

World Journal of *Gastroenterology*

World J Gastroenterol 2018 February 7; 24(5): 549-656



REVIEW

- 549 Behind the curtain of non-coding RNAs; long non-coding RNAs regulating hepatocarcinogenesis
El Khodiry A, Afify M, El Tayebi HM

ORIGINAL ARTICLE

Basic Study

- 573 Hsa-miR-202-3p, up-regulated in type 1 gastric neuroendocrine neoplasms, may target *DUSP1*
Dou D, Shi YF, Liu Q, Luo J, Liu JX, Liu M, Liu YY, Li YL, Qiu XD, Tan HY
- 583 Enteral nutrition combined with glutamine promotes recovery after ileal pouch-anal anastomosis in rats
Xu YY, He AQ, Liu G, Li KY, Liu J, Liu T
- 593 Promotion of Sema4D expression by tumor-associated macrophages: Significance in gastric carcinoma
Li H, Wang JS, Mu LJ, Shan KS, Li LP, Zhou YB

Case Control Study

- 602 Impact of SNP-SNP interactions of DNA repair gene *ERCC5* and metabolic gene *GSTP1* on gastric cancer/atrophic gastritis risk in a Chinese population
Sang L, Lv Z, Sun LP, Xu Q, Yuan Y

Retrospective Cohort Study

- 613 Incidence of hepatocellular carcinoma in patients with chronic liver disease due to hepatitis B or C and coinfectd with the human immunodeficiency virus: A retrospective cohort study
Marcon PS, Tovo CV, Kliemann DA, Fisch P, de Mattos AA

Retrospective Study

- 623 Impaired granulocyte-macrophage colony-stimulating factor bioactivity accelerates surgical recurrence in ileal Crohn's disease
Gathungu G, Zhang Y, Tian X, Bonkowski E, Rowehl L, Krumsiek J, Nix B, Chalk C, Trapnell B, Zhu W, Newberry R, Denson L, Li E
- 631 *PIK3CA* and *TP53* mutations predict overall survival of stage II/III colorectal cancer patients
Li AJ, Li HG, Tang EJ, Wu W, Chen Y, Jiang HH, Lin MB, Yin L

Observational Study

- 641 Faecal calprotectin and magnetic resonance imaging in detecting Crohn's disease endoscopic postoperative recurrence
Baillet P, Cadiot G, Goutte M, Goutorbe F, Brixi H, Hoeffel C, Allimant C, Reymond M, Obritin-Guilhen H, Magnin B, Bommelaer G, Pereira B, Hordonneau C, Buisson A

CASE REPORT

- 651 Sequential spinal and intracranial dural metastases in gastric adenocarcinoma: A case report

Kim H, Yi KS, Kim WD, Son SM, Yang Y, Kwon J, Han HS

ABOUT COVER

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Observational Study

Faecal calprotectin and magnetic resonance imaging in detecting Crohn's disease endoscopic postoperative recurrence

Pierre Baillet, Guillaume Cadiot, Marion Goutte, Felix Goutorbe, Hedia Bixi, Christine Hoeffel, Christophe Allimant, Maud Reymond, Hélène Obritin-Guilhen, Benoit Magnin, Gilles Bommelaer, Bruno Pereira, Constance Hordonneau, Anthony Buisson

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Abstract

AIM

To assess magnetic resonance imaging (MRI) and faecal calprotectin to detect endoscopic postoperative recurrence in patients with Crohn's disease (CD).

METHODS

From two tertiary centers, all patients with CD who underwent ileocolonic resection were consecutively and prospectively included. All the patients underwent MRI and endoscopy within the first year after surgery or after the restoration of intestinal continuity [median = 6 mo (5.0-9.3)]. The stools were collected the day before the colonoscopy to evaluate faecal calprotectin level. Endoscopic postoperative recurrence (POR) was defined as Rutgeerts' index \geq i2b. The MRI was analyzed independently by two radiologists blinded from clinical data.

RESULTS

Apparent diffusion coefficient (ADC) was lower in patients with endoscopic POR compared to those with no recurrence (2.03 ± 0.32 vs $2.27 \pm 0.38 \times 10^{-3} \text{ mm}^2/\text{s}$, $P = 0.032$). Clermont score (10.4 ± 5.8 vs 7.4 ± 4.5 , $P = 0.038$) and relative contrast enhancement (RCE) ($129.4\% \pm 62.8\%$ vs $76.4\% \pm 32.6\%$, $P = 0.007$) were significantly associated with endoscopic POR contrary to the magnetic resonance index of activity (MaRIA) (7.3 ± 4.5 vs 4.8 ± 3.7 ; $P = 0.15$) and MR scoring system ($P = 0.056$). $\text{ADC} < 2.35 \times 10^{-3} \text{ mm}^2/\text{s}$ [sensitivity = 0.85, specificity = 0.65, positive predictive value (PPV) = 0.85, negative predictive value (NPV) = 0.65] and $\text{RCE} > 100\%$ (sensitivity = 0.75, specificity = 0.81, PPV = 0.75, NPV = 0.81) were the best cut-off values to identify endoscopic POR. Clermont score > 6.4 (sensitivity = 0.61, specificity = 0.82, PPV = 0.73, NPV = 0.74), MaRIA > 3.76 (sensitivity = 0.61, specificity = 0.82, PPV = 0.73, NPV = 0.74) and a MR scoring system \geq MR1 (sensitivity = 0.54, specificity = 0.82, PPV = 0.70, and NPV = 0.70) demonstrated interesting performances to detect endoscopic POR. Faecal calprotectin values were significantly higher in patients with endoscopic POR ($114 \pm 54.5 \mu\text{g/g}$ vs $354.8 \pm 432.5 \mu\text{g/g}$; $P = 0.0075$). Faecal calprotectin $> 100 \mu\text{g/g}$ demonstrated high performances to detect endoscopic POR (sensitivity = 0.67, specificity = 0.93, PPV = 0.89 and NPV = 0.77).

CONCLUSION

Faecal calprotectin and MRI are two reliable tools to

detect endoscopic POR in patients with CD.

Key words: Faecal calprotectin; Magnetic resonance imaging; Postoperative recurrence; Crohn's disease; Clermont score; Magnetic resonance index of activity

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Core tip: Performing a colonoscopy within the first year after surgery is now recommended in the management of postoperative Crohn's disease (CD) to decrease the risk of symptomatic recurrence. However, endoscopy is felt as a burdensome procedure by the patients highlighting the need for more convenient tools. In our prospective study from two referral centers, we showed that faecal calprotectin measurement and magnetic resonance imaging with Clermont score or magnetic resonance index of activity calculation are two reliable tools to detect early endoscopic postoperative recurrence in CD and could then be an alternative to colonoscopy.

Baillet P, Cadiot G, Goutte M, Goutorbe F, Brixi H, Hoeffel C, Allimant C, Reymond M, Obritin-Guilhen H, Magnin B, Bommelaer G, Pereira B, Hordonneau C, Buisson A. Faecal calprotectin and magnetic resonance imaging in detecting Crohn's disease endoscopic postoperative recurrence. *World J Gastroenterol* 2018; 24(5): 641-650 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i5/641.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i5.641>

INTRODUCTION

Crohn's disease (CD) is a chronic, progressive and disabling inflammatory disorder, which can highly impacts the patients' quality of life^[1-3]. The natural course of CD can lead to bowel damages such as strictures or fistulas requiring surgical management^[1-3]. Despite an increased use of biologics, surgery is still warranted in half of the patients within ten years after diagnosis^[1]. As intestinal resection is not curative, postoperative recurrence (POR) remains a key issue in the management of patients with CD. Up to 75% of the patients experienced endoscopic POR within the first year after surgery in referral centers^[4]. More than 25 years ago, Rutgeerts and colleagues demonstrated that the postoperative course of CD is very heterogeneous^[5]. They proposed a stratification of the patients according to the early endoscopic findings within the first year after the surgery, namely the Rutgeerts' index, to predict the risk of clinical postoperative recurrence^[5]. Recently, the postoperative Crohn's endoscopic recurrence (POCER) trial confirmed previous retrospective data suggesting that an endoscopy-based strategy with a therapeutic step-up according to the

Rutgeerts' index decreased the risk of clinical POR in CD patients^[6-10]. Even though the best threshold to define endoscopic POR using this index is still debated^[11-13], performing an endoscopy is now recommended for all the patients with CD within the first year after intestinal resection^[14]. However, colonoscopy remains a burdensome procedure for the patients owing to the bowel cleansing, the general anesthesia and the risk of complications^[15,16] highlighting the need to develop more convenient tools.

In this context, magnetic resonance imaging (MRI) is more accepted than endoscopy and has shown a reliable accuracy to detect endoscopic activity in CD patients^[17-21]. The magnetic resonance index of activity (MaRIA)^[17,18,22] and the Clermont score^[20,21,23-25] are the two main MRI scores that have been validated compared to endoscopy in CD. These two scores demonstrated high performances to grade CD severity and to evaluate mucosal healing^[19,26]. However, the MaRIA and the Clermont score have not been investigated so far in the early postoperative course of patients with CD. Only one Austrian group has hitherto proposed an index, so-called the MR scoring system, to detect endoscopic POR. The authors observed promising results compared to the Rutgeerts' index in predicting the risk of clinical POR in patients with CD^[27,28].

Another alternative could be the use of faecal calprotectin measurement to predict the risk of clinical POR. In the last decade, faecal calprotectin demonstrated very reliable performances to diagnose CD, to assess disease activity and to predict clinical relapse^[29-40]. Recently, a few works reported convincing results on the use of faecal calprotectin in the early postoperative phase in CD patients^[41-44].

In the present study, we aimed to assess the performances of MRI and faecal calprotectin to detect endoscopic POR within the first year following surgery in patients with CD.

MATERIALS AND METHODS

Ethical consideration

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements. Informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee. The study was approved by local Ethics Committee (#2014/CE 42).

Patients

All the patients with CD older than 18 years-old, who underwent a CD-related ileocolonic resection, were consecutively enrolled in this prospective study. They were included from two tertiary centers between January 2014 and December 2016. An endoscopic

evaluation was performed for each patient within the first year after surgery (or after restoration of intestinal continuity for the patients with temporary ostomy). The anastomosis was reached by the colonoscope for all the patients. Patients' demographics and clinical activity were collected the same day. We used the Crohn's disease activity index (CDAI)^[45] to grade disease activity. Blood samples were taken prior to the endoscopy to measure high sensitive serum C-reactive protein (CRP) level by immuno-nephelometric method (Vista, Siemens, Berlin, Germany). Stools were collected in the morning the day before the endoscopy. All the patients were also evaluated by magnetic resonance imaging with diffusion-weighted sequences. Colonoscopy and MRI had to be performed within one month. The choice of medication to prevent postoperative recurrence was free and depended on the physician's decision.

Faecal calprotectin testing

Stools were collected in the morning the day before the endoscopy to reduce intra-individual variation, and immediately stored at 4 °C. The bowel cleansing was started in all patients after stool collection. Patients were instructed to transport the stool samples in a dedicated container at 4 °C. Faecal samples were immediately transferred, upon patient arrival, to the local Biochemistry Laboratory. Stool cultures were performed on all inflammatory bowel disease (IBD) samples to exclude gastrointestinal infection. Calprotectin was measured using quantitative immunochromatographic test Quantum Blue High Range (Bühlmann Laboratories AG, Schönenbuch, Switzerland), according to the manufacturer's instructions. All the biochemistry tests were done by individuals blinded from clinical, endoscopic and radiological data.

Endoscopy

After bowel cleansing, endoscopy was performed under anaesthesia with propofol (PROPOFOL DAKOTA PHARM; Sanofi-Aventis, Paris, France). All colonoscopies were performed by experienced IBD endoscopists in each center using column video colonoscopy (QFC L 140; Olympus, Tokyo, Japan). The endoscopists were blinded from biochemistry and MRI data. The endoscopic lesions were graded using the Rutgeerts' index^[5] as routinely used in the two IBD units during the postoperative phase. We defined endoscopic POR as Rutgeerts' index \geq i2b. However, we performed also sensitivity analyses using different cut-off values such as Rutgeerts' index \geq i2 or \geq i3.

MRI examination

On the day of MRI, patients had to have been fasting for at least four h before the examination. An oral ingestion of 500 mL to 1000 mL of PEG (Fortrans®, Ipsen Pharma, Paris, France) was used to achieve an adequate intestinal distension. The MRI imaging examinations with no bowel cleansing the day before the examination and

with no colonic distension (no enema) were performed as previously described^[20,21,23,24] with a 1.5 Tesla GE Optima MR 450w (General Electric HealthCare, Fairfield, CT) in Clermont-Ferrand, France, and with a 1.5 Tesla Avanto MRC1 (Siemens, Erlangen, Germany) in Reims, France.

MRI analysis

Each examination was interpreted independently by two radiologists: one experienced IBD radiologist (CH) and one junior (PB)^[20,21,23,24] who were blinded from endoscopy and biochemistry data. The analyses were focused on the perianastomotic area. The following characteristics were collected: oedema, ulcers, bowel wall thickening (mm), adjacent enlarged lymph nodes (> 8 mm in shortest diameter), comb sign, penetrating complications (fistula, abscess, phlegmon), and Relative Contrast Enhancement (RCE)^[17]. For quantitative assessment, the apparent diffusion coefficient (ADC) was calculated on the ADC map independently in separate sessions by the two radiologists in the peri-anastomotic area or in the area of highest signal intensity in the bowel wall. As previously published, the definition of this area was based on the judgment of the radiologist^[20,21,23-25]. MR scoring system was defined as MR0 (no abnormal features), MR1 (minimal mucosal changes), MR2 (diffuse aphthoid ileitis, moderate recurrence), and MR3 (severe recurrence with trans- and extramural changes)^[27,28]. The Clermont score^[20,21,23-25] was calculated using the following formula: $1.646 \times \text{bowel thickness} - 1.321 \times \text{ADC} + 5.613 \times \text{oedema} + 8.306 \times \text{ulcers} + 5.039$. The MaRIA was calculated using the following formula for each of the five segments: $\text{MaRIA} = 1.5 \times \text{wall thickening (mm)} + 0.02 \times \text{RCE} + 5 \times \text{edema} + 10 \times \text{ulceration}$ ^[17,18,22].

Data managing and statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Clermont-Ferrand University Hospital^[46]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

Statistical analyses were performed using Stata software (version 13, StataCorp, College Station, United States). The tests were two-sided, with a type I error set at $\alpha = 0.05$. Baseline characteristics were presented as mean \pm SD or median (interquartile range) according to statistical distribution (assumption of normality assessed using the Shapiro-Wilk test) for continuous data and as the number of patients and associated percentages for categorical parameters. Comparisons of patients' characteristics between

the independent groups (*i.e.*, Rutgeerts' index) were performed using chi-squared or Fisher's exact tests for categorical variables, and Student's t-test or Mann-Whitney test if assumptions of t-test were not met (1) normality, and (2) assumption of homoscedasticity studied using Fisher-Snedecor test) for quantitative parameters. Receiver operating characteristic (ROC) curves were used to determine the best biomarker to predict Rutgeerts' index. The best thresholds were determined according to biological relevance and to usually recommended indices reported in literature (Youden, Liu and efficiency). Sensitivity (se), specificity (spe) and negative (NPV) and positive predictive values (PPV) were presented with 95% confidence intervals. Concordance has been studied using kappa coefficient and accuracy for categorical parameters. Kappa values were studied in relation to usual recommendations: < 0.2 (negligible), 0.2-0.4 (low/weak consistency), 0.4-0.6 (moderate agreement), 0.6-0.8 (substantial/good agreement) and > 0.8 (excellent agreement). For quantitative parameters, the concordance was studied using correlation coefficient, Lin's concordance coefficient and Bland and Altman graph^[47].

RESULTS

Baseline characteristics of the patients

Overall, 30 CD patients were enrolled in this study. The main characteristics of these patients are provided in Table 1. Among them, half of the patients (15/30) were female and 7 (23.3%) were active smokers. Mean age and mean disease duration at the time of inclusion were 34.9 ± 14.1 years and 9.0 ± 9.5 years, respectively. Fifteen patients presented with pure ileal involvement (L1 according to Montreal classification), only one patient (3.3%) had pure colonic location (L2 according to Montreal classification) and 14 patients had ileocolonic CD (46.7%). Six patients experienced perianal lesions (21.4%). In the current study, the patients were treated with no medication (20.0%), 5-ASA (6.7%), thiopurines (56.7%), anti-TNF agents (20.0%) or several of these drugs for preventing endoscopic POR. The distribution of the endoscopic findings according to the Rutgeerts' index within the first year of surgery is provided in Figure 1.

MRI parameters in detecting endoscopic postoperative recurrence

The median interval between surgery and endoscopy was 6 mo (5.0-9.3). The median interval between MRI and endoscopy was 14 d (6.5-31). We compared all the MRI parameters in patients with or without endoscopic POR. We did not observe any ulceration among the 30 MRI. The bowel wall was not significantly thickened in the patients with endoscopic POR (3.59 ± 1.69 mm vs 2.83 ± 1.55 mm, $P = 0.26$). The detection of oedema was not significantly associated with the occurrence of endoscopic POR (38.5% vs

Table 1 Characteristics at the time of endoscopy of the 30 patients with Crohn's disease enrolled in this study *n* (%)

Patients' characteristics	Value
Age at diagnosis, (yr), mean \pm SD	34.9 \pm 14.1
Disease duration, (yr), mean \pm SD	9.0 \pm 9.5
Female gender	15 (50.0)
Active smokers	7 (23.3)
Montreal classification	
CD location	
L1	15 (50.0)
L2	1 (3.3)
L3	14 (46.7)
CD behaviour	
B1	1 (3.3)
B2	16 (53.3)
B3	13 (43.3)
Perianal lesions	7 (23.3)
Therapy to prevent endoscopic POR ¹	
None	6 (20.0)
5-ASA	2 (6.7)
Thiopurines	17 (56.7)
Anti-TNF agent	6 (20.0)
CDAI, median (interquartile range)	78 (26-86)
CRP, median (interquartile range)	2.9 (2.9-3.9)
Faecal Calprotectin (μ g/g), median (IQR)	100 (100-136)

¹The patients were treated with one or several of these medications. CD: Crohn's disease; POR: Postoperative recurrence; TNF: Tumor Necrosis Factor; CDAI: Crohn's disease activity index; CRP: C-reactive protein.

11.8%, $P = 0.19$). The value of ADC was lower in the patients with endoscopic POR compared to those with no recurrence (2.03 ± 0.32 vs $2.27 \pm 0.38 \times 10^{-3}$ mm²/s, $P = 0.032$). The Clermont score (10.4 ± 5.8 vs 7.4 ± 4.5 , $P = 0.038$) and the RCE ($129.4\% \pm 62.8\%$ vs $76.4\% \pm 32.6\%$, $P = 0.007$) were increased in the patients with endoscopic POR. In contrast, MaRIA (7.3 ± 4.5 vs 4.8 ± 3.7 ; $P = 0.15$) was not significantly higher in the patients with endoscopic POR. The proportion of patients with endoscopic POR was 30.0%, 71.4% and 66.7% in the patients with MR scoring system MR0, MR1 and MR2, respectively ($P = 0.11$). However, the proportion of patients with endoscopic POR seemed to be higher in the patients with MR scoring system MR1 and MR2 vs MR0 (53.8% vs 17.6%, $P = 0.056$).

Using ROC curves, we determined that a value of ADC $< 2.35 \times 10^{-3}$ mm²/s [Se = 0.85 (0.38-0.86), Spe = 0.65 (0.55-0.98), PPV = 0.85 (0.55-0.98), NPV = 0.65 (0.38-0.86)] and a value of RCE $> 100\%$ [Se = 0.75 (0.46-0.91), Spe = 0.81 (0.56-0.91), PPV = 0.75 (0.46-0.91), NPV = 0.81 (0.56-0.91)] were the best cut-off values to identify endoscopic POR (Figure 2). We showed also that a Clermont score > 6.4 [Se = 0.61 (0.35-0.82), Spe = 0.82 (0.58-0.94), PPV = 0.73 (0.47-0.95), NPV = 0.74 (0.46-0.95)] and a MaRIA > 3.76 [Se = 0.61 (0.35-0.82), Spe = 0.82 (0.58-0.94), PPV = 0.73 (0.46-0.98), NPV = 0.74 (0.46-0.96)] demonstrated interesting performances to detect endoscopic POR (Figure 2). In addition, a MR scoring system \geq MR1 showed the following performances to

detect endoscopic POR: Se = 0.54 (0.29-0.77), Spe = 0.82 (0.58-0.94), PPV = 0.70 (0.42-0.98), and NPV = 0.70 (0.50-0.90) (Figure 2).

Clinical and biological markers in detecting endoscopic POR

The CDAI was not significantly higher in patients with endoscopic POR [median values = 80 (51-86) vs 62 (10-85); $P = 0.17$] and the performances of CDAI > 150 to detect endoscopic POR were: Se = 0.08 (0.02-0.36), Spe = 0.94 (0.70-1.00), PPV 0.50 (0.01-0.99) and NPV = 0.56 (0.35-0.75) (Figure 2).

The CRP value was not significantly higher in patients with endoscopic POR (6.2 ± 7.8 vs 3.2 ± 1.6 ; $P = 0.43$). Using a ROC curve, we observed the following performances of CRP level above 5 g/L: Se = 0.31 (0.09-0.61), Spe = 0.88 (0.62-0.98), PPV = 0.67 (0.22-0.96), NPV = 0.61 (0.39-0.80).

Faecal calprotectin values were significantly higher in patients with endoscopic POR (354.8 ± 432.5 μ g/g vs 114 ± 54.5 μ g/g; $P = 0.0075$) (Figure 2). Using a ROC curve, we found that the cut-off value of faecal calprotectin > 100 μ g/g demonstrated high performances to detect endoscopic POR [Se = 0.67 (0.39-0.86), Spe = 0.93 (0.66-1.00), PPV = 0.89 (0.68-1.00) and NPV = 0.77 (0.56-0.97) and accuracy 0.80 (0.66-0.96)] (Figure 2). The exclusive measure of faecal calprotectin level in the postoperative setting would have been able to adequately stratify patients as having no sign of endoscopic POR in most of the patients and therefore might allow in our cohort avoiding 13 colonoscopies *i.e.* 43.3% of the total number (13 true negative patients). However, it would have missed 4 false negative patients (13.3%).

We did not observe any improvement of performances to detect endoscopic POR with concomitant or successive use of MRI and faecal calprotectin (data not shown).

Sensitivity analysis

We performed the same investigations in using different cut-off value of Rutgeerts' index \geq i2 or \geq i3. These results are detailed in Supplementary Tables 1 and 2.

Inter-observer variation study

The inter-observer agreement between the two radiologists was 96.7% for the MR scoring system with a κ -value of 0.933 ± 0.139 . We observed substantial concordances (Lin's concordance coefficient with 95% confidence interval) between the two readers regarding bowel thickness [0.97 (0.94-0.99)], ADC [0.71 (0.53-0.89)], RCE [0.73 (0.55-0.91)], Clermont score [0.990 (0.98-1.00)], and MaRIA [0.99 (0.98-1.00)]. We calculated the median relative variation of ADC [6.5% (5.1-11.0)], RCE [15.0% (8.8-25.5)], Clermont score [9.5% (4.5-9.5)], and MaRIA [9.6% (5.3-13.6)]. The inter-reader agreement was 96.7% using a cut-off value of MaRIA of 3.76 ($\kappa = 0.92 \pm 0.18$) and 93.3% using a

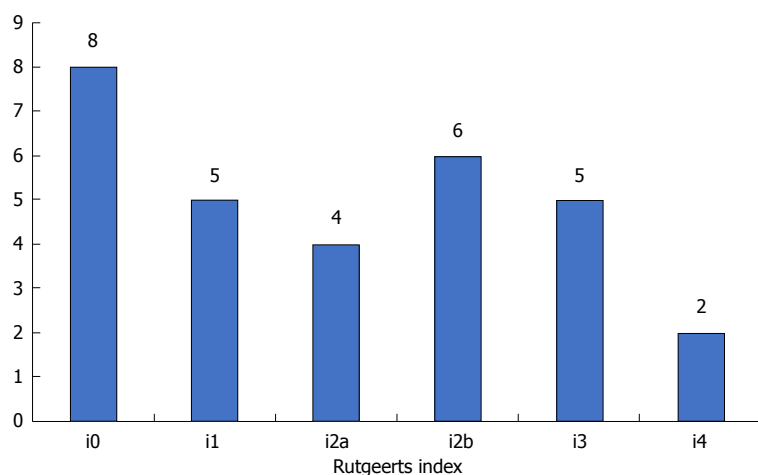


Figure 1 Distribution of the endoscopic findings according to the Rutgeerts' index within the first year of surgery in 30 patients with Crohn's disease.

threshold of Clermont score above 6.4 ($\kappa = 0.86 \pm 0.18$) (no significant difference between the two scores).

DISCUSSION

In this prospective study, we showed, for the first time in the same cohort that faecal calprotectin and MRI are two reliable alternative tools to detect endoscopic POR with CD. In addition, MRI parameters including Clermont score, MaRIA and MR scoring system demonstrated substantial inter-reader agreement.

As surgery is not curative in CD and the rate of endoscopic POR can reach more than 75% within the first year after the surgery in some referral centers^[4], the prevention of POR remains a major concern for the IBD physicians. Recently, the data retrieved from the POCER trial confirmed the positive impact of a tailored therapeutic management based on the early endoscopic findings (within the first year following the intestinal resection) compared to a monitoring based on clinical activity^[6]. A lower rate of endoscopic POR at 18 mo was observed in the active care arm compared to the control group (49% vs 67%, $P = 0.03$)^[6]. Then, performing an endoscopic evaluation within the first week following the surgery (or the restoration of intestinal continuity) is recommended in patients with CD. However, the colonoscopy is felt as a burdensome procedure by most of the patients leading some of them to deny performing this examination. This observation highlights the need to develop more convenient tools for these patients. A nationwide survey including 916 IBD patients recently reported that stools collection for faecal biomarkers and MRI were considered as more acceptable than colonoscopy by CD patients^[15]. Accordingly, investigating the performances of faecal calprotectin and MRI to detect endoscopic POR seemed highly relevant.

The early endoscopic evaluation is performed using the Rutgeerts' index^[5]. The usual definition of endoscopic POR is a Rutgeerts' index $\geq i2$ as the

likelihood of reappearance of symptoms in the five years following the surgery was 40% in i2-patients and more than 75% in i3- or i4-patients compared to less than 15% in patients with Rutgeerts' index $\leq i1$ ^[5]. However, the debate is currently growing regarding this definition owing to the heterogeneity of the i2-subgroup encompassing several conditions such as more than five aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or ulcers up to 1 cm confined to ileocolonic anastomosis. The characterization of the lesions confined to the anastomosis is a problem in daily practice as it is sometimes difficult to exclude alternative diagnosis such as post-surgical or ischemic consequences. Then, the i2-group is now divided into two subgroups *i.e.* i2a (lesions confined to the anastomosis) and i2b (more than 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions). Two teams attempted recently to show a different course of the disease between these two subgroups (i2a vs i2b) but failed to do so^[11,12]. Unfortunately, this question should be very difficult to figure out as a step-up therapeutic strategy is performed in almost all the patients with endoscopic lesions classified as i2a and i2b. Consequently, investigating the natural history of this subgroup of patients will be probably no longer possible. Although it is still matter of debate, we decided to define endoscopic POR as a Rutgeerts' index $\geq i2b$ but we performed a sensitivity analysis using other thresholds including Rutgeerts' index $\geq i2$.

To date, only one team studied the potential role of MRI to replace early endoscopic evaluation in CD patients who underwent ileocolonic resection^[27,28]. They arbitrarily created the MR scoring system dedicated to the postoperative phase as: MR0 (no abnormal features), MR1 (minimal mucosal changes), MR2 (diffuse aphthoid ileitis, moderate recurrence), and MR3 (severe recurrence with trans- and extramural changes)^[28]. The authors observed a good interobserver agreement between the MR scoring system and the Rutgeerts'

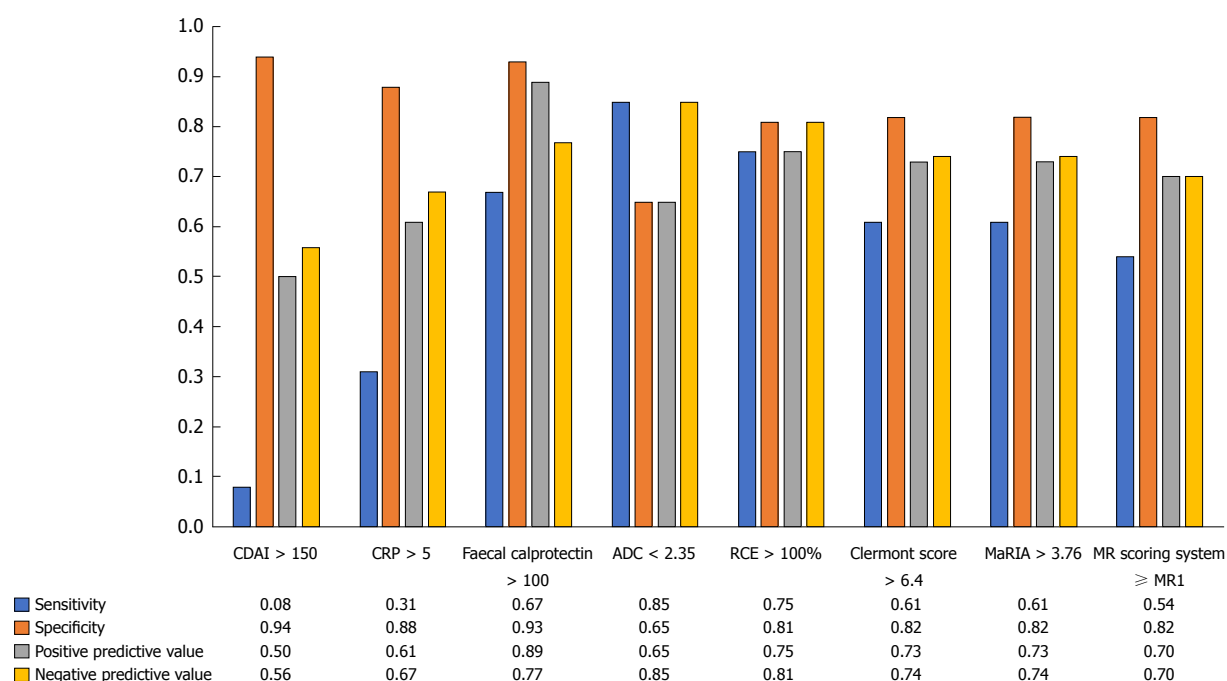


Figure 2 Performances of clinical, biological and magnetic resonance imaging parameters to detect endoscopic postoperative recurrence within the first year after surgery in patients with Crohn's disease.

index (agreement rate = 77.8% and $\kappa = 0.67$). AMR scoring system \geq MR2 showed a trend to be predictive of a higher risk of clinical POR ($P = 0.09$)^[27]. In our cohort, the MR scoring system demonstrated a clear trend to be able to detect the occurrence of endoscopic POR (53.8% vs 17.6%, $P = 0.056$). However, we did not find the same threshold (\geq MR1 rather than \geq MR2). It could be partly explained by the very high level of severe endoscopic POR in the Austrian cohort *i.e.* 5 patients with i3 (16.7%) and 14 patients with i4 (46.7%) contrary to ours: 5 patients with i3 (16.7%) and 2 patients with i4 (6.7%). In our study, we investigated, for the first time, the potential role of each individual MRI item to detect endoscopic POR. We observed that the bowel thickness was not a reliable parameter to distinguish patients with or without endoscopic POR, which is not surprising, as a mildly thickened bowel wall can be seen in CD patients after surgery even in the absence of endoscopic recurrence. We also observed that the presence of oedema was not significantly different between the two groups (38.5% vs 11.8%, $P = 0.19$). Finally, we did not observe any severe lesions on MRI such as ulcerations, fistula or stenosis, which is in line with the early stage of the disease within the first year following the surgery.

The MaRIA^[17-19,22] and the Clermont score^[19-21,23,24,48] are the two available MRI scores validated against endoscopy to assess ileocolonic activity in patients with CD. We investigated the performances of these two validated scores to detect endoscopic POR. We observed substantial positive (0.73 for both) and

negative predictive values (0.74 for both) of these two scores to identify POR. The cut-off values were lower than those usually used to detect inflammatory activity in CD^[18,21]. It is consistent with the fact that the early postoperative lesions are mostly mild and limited to the mucosa. The most sensitive MRI features to detect these minimal shifts are the quantitative parameters assessing the degree of inflammation such as the RCE (for the injected sequences) and the ADC (for the diffusion-weighted sequences), which showed substantial accuracy to detect endoscopic POR in our cohort. However, the impact of these quantitative parameters among the calculation of the MaRIA and the Clermont score remains limited. Even though RCE and ADC demonstrated high inter-reader agreement^[49], these items could be two equipment-dependent metric values, which could be difficult to use alone despite their substantial performances to detect endoscopic POR.

Faecal calprotectin is hitherto the most effective faecal biomarker to assess endoscopic activity in patients with CD^[29-40]. Recently, a French prospective study and a post-hoc analysis of the POCER trial reported that a level of faecal calprotectin > 100 $\mu\text{g/g}$ was the best threshold to detect endoscopic POR (Rutgeerts' index \geq i2) with high negative predictive value between 91 and 93%^[42,43]. Then, the authors calculated that they could avoid from 30% to 47% of unnecessary colonoscopies^[42,43]. In our cohort, we also identified a level of faecal calprotectin > 100 $\mu\text{g/g}$ as the best cut-off value to show an endoscopic POR (Rutgeerts' index

≥ i2b). Contrary to the previous study, we observed a lower negative predictive value (77%) but a higher positive predictive value (89%). The lower level of NPV is consistent with the data from a secondary analysis of the TOPPIC trial^[50] (88 patients) reporting a NPV of 75% even though they observed in the same time a low PPV (58%). Concerning the high PPV, it could be partly explained by the different assays used across the studies and should be confirmed in other larger independent cohorts. In our cohort, the use of faecal calprotectin would have avoided 43.3% of unnecessary colonoscopy (13 true negative patients/30) but would have missed 13.3% of recurrences (4 false negative patients /30). However, we did not observe any severe endoscopic POR (i3 or i4) among these 4 patients. Finally, we confirmed that the CDAI and the CRP level are not accurate enough to monitor patients with CD within the first months after the surgery.

In the same cohort, we investigated the performances of faecal calprotectin and MRI. Our study was not powered to directly compare these two potential alternatives to colonoscopy and then we did not observe any significant difference between these two tools. However, we observed numerically a mild trend favoring faecal calprotectin. Of course, this result has to be confirmed in independent larger cohorts before drawing any conclusion.

The main strengths of our study included its prospective design with concomitant evaluation of faecal biomarker and MRI. In addition, we investigated the potential impact of each MRI parameter including the two most validated scores *i.e.*, the MaRIA and the Clermont score. The main limitation of this study is the sample size even though our sample size calculation was based on the two prior Austrian studies^[27,28] and then remains one of the larger published so far on the role of MRI in the postoperative CD.

Faecal calprotectin and MRI are two reliable options to detect endoscopic POR within the first year after ileocolonic resection in patients with CD and could be used as a more convenient tool than colonoscopy.

ARTICLE HIGHLIGHTS

Research background

Surgical resection is unfortunately not curative in Crohn's disease (CD), and postoperative recurrence (POR) remains a crucial issue in these patients. Performing an endoscopy within the first year after surgery is recommended in clinical practice. However, colonoscopy remains a burdensome procedure for the patients highlighting the need to develop more convenient tools. In this context, MRI and faecal calprotectin are more accepted than endoscopy and have shown a reliable accuracy to detect endoscopic activity in patients with CD. MRI scores such as the magnetic resonance index of activity (MaRIA) and the Clermont score and faecal calprotectin could then be used as an alternative to detect endoscopic POR but their performances remains poorly investigated.

Research motivation

Developing more convenient tools to detect early postoperative recurrence, is a key point in patients with Crohn's disease.

Research objectives

In this study, we assessed the performances of MRI and faecal calprotectin to detect endoscopic postoperative recurrence in patients with Crohn's disease.

Research methods

It was a multicentre prospective observational study.

Research results

ADC < 2.35 × 10⁻³ mm²/s (sensitivity = 0.85, specificity = 0.65, positive predictive value (PPV) = 0.85, negative predictive value (NPV) = 0.65) and RCE > 100% (sensitivity = 0.75, specificity = 0.81, PPV = 0.75, NPV = 0.81) were the best cut-off values to identify endoscopic POR. Clermont score > 6.4 (sensitivity = 0.61, specificity = 0.82, PPV = 0.73, NPV = 0.74), MaRIA > 3.76 (sensitivity = 0.61, specificity = 0.82, PPV = 0.73, NPV = 0.74) and a MR scoring system ≥ MR1 (sensitivity = 0.54, specificity = 0.82, PPV = 0.70, and NPV = 0.70) demonstrated interesting performances to detect endoscopic POR. Faecal calprotectin > 100 µg/g demonstrated high performances to detect endoscopic POR (sensitivity = 0.67, specificity = 0.93, PPV = 0.89 and NPV = 0.77).

Research conclusions

Faecal calprotectin and MRI are two reliable options to detect endoscopic POR within the first year after ileocolonic resection in patients with CD and could be used as a more convenient tool than colonoscopy.

Research perspectives

Additional studies from independent cohorts should be conducted to confirm these data.

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