

Response Letter

Name of journal: World Journal of Gastroenterology

Manuscript Number: 48242

Dear Editors and Reviewers:

Thank you and all the reviewers so much for the comprehensive review of our manuscript entitled **"Quantitative diffusion-weighted MR-Enterography in ileal Crohn's disease: systematic analysis of intra and interobserver reproducibility"** (Manuscript ID: 48242). We appreciate the insightful comments and critiques from you and the reviewers, which help us improve the quality of our manuscript.

We have carefully revised the manuscript based on your suggestions, and the revised manuscript is attached. All the revisions are highlighted using the Track Changes function of Microsoft word. Responses to the reviewers' comments are listed as following. The guidelines and requirements from the editors have been checked or provided throughout the manuscript. We hope this paper in its current revision is acceptable for the publication in *World Journal of Gastroenterology*.

We deeply appreciate your further consideration of our manuscript and look forward to hearing from you.

Thank you and best regards.

Below please find the responses to all comments.

Reviewer 1 (03254879):

SPECIFIC COMMENTS TO AUTHORS

Excellent study team. Important topic. Would be helpful to have better idea of disease severity in the Crohn's disease patients. As this is a retrospective, data on endoscopic scoring (SES-CD or CDEIS) might not be available. I would consider adding the histology severity into the clinical table.

Response: Thank you very much for the thorough review and positive comments of this manuscript. As the superficial biopsy of terminal ileums in endoscopy for analysis, the histology severity of terminal ileum was not reported.

Reviewer 2 (03666823):

SPECIFIC COMMENTS TO AUTHORS

Excellent work. Please add comments in the discussion about other techniques used to evaluate CD activity. The following reference can be interesting: Paredes JM, Ripollés T, Cortés X, Reyes MD, López A, Martínez MJ, Moreno-Osset E. Non-invasive diagnosis and grading of postsurgical endoscopic recurrence in Crohn's disease: usefulness of abdominal ultrasonography and (99m)Tc-hexamethylpropylene amineoxime-labelled leucocyte scintigraphy. J Crohns Colitis. 2010 Nov;4(5):537-45. doi: 10.1016/j.crohns.2010.03.002. Epub 2010 Apr 8. PubMed PMID: 21122557.

Response: Thank you very much for the positive comments. There were lots of techniques used to the evaluation of CD in prior studies [1-3], such as the mentioned abdominal ultrasonography and (99m)Tc-hexamethylpropylene amineoxime-labelled leucocyte scintigraphy as well as CT enterography, and various MR sequences etc. However, the aim of this original study was about the quantitative DWI analysis in CD, so the comparison of different techniques for CD assessment was not included in this article.

References:

1 Miles A, Bhatnagar G, Halligan S, et al. Magnetic resonance enterography,

small bowel ultrasound and colonoscopy to diagnose and stage Crohn's disease: patient acceptability and perceived burden. Eur Radiol 2019; 29: 1083-1093

2 Lee SS, Kim AY, Yang SK, et al. Crohn disease of the small bowel: comparison of CT enterography, MR enterography, and small-bowel follow-through as diagnostic techniques. Radiology 2009; 251: 751-761

3 Catalano O, Maccioni F, Lauri C, et al. Hybrid imaging in Crohn's disease: from SPECT/CT to PET/MR and new image interpretation criteria. Q J Nucl Med Mol Imaging 2018; 62: 40-55

Reviewer 3 (03025513):

SPECIFIC COMMENTS TO AUTHORS

The authors attempt to assess the reproducibility of measurements of ADC and signal intensity (SI) in MRE diffusion-weighted sequences, in patients with ileal Crohn's disease. The results of the study demonstrate a high intra and interobserver agreement for signal ratio (SR) and ADC. A high accuracy of both measurements for detection of ileal inflammation (assessed endoscopically) was also demonstrated. However, there are some challenges that I would like to see assessed: (I will not comment on to the sections in which there are no objections).

Response: Thanks very much for your review and the comments.

Methods.

Page 7, lines 25-6. The definition of terminal ileum as the final 10 cm of small bowel seems quite subjective.

Page 8, 16-17. The reference standard (endoscopy) is assessed qualitatively. It should have been better an assessment via an endoscopic score such as CDEIS or SES-CD (see below).

Response: Thanks for your comments. The terminal ileum is relatively stationary in the right lower quadrant. And terminal ileum can be easily identified in endoscopy or MR enterography by the marker of ileocecal valve.

As our aim was to assess the reproducibility of measurements in quantitative diffusion weighted MR enterography, the endoscopic score was not acquired in this retrospective study.

Discussion.

The authors have to accept the limitation of having subjectively evaluated the endoscopic activity. It should have been better an assessment via an endoscopic score such as CDEIS or SES-CD. Such an approach had also allowed the correlation between endoscopic score and ADC or SR figures.

Response: Thanks very much for the advice. The limitation of subjective evaluation of endoscopic activity was added in the text. Our primary aim was to assess the reproducibility of measurements in quantitative diffusion weighted MR enterography, so the endoscopic score was not acquired in this retrospective study. The correlation between endoscopic score and ADC or SR derived from DWI is worthwhile for further exploration in prospective studies with large samples.

In page 11, lines 8-9, the authors state that “the measurement agreement for DW-MRE quantitative parameters has not been ascertained to date”. Considering that the figures of agreement are provided in the manuscript, the authors should have included that information in the “Conclusions” of the study.

Response: Thank you very much for the comment. According to your suggestion, the information was added in the “Conclusions” of the text as following: “In conclusion, the intra and interobserver agreements of quantitative ADC and SR analysis from DW-MRE images were found to be good or excellent from this initial study. Both the ADC and SR demonstrated high diagnostic yield for distinguishing inflamed terminal ileum in CD patients from the normal. Thereby, ADC value or SR could serve as robust and efficient biomarkers to aid in the noninvasive evaluation of CD.”

On the other hand, I miss an explanation about the poor correlation between SR and ADC ($r=0.45$) in CD patients. Does the degree of possible coexistent fibrosis play any role on this differences? The different behavior, on DWI, of inflammatory and fibrous tissues has not been mentioned in the manuscript.

Response: Thank you very much for the query. The moderate and negative correlations between SR and ADC values were both observed in the two radiologists. And the relatively low correlation coefficients between SR and ADC could be due to the small sample in this study. As the superficial biopsy of terminal ileums in endoscopy, the histologic severity of inflammations and fibrosis from all layers of the bowel wall could not be acquired. From this initial study, ADC and SR analysis of DW-MRE images achieved good to excellent observer agreements for CD evaluation, and could be acted as the robust quantitative biomarkers in clinic. The exploration of ADC and SR in the differentiation of CD inflammations and fibrosis as well as medical therapy assessment during CD course is worthwhile in the future study.

References.

The references 15 & 16, correspond to the same document, although published in two different journals.

Response: Thank you very much for pointing this out. As the document was published in both two journals, the references 15 & 16 were cited just like the references 3 & 4 in the prior study [1].

References:

1 Park SH, Ye BD, Lee TY, Fletcher JG. Computed Tomography and Magnetic Resonance Small Bowel Enterography: Current Status and Future Trends Focusing on Crohn's Disease. *Gastroenterol Clin North Am* 2018; 47: 475-499

Thank you again for your time and comments to our manuscript.