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A MAGNETIC RESONANCE IMAGING INDEX TO PREDICT CROHN'S DISEASE POSTOPERATIVE RECURRENCE: THE MONITOR INDEX

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Short title: MRI to predict Crohn's disease recurrence

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ABSTRACT

Background and Aims: We developed and validated a magnetic resonance imaging (MRI-)based index to predict Crohn's disease (CD) post-operative recurrence (POR).

Methods: Patients with CD having undergone a post-operative evaluation for recurrence (with colonoscopy and MRI no longer than 105 days apart) were included between 2006 and 2016 in university hospital of Nancy, France. MRI-items with good levels of intra and inter-rater agreement (Gwet's coefficient ≥ 0.5) were selected. The MONITOR index's performance was assessed in terms of the area under the receiver operating characteristic curve (AUROC) and accuracy, by considering the Rutgeerts score as the gold standard. The MONITOR index was validated with a bootstrap method and an independent cohort.

Results: Seventy-three MRI datasets were interpreted by two radiologists. Seven items (bowel wall thickness, contrast enhancement, T2 signal increase, diffusion-weighted signal increase, edema, ulcers, and the length of the diseased segment) had a Gwet's coefficient ≥ 0.5 and were significantly associated with the Rutgeerts score, leading to their inclusion in the MONITOR index. All the items had a weighting of 1, except the "ulcers" item weighting 2.5, reflecting the

higher adjusted odds ratio. The AUROC [95% confidence interval] for the prediction of endoscopic POR (Rutgeerts score >1) was 0.80 [0.70; 0.90]. The optimal threshold was a MONITOR index ≥ 1 , giving a sensitivity of 79%, a specificity of 55%, a predictive positive value of 68%, and a predictive negative value of 68%. The bootstrap validation gave an AUROC of 0.85 [0.73; 0.97]. In the validation cohort, a MONITOR index ≥ 1 gave a sensitivity of 87%, a specificity of 75%, a predictive positive value of 84,6%, and a predictive negative value of 75%.

Conclusions: The MONITOR index is an efficient, reliable, easy-to-apply tool that can be used in clinical practice to predict the POR of CD.

Keywords: Crohn's disease; inflammatory bowel disease; magnetic resonance imaging; radiology; surgery; post-operative recurrence

INTRODUCTION

Crohn's disease (CD) is a chronic, disabling condition that can lead to bowel damage and complications related to stricturing or penetrating lesions [1]. Between one third and a half of all patients will require surgical resection of a segment of the intestine (most frequently ileocolonic resection) in the 10 years following disease onset [2–5]. Unfortunately, surgery is not a curative solution, and endoscopic and clinical post-operative recurrence (POR) occurs in respectively 85% to 100% and 34% to 86% of patients within 3 years [6]. Thirty-five percent of operated patients undergo a second intestinal resection within 10 years of the first [7]. The patient management objectives are thus to (i) prevent POR taking into account each patient's individual risk factors, (ii) predict the course of the disease, and (iii) identify disease relapse as early as possible, ideally before the appearance of irreversible damage.

Rutgeerts et al. developed an endoscopic score to predict the post-operative course of CD [8]. Even though this score has not been formally validated, endoscopic evaluations are widely practiced and are recommended in the European Crohn's and Colitis Organization (ECCO) guidelines [9]. However, colonoscopy is an invasive examination and is the least well accepted monitoring tool for inflammatory bowel disease (IBD) [10]. Magnetic resonance imaging (MRI) is an alternative, reliable tool for evaluating the activity and severity of CD, and several MRI-based luminal disease activity scores have been

described [11]. These scores are based on either conventional MRI sequences or a combination of conventional and diffusion-weighted sequences. Furthermore, the bowel preparation protocols differ greatly from one score to another. As present, a standardized procedure is not available, and the published MRI scores are not used widely in clinical practice. In a post-operative setting, data are even more scarce, and the MaRIA or the Clermont scores are not designed and validated for POR assessment[12,13]. Sailer et al. used the Rutgeerts score to build an MR enteroclysis score [14]. However, to the best of our knowledge, a validated index of POR in cases of ileocolonic anastomosis has not been previously developed.

Hence, the objective of the present study was to develop and validate a clinically relevant MRI index of POR, as assessed by the Rutgeerts' score.

METHODS

Study population

We performed an observational study of all adult patients in the Nancy IBD cohort having undergone ileocecal or ileocolonic resection for CD between January 1st, 2006 and December 31st, 2019, and then a post-operative evaluation for recurrence (with colonoscopy and MRI no longer than 105 days apart). The main inclusion criteria were age 18 or more, a confirmed diagnosis of ileal or ileocolonic CD, ileocecal or ileocolonic resection, and the presence of ileocolonic anastomosis at time of evaluation. Two independent cohorts were constituted as a development cohort and a validation cohort. The Nancy IBD cohort was registered with the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*, Paris, France; reference: N81404720).

Endoscopy and MRI techniques are described in supplementary material. The Rutgeerts scoring was prospectively done by the endoscopist according to routine practice. This was reviewed and confirmed by the first author (MS) based on endoscopic pictures and written detailed report.

Choice and selection of candidate MRI signs

The candidate MRI signs were defined on the basis of (i) a preliminary review of the literature data on existing MRI indices of CD activity [12,13] and POR

[14], and (ii) expert opinion. Items which were previously considered as relevant and accurate in the evaluation of ileal disease were considered (supplementary materials). Two senior reviewers with more than ten years experience of abdominal radiology (VL and XO) rated the MRI datasets. The reviewers were blinded to the clinical and endoscopic data. The MRI datasets were rated again (by VL only) 45 days after the first rating. For the item “wall thickening”, the grading was left to the radiologist, defined by an increasing wall thickness compared to the non-involved small bowel.

The new “MRI in Crohn’s Disease To Predict Post-Operative Recurrence” (MONITOR) index was built in two steps. Firstly, we selected the items that had a high level of intra- and inter-rater agreement (defined as a Gwet’s coefficient ≥ 0.5). Items with insufficient reliability were discarded. The selected items were then tested for association with the Rutgeerts score. Secondly, we included reliable MRI items that were significantly correlated with the Rutgeerts score.

Statistics

Calculation of the MONITOR index

The MONITOR index was calculated by summing the responses for the selected items (sign present = a score of 1; sign absent = a score of 0). The weight given to each item depended on the strength of the association with the Rutgeerts score.

Prediction of POR

The MONITOR index's ability to accurately predict POR was tested by reference to the Rutgeerts score. Endoscopic postoperative recurrence was defined as a Rutgeerts score of ≥ 2 or higher.

Candidate items were selected on the basis of (i) their intra- and inter-rater reliability (Gwet's coefficient ≥ 0.5), and (ii) a statistically significant association with the Rutgeerts score in a logistic regression (expressed as the crude odds ratio (OR) [95% confidence interval (CI)]). As mentioned above, the strength of the association (i.e. the OR) was used to set the weight applied to the corresponding item in the MONITOR index. The index's predictive performance was assessed by calculation of the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV), with their respective 95% confidence intervals (CIs).

Four thresholds for the MONITOR index were used to construct a receiver operating characteristic (ROC) curve: 0 (0 vs. >0), 1 (0/1 vs. >1), 2 (0/1/2 vs. 3/4) and 3 (0/1/2/3 vs. 4). The area under the ROC curve (AUROC) was then compared with a value of 0.5 in a statistical test.

External validation

Baseline characteristics were collected. An expert reviewer (VL) and a fellow radiologist (AM) rated the MONITOR index for each MRI examination and

intra- and inter-rater agreement of the MONITOR index was calculated. The index's predictive performance was assessed by calculation of the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV).

Categorical variables were described as the frequency (percentage), and quantitative variables were described as the mean (standard deviation (SD)), the median [interquartile range (IQR)], and the range.

Internal validation using a bootstrap model is described in supplementary materials.

RESULTS

Study population

Development cohort

Between January 1st, 2006, and December 31st, 2016, 61 patients underwent 73 concomitant endoscopic and MRI evaluations. Baseline characteristics, characteristics at time of evaluation and Rutgeerts scores are summarized in Table 1. Rutgeerts score could not be evaluated in 4 cases. These 4 patients were included in the intra-and inter-reader reliability analysis of MRI items but were excluded for the analysis of correlation with the Rutgeerts. The mean quality of the 73 MRI datasets was 4.5 out of 5 according to VL and 4.1 out of 5 according to XO. No MRI examinations were excluded because of insufficient quality.

Validation cohort

Seventeen other patients who underwent 21 concomitant colonoscopy and MRI evaluations of POR within 3 months between August 1st, 2013 and December 31st, 2019, were included as an independent cohort. Characteristics are presented in Table 1.

Selection of the candidate MRI items

The levels of intra- and inter-rater agreement for all the candidate MRI items are given in Table 2. Seven items displayed both a good intra- and inter-rater

agreement (Gwet's coefficient ≥ 0.5) and a good ability to predict the Rutgeerts score: wall thickening, contrast enhancement, T2 signal increase, diffusion-weighted signal increase, edema, ulcers, and lymph nodes > 15 mm. The strength of the association between each item and the Rutgeerts score is shown in Table 3. The "ulcers" item was most strongly associated with POR.

Index construction

The MONITOR index was built by summing the 7 items scored as 0 for the absence of the MRI sign, 1 for the presence of wall thickening, contrast enhancement, T2 signal increase, diffusion-weighted signal increase, edema, and length of diseased segment ≥ 20 mm, and 2.5 for the presence of ulcers. Accordingly, the MONITOR index ranged from 0 (the lowest probability of POR) to 8.5 (the highest probability) (Table 4).

Prediction of POR

Sixty-nine examinations were included to assess the accuracy of our index, since Rutgeert's score was unavailable in 4 cases. The MONITOR index's AUROC [95%CI] for predicting POR was 0.80 [0.70; 0.90] (Figure 1). The optimal cut-off for the MONITOR index was 1, giving a sensitivity of 79% [64; 89], a specificity of 55% [38; 71], a predictive positive value of 68% [53; 80], and a predictive negative value of 68% [48; 83].

When the MONITOR index was >1 , contrast enhancement was present in 100% of the patients, with a diffusion weighted-signal increase in 100%, wall thickening in 63%, a T2 signal increase in 47.8%, edema in 34.8%, ulcers in 58.7% and a diseased segment ≥ 20 mm in 76.1%.

External validation

Both intrareader and interreader reliability were good with an ICC [95%CI] of 0,67 [0,36-0,85] and 0,67 [0,34-0,85] respectively.

MONITOR index ≥ 1 gave a sensitivity of 87%, a specificity of 75%, a predictive positive value of 84,6%, and a predictive negative value of 75% for POR prediction. The AUROC was 0.80.

DISCUSSION

POR after ileocolic resection is frequent but unpredictable [16]. The ECCO consensus statement recommends endoscopic follow-up within 6 to 12 months of surgery, and this follow-up may affect treatment decisions [17]. The POCER trial confirmed that close monitoring with early colonoscopy after surgery was associated with less frequent clinical and endoscopic recurrence [18]. Although the early detection of POR enables a post-operative treat-to-target strategy, iterative colonoscopy may reduce the patient's quality of life and treatment adherence. Furthermore, endoscopy only provides an evaluation of the mucosa and does not take transmural changes into account. After surgery, the anastomosis can become fibrous and stenotic, even in the absence of any inflammatory activity. This is a challenging situation because the corresponding Rutgeerts score (i4) does not reflect the absence of recurrent inflammatory disease.

To construct a reliable score, we specified that each item had to have a Gwet's correlation coefficient of at least 0.5. The levels of intra- and inter-rater agreement in the process used to build the MONITOR index were higher than for some other validated scores in the fields of IBD. For example, the level of inter-rater agreement in the initial validation of the Ulcerative Colitis Endoscopic Index of Severity index was only moderate ($\kappa = 0.50$) [19]. Each item composing the MONITOR index was also significantly associated with the Rutgeerts score.

Our MRI-based index was sensitive for predicting endoscopic POR but the specificity and the PPV were less outstanding. This was probably due to subtle post-surgical rearrangements that can lead to slight abnormalities on MRI. Construction of the MONITOR index was based on the rating of MRI datasets by two radiologists with more than ten years; the levels of intra- and inter-rater agreement were high. However, the index is composed of simple items and should therefore also be easily applied by less experienced radiologists. A young fellow reviewed the MRI of the external validation cohort and the inter-reader reliability remained indeed high.

In view of our small sample size, we proceeded internal bootstrap validation to split-sample validation. However, it has been shown that the bootstrap method can be at least as efficient as the split-sample technique [20]. Our results were strengthened by an external validation on an independent cohort.

Although the endoscopy-based Rutgeerts score is widely used and recommended, it has not been formally validated. The diagnosis, the management and the natural history of patients with i2 POR is subject to debate. Hence, the i2 group has been subdivided into i2a (for lesions limited to the anastomosis) and i2b (for ulcerations with normal mucosa interval of neoterminal ileum). Nevertheless, it seems that there is not a significant difference of the disease course between these two patient subgroups[21,22]. Moreover, a recent study showed that the Rutgeerts score was only moderately

reproducible - especially when differentiating between i0/i1/i2 from i3/i4 [23], which might lead to overtreatment. In view of these data, management of i2 patients remains subject to debate, and recent publications have suggested that endoscopic POR should correspond to scores $>i2$ [24]. Studies of POR tend to focus on severe endoscopic recurrence (i.e. i3 and i4), which provides a more meaningful distinction [25–27]. Further studies with a focus on the i2 group are needed to clarify the management in this context. In our study, we could not divide i2 in two groups because of sample size. We did not study the performance of our score for $> i3$ because the sub-group of patients with an i4 score is very easy to identify and characterize by MRI. We do not believe that identifying i4 patients is the goal of an MRI index in the postoperative setting as it is an extreme situation. Also, due to small sample size, this subgroup analysis could not be performed.

To the best of our knowledge, the present study is the second study to have developed an MRI index for the prediction of POR in CD. To date, four MRI-based scores of luminal CD activity have been developed [12,13,28,29] and only one of these was specifically developed for the evaluation of POR [14,30]. Sailer and colleagues [14] developed a simple index (based on magnetic resonance enteroclysis) that was correlated with clinical recurrence [30]. However, the index has not been formally validated and the reliability of some of its items was not assessed. The items included in the score were defined *a priori*. Even though the degree of interobserver reproducibility was substantial,

the intra-observer reproducibility was not reported. Furthermore, the development cohort comprised only 30 patients, most of whom had severe recurrence (65% ≥ 3). One other weakness of Sailer et al.'s index is the use of enteroclysis, with the administration of methylcellulose solution through a nasojejunal catheter. This may be poorly tolerated by some patients, as previously described for CT enteroclysis [31]. Furthermore, Sailer et al.'s index does not take account of diffusion-weighted sequences which is a promising technique that should now always be implemented in MRI evaluations of CD [11].

The MaRIA score [12] and the Clermont score [13] have recently been studied with regard to POR, but were not originally designed for this purpose, and were less sensitive [32] than the MONITOR index. These two scores are rarely used in clinical practice because of their complexity and the time needed for scoring. A simplified MaRIA score was recently described, but has not been used to study POR [33]. In this study, we were not able to calculate Clermont score due to the lack of ADC with our MRI technique. Indeed, it is now well-established that ADC values vary across MRI machines[11]. All the items included in the simplified MaRIA score were tested for reliability and association with the Rutgeerts score.

Calprotectin is another useful tool for the monitoring of CD [34], and has also been studied for the prediction of POR after ileocolic resection. The fecal level of calprotectin is correlated with the severity of endoscopic POR, [35] and

it has been suggested that a threshold of 100 µg/g detects recurrence with good sensitivity and a high PPV. A post-hoc analysis of the POCER trial [36] also confirmed the benefit of fecal calprotectin monitoring. To avoid iterative follow-up colonoscopies after CD-related surgery, a combination of a rapid, specifically designed MRI assessment tool and fecal calprotectin monitoring might be a useful way of predicting POR [32]. In our study, fecal calprotectin was available only in 6 cases, and the potential added value of combining fecal calprotectin monitoring and MRI above MRI monitoring alone could therefore not be analyzed. The negative predictive value of the MONITOR index of 68% is not high enough to avoid every colonoscopy, but an associated negative calprotectin would be against a recurrence. In the external validation cohort, negative predictive value increased to 75%. Further prospective studies with both MONITOR index and fecal calprotectine measurement are necessary.

The present study had a number of strengths, including its thorough methodology (with central rating of the MRIs by experts blinded to the clinical, endoscopic and laboratory data) and a short time interval between colonoscopy and MRI examination (median: 25 days). We are also aware of some limitations of this study, such as the absence of central reading of colonoscopies or the retrospective design. Despite the absence of colonoscopy records, pictures of ileocolonic anastomosis and detailed written reports were checked to ensure the correct grading of Rutgeerts score. The delay between colonoscopy and MRI examination was up to 105 days, which is a little longer than 3 months. This

cut-off was chosen to allow sufficient number of patients eligible for inclusion, and add power to the statistical analysis. However, no therapeutical changes were done between the two examinations and patients did not report modification of symptoms. In the early post-operative course, changes of mucosal status can appear in a short time, but in our study, some evaluations were not the immediate first post-operative assessment. The median time between surgery and colonoscopy was 17 months, and only 22/73 examinations were the first POR evaluation after surgery. For patients who underwent surgery a longer time ago, it could be thought that CD activity was less likely to change between endoscopy and MRI. Moreover, this is a cross-sectional study using the Rutgeerts' score as gold standard and assessing the performance of MRI in this setting to predict Rutgeerts' score values. Hence, by definition, time from surgery cannot influence our findings. One other weakness of our study is that physicians were aware of clinical data when performing colonoscopy, and also of MRI findings if MRI performed before colonoscopy (44/73). Our sample was not sufficient to show any difference according to the type of anastomosis among side-by-side, end-to-end or end-side.

In conclusion, we have developed and validated a simple, easy-to-use, reliable MRI index for predicting endoscopic POR in CD with high sensitivity and a high NPV.

Table 1. Baseline characteristics and characteristics at time of post-operative evaluation

	Development cohort	Validation cohort
Patients	n = 61	n = 17
Female (%)	35 (57.4)	14 (82.3)
Age (SD)*	27.4 (12.5)	38.6 (13.9)
Ileal disease (%)	41 (67.2)	9 (52.9)
Ileocolonic disease (%)	20 (32.8)	8 (47.1)
More than 1 surgery (%)	15 (25)	8 (47.1)
Post operative evaluations	n = 73	n = 21
Tobacco at time of evaluation	22 (30.1)	1 (4.8)
Days between MRI and colonoscopy (IQR) ^f	24 (44)	49 (27)
Months between surgery and coloscopy (IQR) ^f	17 (47.5)	30 (29)
Biologic alone (%)	35 (47.9)	10 (47.6)
Immunosuppressant alone (%)	10 (13.7)	0 (0)
Combination therapy (%)	8 (11.0)	6 (28.6)
Absence of treatment (%)	20 (27.4)	5 (23.8)
i0 (%)	23 (31.5)	7 (33.3)
i2 (%)	8 (11.0)	1 (4.8)
i3 (%)	20 (27.4)	2 (9.5)
i4 (%)	12 (16.4)	3 (14.3)
not assessed (%)	6 (8.2)	8 (38.1)

*Mean. ^fMedian

Table 2. Intra- and inter-rater agreement for the MRI items in the development cohort

	Intra-rater reliability		Inter-rater reliability	
	Gwet's coefficient	[95% CI]	Gwet's coefficient	[95% CI]
Wall thickening	0.73	0.57; 0.89	0.59	0.40; 0.78
Contrast enhancement	0.75	0.60; 0.90	0.67	0.50; 0.84
T2 signal increase	0.80	0.67; 0.94	0.76	0.62; 0.91
Diffusion-weighted signal increase	0.71	0.55; 0.87	0.63	0.45; 0.81
Edema	0.81	0.68; 0.94	0.67	0.50; 0.84
Ulcers	0.70	0.53; 0.86	0.63	0.45; 0.81
Lymph nodes ≥ 15 mm	0.93	0.86; 0.99	0.92	0.86; 0.99
Comb sign	0.99	0.96; 1	0.94	0.88; 1
Luminal narrowing or stenosis	0.70	0.54; 0.85	0.83	0.72; 0.94
Upstream dilation	0.96	0.90; 1	0.93	0.86; 0.99
Anastomotic limited disease	0.76	0.55; 0.96	0.72	0.49; 0.94
Other sites	0.83	0.71; 0.95	0.80	0.67; 0.92
Length of diseased segment ≥ 20 mm	0.77	0.59; 0.96	0.57	0.31; 0.82

Table 3. Correlation between MRI items and the endoscopic Rutgeerts score

	N	Rutgeerts score \geq i2		Bivariate regression		
		n	%	Odds ratio	95%CI	p
Wall thickening						
Absence	43	19	44.2	1.0		
Presence	26	19	73.1	3.4	1.2-9.8	0.0221
Contrast enhancing						
Absence	25	8	32.0	1.0		
Presence	44	30	68.2	4.6	1.6-13.0	0.0048
T2 signal increase						
Absence	50	22	44.0	1.0		
Presence	19	16	84.2	6.8	1.8-26.3	0.0056
Diffusion weighted signal increase						
Absence	27	8	29.6	1.0		
Presence	42	30	71.4	5.9	2.1-17.2	0.001
Edema						
Absence	56	27	48.2	1.0		
Presence	13	11	84.6	5.9	1.2-29.1	0.0291
Ulcer						
Absence	45	17	37.8	1.0		
Presence	24	21	87.5	11.5	3.0-44.5	0.0004
Lymph nodes >15 mm						
Absence	66	35	53.0	1.0		
Presence	3	3	100.0	6.2	0.2 -197.1	0.3002
Comb Sign						
Absence	68	37	54.4	1		
Presence	1	1	100	2.5	0.03-239.9	0.6901
Luminal narrowing/stenosis						
Absence	63	34	54	1		
Presence	6	4	66.7	1.7	0.3-10	0.5539
Upstream dilation						
Absence	67	36	53.7	1		
Presence	2	2	100	4.3	0.1-183.1	0.4448
Anastomotic limited disease						
Absence	7	3	42.9	1		
Presence	39	28	71.8	3.4	0.7-17.7	0.147
Other sites						
Absence	60	34	56.7	1		
Presence	8	4	50	0.8	0.2-3.3	0.7218

Length of diseased segment

<20 mm	14	5	35.7	1		
\geq 20 mm	32	26	81.3	7.8	1.9-31.9	0.0043

Table 4. Scoring for the MONITOR index

The MONITOR index

Wall thickening	
Absent	0
Present	1
Contrast enhancement	
Absent	0
Present	1
T2-signal increase	
Absent	0
Present	1
Diffusion weighted-signal increase	
Absent	0
Present	1
Edema	
Absent	0
Present	1
Ulcers	
Absent	0
Present	2.5
Length of diseased segment	
<20 mm	0
≥20 mm	1

TOTAL out of 8.5

Figure 1. Ability of the MONITOR index to predict POR (defined as an endoscopic Rutgeerts score ≥ 2).

Figure 2. MRI showing POR. (A) Axial diffusion-weighted MRI showing a signal increase at the anastomosis. (B) Axial T1-VIBE MR sequence in the portal phase, showing contrast enhancement, wall thickening (arrowhead) and an ulcer (arrow). (C) Axial and (D) coronal T2 single-shot fast spin echo MRI sequences, showing edema, wall thickening, an ulcer (arrow), and a diseased segment longer than 20 mm.

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