

How Reliable Is Endoscopic Scoring of Postoperative Recurrence in Crohn Disease?

A Systematic Review and Meta-Analysis

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Objective: Guidelines advise to perform endoscopic surveillance following ileocolic resection (ICR) in Crohn disease (CD) for timely diagnosis of recurrence. This study aims to assess the variation in endoscopic recurrence (ER) rates in patients after ICR for CD using the most commonly used classification systems, the Rutgeerts score (RS) and modified Rutgeerts score (mRS) classifications.

Methods: A systematic literature search using MEDLINE, Embase, and the Cochrane Library was performed. Randomized controlled trials and cohort studies describing ER < 12 months after an ICR for CD were included. Animal studies, reviews, case reports (<30 included patients), pediatric studies, and letters were excluded. The Newcastle–Ottawa Quality Assessment Scale and Cochrane Collaboration’s tool were used to assess risk of bias. Main outcome was the range of ER rates within 12 months postoperatively, defined as RS \geq i2 and/or mRS \geq i2b. A proportional meta-analysis was performed. The final search was performed on January 4, 2022. The study was registered at PROSPERO, CRD42022363208.

Results: Seventy-six studies comprising 7751 patients were included. The weighted mean of ER rates in all included studies was 44.0% (95% confidence interval, 43.56–44.43). The overall range was 5.0% to 93.0% [interquartile range (IQR), 29.2–59.0]. The weighted means for RS and mRS were 44.0% and 41.1%, respectively. The variation in ER rates for RS and mRS were 5.0% to 93.0% (IQR, 29.0–59.5) and 19.8% to 62.9% (IQR, 37.3–46.5), respectively. Within studies reporting both RS and mRS, the weighted means for ER were 61.3% and 40.6%, respectively.

Conclusions: This study demonstrates a major variation in ER rates after ICR for CD, suggesting a high likelihood of inadequate diagnosis of disease recurrence, with potentially impact on quality of life and health care consumption. Therefore, there is an important need to improve endoscopic scoring of recurrent disease.

Keywords: Crohn disease, ileocolic resection, postoperative endoscopic recurrence, (modified) Rutgeerts score

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INTRODUCTION

The main localization of enteral Crohn disease (CD) is the terminal ileum. A laparoscopic ileocolic resection (ICR) is indicated in both complicated disease and as an alternative for patients with uncomplicated disease not responding to immune modulators.^{1–3} Unfortunately, surgery is not curative, and the majority of the patients develop recurrent disease.^{4,5} According to guidelines (ie, European Crohn’s and Colitis Organisation), patients should be assessed by endoscopy at 6 to 12 months postoperatively to diagnose endoscopic recurrence (ER). In case of ER, therapeutic medical therapy is (re)initiated; and if prescribed prophylactically, optimized in order to prevent long-term complicated disease.³ The guidelines recommend the use of the Rutgeerts classification to assess recurrence severity. Lesions in the category i2–i4 are considered ER.^{4,6,7} The classification was modified to discriminate pure anastomotic lesions, which are considered more likely due to postoperative changes (i2a), from the presence of more than 5 aphthous lesions in the neo-terminal ileum, with or without anastomotic lesions (i2b).^{8,9} Despite this modification, the reproducibility of the classification is disputed.^{10–12} Moreover, the mRS is (yet) not advised in European Crohn’s and Colitis Organisation guidelines.

Adequate endoscopic scoring is important, as it is used to tailor medical therapy and to monitor its effect. Especially in this asymptomatic patient group, where endoscopy is used as postoperative surveillance, a reliable scoring system is of utmost importance. After all, improper diagnosis of recurrent disease results in unnecessary prescribing of medical therapy. This potentially impairs quality of life and increases health care consumption. Moreover, the Rutgeerts classification is used as a

primary outcome in clinical trials. However, the Rutgeerts score was initially neither designed nor validated for this purpose.

For these reasons, the objectives of this study are to assess the variation in ER rates in patients after ICR for CD, using the most common classification systems, the Rutgeerts and/or modified Rutgeerts classifications, and to assess the variation and the difference in ER rates when comparing the original Rutgeerts with the modified Rutgeerts classifications.

METHODS

The study protocol was prospectively registered at PROSPERO (registration number: CRD42022363208), and the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidance was followed throughout the process.¹³ The final search was performed on January 4, 2022.

Search Strategy

MEDLINE (PubMed), Embase (Ovid), and the Cochrane Library were searched systematically with the assistance of a clinical librarian.

Medical subject headings and free-text terms used included 'Crohn's Disease', 'ileocolic resection', 'ileocecocolic resection', 'ileo-caecal resection', 'modified Rutgeerts score', 'Rutgeerts score', 'anastomotic ulcer'. There were no restrictions considering the publication date or language in the initial search, and no other methodological filters were applied. Further details of the search terms are provided in Supplemental Table 2, see <http://links.lww.com/AOSO/A297>.

Study Selection

All studies describing primary ileocecal or ileocolic resection in patients with CD with ER rates were included. ER was defined as Rutgeerts score (RS) ≥ 2 or modified Rutgeerts score (mRS) ≥ 2 at 6 to 12 months postoperatively.

Studies not reporting primary ICR or ER defined as RS or mRS within 12 months after surgery were excluded. Animal studies, reviews, case reports, and letters were excluded. Other exclusion criteria were patients aged less than 18 years and less than 30 patients included in the study. In case of overlapping study cohorts, the original study or, if postoperative endoscopic recurrence (POR) was not reported, the study with the most included patients was included.

Two reviewers (E.M.L.D.W., V.B.) separately screened the titles and abstracts of the retrieved articles and independently assessed the full text of the remaining articles. Disagreements concerning the selection were resolved by joint discussion and, when necessary, the opinion of a third researcher (W.A.B.) was obtained. Studies without a retrievable English full text were excluded.

Outcomes

The primary outcome was the overall variation in ER rates and the interquartile range (IQR) (to correct for outliers) of ER rates defined as RS ≥ 2 or mRS ≥ 2 within 1 year after ICR.

Secondary outcomes were (1) the overall range (and IQR) of ER rates defined as RS ≥ 2 within 1 year after surgery; (2) the overall range (and IQR) of ER rates defined as mRS ≥ 2 within 1 year after surgery; (3) the overall range (and IQR) of ER according to subcategories (i0, i1, i2a, i2b, i3, and i4); and (4) the difference in ER rates, presented as weighted means, comparing RS and mRS in studies reporting mRS.

Risk of Bias Assessment

Risk of bias was assessed by 2 reviewers (E.M.L.D.W., V.B.) separately. The methodological quality of cohort studies was assessed

by the Newcastle–Ottawa Quality Assessment Scale. In 3 different domains (selection, comparability, and outcome), stars were assigned, with a total maximum of 9 stars. In the outcome domain, a minimum follow-up period of 12 months and a maximum proportion of 5% of subjects lost to follow-up were considered acceptable. Studies were rated as good, fair, or poor depending on the number of stars, following the Agency for Healthcare Research and Quality standard.¹⁴ For randomized controlled trials, the Cochrane Collaboration's tool for assessing risk of bias was used.¹⁵ This tool focuses on selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias, rated as low, high, or unclear risk (Supplemental Tables 3 and 4, see <http://links.lww.com/AOSO/A297>). Three of the randomized controlled trials were considered high risk. In 2 studies, the primary reason was the lack of blinding of endoscopists to the treatment. In the third study, 56% of patients withdrew before the primary outcome assessment.

Data Extraction and Statistical Analysis

Study and patient characteristics collected included first author, year of publication, number of patients, design, single- versus multicenter, and ER rates within 12 months. The ER rates were extracted directly from the results or calculated by subtracting number of recurrences from the recurrence rates. Within the group of patients with ER defined as ≥ 2 , the ER rates according to the Rutgeerts score (≥ 2) for each study individually were calculated manually. Studies reporting mRS were divided into subcategories in order to calculate the range of ER according to subcategories. The per protocol analysis was selected if both the intention to treat and per protocol analysis were available.

Data analysis was done using IBM SPSS Statistics Data Editor, version 28. Weighted mean differences of the percentage of POR with 95% confidence intervals (CIs) were computed and reported including the total range and IQR. A histogram was computed to show the distribution of the percentages reported by the included studies, weighted by the number of patients evaluated. A meta-analysis with forest plot was not preferable due to the large number of included studies.

RESULTS

Included Studies

The initial literature search identified 966 studies in PubMed, in Embase, and from the Cochrane Library, after removal of duplicates 618 studies remained. Subsequently, titles and abstracts were screened. Eventually, 222 potentially eligible publications were assessed based on full text, of which 76 studies met the inclusion criteria and were included in this review and meta-analysis (Fig. 1), including 11 randomized controlled trials^{16–26} and 65 cohort studies.^{4,7,27–89}

Primary Outcome Endoscopic Recurrence

In total, 76 studies including 7751 patients investigated ER defined by RS ≥ 2 , mRS ≥ 2 , or both, within 1 year after primary ICR for CD (Supplemental Table 1, see <http://links.lww.com/AOSO/A297>). A pooled analysis showed a weighted mean of the ER rates of 43.99% (95% CI, 43.56–44.43). The overall range of reported ER was 5.0% to 93.0% (IQR, 29.2–59.0). A histogram shows the distribution of the ER percentages weighted by number of patients as reported in the included studies (Fig. 2).

Secondary Outcomes

Range of ER Rates Defined as RS ≥ 2

Of the 76 included studies, 64 studies including 6562 patients investigated ER according to RS (≥ 2). The weighted mean of

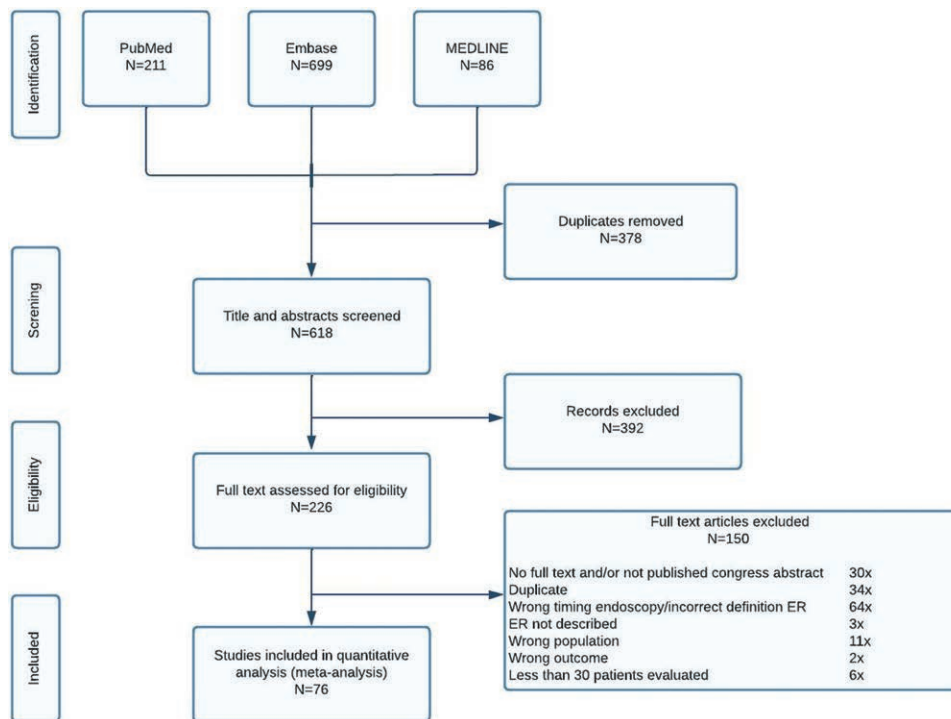


FIGURE 1. PRISMA flowchart.

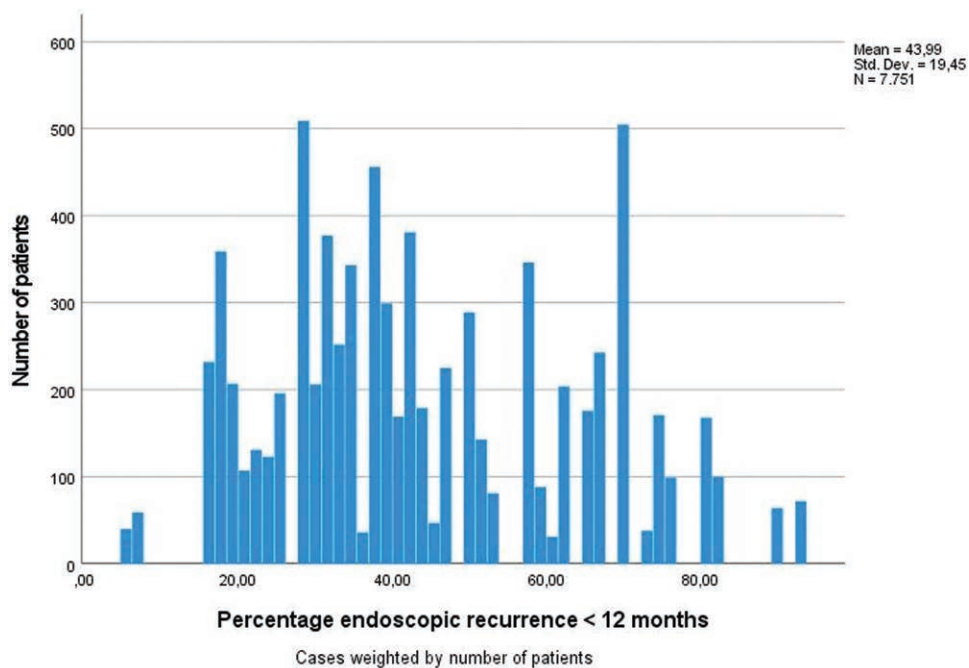


FIGURE 2. Histogram of distribution reported ER percentages weighted by number of patients in included studies, defined as either RS \geq 2 or mRS \geq i2b.

the ER rates was 44.02% (95% CI, 43.53–44.51). The overall range was 5.0% to 93% (IQR, 29.0–59.5) (Fig. 3).

Range of ER Rates Defined as RS \geq i2b

Seventeen studies, including 2083 patients, investigated ER rates according to mRS (\geq i2b). The weighted mean of the ER rates for this group was 41.06% (95% CI, 40.60–41.52). The overall range was 19.8% to 62.9% (IQR, 37.3–46.5) (Fig. 4).

Range of ER According to Subcategories (i0, i1, i2a, i2b, i3, and i4)

Within 17 studies reporting mRS (Table 1), the weighted mean and range of ER were evaluated per subcategory: 9 studies reported the percentages for all categories, 1 study reported i2a and i2b, and 1 other study only reported the percentage for i2b. A minimum of 1209 patients was evaluated for each category and weighted means were calculated (Table 2).

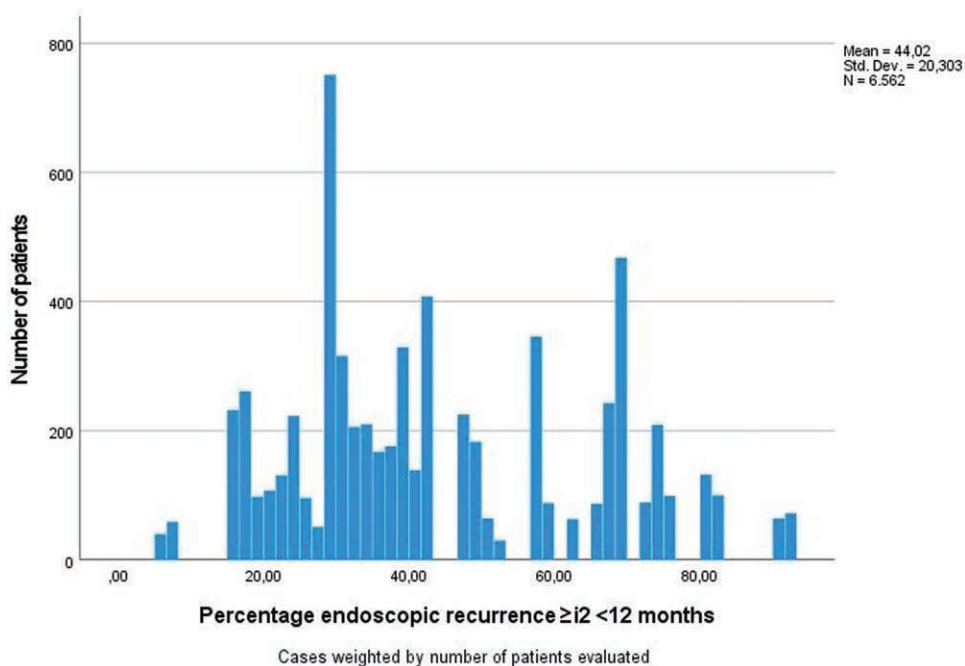


FIGURE 3. Histogram of distribution reported ER percentages weighted by number of patients in included studies according to the RS classification.

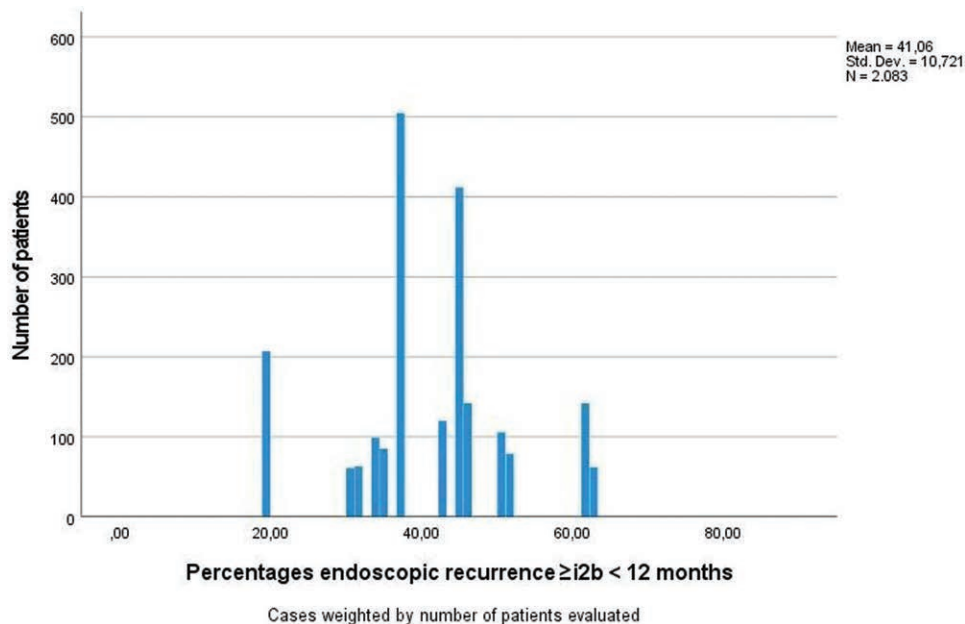


Figure 4. Histogram of distribution reported ER percentages weighted by number of patients in included studies according to the mRS classification.

ER Rates for mRS Versus RS

Of 11 studies who reported the recurrence percentages for mRS and RS (reported or calculated), including 1497 patients, the difference in ER rates was calculated for $\geq i2$ versus $\geq i2b$.^{19,21,27,34,35,39,44,45,51,59,64} In studies reporting ER defined as $\geq i2$, the weighted mean was 61.32% (95% CI, 60.61–62.03). The overall range was 39.1% to 84.7% (IQR, 47.0–69.6). In those reporting POR defined as $\geq i2b$, the weighted mean of ER was 40.60% (95% CI, 40.01–41.18). The overall range was 19.8% to 62.0% (IQR, 34.0–46.5).

Data on the use of medication within the 2 different groups could not be determined, as this was either not reported or not reported unambiguously in all included studies. Therefore, no reliable analysis could be performed.

DISCUSSION

This systematic review and meta-analysis, consisting of 76 articles, showed a wide range of ER rates according to both the RS and mRS within 1 year after ICR for CD (ranging from 5% to 93%). Moreover, data from this study suggest that scoring ER according to the original RS could even lead to a 20% increase in diagnosis of disease recurrence compared to using the mRS.

Earlier studies showed that the interobserver agreement and reproducibility of the original Rutgeerts were suboptimal. Recently, studies have suggested an update of the postoperative ER score.^{10,90,91} The agreement on the distinction between lesions classified as $< i2$ versus $> i2$ was low.^{8,11,92,93} The original Rutgeerts considers < 5 lesions in the terminal ileum, an $i1$.

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TABLE 1.
Studies Reporting mRS

Author	Year	Patients (n)	Endoscopic Recurrence <1 yr (%)
Djelouah et al ⁵⁹	2021	40	37.5
Lopez-Sanroman et al ²¹	2017	61	31.1
Buisson et al ⁶⁴	2021	63	44.4
Lemmens et al ⁴⁵	2017	74	50.0
Primas et al ³⁵	2021	79	51.9
Lopes et al ⁴⁴	2016	99	76.0
Ollech et al ³⁹	2019	207	19.8
Joustra et al ⁵¹	2022	142	67.6
de Bruyn et al ¹⁹	2021	142	62.0
Auzolle et al ²⁷	2018	225	47.0
Riviere et al ³⁴	2021	365	69.6
Cerrillo et al ⁶²	2019	32	50.0
Bachour et al ⁷²	2022	240	37.5
Bisleri et al ⁷⁰	2021	47	44.7
Bommelaer et al ¹⁶	2020	62	62.9
De Cruz et al ⁶¹	2022	85	35.3
Machiels et al ⁴³	2020	120	43.0

TABLE 2.
Weighted Mean and Range of POR Rates According to Subcategory

mRS	Patients Evaluated (n)	Weighted Mean (95% CI)	Range
i0	1209	23.61% (22.94–24.29)	8.5%–45.9% (IQR, 19.0–27.5)
i1	1209	11.88% (11.58–12.17)	4.2%–22.0% (IQR, 10.0–14.9)
i2a	1449	22.20% (21.85–22.55)	11.4%–42.0% (IQR, 19.3–25.0)
i2b	1481	20.86% (20.54–21.18)	10%–34.3% (IQR, 16.5–24.0)
i3	1209	9.16% (8.94–9.37)	3.5%–15.0% (IQR, 4.8–12.0)
i4	1209	10.04% (9.77–10.32)	2.9%–22.8% (IQR, 9.0–12.7)

One explanation for the large variation in ER rates might be that patients with <5 lesions in the neo-terminal ileum in combination with lesions at the anastomosis were not considered i1, but interpreted and therefore overscored as i2. The same might be the case in scoring according to the mRS, where the variation in ER rates in subcategories i2a and i2b is up to 30%. A combination of anastomotic ulcerations with <5 neo-terminal ileum lesions might be overscored as i2b instead of i2a.

The weighted means for subcategories i2a and i2b were doubled compared to subcategories i1, i3, and i4: 20% versus 10%, respectively, with a wider range for i2a and i2b compared to the others. This may suggest that the definitions for subcategories i1, i3, and i4 are less prone to interobserver variability in comparison with the i2 subcategories i2a and i2b.

It can be debated whether the discrimination between i2a and i2b is clinically significant.^{39,53,90,94} A recent individual patient data meta-analysis concluded that the probability of both surgical and clinical recurrence is not different in patients with i2a compared with patients with i2b.¹² This could be explained by the fact that the variance in scoring of i2a and i2b was large because of inadequate scoring. Not surprisingly, the postoperative course was not affected by type i2 (i2a or i2b).

The other subcategory that showed a wide variation was subcategory i4, both in RS and mRS. Large ulcers with diffuse mucosal inflammation in between, as well as an unpassable stricture, are classified as i4. In the case of an anastomotic stricture, it may have been caused by a sealed anastomotic leak healed stricture formation or stricture, as seen in stapled anastomoses. If these strictures do not show inflammation in the terminal ileum, they should theoretically be scored as i0.

Finally, this study even showed some variation in category i0. This could be due to the differences in pre- and postoperative treatment and monitoring strategies in the included studies in

this review. What could be seen as the main limitation of this review is the heterogeneity observed in the included studies, which may hinder an objective comparison of study results. This diversity is a natural consequence of including studies over several years, during which there were changes in both endoscopic scoring (RS vs mRS) and shifts in practice patterns (such as initiation of medical therapy based on risk factors and variations in the timing of colonoscopies). In addition, information on the type of anastomosis was often not reported. Subanalyses were not performed to examine the impact of postoperative treatment and monitoring, as these aspects were often inadequately reported.

Since the primary outcome of this study was the presentation of variations in ER rates, perioperative management is less relevant. A separate analysis was performed focusing only on studies presenting the mRS, which also showed a substantial variation. The only endpoint related to any aspect of performance, specifically the comparison of the 2 scoring systems, was performed within the same population, reducing heterogeneity. These studies were all conducted in the same time frame.

In the statistical analyses, the CI is narrow due to the large number of included studies. The “poor performance” of ER classification shown by this meta-analysis is not reflected in the CI, but it is reflected in the wide range and the relatively large variation in IQR.

Interpretation of the ER and classification according to the mRS are clearly not easy. Considering the clinical impact of recurrence on patients’ quality of life and health care consumption, there seems to be an unmet need to improve the diagnosis of ER. Gastroenterologist should be trained in the correct assessment of anastomoses. Standard operating procedures for videotaping the anastomosis are important to allow central reading by an expert panel to reduce the unacceptable variation in recurrence rates.⁹⁵

Another explanation for the variation could be due to a wound healing phenomenon. Dziki et al described in 1991 that stapled anastomoses (serosa-serosa adaptation) heal differently compared to handsewn anastomoses (mucosa-mucosa adaptation). The inverted staple line heal with linear ulcers on the staple line due to ischemia and secondary wound healing.⁹⁶ Recently, we demonstrated that both patients with stapled anastomoses after resection for colorectal cancer and for CD show these ulcerations at 6 months after surgery.⁹⁷ These ulcerations might influence endoscopic scoring of recurrence and might lead to overscoring. In fact, when handsewn and Kono-S anastomoses are compared with stapled anastomoses, this normal wound healing phenomenon of the stapled anastomosis may even interfere with the diagnosis disease recurrence when assessing ER.²² Therefore, the distinction between handsewn and stapled anastomoses holds significant relevance. Unfortunately, only in 25 of 76 papers included in this review, the type of anastomosis was reported. As a result, in this study a potential impact of the configuration of the anastomosis on outcomes could not be calculated.

The message of this meta-analysis is of great significance to the surgical society. The optimal anastomosis after ileocecal resection for CD is currently a frequently debated and studied topic. There are many studies nowadays investigating the role of the type of anastomosis on disease recurrence after resection; and ER is in most studies the primary endpoint. Luglio et al,²² for example, demonstrated (in the SUPREME trial) a significant reduction in postoperative ER for patients who underwent Kono-S anastomosis compared to a conventional anastomosis. This systematic review shows a huge variation in ER rates, confounding the results of these studies. It is of utmost importance for surgeons performing these studies to realize that endoscopic scoring is inherently subject to a huge variation in ER rates, as demonstrated in this meta-analysis.

In conclusion, this study demonstrates a major variation in ER rates after ICR for CD. This indicates a high likelihood of

inadequate diagnosis of disease recurrence, with major implications for quality of life of the patient and health care consumption. The wider range of recurrence when using the RS compared to the mRS, as well as the higher weighted mean in the RS, suggests that there is an unmet need to improve endoscopic scoring of recurrent disease using training programs and central reading. Since the greatest variation and overscoring were observed when using the original Rutgeerts classification, consideration may be given to using the modified Rutgeerts score (contrary to what the current guidelines recommend). Moreover, since the type of anastomotic healing of stapled anastomoses might influence the discrimination of i2a from i2b and the diagnosis i4, it should be considered to neglect pure anastomotic lesions or pure anastomotic stricturing to avoid overdiagnosis of recurrent CD, with all its consequences.

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E.M.L.D.W., V.B., and W.A.B. wrote the study protocol. E.M.L.D.W. and V.B. collected the data. E.M.L.D.W., V.B., and W.A.B. drafted the article. E.M.L.D.W. performed statistical analyses. S.D. (senior epidemiologist) revised the statistical analysis. M.D., S.D., C.J.B., P.S., A.V., and W.A.B. interpreted data and critically revised the article for important intellectual content. All authors agreed with the final version of the article.

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