Radiology

MR Enterography for the Evaluation of Small-Bowel Inflammation in Crohn Disease by Using Diffusion-weighted Imaging without Intravenous Contrast Material: A Prospective Noninferiority Study[1]

Nieun Seo, MD
Seong Ho Park, MD
Kyung-Jo Kim, MD
Bo-Kyeong Kang, MD
Yedaun Lee, MD
Suk-Kyun Yang, MD
Byong Duk Ye, MD
Sang Hyoung Park, MD
So Yeon Kim, MD
Seunghee Baek, PhD
Kyunghwa Han, PhD
Hyun Kwon Ha, MD

Purpose: To determine whether magnetic resonance (MR) enterography performed with diffusion-weighted imaging (DWI) without intravenous contrast material is noninferior to contrast material–enhanced (CE) MR enterography for the evaluation of small-bowel inflammation in Crohn disease.

Materials and Methods: Institutional review board approval and informed consent were obtained for this prospective noninferiority study. Fifty consecutive adults suspected of having Crohn disease underwent clinical assessment, MR enterography, and ileocolonoscopy within 1 week. MR enterography included conventional imaging and DWI (b = 900 sec/mm^2). In 44 patients with Crohn disease, 171 small-bowel segments that were generally well distended and showed a wide range of findings, from normalcy to severe inflammation (34 men, 10 women; mean age ± standard deviation, 26.9 years ± 6.1), were selected for analysis. Image sets consisting of *(a)* T2-weighted sequences with DWI and *(b)* T2-weighted sequences with CE T1-weighted sequences were reviewed by using a crossover design with blinding and randomization. Statistical analyses included noninferiority testing regarding proportional agreement between DWI and CE MR enterography for the identification of bowel inflammation with a noninferiority margin of 80%, correlation between DWI and CE MR enterography scores of bowel inflammation severity, and comparison of accuracy between DWI and CE MR enterography for the diagnosis of terminal ileal inflammation by using endoscopic findings as the reference standard.

Results: The agreement between DWI and CE MR enterography for the identification of bowel inflammation was 91.8% (157 of 171 segments; one-sided 95% confidence interval: ≥88.4%). The correlation coefficient between DWI and CE MR enterography scores was 0.937 ($P < .001$). DWI and CE MR enterography did not differ significantly regarding the sensitivity and specificity for the diagnosis of terminal ileal inflammation ($P > .999$). DWI and CE MR enterography concurred in the diagnosis of penetrating complications in five of eight segments.

Conclusion: DWI MR enterography was noninferior to CE MR enterography for the evaluation of inflammation in Crohn disease in generally well-distended small bowel, except for the diagnosis of penetration.

Online supplemental material is available for this article.

[1] From the Department of Radiology and Research Institute of Radiology (N.S., Seong H. Park, S.Y.K., H.K.H.), Department of Gastroenterology (K.J.K., S.K.Y., B.D.Y., Sang H. Park), and Department of Clinical Epidemiology and Biostatistics (S.B.), University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul, South Korea; Department of Radiology, Hanyang University Medical Center, Seoul, South Korea (B.K.K.); Department of Radiology, Inje University College of Medicine, Busan, South Korea (Y.L.); and Biostatistics Collaboration Unit, Gangnam Medical Research Center, Yonsei University College of Medicine, Seoul, South Korea (K.H.). Received April 4, 2015; revision requested May 18; revision received June 3; accepted June 29; final version accepted June 29. Supported by a grant from Dongkook Pharmaceutical, Seoul, South Korea. The funder had no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication. The corresponding author had full access to all of the study data and had final responsibility for the decision to submit the manuscript for publication. **Address correspondence to** Seong Ho Park (e-mail: *parksh.radiology@gmail.com*).

Magnetic resonance (MR) enterography plays an important role in the evaluation of Crohn disease (CD). The current standard MR enterography method for the evaluation of CD involves the use of intravenous contrast material. Intravenous contrast material–enhanced (CE) MR enterography is difficult to perform in patients who are at risk for contrast material allergy or other adverse reactions, those with impaired renal function, or those with contraindications to intravenous contrast material administration, such as pregnancy. These risks are relevant to patients with CD because the occurrence of renal insufficiency is not rare in CD for various reasons (18% in a recent study [1]), and many patients with CD are of reproductive age. Additionally, intravenous MR contrast material carries a small but genuine risk of nephrogenic systemic fibrosis, and young patients may be at a higher risk because of long-term gadolinium retention from repeated examinations (2,3). Therefore, performing MR enterography without using intravenous contrast material in patients with CD would allow for increased flexibility in clinical practice, not to mention cost savings. Diffusion-weighted imaging (DWI) has been recognized as a new imaging biomarker for the assessment of bowel inflammation in CD (4–15). Several studies demonstrated strong correlations between diffusion restriction in the bowel wall assessed by using DWI or a composite index derived from diffusion restriction and the severity of bowel inflammation assessed by using CE MR enterography in patients with CD; therefore, it was suggested that DWI may potentially allow the performance of MR enterography without intravenous contrast material for the evaluation of CD (5,6,9). This issue, whether MR enterography can be performed by using DWI without intravenous contrast material while maintaining diagnostic capability, should be investigated properly by using a noninferiority study design (16). To our knowledge, relevant noninferiority studies have not yet been reported. Moreover, in previous studies, investigators did not report correlations with endoscopy findings (6,9) or only reported retrospective correlations with endoscopy findings (5). The purpose of this study was to determine whether MR enterography performed by using DWI without intravenous contrast material is noninferior to conventional CE MR enterography for the evaluation of small-bowel inflammation in CD.

Advances in Knowledge

- MR enterography performed by using diffusion-weighted imaging (DWI), involving T2-weighted sequences with DWI without the use of intravenous contrast material, was noninferior to contrast material–enhanced (CE) MR enterography with the use of T2-weighted sequences and CE T1-weighted sequences to distinguish the presence or absence of small-bowel inflammation in Crohn disease (CD); 91.8% agreement was achieved (157 of 171 segments; one-sided 95% confidence interval: ≥88.4%).
- DWI and CE MR enterography did not differ significantly regarding the sensitivity and specificity of the diagnosis of endoscopically confirmed (defined as a segmental CD endoscopic index of severity [CDEIS] score of ≥3) terminal ileal inflammation in CD ($P > .999$).
- Semiquantitative scores of inflammation severity in the small bowel in CD assessed by using DWI and CE MR enterography demonstrated strong correlation (correlation coefficient, 0.937; $P < .001$).
- DWI and CE MR enterography scores of small-bowel inflammation did not differ significantly regarding the correlation with CDEIS scores in the terminal ileum (correlation coefficients of 0.606 and 0.706, respectively; $P = .110$).

Implication for Patient Care

- MR enterography performed by using DWI without intravenous contrast material can be a viable option for the evaluation of small-bowel inflammation in CD that is unassociated with penetrating complications and can be particularly helpful when a CE examination is difficult to perform.

Materials and Methods

This prospective study was supported by a grant from Dongkook Pharmaceutical in Seoul, South Korea. The authors had full control of the data and the information submitted for publication. The institutional review board of Asan Medical Center approved this study. Informed patient consent was obtained.

Patients

Patients who were examined in the Inflammatory Bowel Disease Center of Asan Medical Center, an academic referral institution, and who fulfilled the following criteria were

Published online before print
10.1148/radiol.2015150809 **Content codes:** GI MR

Radiology 2016; 278:762–772

Abbreviations:
ADC = apparent diffusion coefficient
CD = Crohn disease
CDEIS = CD endoscopic index of severity
CE = contrast material enhanced
CI = confidence interval
DWI = diffusion-weighted imaging

Author contributions:
Guarantors of integrity of entire study, N.S., Seong H. Park; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, N.S., Seong H. Park, K.J.K., B.K.K., H.K.H.; clinical studies, N.S., Seong H. Park, K.J.K., B.K.K., Y.L., S.K.Y., B.D.Y., Sang H. Park, S.Y.K.; statistical analysis, N.S., K.J.K., S.B., K.H.; and manuscript editing, N.S., Seong H. Park, K.J.K., Sang H. Park, S.Y.K., H.K.H.

Conflicts of interest are listed at the end of this article.

contacted regarding study participation: *(a)* adults (≥18 years old) who were referred for suspicion of CD or initial diagnosis of CD, *(b)* no history of bowel resection, *(c)* no emergency care required, and *(d)* no contraindications to MR enterography. Of 54 consecutive patients between October 2012 and December 2013, 50 patients (38 men and 12 women; mean age ± standard deviation, 27.7 years ± 6.4) agreed to participate (Fig 1). The same cohort was reported elsewhere, where it was addressed whether DWI had incremental diagnostic value compared with conventional CE MR enterography in the colorectum and terminal ileum (4). Apart from the main study cohort, a group of 30 similar patients with CD (25 men and five women; mean age, 24.4 years ± 5.5) were randomly chosen from our clinical MR enterography registry (the study was performed between August 2013 and July 2014 by using the same technique as that in the present study) for supplemental analysis of observer reproducibility.

Study Procedures

All 50 prospective patients underwent clinical assessment, including CD activity index, MR enterography, and colonoscopy within 1 week (median time between assessments, 1 day). Patients were not allowed to take medications to modify bowel inflammation in CD in between these examinations.

MR enterography.—MR enterography was performed after oral administration of 1500 mL of 2.5% sorbitol solution. A 3-T imaging unit (Ingenia; Philips Healthcare, Best, the Netherlands) was used. Briefly, the following sequences were performed: coronal T2-weighted half-Fourier sequences with and without fat suppression; coronal and axial T2-like steady-state gradient-echo sequences with fat suppression; coronal free-breathing DWI (with *b* factors of 0 and 900 sec/mm^2) and apparent diffusion coefficient (ADC) mapping; coronal T1-weighted spoiled gradient-echo sequences with fat suppression, including unenhanced imaging and enteric phase and portal venous phase sequences performed after intravenous administration of 0.2 mL per kilogram of body weight of gadoterate meglumine (Dotarem; Guerbet, Villepinte, France) at a rate of 2 mL/sec followed by a saline flush; and an axial delayed CE T1-weighted spoiled gradient-echo sequence with fat suppression. To avoid bowel peristalsis, 10 mg of scopolamine-*N*-butyl bromide (Buscopan; Boehringer Ingelheim, Ingelheim, Germany) was administered intravenously three times at intervals during the imaging examination. Further technical details, including injection timing, are provided in Appendix E1 and Table E1 (online).

Ileocolonoscopy.—Endoscopy was performed after bowel preparation by using 4 L of polyethylene glycol. Three experienced gastroenterologists (K.J.K., S.K.Y., and Sang H. Park, each with experience in performing more than 1000 colonoscopy examinations in patients with CD) performed the examinations by using a video colonoscope (CF H260AL or CF H260AI; Olympus Optical, Tokyo, Japan). They knew that the patients were undergoing endoscopy with regard to CD but were unaware of the MR enterography findings or other clinical findings. The terminal ileal findings were used as the reference

Figure 1

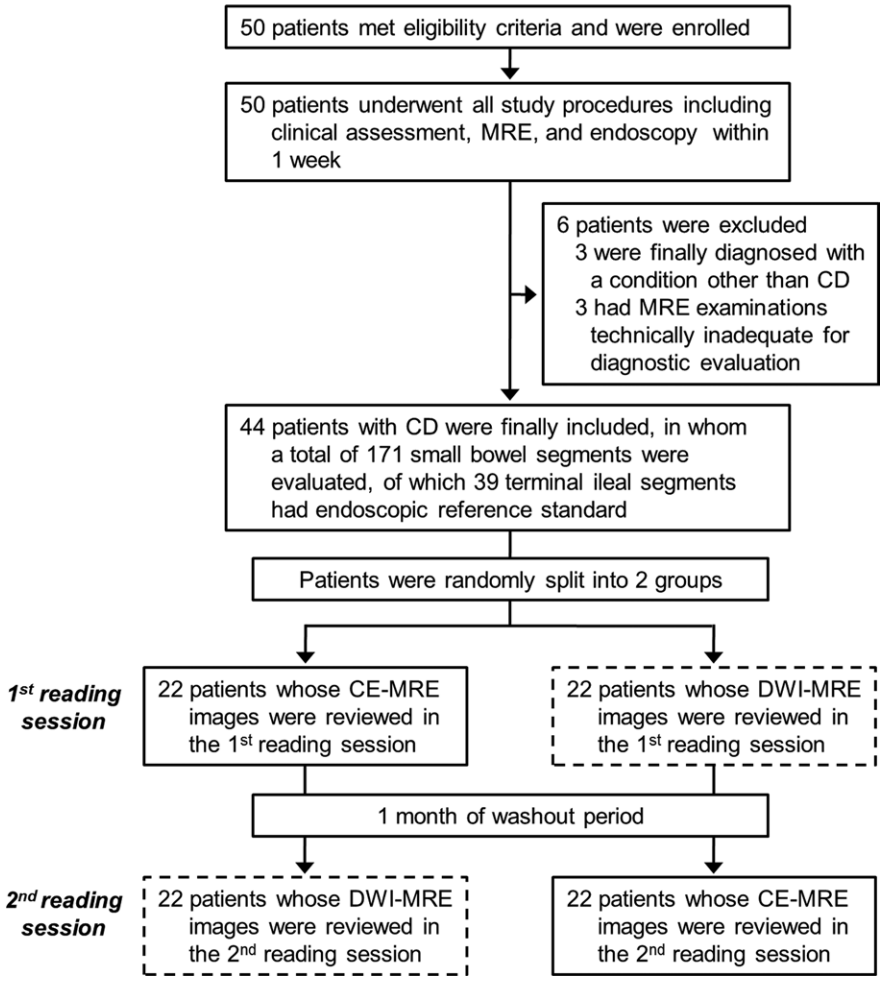


Figure 1: Study flow diagram. *MRE* = MR enterography.

standard for the analysis with regard to the terminal ileum. The length of the terminal ileum that was evaluated was recorded, and its segmental CD endoscopic index of severity (CDEIS) (17) was determined. The small bowel proximal to the terminal ileum was not evaluated endoscopically.

MR Enterography Review

We identified patients who received a final diagnosis of CD according to established clinical, radiologic, endoscopic, and histopathologic criteria (18). A radiologist (S.Y.K., with 2 years of experience in MR enterography) checked the technical adequacy of MR enterography. Three examinations deemed inadequate for diagnostic evaluation were excluded. Then, another radiologist (Seong H. Park, with 5 years of experience in MR enterography) who did not participate in any other image review in the study selected small-bowel segments to be used in the comparison between conventional MR enterography (ie, T2-weighted imaging with CE T1-weighted sequences, subsequently referred to as *CE MR enterography*) and MR enterography without intravenous contrast material (ie, T2-weighted imaging with DWI, subsequently referred to as *DWI MR enterography*) by using CE MR enterography images alone according to the following predetermined criteria: *(a)* the terminal ileum, *(b)* a "severely" inflammatory segment (typically demonstrating multiple cardinal findings of bowel inflammation and involving most of the bowel wall in the segment of interest), *(c)* a segment with "mild" inflammation (the segment with the least remarkable CE MR enterography findings), *(d)* a segment with penetrating complications, and *(e)* well-distended normal-appearing small bowel (one segment each for the ileum and the jejunum, if applicable). The bowel segments were spatially separated by selecting them from different vascular territories or different quadrants of the abdomen. Since one segment could fulfill multiple criteria and some criteria could not be met by any segments, the actual number of segments selected in each patient varied. We chose this approach instead of free-response image interpretation according to some anatomic or arbitrary subdivisions of the small bowel for several reasons. Free-response interpretation has a substantial risk of exaggerating the agreement between DWI and CE MR enterography by falsely rendering a "concordant" interpretation of two findings of inflammation determined by using two MR enterography methods for two different sites in any bowel subdivision (ie, two discordant interpretations). Our method enables accurate location-by-location comparison between DWI and CE MR enterography images but may have a risk of selection bias. To minimize the selection bias, we preplanned the aforementioned criteria, aiming at assembling bowel segments by demonstrating a broad spectrum of findings, from severe inflammation to normalcy, as seen at CE MR enterography. Furthermore, the terminal ileum was included for all patients without any artificial selection to enable a more generalizable unbiased subanalysis. The length of the terminal ileum that was evaluated endoscopically was revealed to the readers (for precise location-wise matching with endoscopy findings). For other segments, a bowel length of approximately 10 cm was marked electronically on the coronal T2-weighted half-Fourier images in the same manner by using short lines traversing the bowel at the start and the end of each segment. The markings were placed carefully to avoid inadvertently pointing to any particular disease processes, such as a fistulous tract.

Main review.—Images of the small-bowel segments were interpreted in consensus by two other radiologists (N.S. and B.K.K., each with 2 years of experience in MR enterography) to make a factual comparison between DWI and CE MR enterography while minimizing confounding effects. Instead, we separately analyzed observer reproducibility of DWI MR enterography. The readers were blinded to the endoscopy findings or other clinical findings, except for the diagnosis of CD. They were also unaware how the bowel segments were selected, which, together with the varying number of segments per patient, helped achieve impartial image review. The patients were randomly assigned to one of two groups, and the images were reviewed during two sessions by using a crossover design (Fig 1). In the first session, one group of images was interpreted by using either CE or DWI MR enterography. After a month of washout period and random reshuffling of the image review order, the examination data were interpreted by using the opposite MR enterography methods in the second session. The readers recorded the following findings and scored bowel inflammation severity according to the methods established in previous studies (Table 1) (4,19,20) for each segment: *(a)* mural thickening (score of 0–3); *(b)* mural hyperenhancement (score of 0–3, CE MR enterography only); *(c)* increased mural or perimural signal intensity on T2-weighted images, representing enteric or perienteric edema (score of 0–3); *(d)* increased vasa recta (not included in the severity scoring, CE MR enterography only); *(e)* restricted mural diffusion (score of 0–3, DWI MR enterography only), defined as hyperintensity on DWI images (b = 900 sec/mm^2) and hypointensity on ADC maps through a comparison with lymph nodes and the spleen (4); and *(f)* penetrating complications and their specific nature (not included in the severity scoring). Distinction of perienteric abscess from inflammation and/or phlegmon at CE and DWI MR imaging was made according to the presence of apparent rim enhancement and marked diffusion restriction at DWI (Fig 2) (21), respectively. We did not measure ADC values, since ADC measurement in the bowel is presumably seldom used in clinical practice, although it has appeared in research studies. Bowel segments that demonstrated one or more of the findings were considered actively inflammatory. MR enterography scores

Table 1

MR Enterography Scores of Bowel Inflammation Severity

Parameter	Score of 0	Score of 1	Score of 2	Score of 3
Mural thickness (mm)*	1–3	>3–5	>5–7	>7
Mural signal intensity on T2-weighted images*	Equivalent to that of normal bowel wall	Minor increase in signal intensity: Bowel wall appears dark gray on fat-saturated images	Moderate increase in signal intensity: Bowel wall appears light gray on fat-saturated images	Marked increase in signal intensity: Bowel wall contains areas of high signal intensity, approaching that of the luminal content
Perimural signal intensity on T2-weighted images*	Equivalent to that of normal mesentery	Increase in mesenteric signal intensity but no fluid	Small fluid rim (≤2 mm)	Larger fluid rim (>2 mm)
Enhancement on T1-weighted images (scored at CE MR enterography only)*	Equivalent to that of normal bowel wall	Minor enhancement in bowel-wall signal intensity that is greater than that of normal small bowel but markedly less than that of nearby vascular structures	Moderate enhancement: Bowel-wall signal intensity increased but somewhat less than that of nearby vascular structures	Marked enhancement: Bowel-wall signal intensity approaches that of nearby vascular structures
Signal intensity on DWI images (scored at DWI MR enterography only)†	No increased diffusion restriction	Increased DWI signal intensity that is similar to but slightly lower than that of lymph nodes	Increased DWI signal intensity, indistinguishable from that of lymph nodes	Increased DWI signal intensity, higher than that of lymph nodes and the spleen

Note.—Scores of at least 1 indicate signs of active inflammation.

* According to references 19 and 20.

† According to reference 4.

of bowel inflammation severity (scores of 0–12) were derived by adding the individual scores.

Review for observer reproducibility.—Thirty bowel segments were randomly chosen from the main study cohort and were mixed with the 30 additional registry patients whose terminal ilea (10 cm in length) were used for analysis. The 60 bowel segments were reviewed by the two study readers independently, twice in two sessions 1 month apart, with random reshuffling of image review order. This review was conducted more than 6 months apart from the main image review and clinical interpretation of the additional registry patient examination data to avoid recall bias.

Figure 2

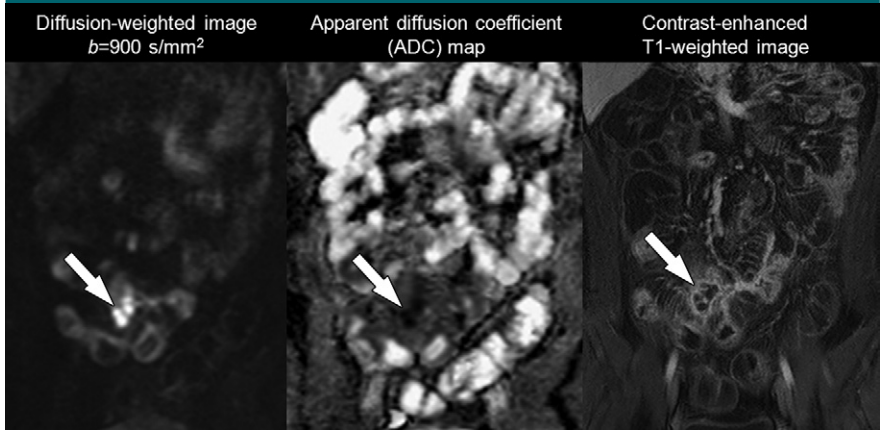


Figure 2: MR enterography images of a perienteric abscess in a 25-year-old man with CD. A 2.7-cm rim-enhancing perienteric mass (arrows) adjacent to an ileal segment as seen on the CE T1-weighted image shows marked diffusion restriction at DWI and on the ADC map.

Statistical Analysis

Sample size.—Sample size was estimated regarding the primary study end point, the percentage agreement between DWI and CE MR enterography in the dichotomous interpretation of bowel inflammation. Expected agreement of 90%, noninferiority margin of 80% (ie, delta of 10%), power of 80%, α of 5%, and adjustment for clustered data structure by using the design effect $n' = n \cdot [1 + (m - 1)\rho]$ (22,23) yielded 45 patients (where where n' is the adjusted sample size, n is the unadjusted sample size, m is the mean cluster size, and ρ is the intracluster correlation). The noninferiority margin was chosen by considering the following factors. In a similar noninferiority study on the investigation of computed tomographic (CT) enterography, the same margin was adopted by considering the reliability of CT enterography in CD (24), while MR enterography reportedly has a slightly lower reliability when compared with

CT enterography (25,26). A 10% decrease in diagnostic outcomes has typically been adopted as delta in published noninferiority diagnostic imaging studies (27). We enrolled 50 patients and assumed a 10% dropout rate. More details are provided in Appendix E1 (online).

Dichotomous interpretation of bowel inflammation.—The proportional agreement between DWI and CE MR enterography and its one-sided 95% confidence interval (CI) was estimated by using generalized estimating equations. The statistical noninferiority of DWI MR enterography to CE MR enterography was established if the lower boundary of the CI was more than 80%. The analysis was performed for all segments and, as subanalyses, for the terminal ilea (to obtain results unaffected by the bowel selection) and inflamed segments only (for a conservative analysis, since normal-appearing segments, in large numbers, were likely to inflate the agreement). In the terminal ileum, the sensitivity and specificity for diagnosis of active inflammation, defined as a segmental CDEIS score of at least 3 at endoscopy (28,29), were compared between DWI and CE MR enterography by using the McNemar test.

Assessment of bowel inflammation severity.—The correlation between DWI and CE MR enterography scores of bowel inflammation severity was estimated by using the linear mixed model for all segments, as well as for the terminal ilea and inflamed segments. In the terminal ileum, the correlation between the MR enterography scores and endoscopic CDEIS scores was also analyzed by using the Spearman coefficient, and the results were compared between DWI and CE MR enterography by using a modified *z* statistic (30).

Observer reproducibility of DWI *MR enterography.*—Intra- and interobserver reproducibility was determined by using proportional agreement and intraclass correlation coefficients for the 60 segments and for the 30 terminal ilea of additional patients from our registry (to obtain more generalizable results unaffected by the bowel selection).

Table 2

Characteristics of Study Subjects

Parameter	Value
Mean age (y)*†	
All subjects	26.9 ± 6.1
Men	26.9 ± 5.6
Women	27.1 ± 7.9
Patient sex	
No. of men	34
No. of women	10
Body mass index (kg/m^2)†	20.0 ± 2.9
CD activity index†	201.53 ± 111.14
Small-bowel segments analyzed	
Total no. of segments	171
Median CE MR enterography score of bowel inflammation severity	2 (0–12) for all segments, 6 (1–12) for 90 segments with scores ≥ 1
Terminal ileum with endoscopic reference standard‡	39
Median segmental CDEIS score	15.5 (0–34)
Segmental CDEIS score ≥ 3‡	30
Segmental CDEIS score < 3‡	9

Note.—Numbers in parentheses are ranges.

* There was no significant age difference between men and women ($P = .745$ according to results of the Mann-Whitney *U* test).

† Data are means ± standard deviations.

‡ Data are the number of small-bowel segments.

For sample size estimation, PASS 2008 software (NCSS, Kaysville, Utah) was used, and SAS version 9.2 was used (SAS Institute, Cary, NC) for other analyses. A *P* value less than .05 was considered to indicate a statistically significant difference.

Results

Subjects

Of the 50 patients enrolled, 47 received a final diagnosis of CD (Table 2). Three patients with CD underwent MR enterography examinations that were technically inadequate for diagnostic evaluation, primarily owing to bowel peristalsis during CE imaging in two patients and a large amount of colonic air that caused artifacts at DWI in one patient. The remaining 44 patients (34 men and 10 women; mean age, 26.9 years ± 6.1) constituted the final cohort for analysis, and a total of 171 small-bowel segments were evaluated (Fig 1). The inflammation severity of the selected bowel segments as assessed with the CE MR enterography score were distributed diffusely across the entire value range (Fig 3), except for uninflamed segments, indicating that unskewed sampling of bowel segments was achieved. All 44 patients underwent endoscopy, but the terminal ileum was evaluated successfully in 39 patients for a length of at least 5 cm (range, 5–20 cm; median length, 10 cm). Thirty patients had active terminal ileal inflammation at endoscopy (segmental CDEIS score ≥ 3), while the remaining nine did not.

Dichotomous Interpretation of Bowel Inflammation

The agreement between DWI and CE MR enterography was 91.8% for all segments (157 of 171 segments; one-sided 95% CI: ≥88.4%; Table 3), establishing the statistical noninferiority of DWI MR enterography. There were 14 segments where the two MR enterography methods yielded discordant interpretations, and the CE MR enterography inflammation severity scores ranged from

0 to 4 (including two terminal ilea, for which CDEIS scores were 0 and 2). Thirteen of the 14 segments were interpreted as having negative findings at DWI MR enterography and positive findings at CE MR enterography for bowel inflammation. The agreement was 95% (37 of 39 segments; one-sided 95% CI: ≥85%) for the terminal ilea that were evaluated endoscopically (Table 3), which also fulfilled the noninferiority criterion, and was 86% (77 of 90 segments; one-sided 95% CI: ≥79.7%) for inflamed segments. DWI and CE MR enterography did not differ significantly with regard to the sensitivity and specificity for the diagnosis of endoscopy-proven terminal ileal inflammation ($P > .999$; Table 4). Representative patient examinations are shown in Figures 4–6.

Figure 3

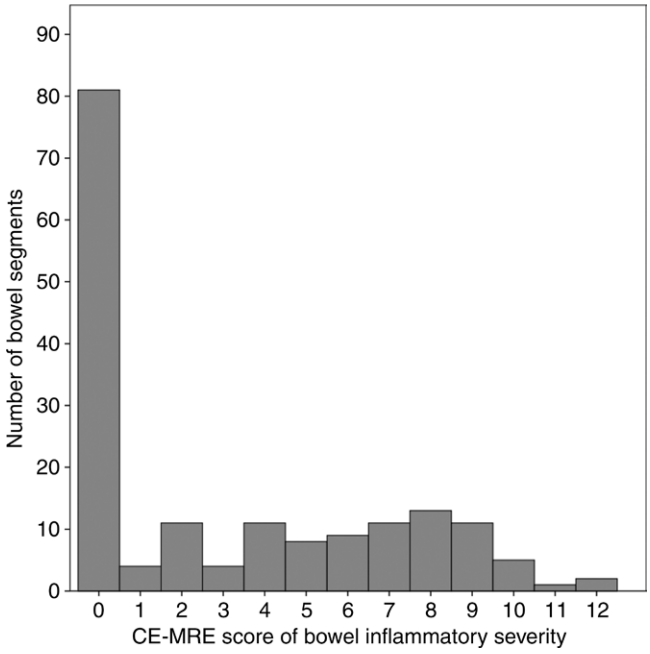


Figure 3: Histogram of CE MR enterography *(MRE)* (including T2-weighted sequences and CE T1-weighted sequences) scores of bowel inflammation severity of the small-bowel segments selected for analysis. The inflammation severity scores for 90 segments that had inflammation at CE MR enterography distribute diffusely across the entire value range, indicating an effective sampling of a broad spectrum of bowel inflammation findings.

Assessment of Bowel Inflammation Severity

The correlation coefficient between DWI and CE MR enterography scores of bowel inflammation severity was 0.937 ($P < .001$) for all segments, 0.869 ($P < .001$) for the terminal ilea that were evaluated endoscopically, and 0.870 ($P < .001$) for inflamed segments (Fig 7). The DWI and CE MR enterography scores did not differ significantly with regard to the correlation with CDEIS scores in the terminal ileum ($P = .110$), with the correlation coefficient being 0.606 ($P < .001$) and 0.706 ($P < .001$), respectively.

Observer Reproducibility in DWI MR Enterography

The reproducibility of DWI MR enterography is summarized in Table 5. Intra- and interobserver reproducibility was fairly high and tended to be slightly lower when the terminal ilea of the external patients were considered separately.

Assessment of Penetrating Complications

Eight bowel segments showed penetrating complications at CE MR enterography: four segments with 1.7- to 2.7-cm abscesses, two segments with enteroenteric fistula, and one segment each with sinus tract and

Table 3

Agreement between MR Enterography Methods in the Dichotomous Interpretation of Small-Bowel Inflammation

	Findings in All Segments Imaged with DWI MR Enterography (DWI with T2-weighted sequences) ($n = 171$)			Terminal Ileum Imaged with DWI MR Enterography (DWI with T2-weighted sequences) and Endoscopy as the Reference Standard ($n = 39$)		
CE MR Enterography Finding	Inflammation	No Inflammation	Total	Inflammation	No Inflammation	Total
Inflammation	77	13	90	30	1	31
No inflammation	1	80	81	1	7	8
Total	78	93	171	31	8	39

Note.—Data are the number of small-bowel segments.

Table 4

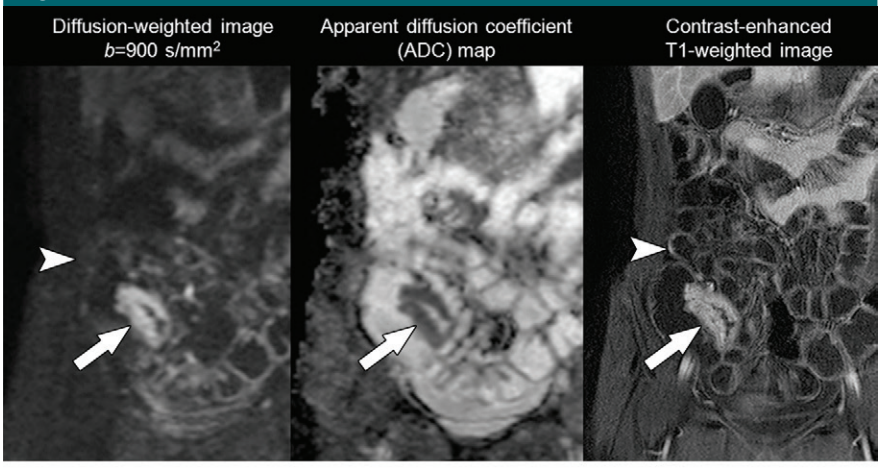
Accuracy of MR Enterography for the Diagnosis of Endoscopically Proven (CDEIS Score ≥ 3) Active Inflammation in the Terminal Ileum

Parameter	CE MR Enterography (%)	DWI MR Enterography (%)	*P* Value
Sensitivity*	93 (28/30)	93 (28/30)	>.999
Specificity	67 (6/9)	67 (6/9)	>.999
Accuracy	87 (34/39)	87 (34/39)	Not applicable
Positive predictive value	90 (28/31)	90 (28/31)	Not applicable
Negative predictive value	75 (6/8)	75 (6/8)	Not applicable

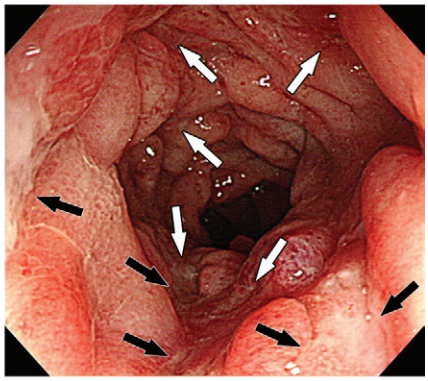
Note.—Numbers in parentheses are the number of segments used to calculate the percentages.

* The interpretive results of CE and DWI MR enterography were exactly the same with regard to sensitivity for segments with inflammation (CDEIS ≥ 3), whereas, with regard to the other diagnostic parameters, the MR enterography interpretations in individual bowel segments were not exactly the same despite the same outcome values, owing to the presence of two discordant interpretations between CE and DWI MR enterography.

Figure 4



a.



b.

Figure 4: DWI MR enterography (T2-weighted sequences with DWI without intravenous contrast material) and CE MR enterography images demonstrate a concordant interpretation and a discordant interpretation of small-bowel inflammation in a 23-year-old woman with CD. **(a)** The terminal ileum (arrows) shows remarkably increased signal intensity on DWI images and hypointensity on the ADC map, indicating diffusion restriction. It concordantly shows marked mural thickening and hyperenhancement on the CE T1-weighted image. In contrast, another ileal segment (arrowheads) with only mild inflammation as seen on the CE T1-weighted image does not show diffusion restriction. **(b)** Colonoscopic image of the terminal ileum shows multiple deep ulcers (arrows) and markedly swollen intervening mucosa.

phlegmon. With DWI MR enterography, the penetrating complications were found in seven of eight segments, there was a failure to detect a thin 2-cm-long sinus tract, and no penetrations were reported as unseen at CE MR enterography. When the specific nature of the penetrating complications was also considered, DWI and CE MR enterography findings were discordant in two of the seven segments: A 2.2-cm perienteric abscess and a phlegmon as seen at CE MR enterography were interpreted as a phlegmon and an enteroenteric fistula, respectively, at DWI MR enterography.

Discussion

The results of this study suggest that MR enterography performed with DWI without intravenous contrast material can be a viable option for the evaluation of inflammation of generally well-distended small bowel in CD. Although the results from all 171 bowel segments may lead to some overestimation of the similarity between DWI and CE MR enterography, the coherent results in the terminal ileum and in the inflamed segments indicate the robustness of the study results. Our results agree with those of recent studies in which a high correlation was demonstrated between absolute ADC values (correlation coefficient of −0.77 and −0.8, respectively) (5,9) or a composite index ("Clermont score") derived from ADC values (correlation coefficient of 0.91 and 0.99, respectively) (5,6) and a CE MR enterography index of bowel inflammation severity (Magnetic Resonance Index of Activity, or MaRIA, score) (31,32) in the small bowel of patients with CD.

Our study results should be extrapolated to clinical practice with some caution. This study was focused on proving the similarity between DWI and CE MR enterography for assessment of bowel inflammatory activity in CD rather than diagnosis of bowel inflammation in a broader sense, which first requires identification of bowel areas that are suspicious for inflammation before assessment of inflammatory

Figure 5

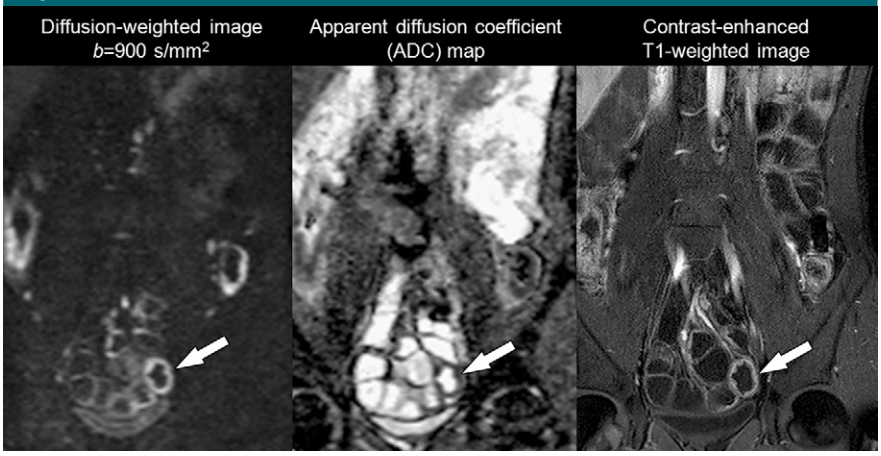
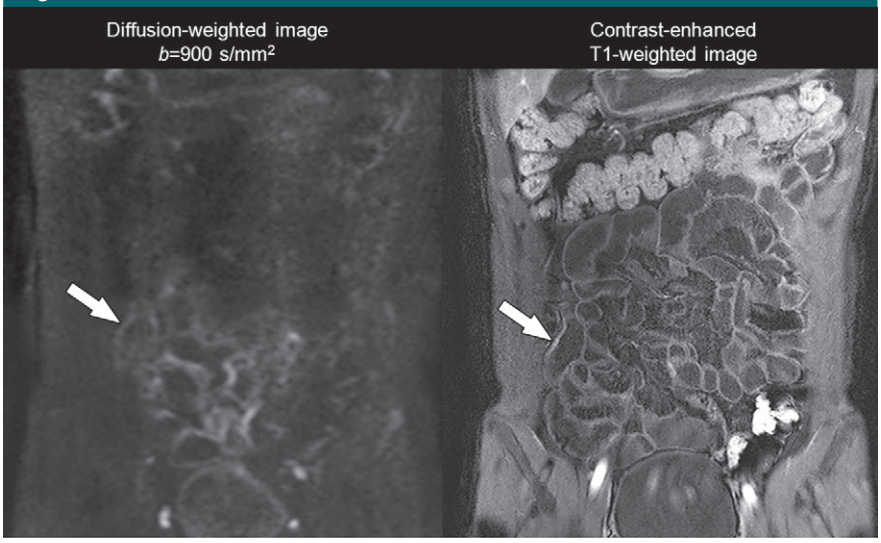
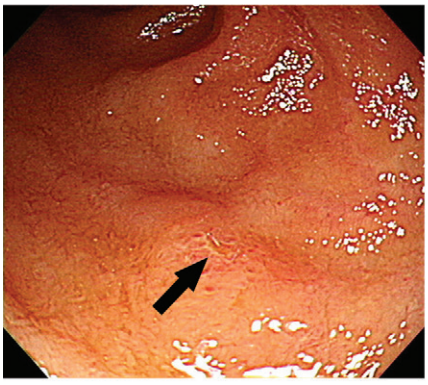


Figure 5: DWI and CE MR enterography images demonstrate a concordant interpretation of small-bowel inflammation in a 27-year-old man with CD. A pelvic ileal segment (arrows) shows remarkable diffusion restriction and concordantly shows mural thickening and hyperenhancement on the CE T1-weighted image.

Figure 6



a.



b.

Figure 6: DWI and CE MR enterography images demonstrate a discordant interpretation of small-bowel inflammation in a 26-year-old man with CD. **(a)** The lateral wall of the terminal ileum (arrows) shows increased enhancement and slight thickening on the CE T1-weighted image but does not show diffusion restriction. **(b)** Colonoscopic image of the terminal ileum shows scattered aphthoid lesions (arrow).

activity. Most of the discordant interpretations between DWI and CE MR enterography in this study were negative bowel inflammation findings at DWI MR enterography and positive bowel inflammation findings at CE MR enterography. This is likely because we investigated bowel segments that were generally well prepared and/or distended. Positive DWI MR enterography findings and negative CE MR enterography findings may occur more frequently in less well prepared, less distended bowel segments, which are typically reported to have false-positive findings at DWI (4,14,15). Furthermore, although small, some observer variability existed in the interpretation of DWI MR enterography findings. Therefore, the discrepancy between DWI and CE MR enterography may be a bit greater in real-world practice. Our study may provide a solid reason to use DWI as an alternative to imaging with intravenous contrast material when performing MR enterography for patients with CD in whom intravenous contrast material cannot be applied or is difficult to apply. However, omitting the use of intravenous contrast material in a standardized fashion is not suggested.

According to the bowel segments associated with penetrating complications in this study, there seems to be a greater discrepancy between DWI and CE MR enterography in the evaluation of penetrating complications. This result may underscore the fact that evaluation of penetrating complications is heavily dependent on examination of anatomic details, for which DWI falls short. CE MR enterography is accepted as a reliable diagnostic tool for the diagnosis of penetrating complications in CD (33). In contrast, there is a paucity of data in the literature regarding DWI for the evaluation of penetrating complications of CD, and the results of our study, as well as those in previous studies, may not yet indicate a clear effectiveness of DWI for this task (6,10,11,34,35). Considering that our sample size was small for the investigation of penetrating complications and yet the discordance was considerable, this is an important limitation of this

Figure 7

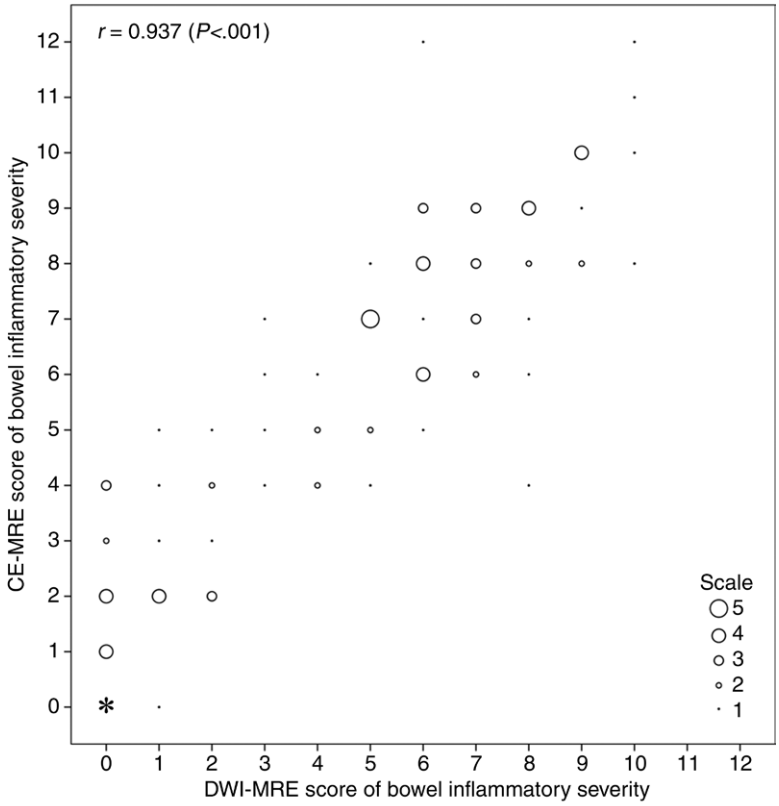


Figure 7: Scatterplot shows the correlation between DWI and CE MR enterography *(MRE)* scores of bowel inflammation severity. The dot size represents the number of bowel segments (one to five). Eighty segments that had a score of 0 at both DWI and CE MR enterography (*) are not directly shown because of scaling.

Table 5

Intra- and Interobserver Reproducibility in the Evaluation of Small-Bowel Inflammation with DWI MR Enterography

	Intraobserver Reproducibility		Interobserver Reproducibility	
Parameter	Reader 1	Reader 2	Session 1	Session 2
All segments (n = 60)				
Dichotomous assessment, proportional agreement (%)	88 (53/60)	100 (60/60)	88 (53/60)	93 (56/60)
Semiquantitative assessment (scoring), intraclass correlation coefficient	0.881*	0.908*	0.855†	0.858†
Terminal ilea from patients in the registry group (n = 30)				
Dichotomous assessment, proportional agreement (%)	87 (26/30)	100 (30/30)	87 (26/30)	93 (28/30)
Semiquantitative assessment (scoring), intraclass correlation coefficient	0.745*	0.836*	0.721†	0.749†

Note.—Numbers in parentheses are the number of segments used to calculate the percentages.

* Calculated by using a one-way random-effects model.

† Calculated by using a two-way random-effects model.

study, as well as, potentially, DWI MR enterography. The role of DWI in the diagnosis of penetrating complications of CD should be further defined in large cohorts.

This study had limitations. First, the identification of the bowel segments to be analyzed may have introduced some selection bias. However, as explained earlier, since we tried to minimize and resolve the bias throughout the preplanned study design and analysis, we believe that the intended purpose was fairly adequately addressed in the study. Second, the endoscopic reference standard was available only in the terminal ileum. Nonetheless, this is an unavoidable limitation of any small-bowel imaging studies, since location-matched endoscopic correlation is essentially impossible for other parts of the small bowel. Last, in our study, we did not compare DWI and CE MR enterography with regard to the evaluation of strictures, since no relevant patients existed in the study cohort.

In conclusion, DWI MR enterography was noninferior to CE MR enterography for the evaluation of inflammation of generally well-distended small bowel in CD, but considerable discordance was shown in the diagnosis of penetrating complications.

Disclosures of Conflicts of Interest: N.S. disclosed no relevant relationships. **Seong H. Park** Activities related to the present article: author received a grant from Dongkook Parmaceutical. Activities not related to the present article: disclosed no relevant relationships. Other relationships: disclosed no relevant relationships. **K.J.K.** disclosed no relevant relationships. **B.K.K.** disclosed no relevant relationships. **Y.L.** disclosed no relevant relationships. **S.K.Y.** disclosed no relevant relationships. **B.D.Y.** disclosed no relevant relationships. **Sang H. Park** disclosed no relevant relationships. **S.Y.K.** disclosed no relevant relationships. **S.B.** disclosed no relevant relationships. **K.H.** disclosed no relevant relationships. **H.K.H.** disclosed no relevant relationships.

References

1. Lewis B, Mukewar S, Lopez R, Brzezinski A, Hall P, Shen B. Frequency and risk factors of renal insufficiency in inflammatory bowel disease inpatients. Inflamm Bowel Dis 2013;19(9):1846–1851.

2. Daftari Besheli L, Aran S, Shaqdan K, Kay J, Abujudeh H. Current status of nephro-

genic systemic fibrosis. Clin Radiol 2014; 69(7):661–668.

3. Thomsen HS, Morcos SK, Almén T, et al. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol 2013;23(2):307–318.
4. Kim KJ, Lee Y, Park SH, et al. Diffusion-weighted MR enterography for evaluating Crohn's disease: how does it add diagnostically to conventional MR enterography? Inflamm Bowel Dis 2015;21(1):101–109.
5. Caruso A, D'Incà R, Scarpa M, et al. Diffusion-weighted magnetic resonance for assessing ileal Crohn's disease activity. Inflamm Bowel Dis 2014;20(9):1575–1583.
6. Hordonneau C, Buisson A, Scanzi J, et al. Diffusion-weighted magnetic resonance imaging in ileocolonic Crohn's disease: validation of quantitative index of activity. Am J Gastroenterol 2014;109(1):89–98.
7. Sirin S, Kathemann S, Schweiger B, et al. Magnetic resonance colonography including diffusion-weighted imaging in children and adolescents with inflammatory bowel disease: do we really need intravenous contrast? Invest Radiol 2015;50(1):32–39.
8. Tielbeek JA, Ziech ML, Li Z, et al. Evaluation of conventional, dynamic contrast enhanced and diffusion weighted MRI for quantitative Crohn's disease assessment with histopathology of surgical specimens. Eur Radiol 2014;24(3):619–629.
9. Buisson A, Joubert A, Montoriol PF, et al. Diffusion-weighted magnetic resonance imaging for detecting and assessing ileal inflammation in Crohn's disease. Aliment Pharmacol Ther 2013;37(5):537–545.
10. Ream JM, Dillman JR, Adler J, et al. MRI diffusion-weighted imaging (DWI) in pediatric small bowel Crohn disease: correlation with MRI findings of active bowel wall inflammation. Pediatr Radiol 2013;43(9):1077–1085.
11. Neubauer H, Pabst T, Dick A, et al. Small-bowel MRI in children and young adults with Crohn disease: retrospective head-to-head comparison of contrast-enhanced and diffusion-weighted MRI. Pediatr Radiol 2013; 43(1):103–114.
12. Oto A, Kayhan A, Williams JT, et al. Active Crohn's disease in the small bowel: evaluation by diffusion weighted imaging and quantitative dynamic contrast enhanced MR imaging. J Magn Reson Imaging 2011;33(3):615–624.
13. Oussalah A, Laurent V, Bruot O, et al. Diffusion-weighted magnetic resonance without bowel preparation for detecting colonic inflammation in inflammatory bowel disease. Gut 2010;59(8):1056–1065.
14. Kiryu S, Dodanuki K, Takao H, et al. Free-breathing diffusion-weighted imaging for the assessment of inflammatory activity in Crohn's disease. J Magn Reson Imaging 2009;29(4):880–886.
15. Oto A, Zhu F, Kulkarni K, Karczmar GS, Turner JR, Rubin D. Evaluation of diffusion-weighted MR imaging for detection of bowel inflammation in patients with Crohn's disease. Acad Radiol 2009;16(5):597–603.
16. Ahn S, Park SH, Lee KH. How to demonstrate similarity by using noninferiority and equivalence statistical testing in radiology research. Radiology 2013;267(2):328–338.
17. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut 1989;30(7):983–989.
18. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol Suppl 1989;170:2–6; discussion 16–19.
19. Steward MJ, Punwani S, Proctor I, et al. Non-perforating small bowel Crohn's disease assessed by MRI enterography: derivation and histopathological validation of an MR-based activity index. Eur J Radiol 2012; 81(9):2080–2088.
20. Tielbeek JA, Makanyanga JC, Bipat S, et al. Grading Crohn disease activity with MRI: interobserver variability of MRI features, MRI scoring of severity, and correlation with Crohn disease endoscopic index of severity. AJR Am J Roentgenol 2013;201(6):1220–1228.
21. Oto A, Schmid-Tannwald C, Agrawal G, et al. Diffusion-weighted MR imaging of abdominopelvic abscesses. Emerg Radiol 2011;18(6):515–524.
22. Zhou XH, Obuchowski NA, McClish DK. Statistical methods in diagnostic medicine. 2nd ed. Hoboken, NJ: Wiley, 2011; 198–199.
23. Barratt H, Kirwan M. Clustered data—effects on sample size and approaches to analysis. HealthKnowledge: Public Health Action Support Team. http://www.healthknowledge.org.uk/public-health-textbook/research-methods/1a-epidemiology/clustered-data. Accessed June 2015.
24. Lee SJ, Park SH, Kim AY, et al. A prospective comparison of standard-dose CT enterography and 50% reduced-dose CT enterography with and without noise reduction for evaluating Crohn disease. AJR Am J Roentgenol 2011;197(1):50–57.
25. Jensen MD, Ormstrup T, Vagn-Hansen C, Østergaard L, Rafaelsen SR. Interobserver and intermodality agreement for detection of small bowel Crohn's disease with MR enterography and CT enterography. Inflamm Bowel Dis 2011;17(5):1081–1088.
26. 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(3):751–761.
27. Park SH, Ahn S, Hong N, Park JH, Hwang SS, Lee KH. Quality of reporting noninferiority/similarity in research studies of diagnostic imaging. Radiology 2014;270(1):241–247.
28. Sipponen T, Nuutinen H, Turunen U, Färkkilä M. Endoscopic evaluation of Crohn's disease activity: comparison of the CDEIS and the SES-CD. Inflamm Bowel Dis 2010;16(12):2131–2136.
29. Sipponen T, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. Inflamm Bowel Dis 2008;14(1):40–46.
30. Steiger JH. Tests for comparing elements of a correlation matrix. Psychol Bull 1980; 87(2):245–251.
31. Rimola J, Rodriguez S, García-Bosch O, et al. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. Gut 2009;58(8):1113–1120.
32. Rimola J, Ordás I, Rodriguez S, et al. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. Inflamm Bowel Dis 2011;17(8):1759–1768.
33. Allen BC, Leyendecker JR. MR enterography for assessment and management of small bowel Crohn disease. Radiol Clin North Am 2014;52(4):799–810.
34. Schmid-Tannwald C, Agrawal G, Dahi F, Sethi I, Oto A. Diffusion-weighted MRI: role in detecting abdominopelvic internal fistulas and sinus tracts. J Magn Reson Imaging 2012;35(1):125–131.
35. Braithwaite KA, Alazraki AL. Use of the star sign to diagnose internal fistulas in pediatric patients with penetrating Crohn disease by MR enterography. Pediatr Radiol 2014;44(8):926–931.