript in line with the comments. These changes will not influence the content and framework of the paper. We hope that the correction will meet with approval. Thank you very much for your comments and suggestions.

We are looking forward to your approval.

Best regards,

Yours sincerely,

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