



# Assessment of presence and grade of activity in ileal Crohn's disease

## SMALL INTESTINE

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### ABSTRACT

**Background/Aims:** To assess the sensitivity of magnetic resonance enterography (MRE) in the diagnosis of Crohn's disease (CD) activity and correlation between endoscopic and MRE scores in predicting the activity grade.

**Materials and Methods:** Twenty-five ileal CD patients with clinical and biochemical evidence of activation underwent ileocolonoscopy and MRE within 7 days of their application. Simplified endoscopic scoring of CD (SES-CD) and MRE scores was done and compared with each other and other parameters of activation (CRP, leukocyte count, platelet count).

**Results:** The sensitivity of MRE scoring was found to be 92%; however, the statistical correlation with SES-CD was not significant ( $p=0.83$ ) for the grading of the activity.

**Conclusion:** MRE scoring is sensitive enough to use in CD activity evaluation; however, it can not be used alone, and it is rather a complementary technique to endoscopy and is especially valuable for patients with extraluminal disease.

**Keywords:** Crohn's disease, activation, ileocolonoscopy, magnetic resonance enterography

### INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) affecting all segments of the digestive tract. The incidence is around 3.1-14.6/100,000 in the north of the United States and 0.7-9.8/100,000 in Europe (1). Management of CD is a challenging issue, and morbidity and mortality rates increase unless the patient is followed up precisely. Deep remission should be the main goal in order to improve the quality of life, increase the time interval free of complications, and diminish surgery indications and malignancy risks.

Endoscopic evaluation by an experienced endoscopist differentiates correctly between CD and ulcerative colitis (UC) in 89% of the patients (2). Endoscopy is required for management of CD as well. Evidently, mucosal healing has been emphasized rather than clinical well-being

(Crohn Disease Activity Index) and biologic markers, such as C-reactive protein (CRP) and fecal calprotectin in recent years. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID) developed and validated the Crohn's disease endoscopic index of severity (CDEIS) in 1989 (3). This scoring was complicated and cumbersome, because it possessed further evaluations and calculations. Moreover, GETAID published another study declaring that the predictive value of CDEIS was not significant in making the decision of corticosteroid treatment (4). Simplified endoscopic scoring of CD (SES-CD) was validated and reported in 2004 (5). Ulcer size, ulcerated surface, affected surface, and luminal narrowing were scored separately in five segments (ileum, right colon, transverse colon, left colon, and rectum), and the scores were added to find the overall score. The main difference between the

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variables of CDEIS and SES-CD is that the first one contains the depth of the ulcer, whereas the other one uses the size of the ulcer. Daperno et al. (5) demonstrated a strong correlation between SES-CD and CDEIS in 121 patients. Additionally, SES-CD was also correlated with both clinical findings and serum CRP levels. Besides, after the development of biologic agents, endoscopic healing scores significantly correlated more with the outcome of CD (6). It was thought that mucosal assessment was of little use in directing the treatment until the introduction of biologic agents. The publications about the impact of biologic agents on mucosal healing were the cornerstone of CD surveillance (6,7). Fewer hospitalizations and fewer surgical procedures were needed with the introduction of biologic agents. The therapy for patients with active endoscopic scores and normal clinical manifestations and CRP was successfully adjusted in 50% of the total study population (8).

It is evident that ileocolonoscopy is the gold standard for the diagnosis and maintenance of IBD. On the other hand, it is an invasive technique that needs at least 3 days of preparation, and there is a risk of not being able to intubate the ileocecal valve, since the valve is usually edematous or stenotic in active small bowel CD. Furthermore, there is a risk of underestimating the disease activity, because the endoscope can not reach all of the small bowel segments, and a narrower colonoscope may be traversed easily through a stenosis skipping it. At this point, radiologic imaging seems to have more advantages over colonoscopy. However, the methods except ultrasonography (US) and magnetic resonance imaging (MRI) possess high amounts of ionizing radiation risk if they are used routinely for the follow-up, and patients with CD are usually young patients who are more vulnerable to radiation. Martinez et al. (9) conducted a study to compare the values of US and magnetic resonance enteroclysis (MRE) in CD, taking endoscopic results, clinical scores, and biomedical parameters as references. They did not find a significant difference between the diagnostic values of US and MRI. Therefore, the choice of the imaging modality (US versus MRI) should depend on the availability of the tools and experience of the radiologist.

In the 1990s, MRI was used to evaluate perianal fistulas in CD (10), while suboptimal image quality limited the usage of MRI in small bowel and colon assessment. In the following years, new MRI techniques contributed to high-quality images (11-13). Giromette et al. (14) classified disease activity into 3 categories (no activity, mild activity, moderate to severe activity) and investigated MRE findings for positive and negative predictive values (PPV, NPV), sensitivity and specificity, and overall accuracy in evaluating CD activity of an MRI scoring system, considering the histologic score as the standard reference. All the calculated values (PPV, NPV, sensitivity, and specificity) were around or over 80%, which is reasonably good. They concluded that the overall score is more valuable than a single parameter, such as bowel wall thickness (14).

Since mucosal healing is the target in the treatment of CD, endoscopic surveillance is the mainstay of the management. However, ileocolonoscopy has same drawbacks, which were mentioned previously. Hence, other techniques and scores must be improved as an alternative, such as MRE. Thus, the aim of our study was to determine the sensitivity of MRE in the diagnosis of the activity and MRE scoring in predicting the activity grade in CD, taking endoscopic findings as reference, and if MRE can replace ileocolonoscopy in the surveillance of CD.

## MATERIALS AND METHODS

This was a prospective study with 25 ileal CD patients who were referred to Izmir Ataturk Teaching and Research Hospital, Gastroenterology Department. The study was approved by the institutional review board. Patients were informed about the study and were asked to sign a consent form. The expenses were met by the health insurance companies of the individuals, since the investigations were indicated because of their health conditions.

### Patients

Twenty-five CD patients with only terminal ileum involvement were enrolled in the study. Patients with colonic CD and contraindications for MRI were excluded. All of them were diagnosed previously and on medication. They all underwent ileocolonoscopy due to any symptoms or findings of activation, such as fever, stomach ache, severe changes in the pattern of defecation, and elevated acute phase reactants (C-reactive protein-CRP, leucocytes or platelets).

### Endoscopy

Blood samples for CRP, leukocytes, or platelet count were obtained from all of the patients, and then they were prepared for ileocolonoscopy with 3 days of soft and liquid diet and 100 ml phospho-soda taken 12 hours prior to the procedure. They were sedated with varying (5-10 mg) doses of midazolom (Dormicum, Roche) intravenously and propofol (Diprivan, Astra Zeneca) 1.5-2.5 mg/kg intravenously. Endoscopic scoring (SES-CD) was performed during all of the procedures by two experienced endoscopists. The endoscopic variables were assessed in 5 segments (ileum, right colon, transverse colon, left colon, and rectum), and then, the scores for each segment were added to find out the overall score. The disease endoscopic activity was interpreted as remission for scores 0-2, mild for scores 3-6, moderate for scores 7-9 and severe for scores more than 9. The ileum was scored for the extent that was reached during the procedure. An ileocecal valve or an ileocolonic anastomosis lesion was grouped as right colon involvement; hence, those types of patients were excluded prior to the study, as were the colon involvement patients. Biopsies were taken from areas with lesions, such as erythema, ulcerations, and cobblestone appearance, and patients with different histopathological diagnoses other than CD were excluded.

**MRE**

After ileocolonoscopy, MRE was performed in all of the individuals in 7 days. Two radiologists evaluated the results, blinded to the ileocolonoscopy results. The MRE protocol included pre-examination overnight fasting and oral up-take of 1500-2000 ml of aqueous 3% mannitol. All patients were instructed to drink this solution continuously over a period of 45 minutes to 1 hour prior to the MR examination. Nearly 10 minutes before the imaging, 10 mg hyosin n-butyl bromid (Buscopan®, Boehringer Ingelheim, Germany) was injected intravenously in order to reduce bowel peristalsis and to avoid motion artifacts. Most patients were placed in the prone position; this position produces a degree of abdominal compression and reduces the number of sections required for each coronal acquisition. However, the supine position is normally required in patients with stomas and abdominal wall fistulas.

Magnetic resonance enteroclysis was performed on a 1.5 Tesla MR system (Signa, GE HDxt 1.5 T) with an 8-channel phase-array body coil using the following protocol: coronal T2-weighted single-shot fast spin echo (SSFSE) (TR/TE 494/2298, matrix size 384x320, slice thickness 5 mm, gap 0 mm), coronal T2-weighted 2D true fast imaging with steady state precession (true-FISP) (TR/TE 4.2/1.9, matrix 256x192, slice thickness 5mm, gap 0 mm), and axial and coronal T1-weighted post-contrast 2D ultrafast gradient echo sequence (FLASH) (TR/TE 1.5/3.3, matrix 224X224, slice thickness 5 mm, gap 0 mm). A single dose of gadolinium (Gd) (0.1 mmol/kg) was administered intravenously, and postcontrast images were acquired after 60 seconds of contrast administration.

We have used the MRE scoring system of disease activity described by Girometti et al. (14). Terminal ileum was defined as the 30-cm-long bowel loop proximal to the ileocecal valve or ileocolic anastomosis in cases of previous surgical resection. Quantitative assessment of bowel wall contrast enhancement (WCE) was calculated by applying a particular equation, according to Sempere et al. (15), with the parameters acquired before and after the gadolinium injection. WCE was also qualitatively defined as homogeneous or layered, as described by Koh et al. (16). We have also qualitatively evaluated the presence (1 point) or absence (0 points) of mucosal abnormalities (wall nodularity and/or ulcers and/or cobblestoning) and extraviseral disease (17): mesenteric involvement (including comb-sign and/or fibrofatty proliferation), presence of more than three mesenteric enlarged lymph nodes (short diameter on the axial plane >10 mm), inflammatory masses, and sinus tract fistulas. In correlation with conventional fluoroscopy, bowel wall motility was evaluated considering both peristalsis (present or absent) and distensibility (present or absent). Changes in the diameter of the lumen in the consecutive images revealed peristalsis. The subjects were divided into three categories of disease activity according to the sum of the scores: no activity (score 0-1), mild activity (score 2-6), and moderate-to-severe activity (score ≥7).

**Statistical analysis**

Endoscopic and MRE scores of ileal CD were compared. Statistical analysis was conducted using R, version 2.15.0. R is a statistical computing and graphics programme which was developed at Bell Laboratories (formerly AT&T, now Lucent Technologies in USA) by John Chambers and colleagues. R is available as Free Software under the terms of the Free Software Foundation's GNU General Public License. Continuous variables were summarized using the median, 25<sup>th</sup>, and 75<sup>th</sup> percentiles, and categorical variables were summarized using percentages. Spearman's rank correlation was used to estimate pairwise associations among endoscopy score, MR scores, leukocytes, platelets, and CRP. Scatterplot matrices with lowess smooth lines were used to depict the associations among variables. P<0.05 was considered statistically significant.

**RESULTS****Patient characteristics**

Nine patients out of 25 were female. The mean age was 38 (26-61). All of them were Caucasians. One patient previously had a right hemicolectomy and ileotransversostomy operation due to obstruction (the neoterminal ileum was assessed). All of the patients had ileal disease without any colonic involvement. The median duration of the disease was 7 years (1-12). None of them was smoking actively; however, 18 of them were ex-smokers. None of them was under remission. The median and range values were CRP 3.2 (0.17-18.83), leukocytes 9.590 (5.440-16.900), platelets 364,000 (83,000-631,000), albumin level 4.1 (2.6-5.1), and hemoglobin level 12.3 (8.4-15). Also, 17 (68%) patients were assessed as mild, 5 (20%) as moderate, and 3 (12%) as severe according to SES-CD; 2 (8%) patients were categorized as inactive, 20 (80%) as mild, and 3 (12%) as moderate-to-severe according to MR activity score.

**Disease activity evaluation**

Two patients with mild CD according to SES-CD were diagnosed as having inactive disease in MRE; 23 patients with endoscopically active CD were also verified as active in MRE, demonstrating the sensitivity of MRE in ileal CD as 92% for the presence of activation but not the stage of relapse. Further, 82% of the endoscopically proven mild-stage patients were also scored as mild by MRE. On the contrary, only 25% of the endoscopically moderate-to-severe patients were also scored as so by MRE. These results show that MRE seems to underestimate the activity of the disease. The MRE scores that did not overlap with endoscopic scores tended to be in the lower stage than SES-CD. The overlapping results appeared to accumulate in the mild stage. Table 1 shows the SES-CD and MRE activity scores in detail. Table 2 demonstrates the correlation between the scores and laboratory findings. SES-CD and MRE scoring were not correlated statistically for the prediction of CD activity grade (p=0.83). On the other hand, MRI scoring correlated with CRP (p=0.029). Platelet count correlated with leukocyte count (p=0.031) and CRP (p=0.003). Figures 1, 2, and 3

**Table 1.** Detailed scoring results (MRI scoring; 0-1 no activity, 2-6 mild, >=7 moderate to severe and SES-CD; 0-2 no activity, 3-6 mild, 7-9 moderate, >9 severe)

Age	Gender	MRI scoring	SES-CD
44	female	3-mild	6-mild
26	female	0-no activity	4-mild
34	male	3-mild	4-mild
54	female	5-mild	4-mild
39	male	4-mild	5-mild
48	male	2-mild	5-mild
32	female	3-mild	6-mild
29	female	6-mild	4-mild
35	male	4-mild	6-mild
41	male	5-mild	4-mild
36	male	5-mild	4-mild
61	female	5mild	4-mild
53	male	7-moderate to severe	8-moderate
45	male	2-mild	8-moderate
28	male	3-mild	7-moderate
49	female	2-mild	11-severe
29	male	0-no activity	5-mild
31	male	4-mild	8-moderate
32	female	3-mild	6-mild
24	male	6-mild	7-moderate
53	male	6-mild	11-severe
34	female	7-moderate to severe	11-severe
54	male	4-mild	4-mild
27	male	7-moderate to severe	5-mild
51	male	6-mild	5-mild

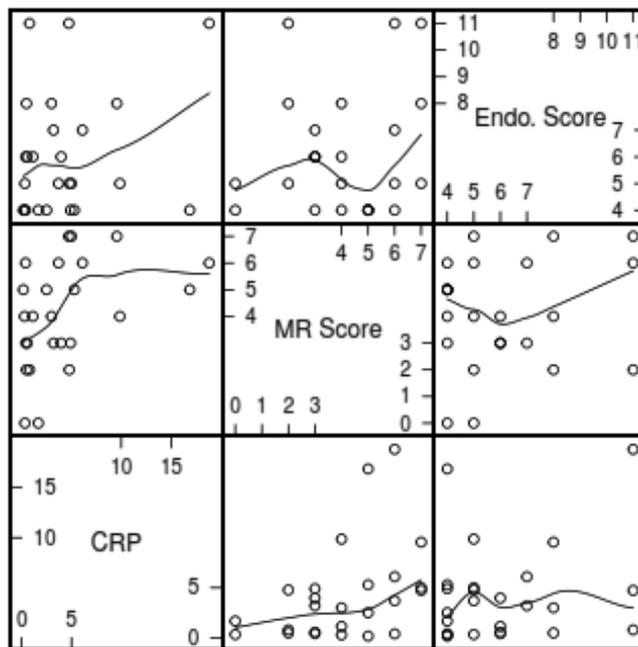
Endoscopically higher scores are colored in dark gray; radiologically higher score is colored in light gray

**Table 2.** Correlation between scores and laboratory results (p<0.05 shows statistical significance) in predicting the presence of activation

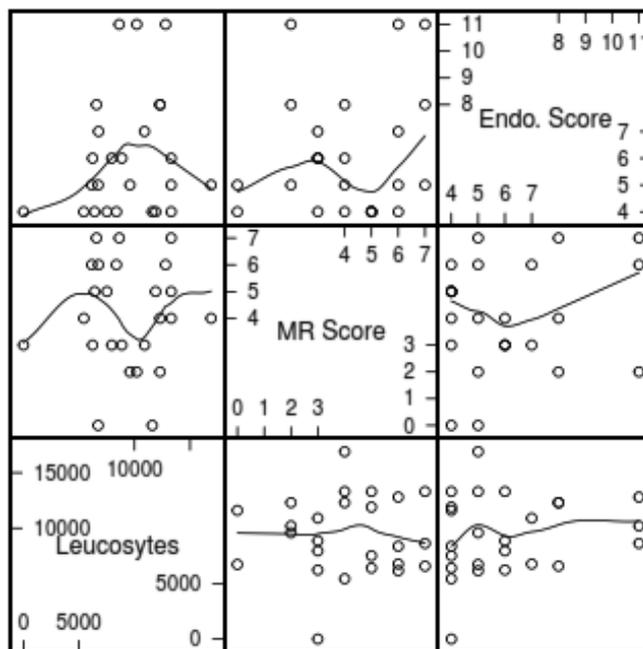
	CRP	Leucocytes	Platelet count	SES-CD count	MRE scoring
CRP		0.065	0.003	0.41	0.029
Leukocyte count	0.065		0.031	0.31	1
Platelet count	0.003	0.031		0.79	0.39
SES-CD	0.41	0.31	0.79		0.83
MRE scoring	0.029	1	0.39	0.83	

CRP: c-reactive protein; MRE: magnetic resonance enterography; SES-CD: simplified endoscopic scoring of CD

illustrate the scatterplot matrices for the correlations of scores and laboratory findings. Figure 4 demonstrates the graph of the results of 25 patients.



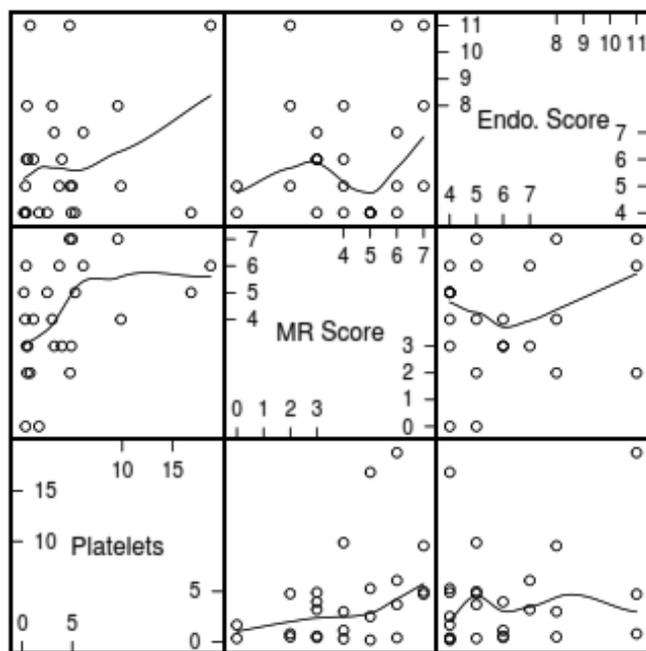
**Figure 1.** Scatterplot matrix of the correlation between SES-CD, MRE scoring, and CRP.



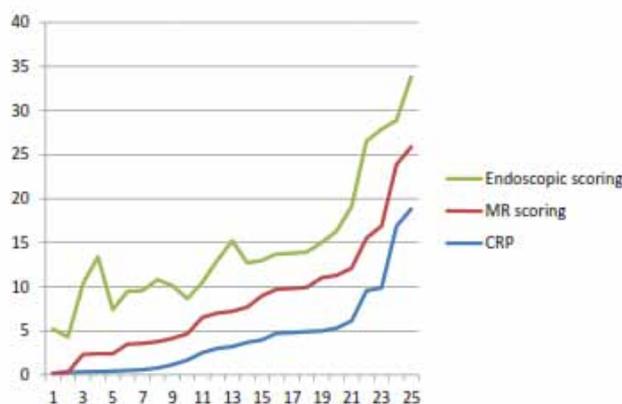
**Figure 2.** Scatterplot matrix of the correlation between SES-CD, MRE scoring, and leukocyte counts.

**DISCUSSION**

We sought to determine the efficacy of activity scoring systems among CD patients with only ileal involvement. MR enterography technique has started to be used very recently in our institution; it appears to be effective in determining the presence of activity in CD despite the 'learning curve' fact. The technique was successful in 92% of the patients in demonstrating the presence of activation. However, it predicted the correct grade of activity in only 64% of the total. SES-CD and MRE scor-



**Figure 3.** Scatterplot matrix of the correlation between SES-CD, MRE scoring, and platelet count.



**Figure 4.** Illustrates the graph of the SES-CD, MRE scoring and CRP results of 25 patients. Each number in the x-axis represents a patient. Patients are in the order of the ones having the lowest values towards the ones having the highest values of scores and CRP. y-axis represents results.

ing were not statistically correlated for the detection of activity grade; this can be attributed to the distinction between the variables in the two scoring systems. Endoscopic scoring focuses on luminal changes, whereas MRE scoring contains both mucosal and extraluminal alterations.

Crohn's Diseases Activity Index (CDAI), Perianal Disease Activity Index (PDAI), fistula drainage assessment, quality of life scores (Inflammatory Bowel Disease Questionnaire [IBDQ]), sub-clinical markers (C-reactive protein, fecal calprotectin, intestinal permeability), and endoscopic scores (CDEIS, SES-CD, Rutgeerts score for postsurgical recurrence) are used to assess the activity of CD (18). However, most of them are not adequate if used alone. For instance, CRP usually does not correlate well with the clinical score in CD (19). Physicians usually tend to rely

on their global clinical judgment, which has great intra- and inter-observer variability (18). Besides, mucosal healing seems to be the main goal in treatment.

The relationship between endoscopic activity and long-term outcomes was examined in patients with CD who underwent ileocolonic resection at the end of the 1980s by Rutgeerts et al. (20,21). They showed that any endoscopic evidence of mucosal inflammation or stenosis 1 year after surgery was a predictor of recurrence in the surveillance. These studies were the prototypes of recent studies, such as the one involving treatment-naïve CD patients. Baert et al. (22) proved that 70.8% of patients with complete mucosal healing at year 2 were still in remission at years 3 and 4, whereas only 27.3% of patients with endoscopic activity at year 2 were in remission in the long term. By the introduction of antimetabolites and biologic agents, the therapeutic landscape has changed. The ACCENT I trial determined the efficacy of anti-TNF therapy on mucosal healing at week 10, which is clearly correlated with a sustained response (23). The SONIC study found the best treatment results in infliximab and infliximab-azathioprine combination groups rather than the azathioprine group; the presence of mucosal lesions prior to the treatment was the best determinant of response in the post hoc analysis (24). Consequently, endoscopic healing appears to be the main goal of the therapy, and probably, it will be replaced by histological healing in the future with the use of confocal endoscopes. Indeed, it is hard to achieve a clinical endpoint, but controlled studies provide evidence that with use of infliximab, adalimumab, and certolizumab pegol, mucosal healing seems to be an attainable goal for CD patients (25).

Capsule endoscopy (26) and push-and-pull enteroscopy are the two techniques that gastroenterologists use to evaluate the small bowel thoroughly, but both of them are cumbersome and can cause complications in the presence of strictures. Today, MRI imaging of small bowel (MRE) is successfully used with the combination of ileocolonoscopy. In 2001, Koh et al. (16) obtained low sensitivity but high specificity of MRI for the assessment of activity in CD, and of the 17 actively inflamed segments missed on MR imaging, 16 were in the colon. After 9 years, the imaging techniques improved, so that contrast enhancement has become a key criterion in assessing inflammation in MRI of the small bowel (27). Now, it is even possible to capture the presence of activity in the mucosal phase by MRI. Contrast enhancement patterns may be useful in differentiating active disease from remission (28) or even chronic inflammatory disease. Hafeez et al. (1) showed that MRE in CD has a positive diagnostic impact and influenced therapeutic strategy in 61% of their patients. Additionally, small bowel adenocarcinoma screening in CD is substantial (29) and can be accomplished by MRE.

Our study is unique in that the endoscopic scores and MRE scores established by Girometti et al. (30) using 11 MRI parameters were calculated in ileal CD and were compared, whereas

other studies have focused mostly on the correlation between imaging modalities. In fact, there is one individual study that seems to be similar to ours. However, they used a scoring system that was a modification of that developed by Girometti et al. Some parameters, such as “mesenteric involvement” and “layered enhancement,” were removed. In contrast, “bowel wall edema” was included. Additionally, there is a meta-analysis that systematically reviewed the evidence on the accuracy of MRI for grading disease activity in CD (31). Seven studies were included from a search resulting in 253 articles (32-38). Nonetheless, these seven studies are indeed diverse from our study, taking the methods, inclusion criteria, and study population into consideration.

On the other hand, some limitations of our study should also be highlighted. First, none of the patients was in the beginning stage. Second, there were no controls to validate the specificity of our MRE findings. Although the two scoring systems did not correlate significantly for the determination of the presence of activity, MRE was supplementary to the endoscopic findings and had a sensitivity of 92% in predicting the presence of activity. Understaging with MRI was detected, contrary to the two publications mentioned above. The possible causes of this understaging in our study can be summarized as the different parameters used in the MR scoring, the relative inexperience with evaluation of abdominal MRI for CD, the variation in definitions used in the different studies, and the subjective nature of evaluation of bowel loops for assessment of enhancement and thickening. Another explanation for the inaccuracy of MRI in staging is the fact that MRI and the reference standard are essentially different methods. With ileocolonoscopy, only the lumen and the inner surface of the bowel wall can be assessed; meanwhile, on MRI, the entire bowel wall with all its layers and the extraintestinal abdomen (e.g., the mesenteric vessels, mesenteric lymph nodes, mesenteric fat) are evaluated, as CD is a transmural disease. Although this fact seems to be in conflict with our results, our study population was mostly composed of patients with the luminal type of CD.

In conclusion, we recommend caution in the interpretation of MRE findings in CD but find it to be a very useful and less invasive tool. Both modalities are complementary, and MRE should be used in more severe cases of CD and in patients who might have involvement beyond the mucosa of the small bowel.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the institutional review board.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** Concept - E.S.Y., S.İ.; Design - E.S.Y., S.İ., F.T., G.K.; Supervision - O.O., B.Ü.; Resource - E.S.Y., S.İ., F.T., G.K., Z.A., J.C.S.; Materials - E.S.Y., S.İ., F.T., G.K., Z.A., J.C.S.; Data Collection&/or Processing - E.S.Y., S.İ., F.T., G.K., Z.A.; Analysis&/or Interpretation - J.C.S.; Literature Search - E.S.Y., S.İ., F.T., G.K., Z.A.; Writing - E.S.Y.; Critical Reviews - E.S.Y.

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