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Observations and Research

Development of a New Index to Assess Small Bowel Inflammation Severity in Crohn's Disease Using Magnetic Resonance Enterography

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Background: The severity of small bowel (SB) inflammation in Crohn's disease (CD) patients is a key component of the therapeutic choice. We aimed to develop a SB-CD Magnetic Resonance Enterography (MRE) index of Inflammation Severity (CDMRIS).

Methods: Each gastroenterologist/radiologist pair in 13 centers selected MREs from 6 patients with SB-CD stratified on their perceived MRE inflammation severity. The 78 blinded MREs were allocated through balanced incomplete block design per severity stratum to these 13 pairs for rating the presence/severity of 13 preselected items for each SB 20-cm diseased segment. Global inflammation severity was evaluated using a 100-cm visual analog scale. Reproducibility of recorded items was evaluated. The CDMRIS was determined through linear mixed modeling as a combination of the numbers of segments with lesions highly correlated to global inflammation severity.

Results: Four hundred and forty-two readings were available. Global inflammation severity mean ± SD was 21.0 ± 16.2. The independent predictors explaining 54% of the global inflammation severity variance were the numbers of segments with T1 mild–moderate and severe intensity of enhancement, deep ulceration without fistula, comb sign, fistula, and abscess. Unbiased correlation between CDMRIS and global inflammation severity was 0.76.

Conclusions: The CDMRIS is now available to evaluate the severity of SB-CD inflammation. External validation and sensitivity-to-change are mandatory next steps.

Lay Summary

Small bowel inflammation in Crohn's disease (CD) patients is a key component of the therapeutic choice. We developed a Magnetic Resonance Enterography (MRE) index of Inflammation Severity (CDMRIS) based on intensity of enhancement, deep ulceration, comb sign, fistula, and abscess.

Key Words: CDMRIS, MRE, small bowel, Crohn

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Introduction

Crohn's disease (CD) is characterized by an inflammation that can involve the entire digestive tract. Quantifying the severity of inflammation of the lesions is a key step in the management of patients, as inflammatory lesions could lead to intestinal and extraintestinal complications that can be prevented by efficient medications.[1]

Several studies comparing preoperative radiological data with anatomopathological lesions from surgical specimens showed that magnetic resonance enterography (MRE) was reliable in recognizing inflammation of small bowel (SB) CD.[2–4] Anti-inflammatory therapies target inflammation that is potentially reversible while fibrosis is considered irreversible, and generally considered an indication for surgery.[5] Moreover, SB CD including (L3) or not (L1) colonic involvement is the most common location of the disease in about two-thirds of CD patients.[6] Approximately 10% of them have normal ileoscopy,[7] either because the disease had skipped the distal ileum (30%), developed only in the intramural and mesenteric distal ileum (65%), or appeared only in the upper gastrointestinal region (5%).[8] Therefore, there is a need for objective tools to evaluate the degree of SB inflammation. Ileocolonoscopy is the gold standard to evaluate colonic inflammation, whereas computed tomography enterography and MRE with bowel distension are the reference techniques to explore the SB because it is inaccessible by conventional endoscopy, according to the American and European guidelines.[9,10] Moreover, these imaging techniques give possibility to assess intramural disease and extramural penetrating complications.

These 2 cross-sectional imaging techniques have a similar diagnostic accuracy,[11,12] but MRE should be chosen when possible to minimize use of radiation, which is of concern to providers and patients.[13] MRE is already commonly used in clinical practice to evaluate the SB disease severity at initial diagnosis and also to monitor patients under treatment.[14]

To date, several MRE activity scores have been developed in patients with ileocolonic CD, but have major limitations. The most important one, the MaRIA (Magnetic Resonance Index of Activity), was developed and further validated at the segmental level, in 5 colonic segments and terminal ileum,[15,16] from the corresponding segmental adaptation of the Crohn's Disease Endoscopic Index of Severity (CDEIS).[17] By construction, the MaRIA is a MRE measure of disease activity in several segments of the colon and restricted to 1 segment of the SB, the terminal ileum. Indeed, the CDEIS is strictly limited to the visualization of the mucosa in the colon and the last part of terminal ileum, and its correlation with an examination able to explore the entire bowel wall and its environment such as MRE should be considered with caution. The Clermont score has the same limitations as the MaRIA score on the basis of which it was developed,[18] while the London score was developed on the basis of histopathology,[19] but using a not validated histopathological score of acute inflammation in patients with terminal ileum resection.[20]

Thus, we aimed to develop an index dedicated to specifically evaluate the severity of inflammation in SB CD tied to global inflammation severity evaluation by the gastroenterologist/radiologist pairs based on observed imaging findings, rather than tied to endoscopic or histologic sampling.

Materials and Methods

Study Design

Thirteen centers took part in this cross-sectional multicenter study. A pair of gastroenterologist and radiologist in each of the 13 centers was asked to select 6 MREs from patients with known CD involving the SB including (L3) or not (L1) colonic involvement, stratified on his/her perceived overall evaluation of SB inflammation severity, 2 nil/mild (m), 2 intermediate (i), 2 severe (s), in order to have a large range of inflammatory severities in the study sample within each center, and without any a priori about clinical, biological, endoscopic, or histological data.

The corresponding 78 MREs were centralized, anonymized, and then allocated through balanced incomplete bloc design per stratum of severity to pairs of gastroenterologist and radiologist, 1 pair per center, as shown in Figure 1 and as detailed in the supplementary method, study design. Globally, there were 442 readings and 104 rereadings, and each reader pair had to evaluate 34 MREs and to reevaluate 8 MREs, the MREs being sent to readers in 3 successive sets at a 2-month interval.

The study protocol was approved by the Institutional Review Boards of all participating centers.

MRE Protocol

MRE protocol had to be performed as recommended with bowel distension using approximately 1000 mL of oral contrast followed by spasmolytic administration, and necessarily included single-shot axial and coronal fast spin echo and steady state free precession gradient echo T2-weighted sequences without saturation, a single-shot axial or coronal fast spin echo T2-weighted sequence with fat saturation, and axial and coronal T1-weighted sequences with fat saturation before and approximately 70 s after administration of intravenous gadolinium, with the use of phased array coils at 1.5 T.[21] The slice thickness should be 5 mm for T2-weighted sequences and 3 mm for T1-weighted sequences.

Selection of the Items for Reading

The selection of items to be evaluated was based on a review of the literature performed by M.Z. to identify all the radiological items that have been associated with inflammation. A committee composed of 3 gastroenterologists and 3 radiologists proposed an initial definition of these lesions and selected MRE pictures to illustrate them. Then, they organized 2 meetings of presentation of the different items and discussions with all gastroenterologists and radiologists participating into the study in order to homogenize the definitions of all lesions. A CD-ROM containing multiple examples including the lesions discussed during the 2 meetings was given to all participants.

The following 13 items were finally selected: (1) maximal wall thickness and (2) minimal luminal diameter, as continuous items (mm); (3) mural hyperintensity in T2-weighted sequences meaning higher intensity when compared with normal loop, as absent or present; (4) lymph nodes along the intestinal loops, as absent or present; (5) lymph nodes along vascular axis, as absent or present; (6) deep ulceration without fistula meaning mucosal intramural defect visible, as absent or present; (7) "comb sign" (engorged vasa recta), as absent or present; (8) abscess, as absent or present; (9) sclerolipomatosis, as absent or present; (10) intensity of

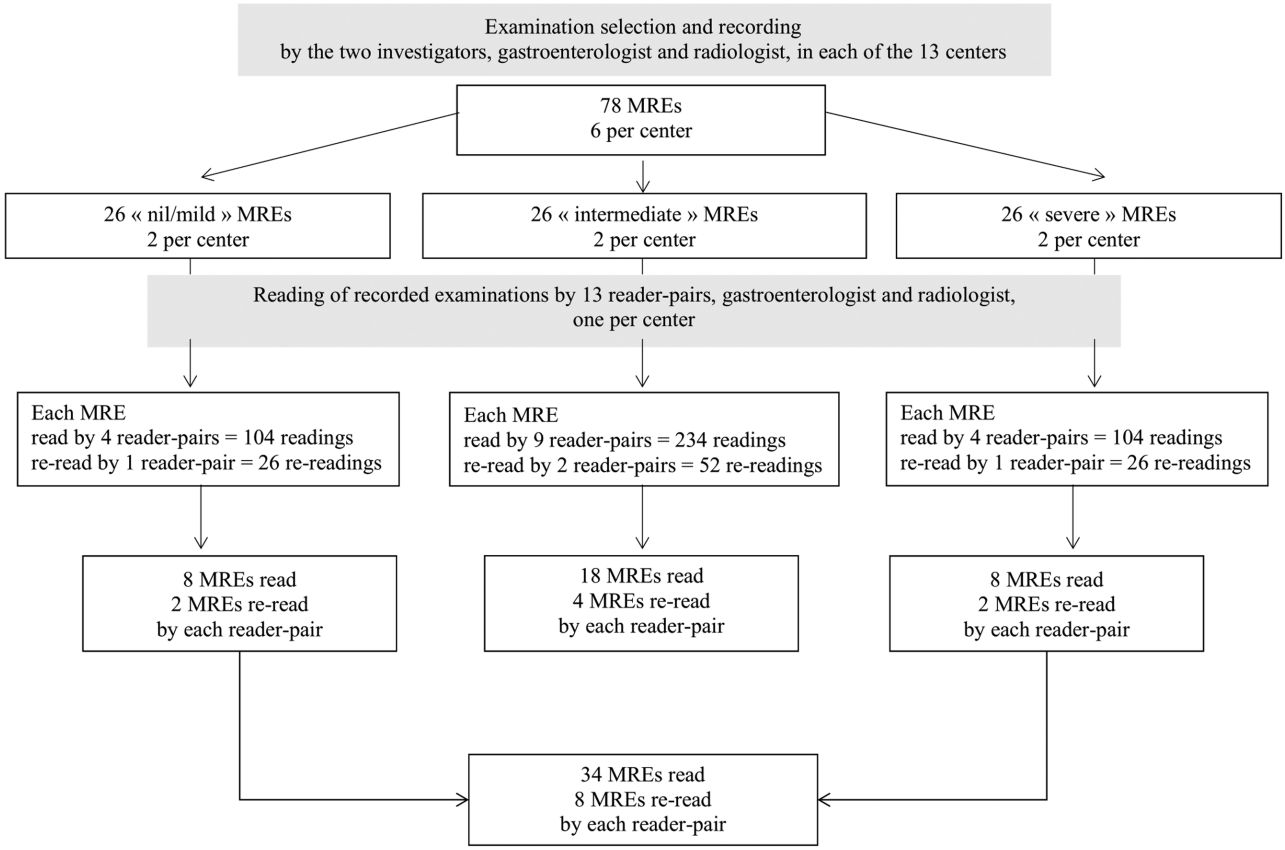

Figure 1. Flow diagram illustrating the study protocol.

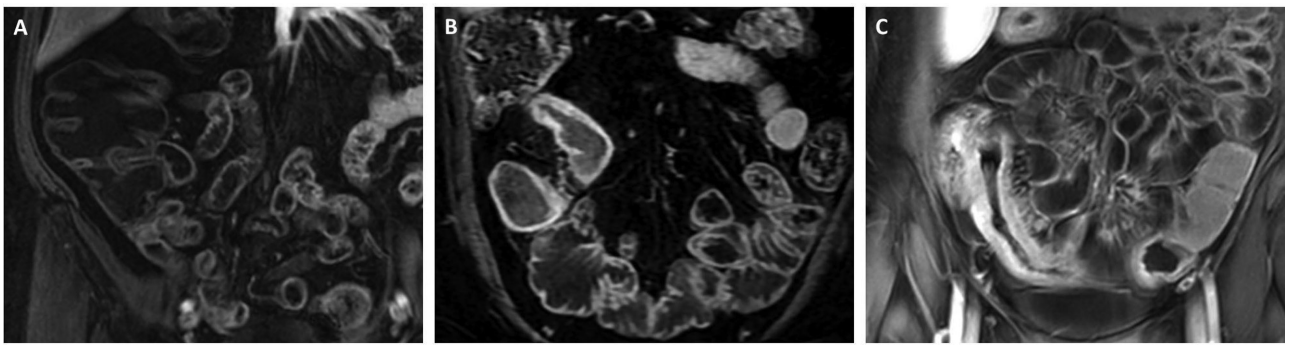

Figure 2. Examples of intensity of enhancement (IE) in T1-weighted sequences when compared to normal bowel loops, as absent (A), mild–moderate (B), or severe (C).

enhancement (IE) in T1-weighted sequences when compared to normal bowel loops, as absent, mild–moderate, or severe, subjective evaluation as usually performed in clinical practice (as illustrated in Figure 2); (11) pattern of this enhancement, as absent, homogeneous, or layered; (12) type of fatty proliferation as absent, blurred wall, or inflammatory mass; (13) fistula, as absent, blind (sinus tract), internal, or cutaneous, only the responsible segment and not the "victim" segment being considered.

Readings of MREs

The 2 investigators having selected the MREs within a center constituted the center pair in charge of MREs readings. A pair from a center did not read an MRE selected in its own center. Pairs were not aware of possible reevaluations, which did not belong to the same set than the corresponding first evaluation.

First, each reader pair had to determine the total length of diseased SB. Only the diseased SB was then evaluated. For the reading, the cumulative diseased SB was divided into 20-cm segments in retrograde fashion. The first segment started from the most distal lesion, that is the nearest to the ileocecal valve, and ended 20 cm proximally. If the lesions were contiguous, the second segment started at the end of the first segment and ended 20 cm proximally. For example, if the disease involved 30 cm of distal ileum from 15 cm before the ileocecal valve, this corresponded to 2 20-cm segments, the first one from 15

to 35 cm before the ileocecal valve with 20 cm involved by lesions, the second one from 35 to 55 cm before the ileocecal valve with 10 cm involved by lesions (from 35 to 45 cm before the ileocecal valve). If lesions were not contiguous, the second segment started from the most distal lesion not included in the previous segment and ended 20 cm proximally. For example, if the disease involved 25 cm of distal ileum from 15 cm before the ileocecal valve, and 15 cm of proximal jejunum, this corresponded to 3 20-cm segments, the first one from 15 to 35 cm before the ileocecal valve with 20 cm involved by lesions, the second one from 35 to 55 cm before the ileocecal valve with 5 cm involved by lesions (from 35 to 40 cm before the ileocecal valve), and the third one in the proximal jejunum including 15 cm involved by lesions. Apart from the segments identified, the rest of the SB was considered as normal.

Once the segments identified, the reading was made in anterograde fashion. For each identified diseased 20-cm segment, the reader pair noted all the items present in this segment among the 13 items described above. Within each segment, the readers recorded the item with the most severe grade for each item.

Finally, at the end of each MRE reading, global inflammation severity was evaluated between 0 and 100 using a 10-cm visual analog scale (VAS) in anterograde fashion, from duodenum to distal ileum, a global appraisal according to the items recorded in the different segments identified.

For each reading, the characteristics recorded per segment were synthetized as follows: extreme values of maximal thickness and minimal diameter were calculated across segments; the presence of the item in at least 1 segment and the number of segments involved by the item, at each of its levels (such as absent or present for abscess; absent, mild–moderate, or severe for IE in T1-weighted sequences), among the diseased segments for qualitative items.

Statistical Methods

Characteristics at MRE examination

The characteristics derived from observations at MRE examination were described from the different readings, ignoring rereadings, as mean ± SD, median–interquartile range (IQR) across the different readings of the examination. In addition, the total number of segments displaying the lesion across all readings and all examinations was presented due to its simplicity.

Inter- and intrareader variation study of characteristics at MRE examination

Interreader agreement level was assessed from the multiple readings of each MRE, excluding rereadings, through the intraclass correlation coefficient (ICC) taking into account the balanced incomplete block design.[22] Intrareader agreement level was assessed from the reading and rereadings of each pair, through the classical ICC using the 2-way random model.[23] Since it was demonstrated that the quadratic weighted Kappa is identical to the ICC,[24] most authors used for ICC the limits initially proposed for Kappa by Landis and Koch[25] to quantify the level of agreement, "slight" agreement for a value between 0 and 0.20, "fair" agreement for a value between 0.21 and 0.40, "moderate" agreement for a value between 0.41 and 0.60, "substantial" agreement for a value between 0.61 and 0.80, "almost perfect" agreement for a value above 0.80. We used these references between quotes to indicate that these divisions were somewhat arbitrary, but do provide useful benchmarks, as recognized by the authors themselves.

Index construction

To construct the inflammation severity index, a multiple linear mixed model was used.[26] The dependent variable was the global inflammation severity as evaluated by a pair of radiologist and gastroenterologist and measured on a VAS. The independent predictors were the presence of each item in at least 1 segment and the number of segments in which each item was observed (dichotomous item), the presence of each item in at least 1 segment and the number of segments in which each item was observed, at each level of severity or above (polytomous item), the maximal wall thickness, the minimal luminal diameter (continuous items). Two qualitative items were added, maximal wall thickness and minimal luminal diameter relatively to their median estimate (8.0 and 3.0 mm, respectively). In addition, reader pair and examination were considered as random factors to take into account the dependency between data obtained by different pairs on the same MRE or between data obtained by the same pair on different MREs.

The multiple linear mixed model allowed estimation of the linear combination of independent variables, as well as the random factor variances, through restricted maximum likelihood. The independent variables were selected using forward selection, likelihood ratio test and a P value of .01 (as justified in the supplementary method, index construction). The quality of the predicted index was assessed through the proportion of the variance of the dependent variable explained by the multiple linear mixed model (as explained in the supplementary method, index construction) and illustrated by the scatterplot of the predicted index as a function of the reader pair global inflammation severity evaluation (measured on VAS). In addition, the scatterplot of the residual as a function of the predicted inflammation severity index is shown in Supplementary Figure 1. An internal cross-validation of the correlation between global inflammation severity evaluation and predicted index, calculated without taking account of the random factors, was obtained through the bootstrap method as detailed in the supplementary method, index construction.

Results

Description of MRE Characteristics

The characteristics of the various items as derived from observations at MRE examinations by the different pairs of gastroenterologist–radiologist are described in Table 1 for continuous ones and in Table 2 for qualitative ones (dichotomous or ordinal). The mean (±SD) global inflammation severity measured on a VAS between 0 and 100 was estimated by the different pairs at 21.0 (±16.2) (IQR 7.5–30.3), and the mean (±SD) number of diseased segments per reading was 1.55 (±0.21), with 65%, 22%, 9%, and 4% of readings involving 1, 2, 3, and 4 or more segments. Among the 680 segments, 643 had location documented and roughly 40% could be considered as belonging to the last part of terminal ileum.

Table 1. Description of continuous MRE characteristics in 78 examinations (26 initially selected in each category of inflammation severity—nil/moderate, intermediate, severe—with 4, 9, and 4 readings for each MRE, respectively).

	Mean ± SD	Median	IQR
Number of diseased segments	1.55 ± 0.81	1.25	1.00–1.81
Length of diseased small bowel (cm)	18.7 ± 15.1	15.7	8.2–26.7
Maximal wall thickness (mm) across segments	7.9 ± 2.8	8.3	5.9–10.0
Minimal luminal diameter (mm) across segments	3.6 ± 2.6	2.6	2.3–4.4
Global inflammation severity on a visual analog scale between 0 and 100	21.0 ± 16.2	20.1	7.5–30.3

Abbreviations: IQR, interquartile range; MRE, magnetic resonance enterography.

Table 2. Description of MRE characteristics about lesions in 78 examinations (26 initially selected in each category of inflammation severity—nil/moderate, intermediate, severe—with 4, 9, and 4 readings for each MRE, respectively).

	Proportion of readings with the lesion seen in at least 1 segment		Number of segments with the lesion		
	Mean ± SD	Median (mean per reading)	Mean ± SD	Median (mean per reading)	Total among 680 segments
Maximal wall thickness (mm)					
>8	0.47 ± 0.39	0.47	0.65 ± 0.61	0.50	284
Minimal luminal diameter (mm)					
≥3	0.65 ± 0.27	0.67	0.86 ± 0.56	0.75	377
T2 wall hypersignal	0.50 ± 0.30	0.50	0.75 ± 0.57	0.71	334
T1 degree of intensity enhancement					
Mild–moderate	0.54 ± 0.31	0.53	0.81 ± 0.67	0.75	362
Severe	0.39 ± 0.33	0.29	0.59 ± 0.68	0.50	267
T1 pattern of intensity enhancement					
Homogenous	0.45 ± 0.31	0.44	0.63 ± 0.54	0.56	263
Layered	0.51 ± 0.34	0.53	0.77 ± 0.70	0.71	362
Deep ulcer without fistula	0.26 ± 0.25	0.25	0.32 ± 0.34	0.25	152
Type of fatty proliferation					
Blurred wall	0.30 ± 0.28	0.25	0.43 ± 0.43	0.29	194
Inflammatory mass	0.10 ± 0.22	0.00	0.12 ± 0.27	0.00	41
Comb sign	0.53 ± 0.40	0.50	0.83 ± 0.85	0.56	392
Fistula					
Sinus tract	0.07 ± 0.16	0.00	0.07 ± 0.16	0.00	29
Internal	0.17 ± 0.32	0.00	0.23 ± 0.50	0.00	87
Cutaneous	0.03 ± 0.13	0.00	0.03 ± 0.13	0.00	14
Abscess	0.12 ± 0.29	0.00	0.13 ± 0.31	0.00	46
Sclerolipomatosis	0.45 ± 0.33	0.50	0.76 ± 0.76	0.61	344
Lymph node along vascular axis	0.59 ± 0.34	0.61	0.97 ± 0.87	0.75	437
Lymph node along intestinal loops	0.45 ± 0.32	0.33	0.67 ± 0.69	0.50	312
Deep ulcer or sinus tract	0.30 ± 0.28	0.25	0.37 ± 0.37	0.25	172

Abbreviation: MRE, magnetic resonance enterography.

Inter- and Intrareader Variation Study of MRE Characteristics

The level of agreement on the characteristics between MRE multiple readings (interreader pair) and between MRE reading and rereading (intrareader pair) is described in Table 3 for the continuous items and in Table 4 for the number of segments involved by each lesion. The level of agreement on the presence of each lesion in at least 1 segment is described in Supplementary Table 1.

Globally, the interreader pair level of agreement was "moderate" for continuous items, but "substantial" for maximal wall thickness and variable from "fair" to "substantial" for the number of segments involved by a lesion. The numbers of segments involved by some lesions were more subject to an interreader pair variation: the T2 wall hypersignal (inter-ICC estimate of 0.227, "fair" agreement), any type of fatty proliferation (0.248, "fair" agreement), the presence of a deep ulcer without fistula (0.131, "slight"

Table 3. Agreement level on each continuous item between multiple readings (interreader) and between reading and rereading (intrareader) of MREs.

	ICC inter			ICC intra		
	Estimate	95% CI	Total variance	Estimate	95% CI	Total variance
Number of diseased segments	0.551[a]	0.455–0.644	0.93	0.758[b]	0.664–0.829	1.80
Length of diseased small bowel (cm)	0.549[a]	0.454–0.642	315	0.788[b]	0.701–0.852	274
Maximal wall thickness (mm) across segments	0.735[b]	0.664–0.798	8.64	0.775[b]	0.686–0.842	10.52
Minimal luminal diameter (mm) across segments	0.451[a]	0.350–0.554	8.88	0.547[a]	0.396–0.669	10.67
Global inflammation severity measured on a visual analog scale between 0 and 100	0.495[a]	0.396–0.594	339	0.762[b]	0.660–0.832	514

Abbreviations: ICC, intraclass correlation coefficient; MRE, magnetic resonance enterography.
[a]"Moderate" agreement.
[b]"Substantial" agreement.

Table 4. Agreement level on the number of segments involved by each lesion between multiple readings (interreader) and between reading and rereading (intrareader) of MREs.

	ICC inter			ICC intra		
	Estimate	95% CI	Total variance	Estimate	95% CI	Total variance
Maximal wall thickness (mm) >8	0.449[c]	0.342–0.553	0.57	0.633[d]	0.503–0.735	0.77
Minimal luminal diameter (mm) ≥3	0.224[b]	0.127–0.334	0.67	0.366[b]	0.188–0.521	1.01
T2 wall hypersignal (edema)	0.227[b]	0.130–0.337	0.79	0.472[c]	0.310–0.608	0.87
T1 degree of intensity enhancement						
Mild–moderate	0.355[b]	0.252–0.464	0.98	0.632[d]	0.501–0.735	1.01
Severe	0.357[b]	0.255–0.466	0.74	0.560[c]	0.414–0.679	0.92
Any	0.608[d]	0.518–0.693	1.11	0.764[d]	0.669–0.834	1.32
T1 pattern of intensity enhancement						
Homogenous	0.239[b]	0.142–0.350	0.67	0.564[c]	0.417–0.682	0.88
Layered	0.435[c]	0.333–0.539	0.26	0.695[d]	0.580–0.782	0.87
Any	0.604[d]	0.514–0.690	1.12	0.605[d]	0.464–0.715	0.87
Deep ulcer without fistula	0.131[a]	0.042–0.237	0.35	0.501[c]	0.341–0.632	0.46
Type of fatty proliferation						
Blurred wall	0.136[a]	0.047–0.242	0.58	0.548[c]	0.396–0.670	0.45
Inflammatory mass	0.338[b]	0.236–0.448	0.12	0.684[d]	0.567–0.775	0.21
Any	0.248[b]	0.149–0.359	0.63	0.671[d]	0.550–0.765	0.64
Comb sign	0.609[d]	0.519–0.694	0.97	0.741[d]	0.640–0.816	1.13
Fistula						
Sinus tract	0.171[a]	0.078–0.279	0.06	0.323[b]	0.141–0.484	0.10
Internal	0.696[d]	0.618–0.767	0.28	0.805[e]	0.725–0.863	0.37
Cutaneous	0.659[d]	0.575–0.736	0.03	0.651[d]	0.525–0.750	0.03
Any	0.684[d]	0.605–0.757	0.33	0.726[d]	0.622–0.806	0.48
Cutaneous or internal	0.679[d]	0.599–0.753	0.30	0.805[e]	0.725–0.863	0.37
Abscess	0.545[c]	0.449–0.638	0.12	0.677[d]	0.558–0.769	0.09
Sclerolipomatosis	0.463[c]	0.363–0.566	0.89	0.714[d]	0.605–0.797	1.23
Lymph nodes						
Along vascular axis	0.431[c]	0.330–0.536	1.25	0.738[d]	0.637–0.815	1.62
Along intestinal loops	0.426[c]	0.324–0.531	0.88	0.571[c]	0.427–0.687	0.85
Deep ulcer or sinus tract	0.155[a]	0.064–0.262	0.37	0.540[c]	0.388–0.663	0.49

Abbreviations: ICC, intraclass correlation coefficient; MRE, magnetic resonance enterography.
[a]"Slight" agreement.
[b]"Fair" agreement.
[c]"Moderate" agreement.
[d]"Substantial" agreement.
[e]"Almost perfect" agreement.

Table 5. Final model: variables selected by the multiple linear mixed regression method (N = 442 readings), and format for calculation of Crohn's Disease Magnetic Resonance index Inflammation Severity.

Characteristics		Coefficient estimate ± standard error	P	Final coefficients	Total
Number of 20-cm segments (n) with mild–moderate IE in T1-weighted sequences (MMT1)	n_{MMT1}	5.932 ± 0.733	<.001	x2	= Total 1
Number of 20-cm segments (n) with severe IE in T1-weighted sequences (MMT1)	n_{ST1}	8.948 ± 1.502	<.001	x3	= Total 2
Number of 20-cm segments (n) with deep ulcer without fistula (DU)	n_{DU}	2.982 ± 0.994	.003	x1	= Total 3
Number of 20-cm segments (n) with "comb sign" (CS)	n_{CS}	2.768 ± 0.785	<.001	x1	= Total 4
Number of 20-cm segments (n) with any fistula (F)	n_{F}	9.356 ± 1.171	<.001	x3	= Total 5
Number of 20-cm segments (n) with abscess (A)	n_{A}	10.735 ± 1.780	<.001	x4	= Total 6
		CDMRIS = $2n_{MMT1} + 3n_{ST1} + n_{DU} + n_{CS} + 3n_{F} + 4n_{A}$			

Abbreviation: IE, intensity enhancement.

agreement), and the presence of a sinus tract (0.171 "slight" agreement). Inter-ICC after combination of sinus tract with deep ulcer was 0.155, "slight" agreement, thus not increased. The intrareader pair level agreement was globally "moderate" to "substantial" for all analyzed criteria, except for the number of segments with minimal luminal diameter ≥3 mm and the number of segments involved by sinus tract (intrareader pair ICC estimate of 0.366 and 0.323, respectively, "fair" agreement).

Index Construction

Table 5 describes the variables selected by the multiple linear mixed regression method and their coefficient estimates to be used to calculate the inflammation severity index. Supplementary Table 2 describes the univariate association of each characteristic at each level or above with the global inflammation severity measured on VAS, as assessed by each reader pair at MRE reading. Simplification of the coefficients leads to the CDMRIS value as $2n_{MMT1} + 3n_{ST1} + n_{DU} + n_{CS} + 3n_{F} + 4n_{A}$, in which n are the numbers of 20-cm SB diseased segments, n_{MMT1} with mild or moderate intensity enhancement, n_{ST1} with severe intensity enhancement, n_{DU} with deep ulceration without fistula, n_{CS} with "comb sign," n_{F} with any fistula, n_{A} with abscess. The format to calculate the CDMRIS is shown in Table 5. Supplementary Table 3 shows the nonselected variables and their P value if added to the final model.

Figure 3 displays the scatterplot of the CDMRIS index as a function of the global inflammation severity evaluation. The proportion of variance of the global inflammation severity evaluation explained by the linear mixed model was 54%. Supplementary Figure 1 describes the scatterplot of the standardized residuals as a function of the predicted index with no evident deviation to the assumptions used to derive the model. The correlation between CDMRIS and global inflammation severity measured on VAS was about 0.755, after correction of an optimism of 0.011, as estimated from bootstrap method.

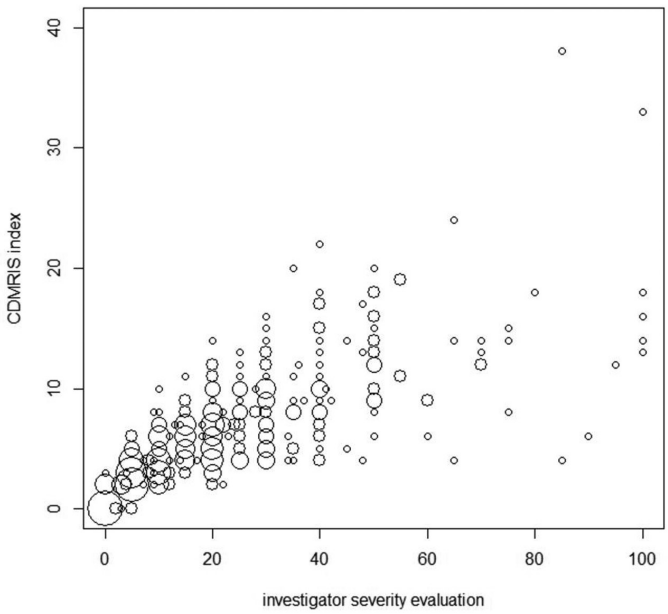

Figure 3. Scatterplot of the CDMRIS index as a function of the investigator global inflammation severity measured on VAS. The area of each circle is related to the number of coincident data plotted there (varying between 1 and 41). Abbreviation: VAS, visual analog scale.

CDMRIS Description

Across the 78 examinations, the CDMRIS was calculated with a mean (±SD) value of 6.1 (±4.9) (median 5.3, IQR: 2.8–8.8). By construction, CDMRIS value is not limited since related to the number of 20-cm segments involved by some lesions. Careful analysis of observed extreme CDMRIS values in our sample, taking into account that some of these values were obtained through the readings of the same MRE and/or by the same reader pair, allows us to suggest that 20 is a reasonable limit to define a very high level of inflammation severity, even if some higher values of CDMRIS can be observed in some particular situations.

Concerning reproducibility, the level of agreement on CDMRIS was "substantial" between multiple readings (interreader pair ICC estimate: 0.720; 95% CI: 0.646–0.786; total variance: 24.7), and between reading and rereading (intrareader pair ICC estimate: 0.783; 95% CI: 0.696–0.848; total variance: 32.4).

Discussion

In this study, we build the CDMRIS which is the first index devoted to the SB for the assessment of inflammation severity in CD by MRE. This index comprises 5 items associated with the severity of inflammation (intensity enhancement, deep ulceration, comb sign, any fistula, and abscess) able to explain 54% of the global inflammation severity variance.

We asked each pair of gastroenterologist and radiologist to select 2 representative MREs according to their perception of each severity level of SB inflammatory lesions, nil-mild, moderate, or severe, to obtain examinations showing a large range of inflammation severities. The objective was to avoid getting for instance only severe cases or only mild cases within each center, rendering the selection of consecutive cases very unlikely. We also doubled the number of readings for the intermediate group, the most difficult to evaluate in practice.

Moreover, the MREs were selected from patients with known SB CD, associated or not with colonic localization, without any a priori about clinical, biological, endoscopic, or histological data in order to avoid selection bias. Whatever the colonic involvement, we limited our analysis to the SB because none of the previously proposed indices was specifically dedicated to the SB, except the last 10–15 cm of the distal ileum. Our population could include patients with either nonstricturing or stricturing CD, especially since inflammation and fibrosis are often associated in CD strictures. However, to be focused on the assessment of SB inflammation, and not on fibrosis, the participants were asked to ignore in their evaluation what they supposed to be "noninflammatory" lesions or intestinal damage lesions, as measured through the Lemann index[27] and usually considered as nonreversible.

To evaluate reproducibility level of the MRE reading and to construct the CDMRIS, MREs were to be read by a pair of gastroenterologist and radiologist. We considered that such reading was more appropriate than the reading of MRE by the radiologist alone, because it is more representative of what happens in clinical practice during multidisciplinary discussions to choose the best management for patients.

Interagreement levels are quite similar to those published in previous works, except for T2 wall hypersignal and ulcers.[28,29] These results could be partly explained by large differences in study design (78 MREs from 13 centers vs. 33 from 1 center and 50 from 3 centers, 13 readers vs. 4, gastroenterologist–radiologist pair of readers vs. radiologist readers alone, only SB segments vs. 4 or 5 colonic segments and only 1 distal ileal segment).

The inter- and intrarater level agreement of the CDMRIS was "substantial." The lesions selected by the regression procedure were among those showing "fair" to "moderate" interrater agreement and "moderate" to "substantial" intrarater agreement. This really makes sense, indicating that radiologists and gastroenterologists reliably recognized the radiological items they felt to be important indicators of inflammation severity. Nevertheless, 1 item included in the index showed a "slight" interrater agreement and a "moderate" intrarater agreement: the number of segments involved by the presence of a deep ulcer without fistula. It might be due to the difficulty of distinguishing a sinus tract from a deep ulcer without fistula, but we could not confirm this hypothesis because the inter-ICC of the number of segments involved by either "deep ulcer without fistula" or "sinus tract" was not higher. The selection of the number of segments with "deep ulcer without fistula" by the regression procedure may be due to the fact that a reader evaluated global inflammation severity higher on a VAS in presence of this item, all other items being equal. Thus, global inflammation severity and the number of segments involved by the presence of a deep ulcer without fistula may be related despite the low reproducibility of this item, potentially explaining its selection in the final index. In addition, the index showed a "substantial" inter- and intrarater agreement, because the number of segments involved by the presence of a deep ulcer without fistula is only 1 component of the index out of 5, the one with the lowest coefficient.

Fistulas and abscesses were selected as major components of the CDMRIS. This may seem surprising at first reading, because there is a tendency to associate inflammation and reversible lesions, while fistulas and abscesses are often considered as irreversible lesions, forming part of the intestinal damage in the Lemann index.[27] In fact, we showed in a study comparing MRE items to the pathological examination of surgical specimens in patients with CD that fistulas and abscesses were associated with the highest pathological inflammatory score, confirming that fistulas are also inflammatory lesions.[2]

The number of segments with mural hyperenhancement was also selected as a component of the CDMRIS which is consistent with other studies demonstrating that it is one of the most consistently useful sign for reflecting inflammation in CD.[30] However, it is nonspecific to inflammation and can also reflect other processes in CD such as fibrosis or chronic mesenteric venous occlusion.[9] However, our MRE protocol did not include a requirement for dynamic or delayed gadolinium enhancement sequences that are known to provide additional information to distinguish inflammation from these other processes, but are not mandatory according to the European consensus statement on the technical performance of MRE in CD.[21]

In the final model, the T2 hyperintensity corresponding to mural edema described by other authors was not selected by the multivariate linear mixed model.[15] This criterion was frequently described, at least by 50% of the pair of readers, nevertheless the interobserver agreement was "fair." Among the 6 other items not retained by the multivariate linear mixed model, the maximal wall thickness and the minimal luminal diameter were not associated with the severity of inflammation. It should be noted that maximal wall thickness >8 mm was highly significantly associated to the severity of inflammation in univariate analysis ($P < .001$, Supplementary Table 2), but not selected into the model ($P = .105$, Supplementary Table 3). Similarly, minimal luminal diameter >3 mm was also significantly associated to inflammation severity ($P = .008$, Supplementary Table 2), but not selected in the multivariate model ($P = .012$, Supplementary Table 3), possibly in relation to our stringent selection procedure. This could be also due

to the categorization of continuous items relatively to their median, but this choice was decided in relation to our sample size, even if several readings were performed. In addition, the minimal luminal diameter measurement is difficult and inaccurate for the lowest values, due in part to technical limitations. Maximal wall thickness has been previously shown to be associated with the activity of the disease,[20,31,32] but this is not equal to inflammation severity. The other items (fatty proliferation, sclerolipomatosis, pattern of T1 enhancement and lymph nodes) were not retained in the final model and have not been clearly associated with either the activity or the severity of the inflammation in previous studies.[2–4,33]

The total length of the diseased SB was never selected probably since this information is already included in the number of segments with each selected item related to global inflammation severity, which contains the length but also the grade of the lesion and its degree of association with inflammation severity.

Several scores have been previously proposed but with the same limitation. The MICD, index of severity in ileal CD, composed of an inflammatory score and an obstructive score, was based on an extensive review of the literature and on a consensus between radiologists and gastroenterologists from 6 centers.[34] The coefficients used to measure each component came from experts and were not validated.[34] The MEGS, MRE global score, was derived from a previously segmental activity score developed on surgical resection specimens using an unvalidated transmural histopathological acute inflammation score[20] applied to 44 sites in a sample of 16 patients and subsequently validated against terminal ileum biopsies in a small sample of 26 patients.[19] This histopathological activity index was expanded to include assessment of segmental disease length, evaluations of haustral loss and evaluation of extraenteric complications. As recognized by the authors, the coefficients used for these expansions were necessarily arbitrary.[35] It appears to us more accurate to derive coefficients to be applied to the various lesions from an objective analysis of the quantitative evaluation of inflammation severity than from the subjective appraisal of a few experts.

The MaRIA was built at the segmental level, 5 colonic segments and terminal ileum, from a linear function of bowel wall thickness, mural edema, mucosal ulceration, and relative contrast enhancement,[15,16] highly correlated with a modified segmental version of the CDEIS.[17] The authors found by construction a strong correlation between MaRIA and CDEIS[17] in the development study,[15] but confirmed in the validation study.[16] Correlation between MaRIA and CDEIS was high as expected in the development study, 0.81 and 0.78, but also in the validation study, 0.80 and 0.84, at the segmental and patient level, respectively. The MaRIA score was applied to deep small intestine in a study using balloon-assisted enteroscopy and an adaptation of the simplified endoscopic index of severity (SES-CD),[36] with 3 segments, terminal ileum (10 cm), proximal ileum and jejunum (approximately 300 cm each), an adaptation that can be questioned with segments of so different lengths, whereas SES-CD was constructed from colonic segments and terminal ileum with relatively similar lengths.[37] Another study showed a modest correlation between videocapsule endoscopy (VCE)—Lewis score[38] and MaRIA global index in patients with quiescent SB-CD.[39]

The Clermont score has been developed on the basis of the MaRIA score by replacing contrast enhancement with apparent diffusion coefficient and showed that it was highly correlated with this score in ileal CD, but not in colonic CD, and share the same limitations.[18,40] As for MaRIA global index, a modest correlation between VCE—Lewis score and MRE—Clermont score of inflammation was observed in patients with quiescent SB-CD.[39]

After studying the reproducibility of the different studied items, the created index called CDMRIS is based on the association between the global inflammation severity evaluation provided by the readers and the numbers of segments involved by selected items observed by the readers on MRE, without any reference to endoscopy, histology, or patient's clinical status. Thus, the CDMRIS is an image-based index. Besides, 2 of the 5 items that affected the perception of inflammation severity by the readers and were thus included in the index are penetrating complications which are not addressed with endoscopy or mucosal biopsies (fistula, abscess).

The strengths of our study are the followings: (1) the design which started from scratch without any a priori, taking into account the usual items described in clinical practice; (2) an index dedicated to SB, the most common localization of CD; (3) a focus on the inflammatory component; (4) an assessment through MRE, considered as the best radiological modality in the field; (5) the recognition and incorporation of penetrating complications into the score, which often trigger additional therapy or surgery but are not addressed in endoscopic or histopathology scores, and which should be considered as critical items when consensus recommendations for treatment response are developed.

However, our study has some limitations: (1) the reproducibility level of 1 selected item in the index deep ulcer without fistula is relatively low; (2) the level of the correlation between the index and the global inflammation severity evaluation by pairs of investigators may appear limited. Nevertheless, the proportion of variance of the global inflammation severity evaluation of 54% is rather similar to the 62% estimated from the raw correlation between the MaRIA and the overall severity evaluated on a VAS in a recent study[29]; (3) external validation in new patients with new readers is lacking; however, we performed an internal validation using bootstrap method.

Conclusion

The Crohn's Disease Magnetic Resonance index of Inflammation Severity (CDMRIS) is the first index devoted to the assessment of SB CD inflammation severity by MRE and allowing a quantitative measurement of the overall inflammatory burden of the small intestine. Provided further validation in new patients by new readers and the assessment of its variations under treatment, the CDMRIS will allow gastroenterologists to better evaluate the degree of inflammation in SB CD and hence, it may be of some help to guide therapeutic strategy in patients in whom lesions are not easily accessible by conventional endoscopy and histology.

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Supplementary Data

Supplementary data is available at *Crohn's and Colitis 360* online.

Authors' Contribution

Conception and design of the study: Y.B., J.C., and J.Y.M. Generation, collection, and assembly of data: all authors, except J.Y.M., and GETAID CDMRIS Study Group. Analysis and/or interpretation of data: J.Y.M. and Y.B. Drafting or revision of the manuscript: Y.B., C.L.B., A.B., and J.Y.M. Approval of the final version of the manuscript: all authors.

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Conflicts of Interest

Yoram Bouhnik received honoraria from AbbVie, Amgen, Biogaran, Biogen, Boehringer Ingelheim, Celltrion, Ferring, Fresenius Kabi, Gilead, Hospira, Janssen, Lilly, Mayoli Spindler, Merck, MSD, Norgine, Pfizer, Roche, Sandoz, Sanofi, Shire, Takeda, and UCB. Magaly Zappa received honoraria from AbbVie. Vered Abitbol received honoraria from Biogen, AbbVie, Takeda, Janssen, Amgen, Pfizer, Amgen, Vifor, Arkopharma, and UCB. Arnaud Bourreille received honoraria from Abivax, AbbVie, Boehringer, Celgene, Gilead, Mauna Kea Technologies, Medtronic, MSD, Janssen, Gilead, Hoffman la Roche Ferring, Janssen, MSD, Pfizer, Takeda, Tillotts, and OSE immunotherapeutics. The other authors have nothing to disclose.

Data Availability

Data available in supplementary material.

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