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Evaluation of Crohn's disease activity by MR enterography: Derivation and histopathological comparison of an MR-based activity index[◇]

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ABSTRACT

Aims: To compose a qualitative magnetic resonance imaging (MRI) activity index showing Crohn disease (CD) activity, and to compare magnetic resonance enterography (MRE) findings with histopathology results.

Materials and methods: Twenty-six patients (11 male and 15 female; mean age 36.7) who had MRE and colonoscopic biopsy between October 2011 and August 2012 were included in the study. On MRE the following parameters were evaluated: bowel wall thickness, bowel wall T2 signal, bowel wall contrast enhancement pattern and degree, length and number of involved bowel segments, perimural T2 signal, mesenteric inflammation, mesenteric lymph nodes and complications of CD. Each parameter was scored to calculate MRI activity index. Biopsy specimens were retrospectively evaluated, histopathologic and endoscopic acute inflammation scores (AIS, eAIS) were calculated. Each parameter and total MRI activity index were compared with the pathology scores (AIS, eAIS) by Mann–Whitney *U* test and Spearman correlation.

Results: Statistically significant positive correlation was found between AIS and eAIS, mural thickness and eAIS. Moderate correlation was found between MRI activity index and eAIS, mural enhancement degree and eAIS; and poor correlation was found between mesenteric inflammation score and eAIS, MRI activity index and AIS, however they were not statistically significant.

Conclusions: In CD, bowel wall thickness measured by MRE is best correlated with the histopathologic results which are accepted as the reference standard. In cases with high MRI activity index, eAIS is also generally high. MRI activity index which is measured simply and noninvasively can be used in the follow up of CD.

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1. Introduction

Crohn disease (CD) is a chronic, autoimmune disorder which may affect any portion of the gastrointestinal tract, most commonly involving the terminal ileum. Enteric involvement tends to be segmental, and inflammation is often transmural [1]. It is characterized histologically by the presence of non-caseating granulomas

and transmural inflammation of the bowel, leading to erosions, ulceration and inflammatory stenosis [2]. Enteric sinuses, fistulae, mesenteric phlegmons and abscess may complicate penetrating disease.

Clinicians often use medical history, laboratory data, and physical examinations to assess disease activity and complications, but these tools are relatively nonspecific. Clinical history of disease activity is subjective and varies from patient to patient. This leads to requirement to collect data from imaging modalities. However, small bowel assessment of the radiological imaging techniques is difficult because of anatomical and physiological characteristics. For many years, the small intestine has been called the blind spot of gastrointestinal tract, due to inaccessibility by endoscopic examination. Ileocolonoscopy with biopsy is still generally assumed as a gold standard. However, these tests only evaluate the mucosa,

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Table 1
MRE acquisition sequences and parameters.

	FAT SAT 2D FIESTA		T2 SSFSE	LAVA BH C(+)	
Imaging plane	Axial	Coronal	Coronal	Axial	Coronal
TR	4	4	1173	4	4
TE	2	2	85	2	2
FA	70	70	90	12	12
Slice thickness(mm)	7	5	5	2.6	2.1
Number of slices	60	30	30	92	76
FOV	266 × 380	410 × 410	288 × 224	360 × 400	396 × 440

and in 27.8% of patients terminal ileum cannot be visualized [3].

Since endoscopic techniques are often limited to more proximal segments of the small bowel, either enteroclysis or small bowel follow-through (SBFT) has been the gold standard for the diagnosis of CD. With these methods, direct information can be obtained about lumen size and function, and also indirect information can be found out about small bowel wall and surrounding tissues. Although new techniques like video capsule endoscopy and double balloon endoscopy eliminate the disadvantages above, their efficiency is low compared to cross-sectional imaging.

Cross-sectional imaging is sensitive enough to detect bowel inflammation and complications of CD, and that allows differentiation acute disease which can be managed medically from surgery required cases. In recent years, thanks to progress in imaging technology, high-resolution multiplanar images can be obtained. By the help of these current techniques, enteroclysis and enterography techniques are commonly used in the diagnosis of the small intestine diseases. According to European Crohn's and Colitis Organization (ECCO) consensus, computed tomography (CT) or magnetic resonance enterography (MRE)/Magnetic resonance (MR) enteroclysis is considered gold standard today due to the high diagnostic accuracy [4]. MRE is preferred versus computed tomography enterography (CTE) because of potential advantages. The most valuable advantage of MRE is the lack of ionizing radiation. Moreover MRE provides high tissue contrast, and enables evaluation of small intestine peristalsis and distension with dynamic sequences.

The aim of this retrospective study is to compose a qualitative magnetic resonance imaging (MRI) activity index showing CD activity. We also aim to compare acute inflammation score (AIS), derived

from histopathological findings of endoscopic biopsies with MR activity index obtained from MRE findings in CD.

We think that our index will be useful for local practice, and it can also be a guide for other radiologists who are interested in MRE of Crohn disease.

2. Material and methods

2.1. Study patients

Between October 2011 and August 2012, patients with endoscopy and concurrent biopsy proven CD, who underwent MRE were included in the study. Eligible patients who did not have colonoscopy or biopsy within 7 days after MRE were excluded from the study. Twenty-six consecutive patients (range 18–66 years, fifteen female, and eleven male), who had both MRE and colonoscopic biopsies within one week, were recruited for the study. Three of our patients underwent terminal ileum resections for complications related to Crohn's disease.

2.2. MRE patient preparation

The accuracy of MRE interpretation is related to appropriate bowel preparation and optimal bowel distention. Therefore bowel preparation was applied in every patient. Patients were asked to drink Fleet Phospho Soda® 45 mL previous evening at 18:00 before examination. Afterwards patients were allowed to receive only clear liquid foods.

Patients fasted for 6 h prior to MRE imaging. Each patient ingested 1500 mL water in one hour interval, starting 2 h before scanning. In the last hour, patients drank 100 mL Osmolak solution (Osmolak 10 g/15 mL 250 mL solution, Biofarma®), mixed with

Table 2
Qualitative MR activity index definition.

Score	0	1	2	3
Mural thickness ^b	1–3 mm	>3–5 mm	>5–7 mm	>7 mm
Mural T2 signal	Equivalent to normal bowel wall	Minor increase	Moderate increase	Marked increase
Enhancement degree ^c	Equivalent to normal bowel wall	Minor enhancement	Moderate enhancement	Marked enhancement
Mural enhancement pattern	Normal	Homogeneous	Mucosal	Layered
Affected segments	Normal terminal ileum <15 cm	>15 cm One segment	2 or 3 segments <15 cm	More than 3 segments or minimum 2 long segments (>15 cm)
Complication ^d	Absent	Present		
Comb sign	Absent	Present		
Lymph nodes	Absent	Cluster less than 1 cm	1 node greater than 1 cm	3 nodes greater than 1 cm
Perimural T2 signal	Equivalent to normal mesentery	Increase in mesenteric signal but no fluid	Small fluid rim (≤2 mm)	Larger fluid rim (>2 mm)

Mesenteric score^a (Comb sign + Lymph nodes + Perimural T2).

^a Presence of comb sign, lymph nodes and presence of mesenteric fluid were considered when calculating mesenteric score.

^b Measured using electronic calipers.

^c Compared to normal small bowel.

^d One point was added for each complication.

Table 3

Transmural histologic scoring of mural acute inflammation in biopsy specimens.

	0	None
	1	Apthous ulcer (<7 mm)
Mucosal ulceration	2	Linear ulcer
	3	Confluent-large ulcer
Oedema	0	None
	1	Mild
	2	Moderate
	3	Severe
Neutrophils	0	No increase
	1	Mild increase
	2	Moderate increase
	3	Marked increase
Depth of neutrophilic penetration	0	None
	1	Mucosa
	2	Submucosa
	3	Muscularis

Neutrophilic penetration of serosa/extramural fat was not evaluated because histologic assessment was not based on surgical specimens, therefore maximum AIS was 12.

1400 mL water, total of 1500 mL. In order to diminish bowel motion artifacts intravenous 0.5 mg glucagon were administered 30 min before imaging.

2.3. MR imaging protocol

All MR examinations were performed using a 1.5 T MR unit (GE Signa® Excite HD). LAVA (Liver acquisition with volume acquisition) sequences were acquired before and 70 s after intravenous administration of 0.1 mmol/kg body weight of gadolinium chelate (Omniscan®, Nycomed Imaging, Oslo, Norway). Table 1 presents MR imaging protocol.

2.4. MRE interpretation

A senior radiologist with experience in interpreting small bowel MR examinations and a radiology resident reviewed the MRE images in consensus, blinded to endoscopy and histopathology results. All of our patients had terminal ileum involvement. For each patient the score was derived from terminal ileum 10 cm proximal to the ileocaecal valve. Mural thickness was measured from coronal T2 single shot fast spin echo (SSFSE) images. By comparing to the normal looking ileal segments, MR images of involved terminal ileum were scored for mural T2 signal, perimural T2 signal and contrast enhancement degree. Enhancement pattern was also scored, classified as homogeneous (with all bowel wall enhancing equally), mucosal only (with only the innermost wall layer enhancing) or layered (with both mucosal and serosal bowel wall layers enhancing, with a central band of relatively reduced enhancement). The presence or absence of increased mesenteric vascularity (the “comb” sign), the presence of lymph nodes (size and number) adjacent to the inflamed bowel and perimural T2 signal were scored to calculate mesenteric inflammation score. Scoring also included number and length of the involved bowel segments. Complications detected in MRE, namely fistula and abscesses were also scored. Eventually a qualitative MR activity index scoring system was achieved (Table 2).

Approximately five biopsies were collected for each patient from different sites including colon also rectum, and terminal ileum. The biopsies were examined by a pathologist with extensive experience in gastrointestinal histopathology. An assessment of the acute inflammation score was made by using the method of Borley et al. This grades AIS, with a maximum of 12, based on mucosal ulceration (grade 0–3), edema (grade 0–3), and quantity (grade 0–3) and depth (grade 0–4) of neutrophilic infiltration (Table 3). However, most of our patients did not have terminal

Table 4

Histological scoring system for acute inflammation in endoscopic biopsies (eAIS).

Histological variable	Grade	
Erosion or ulceration	0 = No	1 = Yes
Polymorphs in lamina propria	0 = No	1 = Yes
Cryptitis	0 = No	1 = Yes
Crypt abscess formation	0 = No	1 = Yes
Inflammatory exudates	0 = No	1 = Yes
Granulomas	0 = No	1 = Yes

Maximum e-AIS was 6.

Table 5

MR activity index score distribution.

MR Score	Min–Max	Average $\pm$ SD	Median
MR Total Score ^a	4–18	11.62 $\pm$ 4.37	12
Mural thickness	1–3	2.07 $\pm$ 0.89	2
Mural T2 Signal	0–3	1.54 $\pm$ 1.24	1
Mural enhancement pattern	1–3	2.04 $\pm$ 0.82	2
Enhancement degree	1–3	2.23 $\pm$ 0.91	3
Mesenteric score	0–3	1.24 $\pm$ 0.83	1
Affected segments	1–3	2.28 $\pm$ 0.84	3

^a Complications (abscess and fistula) were included in MR activity index score.

Table 6

AIS and e-AIS score distribution.

	Min–Max	Ort $\pm$ SD
Acute inflammation score (AIS)	2–10	6.31 $\pm$ 2.29
Endoscopic (eAIS)	0–5	2.73 $\pm$ 1.51

ileum resection; therefore neutrophilic infiltration to serosa fat was not included when scoring.

An endoscopic biopsy acute inflammatory score (eAIS) was also developed based on typical morphological features of CD described in guidelines published by the ECCO. This scoring system with a maximum of 6 points was calculated including variables such as erosion-ulceration, neutrophilic infiltration in lamina propria, cryptitis, crypt abscess formation, inflammatory exudates and granulomas (Table 4).

Correlative statistics for MR activity index and pathologic activity index (AIS and eAIS) were performed by using software (NCSS 2007&PASS 2008 Statistical Software, Utah USA). Mann–Whitney *U* test was used to compare results (mean, standard deviation, median, correlation) and also qualitative data. Spearman's rho correlation coefficient was used for correlation analysis. Best predictive value for the total MR activity index score was assessed by calculating receiver operating characteristic (ROC) curve. Significance was set at $p < 0.05$ and confidence interval estimated at the 95% level.

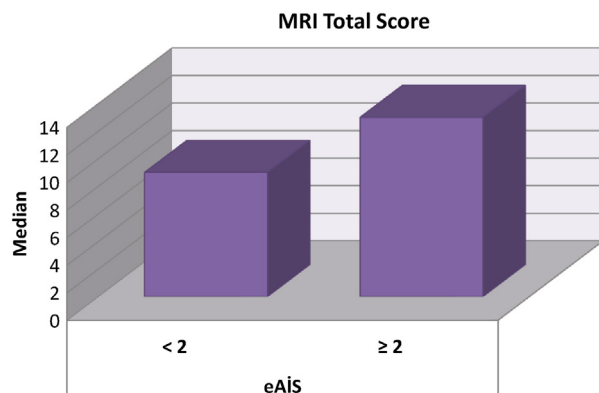
MR activity index parameters; bowel wall thickness, bowel wall enhancement and mesenteric scores, which also influence eAIS, were evaluated with multivariate regression analysis. Our model was established with Backward Stepwise regression analysis.

3. Results

In our study, the average age of 15 female patients was 37.6; the average age of 11 male patients was 35.5; and the total age average was 36.7. All patients were diagnosed with CD after clinical evaluation and colonoscopic biopsy. 26 patients' biopsies from different segments of the colon and almost 130 localizations of the terminal ileum were evaluated histopathologically. MR activity index total score varied between 4 and 18 and its average was 11.62 $\pm$ 4.37; also, its median was 12 (Table 5). AIS varied between 2 and 10 and the average score was 6.31. eAIS varied between 0 and 5 and

Table 7
Correlation between AIS and eAIS.

AIS	eAIS	
	<i>r</i>	<i>p</i>
	0.786	0.001**

r: Spearman's rho correlation coefficient.** *p* < 0.01.**Graphic 1.** MR activity index total score in eAIS groups.

average score was 2.73 (Table 6). There was a significant positive correlation between AIS and eAIS (Table 7).

A 33.6% moderate positive correlation between MR activity index total score and eAIS score was detected but this correlation was not statistically significant.

Univariate correlation showed a statistically significant positive correlation between eAIS and wall thickness. When we evaluated our model with Backward stepwise regression analysis, we found that the model was significant in the 3rd step ($p = 0.034$; $p < 0.05$); and coefficient of determination was 0.189 ($R = 0.435$; $R^2 = 0.189$). Only the effect of the wall thickness on the model was statistically significant.

Our model was established as $eAIS = 1.203 + 0.705$ (wall thickness).

We found a 35% moderate positive correlation between enhancement degree and eAIS score but this correlation was not statistically significant. There was a 29.6% poor positive correlation between mesenteric score and eAIS score, but this correlation was not statistically significant.

No significant correlation was found between mural T2 signal, mural enhancement pattern and eAIS scores.

There was a 42.1% statistically significant positive correlation between wall thickness and AIS score. In the analysis made by wall thickness, the model was found significant ($p = 0.043$; $p < 0.05$); ($R = 0.399$; $R^2 = 0.159$).

Our model was established as $AIS = 45.174 + 1.027$ (wall thickness).

There was a 21.7% poor positive correlation between MR activity index total score and AIS score, but this correlation was not statistically significant.

There was a 23% poor positive correlation between mural T2 signal and AIS score; however it was not statistically significant.

There was no correlation between mural enhancement pattern, enhancement degree, mesenteric score and AIS scores.

eAIS score over 2 was accepted as cut off value to determine highly active disease. The patients were divided into 2 groups (Graphic 1) according to their eAIS ($eAIS \leq 2$, $eAIS > 2$).

MR activity index total score was found higher in the group with $eAIS > 2$ (Figs. 1 and 2) but there was no statistically significant difference ($p > 0.05$). In the cases with 12 or higher MR activity index

total score, the sensitivity to detect highly active disease ($eAIS > 2$) was 70.59% with a specificity of 85.71%; positive predictive value of 92.31%; and negative predictive value of 54.55%.

4. Discussion

CD is an inflammatory bowel disease that has a high morbidity due to severe potential complications and its nature with chronic relapses. Since there is no curative treatment of the disease, the aim of the treatment should provide remission, minimize symptoms, and slow down the progression of the disease [5]. Treatment plan is based on the activity of the disease. Although many various specific tools for the disease have been developed in the last 25 years, it is still difficult to evaluate the activity of the disease [6,7].

Recently, symptom scoring, biochemical markers, endoscopic scoring, histology, and MR have been used to show activity of CD [8]. Clinicians nowadays have been using scoring systems such as Harvey-Bradshaw Index, Crohn's Disease Activity Index (CDAI) and Pediatric Crohn's Disease Activity Index (PCDAI) and fecal markers like fecal calprotectin for disease activity [9,10]. Lately, MR activity index with ileocolonoscopy and histology has been used as a reference to determine the disease activity [11]. While evaluating disease activity by MRE, some parameters such as wall thickness, degree and type of wall contrast enhancement, mural T2 signal, perimural edema, mesenteric vascularity and lymphadenopathy are taken into consideration. However, many studies show that there is no relationship between MRE findings and CDAI [12–15]. The most frequently used systems for histopathological evaluation are AIS and eAIS. Endoscopic scoring system includes disease activity markers [16] and it shows similarities with transmural scoring system.

In this study, we used AIS model, which is generally applied in the terminal ileal resection material, in endoscopic biopsy material. Moreover, we also applied eAIS system in determining histopathological disease activity and compared both systems. We detected significant positive correlation between AIS and eAIS. We found that wall thickness was the single MR finding that had the best correlation with both AIS and eAIS. Thus, we conclude that wall thickness is the parameter that correlates best with active inflammation.

Mural thickness can be measured from noncontrast fast gradient echo or spin echo T2 sequences. In the uncomplicated disease, the activity and treatment response may be followed by measuring mural thickness on noncontrast sequences; yielding safety, time and cost savings. However, contrast enhanced MR sequences are required in the newly diagnosed patients for differential diagnosis, e.g. excluding neoplastic disease. Complications such as fistulas and abscess are also better shown on contrasted studies.

In the literature, it was stated that besides wall thickness, mural T2 signal was also related to pathological activity [17,18]. However, in our study, this data could not be verified. Some researchers found that contrast enhancement degrees were correlated with disease activity [18,19]. Maccioni et al. showed that there was a significant correlation between mural T2 signal and contrast enhancement level; however, this finding was not an independent indicator of the inflammation [18]. Other researchers found that contrast enhancement was less sensitive than wall thickness and T2 signal in determining disease activity [20]. Measurement of contrast enhancement can be incoherent depending on the dynamic imaging protocols and can show differences among researchers [21]. Therefore, in this study, when scoring the degree of contrast enhancement, we scored it by comparing the contrast enhancement in the normal-looking ileum of the same case. CD is characterized by abnormal angiogenesis and latest studies show that microvascular density, disease chronicity, and disease activity

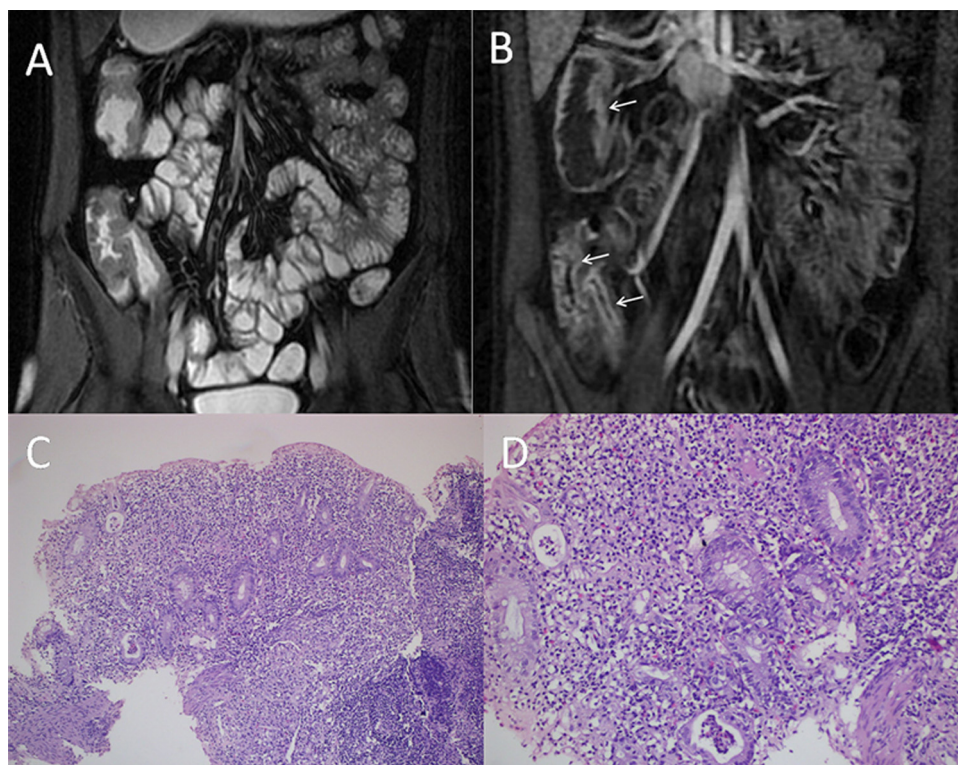


Fig. 1. 28 Year old male patient with chronic abdominal pain and diarrhoe. MRI activity index was 12, whereas AIS was 4 and eAIS was 3. **A.B.** Coronal fat saturated 2D FIESTA (A) and coronal LAVA (B) after contrast administration. Mural thickness and T2 signal was high in the terminal ileum and right colon. Layered contrast enhancement pattern was observed (arrows). **C.D.** H&E $\times 10$ (C) and H&E $\times 20$ (D) sections revealed erosion, cryptitis and crypt abscess. Mucosa and submucosa are infiltrated with mixed inflammatory cells. The epithelium appears regenerative and mucin depleted.

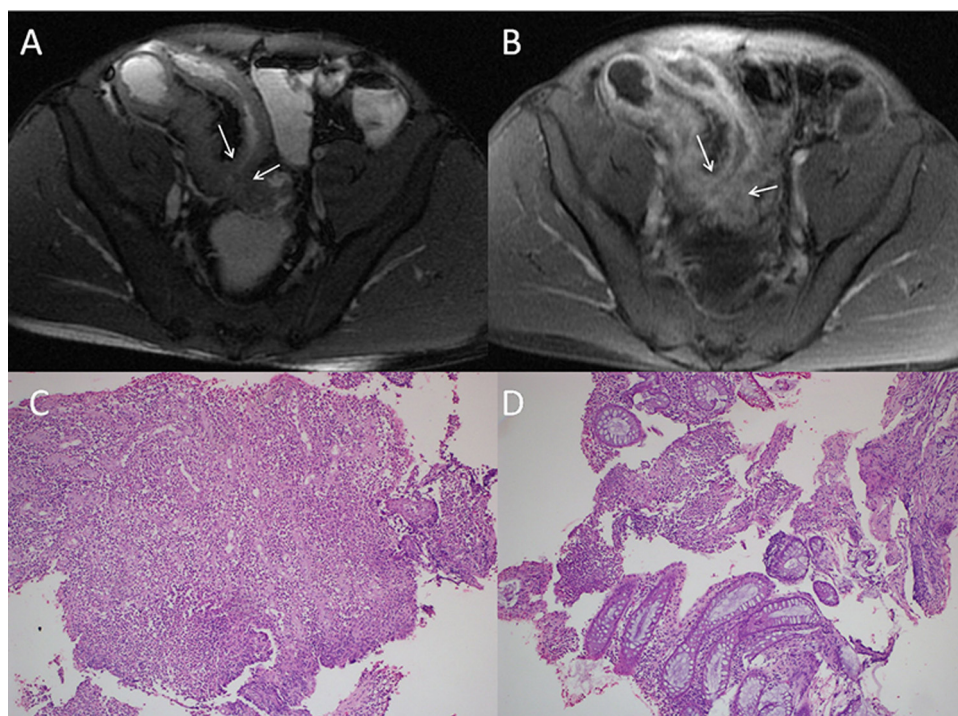


Fig. 2. 24 year old male patient with chronic abdominal pain. MRI activity index was 15, whereas AIS was 9 and eAIS was 4. **A.B.** Axial fat saturated 2D FIESTA (A) and axial LAVA after contrast administration. Mural thickness and T2 signal was high in the distal ileal segments and a fistula was observed between ileum and proximal rectum (arrows). There was prominent and layered contrast enhancement in the involved bowel segments. **C.D.** Ulcer, the colonic mucosa and submucosa are infiltrated with mixed inflammatory cells (C) (H&E $\times 20$). Minimal glandular distortion. The lamina propria is infiltrated with mononuclear cells (D) (H&E $\times 10$).

affect contrast uptake [22]. To choose a specific patient group for MR evaluation affects the results. For instance, contrast enhancement levels of newly-diagnosed disease and contrast enhancement in a long-term following, treated disease are different. A statistically non-significant, moderate correlation between bowel wall contrast enhancement degree and histological activity was also observed in our study. As some other studies have also shown, we believe that contrast enhancement, indicating active inflammation, is probably related to disease activity; however, we could not find statistically significant correlation between bowel wall contrast enhancement degree and histological activity because of small number of patients in our study.

Michael et al. found a significant correlation between AIS and perimural T2 signal. However there was a poor correlation between AIS and comb sign, and there was no correlation between AIS and the number of lymph nodes [23]. In this study there was a statistically non-significant poor correlation between eAIS and mesenteric score that we formed by comb sign, perimural T2 sign, and lymph node number. There was no correlation between mesenteric score and AIS.

In this study, we also considered the number and length of affected bowel segments in MR activity scoring. However, we found no correlation between AIS and eAIS scores and the number and length of affected segments. We also included some complications such as abscess and fistula in MR activity index score. On MRE, we observed complications in 4 patients, all of whom had MR activity index scores >15. MR activity index score of 3 of these 4 patients was 18; AIS and eAIS scores of these 3 patients were also high (average AIS:7, eAIS:3.3). We think that complications developing as a result of Crohn's disease is closely related to disease activity. Thus, we suggest that complications should be included in MR activity score.

The patients were divided into two groups according to eAIS (eAIS ≤ 2, eAIS > 2). MR activity index total score was highest in the group with eAIS > 2, however there was no statistically significant difference ($p > 0.05$). When identifying whether there was a pathologically active disease (eAIS > 2) in the cases with $12 \geq$ MR activity index total score, sensitivity was 70.59%; specificity was 85.71%; positive predictive value was 92.31%; and negative predictive value was 54.55%. Probably because the number of our cases was few, no significant difference was found. Despite, we still think that MR activity index total score can be used to determine disease activity. The major restriction of our study was the number of our patients. We think that in larger patient groups, a significant correlation between histopathological activity index and further MR parameters may be found.

Histopathological evaluation of our patients was done by colonoscopic biopsy material and another restriction was that full-thickness examination could not be made. The most important limitation was the lack of correlation of biopsy site and MRE evaluation site since terminal ileum segments were evaluated with MRE and most of the histopathologic evaluation was performed from colon. Segments exposed to biopsies might not always be the part with the highest disease activity due to the access difficulty to the terminal ileum. Most of our parameters did not correlate with the histopathologic indexes probably because endoscopic biopsies, obtained from eligible sites of the bowel, were limited to show exact activity of the disease.

8. Conclusions

MR activity score, developed to show CD activity, is a simple and non-invasive test. Wall thickness determined in MRE is shown to

be well correlated with histopathological results that are accepted as reference standard. eAIS scores are high in the cases with high MR activity index. Thus, MR activity index obtained by MRE may be useful in CD follow-up.

Conflict of interest

None.

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