Manuscript ID: 37884
Title: MRI and Crohn's Disease Endoscopic Index of Severity: Correlations and concordance
Journal: World Journal of Gastroenterology

Response to Reviewers' comments

Dear Editor,

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback, and made modifications to improve the manuscript. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our results and their discussion, therefore providing a more complete context for the research that may be of interest to your readers.

We hope that you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.

Best regards,
Fei Miao

Department of Radiology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin 2nd Rd, Shanghai 200025, China.

E-mail:mf11066@rjh.com.cn

Tel: +86-13917041205

Fax: +86-21-64085875

Reviewer #1

This is an interesting study which deals with the relevance of MRI in diagnosis, severity assessment, and follow-up monitoring of Crohn's disease. The results are sound and following to the authors the methods applied can be a useful adjunct in monitoring patients' therapy. However, for a reader not so familiar with the details of MR diagnostic it seems to be difficult to keep a clear view on the different parameters (MaRIA, trRCE. and so on). Particularly a gastroenterologist would be interested to hear some remarks on the physiological background of the different parameters. E.g. what is aRCE in physiological terms? What does diffusion measuring by MR mean. Partly this is addressed in the mansuscript for stenoses and strictures.

Response: We thank the Reviewer for the comment. We added some clarification to the manuscript. T2WI can show the intestinal wall thickening, serosal edema (T2WI high signal), and mucosal defects suggesting ulcers. Artery enhancement sequence on T1W1 shows the blood supply of the intestine. aRCE is the enhancement rate during arterial phase and represents the degree of blood supply. pRCE is the blood supply during the portal phase. dRCE is the blood supply during the period of delay. In the presence of acute inflammation, the enhancement rates of the various phases are elevated. If the peak value of the enhancement curve is delayed, the inflammation is likely to be improved or chronic[1-7].

DWI (diffusion-weighted imaging) can be used to measure the movement of water molecules in living bodies. In the presence of acute inflammation, the edema, exudation of intestinal wall tissue, and elevated inflammatory cytokine levels limit the movement of the water molecules in tissues and cells (i.e. the diffusion is limited). Hence, the DWI signals increase and while ADC values decrease. Those values are reversed when inflammation improves[1-7].

The authors should check whether every abbreviation is explained at the first mention in the text.

Response: We thank the Reviewer for the comment. The abbreviations were verified.

How reliable was the endoscopic evaluation? By one endoscopist? Coauthorship of a gastroenterologist?

Response: We thank the Reviewer for the comment. All endoscopic examinations were performed by the same two gastroenterologists. It was clarified in the manuscript.

Is the MR method able to detect fistulas?

Response: We thank the Reviewer for the comment. MRI T2W1 and T1W1 dynamic enhancement sequences can show intestinal fistula. In the present study, the frequency of fistula was low. Therefore, reliable statistical analyses could not be performed. This was noted as a limitation.

Reviewer #2

The authors do not describe how patients were identified for the study. There is a risk of bias if non-consecutive patients are included, so this information is important.

Response: We thank the Reviewer for the comment. All the adult patients meeting the diagnostic criteria were enrolled. The patients were excluded if they had poor MR image quality that could not be used for diagnosis and measurements or if they had incomplete clinical data. This was clarified in the manuscript.

Second, the authors state that all endoscopies were performed within 7 days of MRI. This requires clarification. At our center, for example, patients undergoing both MRI and endoscopic evaluation of CD may have an MRI first, then an endoscopy, or vice versa, and these may occur months apart. Were patients whose exams were greater than 7 days apart excluded? Otherwise, how is it that all patients had their exams within this time frame?

Response: We thank the Reviewer for the comment. In fact, it is routine practice at our hospital that all patients undergo both MRI and endoscopy within 7 days, but the order could vary from a patient to another. This was clarified in the manuscript.

Next, the use of double balloon endoscopy requires clarification. This is not standard practice for evaluation of Crohn's activity, at least in the United States and Europe. Is this standard in China? If so, why? Otherwise, why were patients having these exams?

Response: We thank the Reviewer for the comment. The predilection site of CD is the distal ileum. Colonoscopy can detect the lesions and the diagnosis of CD can be made for most patients. Nevertheless, the diseased sites of some patients can be the jejunum or distal ileum and in these cases, the disease is detected by MRI. In these cases, if the colonoscopy was negative, then double-balloon enteroscopy was performed to confirm the diagnosis of CD. As said above, MRI and endoscopy are performed within 7 days in different order and MRI results maybe not available when the endoscopy is performed. Hence, enteroscopy is performed instead of colonoscopy in order to be sure to see any eventual CD lesions and avoid a second endoscopy.

The fourth paragraph of the methods section ("MR images were independently…") is difficult to understand. The first sentence of the sixth paragraph is also ambiguous – is the ROI the unit of comparison? These should be revised in conjunction with a fluent English writer.

Response: We are sorry for this. This paragraph was edited. The ROI is the region of interest, i.e. the image area that is analyzed for MRI parameters.

Reviewer #3

1. The authors stressed that the follow-up of CD is investigated; there is no primary diagnosis. it is of interest to know the MRI performance in therapeutic sequences/ cycles; is there any data?

Response: We thank the Reviewer for the comment. In fact, all included patients had been diagnosed with CD based on clinical, endoscopic, imaging and histopathological results, according to the WHO criteria[8]. These criteria are: 1) non-contiguous/segmental lesions visible by imaging, endoscopy, and/or the resected specimen; 2) manifesting as paving stones/longitudinal ulcer visible by imaging, endoscopy, and/or the resected specimen; 3) inflammatory lesions of the entire wall based on clinical manifestations and/or resected specimen showing abdominal masses, and stenosis visible by imaging and endoscopy; 4) histopathological manifestations of non-cheese-like granuloma; 5) cleft/fistula visible by imaging, endoscopy, and/or the resected specimen; and 6) anal lesions visible by clinical manifestations and/or biopsy/resected specimen. The diagnosis of CD is made in the presence of: a) criteria 1+2+3 and any one of 4, 5, or 6; or b) criterion 4 and any two of 1, 2, or 3.

If the lesions were improved after medical treatment of CD, the following MRI manifestations could be seen: 1) T2WI showed that the thickening of the intestinal wall was alleviated, edema was alleviated or had disappeared, and mucosal ulcers were healed; 2) dynamic T1W1 enhancement sequence showed that the enhancement of the lesion segment had weakened, and the intestinal wall was no longer stratified; 3) the exudation surrounding the intestines was reduced or had disappeared, and the enlarged lymph nodes surrounding the intestines had shrunk; and 4) DWI sequence showed that the signals of the diseased segment were reduced and ADC values were increased.

Those points were clarified in the manuscript.

2. CD activity is evaluated using CRP levels. The proinflammatory cytokines are not used to evaluate and monitor CD activity; please give reasons.

Response: We thank the Reviewer for the comment. Clinically, CRP is usually combined with ESR to evaluate the disease activity. Elevated CRP is associated with disease activity to a certain degree, but it is not absolute. CRP is a sensitive indicator of systemic inflammatory activity, but the specificity is poor. CRP is not only elevated when CD is active, but it is also elevated in the presence of any other cause of inflammation[9-11]. Therefore, CD activity cannot be evaluated and monitored only based on CRP, hence the need for more specific examinations. Endoscopy is invasive. Hence, MRI could be an ideal method for monitoring CD.

What experiences and lessons can be learnt from this study?
What is the direction of the future research?

Response: We thank the Reviewer for the comment. The lessons from this study are that the results of endoscopy were not completely consistent with results of MR among CD patients. In addition, the most sensitive indicator in evaluating efficacy by MR was relevant indicators during the MR enhanced arterial phase. As for future

research, the most appropriate timing for performing MR evaluation and monitoring disease conditions after treatment of CD remains to be determined.

Comments in the manuscript

Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-59080039, Fax: +86-10-59080039.

Response: We corrected the phone number.

Please read the core tip then provide the audio core tip:
Acceptable file formats: .mp3, .wav, or .aiff
Maximum file size: 10 MB
To achieve the best quality, don't allow to have the noise.

Response: We now provide the Audio Core Tip.

The format should be like this, please revise others.

Response: We are sorry for this. The references were edited accordingly.

The guidelines for writing and formatting Aritcle Highlights are as follows:
1 Research background
The background, present status, and significance of the study should be described in detail.
2 Research motivation
The main topics, the key problems to be solved, and the significance of solving these problems for future research in this field should be described in detail.
3 Research objectives
The main objectives, the objectives that were realized, and the significance of realizing these objectives for future research in this field should be described in detail.
4 Research methods
The research methods (e.g., experiments, data analysis, surveys, and clinical trials) that were adopted to realize the objectives, as well as the characteristics and novelty of these research methods, should be described in detail.
5 Research results
The research findings, their contributions to the research in this field, and the problems that remain to be solved should be described in detail.
6 Research conclusions
The following questions should be briefly answered:
What are the new findings of this study?
What are the new theories that this study proposes?
What are the appropriate summarizations of the current knowledge that this study provided?
What are the original insights into the current knowledge that this study offered?
What are the new hypotheses that this study proposed?

What are the new methods that this study proposed?
What are the new phenomena that were found through experiments in this study?
What are the hypotheses that were confirmed through experiments in this study?
What are the implications of this study for clinical practice in the future?
7 Research perspectives
What experiences and lessons can be learnt from this study?
What is the direction of the future research?
What is/are the best method/s for the future research?

Response: We now provide those points.

Please list and define all abbreviation appearing in the tables or figures. Please check across the text.

Response: We now list all abbreviations below each table.

For the figures with labels, arrows, or other markers, photographs, clinical images, photomicrographs, gel electrophoresis, and the like that include labels, arrows, or other markers must be submitted in 2 versions: one version with the markers; and the other without.

Response: We now provide all figures with and without markers.

Please provide one total title. For example, Figure 1 Pathological changes of atrophic gastritis tissue before and after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ....
Please check across the text.

Response: We edited the figure legends according to the comment.

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