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Prognostic Value of the Modified Rutgeerts Score for Long-Term Outcomes After Primary Ileocecal Resection in Crohn's Disease

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INTRODUCTION: The prognostic value of the modified Rutgeerts score (mRS) in patients with Crohn's disease (CD) needs to be further elucidated. This study assessed the prognostic value of the mRS for long-term outcomes after primary ileocecal resection in patients with CD.

Prognostic value of the modified Rutgeerts' score for long-term outcomes after primary ileocecal resection in Crohn's disease

Study population



652 Crohn's disease patients
Mean follow-up: 6.4 yrs

Methods



Modified Rutgeerts' score at first postoperative ileocolonoscopy (i.e. index mRS) was used for analyses on long-term outcomes: surgical and clinical recurrence, progression to severe endoscopic recurrence.

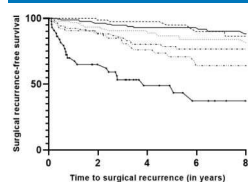
Cox proportional hazard models were used to assess the association between index mRS and outcomes.



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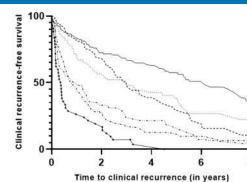
Outcomes

Surgical recurrence



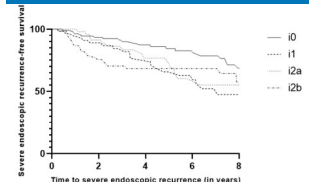
Multivariable analysis:
i2b aHR 3.0 (1.5-5.6), i3 aHR 4.0 (2.0-7.9), i4 aHR 8.0 (4.0-16.0)

Clinical recurrence



Multivariable analysis:
i1 aHR 1.7 (1.5-5.6), i2a aHR 1.7 (1.7-2.4), i2b aHR 4.4 (3.2-6.0), i3 aHR 3.6 (2.5-5.2), i4 aHR 7.3 (4.8-10.9)

Severe endoscopic recurrence



Multivariable analysis:
i1 aHR 2.0 (1.1-3.7); i2b aHR 2.5 (1.4-4.6)

Conclusions

- The increasing mRS corresponds closely with the risk of surgical and clinical recurrence
- Moderate to severe lesions (index mRS \geq i2b) are associated with surgical recurrence
- Ileal lesions (index mRS i1 and i2b) are associated with severe endoscopic recurrence
- These results support tight monitoring of disease activity and treatment optimization in patients with ileal lesions, and a more conservative management in patients with anastomotic lesions

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METHODS: Patients with CD after primary ileocecal resection with an available mRS at first postoperative ileocolonoscopy (index mRS) were retrospectively included. The primary outcome was surgical recurrence. Secondary outcomes were clinical recurrence and progression to severe endoscopic recurrence (≥ 3). Cox proportional hazard models were used to assess the association between index mRS and outcomes.

RESULTS: Six hundred fifty-two patients were included (mean follow-up: 6.4 years, SD: 4.6). Surgical recurrence rates were 7.7%, 5.3%, 12.9%, 19.1%, 28.8%, 47.8% for index mRS i0, i1, i2a, i2b, i3, and i4, respectively. Clinical recurrence occurred in 42.2% (i0), 53.7% (i1), 58.5% (i2a), 80.2% (i2b), 79.4% (i3), and 95.3% (i4) of patients. Progression to severe endoscopic recurrence occurred in 21.1% (i0), 33.9% (i1), 26.8% (i2a), and 33.3% (i2b) of patients. An index mRS of i2b (adjusted hazard ratio [aHR] 3.0; 1.5–5.6), i3 (aHR 4.0; 2.0–7.9) and i4 (aHR 8.0; 4.0–16.0) were associated with surgical recurrence. An index mRS of i1 (aHR 1.7; 1.2–2.4), i2a (aHR 1.7; 1.2–2.4), i2b (aHR 4.4; 3.2–6.0), i3 (aHR 3.6; 2.5–5.2), and i4 (aHR 7.3; 4.8–10.9) were associated with clinical recurrence. An index mRS of i1 (aHR 2.0; 1.1–3.7) or i2b (aHR 2.5; 1.4–4.6) was associated with progression to severe endoscopic recurrence.

DISCUSSION: The increasing mRS corresponds closely with the risk of surgical and clinical recurrence. An index mRS \geq i2b is associated with surgical recurrence, an index mRS \geq i1 is associated with clinical recurrence, and i1 or i2b with progression to severe endoscopic recurrence. These results support tight monitoring of disease activity and treatment optimization in patients with ileal lesions and a more conservative management in patients with anastomotic lesions.

KEYWORDS: Crohn's disease; modified Rutgeerts score; postoperative recurrence

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/AJG/D48>

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INTRODUCTION

Patients with Crohn's disease (CD) are still at considerable risk of an intestinal resection although the risk has declined over the past decades (1). An intestinal resection is an important treatment modality, which is performed in approximately 25% of patients within 10 years after CD diagnosis (2). An ileocecal resection (ICR) is the most common surgical procedure in CD (3). Despite an intestinal resection may induce disease remission and provide relief of CD symptoms, surgery is not curative and recurrence at the ileocolic anastomosis and/or in the neoterminal ileum is common (4–6).

Ileocolonoscopy is considered the golden standard for the diagnosis of postoperative recurrence in patients with CD (7). The Rutgeerts score (RS) was developed as an endoscopic scoring system to assess the severity of recurrence of inflammation at the ileocolic anastomosis and in the neoterminal ileum. The original RS stratifies the endoscopic severity into 5 groups (i0–i4) (8). High indices of the RS (≥ 2) are associated with a higher risk of clinical recurrence and a re-resection when compared with a lower RS (i0–i1) (9). However, the prognostic value per index score of the RS is unknown.

The modified Rutgeerts score (mRS) was proposed to differentiate i2 into lesions confined to the anastomosis (i2a) versus lesions in the neoterminal ileum (i2b) and is currently used to assess the severity of postoperative endoscopic recurrence (10). The nature of anastomotic lesions (i2a) is unknown and may be related to a postischemic surgical phenomenon or related to staples, instead of CD recurrence (11). Several studies have reported conflicting clinical outcomes of anastomotic lesions on several measures of postoperative

recurrence (clinical recurrence, surgical recurrence, and/or progression to [severe] endoscopic recurrence) (12–18). In a recently published individual participant data meta-analysis, no difference was observed between i2a and i2b lesions for clinical recurrence and/or a surgical reintervention (19). However, no adjustment for known risk factors was conducted for the latter outcome. In addition, progression to severe endoscopic recurrence was not assessed. Therefore, the initiation or optimization of medication after an endoscopic diagnosis of ulcerations at the ileocolic anastomosis remains a matter of debate.

In this cohort study, we assessed the prognostic value of the mRS (per index score), after correction for known clinical risk factors, to predict the risk of surgical and clinical recurrence, and progression to severe endoscopic recurrence after primary ICR in patients with CD.

METHODS

Participants and study design

Consecutive patients who underwent a primary ICR for the indication of CD between 2000 and 2019 were identified from a multicenter, retrospective database from 6 academic and 4 teaching hospitals in the Netherlands. All patients with CD (i) aged ≥ 16 years or older, (ii) who underwent ICR with restoration of the intestinal continuity, and (iii) who had ≥ 1 postoperative ileocolonoscopy assessed with the use of the mRS were included. Exclusion criteria were a permanent stoma, a re-resection before the first postoperative endoscopic assessment, prior intestinal resections, other indications for ICR (e.g., gastrointestinal malignancy), and/or absence of follow-up data.

Outcomes

The primary outcome of this study was surgical recurrence (i.e., re-resection of the small bowel and/or colon) for CD recurrence during follow-up. Surgical recurrence within 3 months from primary ICR was considered as a re-resection due to postoperative complications and not considered as surgical recurrence. The secondary outcomes were (i) clinical recurrence defined as CD-related complaints with subsequent endoscopic recurrence (mRS \geq i2b), surgical recurrence, radiologic recurrence (assessed by a local radiologist on ultrasonography, computed tomography, or magnetic resonance imaging), and/or therapeutic optimization (i.e., initiation of corticosteroids, immunomodulators, or biologicals for symptomatic disease) and (ii) progression to severe endoscopic recurrence (mRS \geq i3) in patients with an index mRS i0–i2b.

Data collection

Baseline and clinical data were retrieved from individual medical charts including demographics, surgical and disease characteristics, and prior medical treatment. The date of index ileocolonoscopy (i.e., first operative ileocolonoscopy) was set as start of the follow-up and time at risk of this study. The mRS at the first postoperative ileocolonoscopy (i.e., index mRS) was used to assess the outcomes. The mRS was graded separately by 4 trained physicians (S.B., J.A., E.B., and J.S.) based on available photographs and/or the endoscopy report for all patients. Follow-up time was defined as the interval between the index ileocolonoscopy (t0) and time to event. Patients were censored in case of the event was not observed (i.e., end of follow-up or lost to follow-up).

Statistical analyses

Descriptive statistical analysis (frequency, percentage, mean, SD, median, and interquartile range [IQR]) was used to describe the research sample. Categorical variables were quoted as the number and percentage. Continuous variables were tested for normality using the Shapiro-Wilk test. Normal distributed variables were presented as mean and SD, while non-normal distributed variables were presented as median and IQR. Kaplan-Meier curves, with log-rank test for significance, were used to describe and compare survival probabilities between individual mRS.

Associations between index mRS and known clinical risk factors (according to the current guidelines) and the 3 time-to-event outcomes (surgical and clinical recurrence, and progression to severe endoscopic recurrence) were investigated using Cox proportional hazard models (7,20,21). The following variables were included for multivariable analysis: age at diagnosis, penetrating disease behavior at surgery (according to the Montreal classification), maintenance therapy during follow-up (i.e., continuation of postoperative prophylactic medication or start of medication within 6 weeks after index ileocolonoscopy with an antitumor necrosis factor agent [anti-TNF] and/or an immunomodulator), and time to index ileocolonoscopy (7,20,21). The models included a random effect for the study center to take potential correlation into account between patients treated in the same hospital.

Because severe endoscopic recurrence is not observed directly and only known to lie within the interval between the first ileocolonoscopy at which it was not yet present and the last ileocolonoscopy at which it was diagnosed, sensitivity analysis with interval censoring for severe endoscopic recurrence was performed. Analyses were performed in R version 4.1.3 (R Core

Team 2022) with the help of the packages *icenReg* (version 2.0.15) and *survival* (22).

Ethics

This study was performed in accordance with the Declaration of Helsinki and approved by the Medical Ethical Research Committee of the Erasmus University Medical Centre Rotterdam (MEC-2017-1151).

RESULTS

Baseline characteristics

A total of 652 patients with CD who underwent a primary ICR were included. Most of the patients were female (62.9%) with a mean age of 35.6 years (SD: 13.8) and a median disease duration of 3.1 years (IQR: 0.8–8.2) during ICR (Table 1). Disease localization was restricted to the ileum in 63.8% (n = 418) of patients, and 36.2% (n = 236) of patients had ileocolic disease at ICR. After primary ICR, postoperative prophylactic treatment was initiated in 36.7% (n = 239) of the patients and concerned immunomodulator monotherapy (61.1%, n = 146), anti-TNF monotherapy agent (21.8%, n = 52), combination therapy (immunomodulator and anti-TNF agent) (14.6%, n = 35), ustekinumab (2.1%, n = 5), and vedolizumab (0.4%, n = 1).

Index ileocolonoscopy was performed at a median of 8.7 months (IQR: 5.9–23.9) after primary ICR. The mean follow-up period after index ileocolonoscopy was 6.4 years (SD: 4.6). The index mRS comprised i0 in 195 patients (29.9%), i1 in 113 patients (17.3%), i2a in 101 patients (15.5%), i2b in 131 patients (20.1%), i3 in 66 patients (10.1%), and i4 in 46 patients (7.0%). After the index ileocolonoscopy, maintenance therapy was initiated, within 6 weeks after ileocolonoscopy, in 14.4%, 14.2%, 30.7%, 43.5%, 50.0%, and 58.7% of patients with i0, i1, i2a, i2b, i3, and i4, respectively.

Index modified Rutgeerts score and surgical recurrence

The overall surgical recurrence rate was 15.3% (n = 100) after a mean time to re-resection of 2.3 years (IQR: 0.6–4.5). During follow-up, surgical recurrence occurred in 7.7%, 5.3%, 12.9%, 19.1%, 28.8%, and 47.8% in patients with i0, i1, i2a, i2b, i3, and i4 (Figure 1). Surgical recurrence rates were not significantly higher in patients with an index mRS of i2b when compared with patients with an index mRS of i2a (28.8% vs 19.1%) (log-rank test, $P = 0.16$).

Index modified Rutgeerts score and clinical recurrence

Six hundred twenty-six patients (96.0%) were eligible for the analysis on clinical recurrence. Clinical recurrence occurred in 63.1% (n = 412) of patients and was reported in 42.2%, 53.7%, 58.5%, 80.2%, 79.4%, and 95.3% in patients with i0, i1, i2a, i2b, i3, and i4 (Figure 2). Clinical recurrence rates were significantly higher in patients with an index mRS of i2b when compared with patients with an index mRS of i2a (80.2% vs 58.5%) (log-rank test, $P < 0.001$).

Index modified Rutgeerts score and progression to severe endoscopic recurrence

During follow-up, 55.9% of the patients (n = 304) (57.4% i0, 53.6% i1, 53.9% i2a, 57.3% i2b) with an index mRS i0–i2b underwent >1 postoperative ileocolonoscopy. In this subset of patients, progression to severe endoscopic recurrence (i3–i4) was reported in 27.7% of patients (n = 84). Progression to severe

Table 1. Baseline characteristics of the study cohort (n = 652)

Variables	Outcomes
Female sex, n (%)	410 (62.9)
Age at diagnosis, mean (SD)	30.1 (13.8)
Montreal classification (age), n (%)	
A1: <17 yr	86 (13.2)
A2: 17–40 yr	423 (64.9)
A3: >40 yr	143 (21.9)
Montreal classification (location of disease) at surgery, n (%)	
L1: Ileal	416 (63.8)
L3: Ileocolic	236 (36.2)
Montreal classification (behavior of disease) at surgery, n (%)	
B1: Nonstricturing, nonpenetrating	149 (22.9)
B2: Stricturing	323 (49.5)
B3: Penetrating	180 (27.6)
Perianal disease during surgery, n (%)	83 (12.7)
Active smoking at surgery, n (%)	231 (35.4)
Medication exposure prior to ICR, n (%)	
Corticosteroids	536 (82.2)
Immunomodulator	433 (66.4)
Anti-TNF agent	294 (45.1)
Ustekinumab	7 (1.1)
Vedolizumab	14 (2.1)
Time between diagnosis and ICR (in yr), median (IQR)	3.1 (0.8–8.2)
Age at surgery, mean (SD)	35.6 (13.8)
Postoperative prophylactic treatment, n (%)	239 (36.7)
Immunomodulator monotherapy	146 (61.1)
Anti-TNF monotherapy	52 (21.8)
Combination therapy (immunomodulator and anti-TNF agent)	35 (14.6)
Ustekinumab	5 (2.1)
Vedolizumab	1 (0.4)
Time between ICR and index ileocolonoscopy (in mo), median (IQR)	8.7 (5.9–23.9)
Rutgeerts score at index ileocolonoscopy, n (%)	
i0	195 (29.9)
i1	113 (17.3)
i2a	101 (15.5)
i2b	131 (20.1)
i3	66 (10.1)
i4	46 (7.0)

IBD, inflammatory bowel disease; IQR, interquartile range; ICR, primary ileocecal resection; mRS, modified Rutgeerts score.

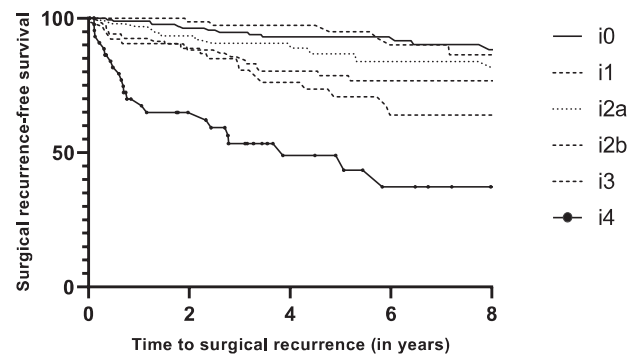


Figure 1. Kaplan-Meier curve of surgical recurrence-free survival (n = 652).

endoscopic recurrence rates occurred in 21.1% (i0), 33.9% (i1), 26.8% (i2a), and 33.3% (i2b) of patients (Figure 3). Severe endoscopic recurrence rates were not significantly higher in patients with an index mRS of i2b when compared with patients with an index mRS of i2a (33.3% vs 26.8%) (log-rank test, $P = 0.47$).

Association of the modified Rutgeerts score with outcomes

After adjusting for the included clinical risk factors, an index mRS of i1 (adjusted hazard ratio [aHR] 0.7; 95% confidence interval [CI] 0.3–1.9) and anastomotic lesions (i2a) (aHR 1.7; 95% CI 0.8–3.5) were not associated with surgical recurrence in multivariable analysis (Table 2). An index mRS of i2b (aHR 2.9; 95% CI 1.5–5.6), i3 (aHR 4.0; 95% CI 2.0–7.9), and i4 (aHR 8.0; 95% CI 4.0–16.0) were independently associated with surgical recurrence during follow-up. An increased time to index ileocolonoscopy was associated with surgical recurrence (aHR 1.1; 95% CI 1.0–1.2). No other associations were reported.

An index mRS of i1 (aHR 1.7; 95% CI 1.2–2.4), i2a (aHR 1.7; 95% CI 1.2–2.4), i2b (aHR 4.4; 95% CI 3.2–6.0), i3 (aHR 3.6; 95% CI 2.5–5.2), and i4 (aHR 7.3; 95% CI 4.8–10.9) were associated with clinical recurrence. Furthermore, active smoking at surgery (aHR 1.4; 95% CI 1.1–1.7) and maintenance therapy with an immunomodulator (aHR 0.6; 95% CI 0.5–0.7) were associated with clinical recurrence.

Concerning progression to severe endoscopic recurrence, an index mRS of i2a was not associated with progression to severe endoscopic recurrence (aHR 1.9; 95% CI 0.9–3.7). An index mRS of i1 and i2b were independently associated with progression to severe endoscopic recurrence (aHR 2.0; 95% CI 1.1–3.7 [i1])

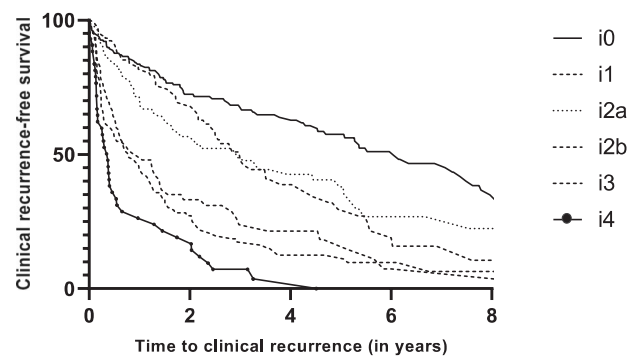


Figure 2. Kaplan-Meier curve of clinical recurrence-free survival (n = 626).

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(14,17,18). The more indolent disease course in patients with anastomotic lesions when compared with ileal inflammation regarding progression to severe endoscopic lesions has also been shown in 2 retrospective multicenter studies (14,17). In addition, Hammoudi et al (18) reported a shorter clinical recurrence-free survival in patients with ileal lesions at index ileocolonoscopy when compared with patients with lesions confined to the anastomosis. These findings are in line with our results showing that an index mRS of i1 is associated with both clinical recurrence and progression to severe endoscopic recurrence, whereas an index mRS of i2a is merely associated with clinical recurrence. These outcomes may be explained by a distinct pathological mechanism of anastomotic lesions when compared with ileal lesions, in which the role of ischemia is debated (18,23). A recent published meta-analysis with individual patient data reported no difference was observed between i2a and i2b lesions on the outcomes of clinical recurrence and/or a surgical reintervention (19). However, the analyses for a surgical reintervention were not corrected for known risk factors associated with recurrence. In this study, after adjusting for known clinical risk factors, an index mRS \geq i2b was found to be independently associated with surgical recurrence and progression to severe endoscopic recurrence, which supports the recommendation to consider therapy optimization in patients with an index mRS of \geq i2b after primary ICR.

Despite the lack of a statistically significant association between anastomotic lesions and surgical recurrence and progression to severe endoscopic recurrence, the risks for both outcomes were still as high as 12.7% and 26.8% during follow-up. Further research to identify risk factors and/or biomarkers for postoperative recurrence is warranted to appropriately manage patients with anastomotic lesions. The need for more accurate biomarkers seems underscored by the lack of association between clinical risk factors, except for active smoking and maintenance therapy with an immunomodulator with clinical recurrence and long-term outcomes in multivariable analysis in this study.

Recently, a new endoscopic scoring system has been proposed in which endoscopic scoring should be adapted to the anastomotic technique (24). The (m)RS has been developed for the assessment of an end-to-end anastomosis. In the modern era, a wide lumen stapled side-to-end or side-to-side anastomosis has been preferred over the end-to-end anastomosis to prevent anastomotic leakage, fecal stasis, and stenosis of the anastomosis. When the (m)RS is applied to endoscopically assess these anastomotic techniques, anatomic locations such as the ileal blind loop and ileal body are disregarded (24,25). Prospective analysis of inflammation at these locations and subsequent refinement of the endoscopic score is awaited.

Our study was the first to assess the predictive value of the mRS on long-term outcomes in postoperative patients with CD. Despite the consideration of objective outcome measures in a large population (from both academic and nonacademic hospitals) of patients who underwent a primary ICR with long-term follow-up, limitations of this study need to be taken into consideration. First, because the indication of subsequent ileocolonoscopies could not be assessed, due to the retrospective design, confounding by indication may be present. Second, because our study concerns a wide period, several changes of postoperative management may have influenced the outcomes including improved access to endoscopy, development of strict and noninvasive monitoring, and medication strategies. This study design did not allow to correct for all these potential confounding factors. Regarding the changes

in the postoperative endoscopic strategy, a substantial number of patients (40%) did not undergo an index ileocolonoscopy within 1 year postoperatively, which is recommended by the current guidelines (7,20,21). To adjust for potential confounding, we have included time to index ileocolonoscopy in the multivariable analysis. Finally, perianal fistulizing disease, proctitis, and/or granulomas in the resection specimen are considered risk factors of postoperative recurrence in current guidelines (7,20,21). Due to the restriction of number of variables that could be included in multivariable analysis, the findings are not corrected for the presence of perianal fistulas. In addition, standardized data on the presence of proctitis and/or granulomas in the resection specimen were unavailable in the pathology reports.

In conclusion, the increasing mRS at index ileocolonoscopy corresponds closely with the risk of surgical and clinical recurrence after primary ICR. Anastomotic lesions (i2a) are not associated with surgical recurrence and progression to severe endoscopic recurrence, in contrast to lesions in the neoterminal ileum (\geq i2b). An index mRS \geq i1 is associated with clinical recurrence. In addition, i1 lesions are associated with progression to severe endoscopic recurrence. These results support conservative management and no need for escalation of therapy in patients with anastomotic lesions and tight monitoring of disease activity and treatment optimization in patients with ileal lesions.

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CONFLICTS OF INTEREST

Guarantor of the article: Annemarie C. de Vries, MD, PhD.

Specific author contributions: M.T.J.B., S.t.B.H., A.C.d.V.: conception and design; M.T.J.B., S.t.B.H., F.H., A.G.L.B., G.D., M.J.R.-C., N.K.H.d.B., L.P.S.S., A.E.v.d.M.d.-J., R.L.W., O.v.R., C.v.d.W., A.C.d.V.: acquisition and interpretation of data; M.T.J.B., S.t.B.H., N.S.E., A.C.d.V.: analysis of data. All authors have participated in drafting or critically revising the manuscript and gave their final approval of the current version.

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Janssen, and Ferring, outside the submitted work. O.v.R. has served as invited speaker for Janssen-Cilag and has received nonfinancial support from Takeda, outside the submitted work. A.C.d.V. has served on advisory boards for Takeda, Janssen, Bristol Myers Squibb, Abbvie, Pfizer, and Galapagos and has received unrestricted research grants from Takeda, Janssen, and Pfizer, outside the submitted work. All other authors report no conflicts of interests.

Ethical approval statement: The RAP-CD study was approved by the Medical Ethics Review Committee of the Erasmus Medical Center (METC-2017-482). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Study Highlights

WHAT IS KNOWN

- ✓ The modified Rutgeerts score (mRS) is used for the assessment of postoperative recurrence in Crohn's disease.
- ✓ The prognostic value of the mRS for long-term outcomes needs to be further elucidated, especially the impact of anastomotic lesions needs clarification.

WHAT IS NEW HERE

- ✓ The increasing mRS corresponds closely with the risk of surgical and clinical recurrence.
- ✓ Moderate-to-severe lesions ($\geq i2b$) are associated with surgical recurrence and mild-to-moderate lesions are associated with progression to severe endoscopic recurrence (i1 and i2b).
- ✓ An mRS $\geq i1$ is associated with clinical recurrence.

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