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Original Article

Histologic and Endoscopic Findings Are Highly Correlated in a Prospective Cohort of Patients With Inflammatory Bowel Diseases

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Abstract

Background and Aims: The advantages of endoscopic vs histologic assessments of inflammation in inflammatory bowel disease remain unclear. We compared endoscopic and histologic inflammation in a prospective cohort. Furthermore, in patients with discordant findings, we compared the ability of endoscopy vs histology to predict disease course.

Methods: Ulcerative colitis (UC) or Crohn's disease (CD) patients underwent routine colonoscopies with intestinal biopsies, which included ratings of inflammation severity. Tetrachoric correlation analysis between the endoscopic and histologic inflammation ratings was performed. In postsurgical CD patients, major adverse outcomes (MAOs) were recorded.

Results: The analysis included 749 patients (60.2% CD patients), with 2807 biopsied segments. We found high concordance between endoscopist and pathologist inflammation ratings (0.84, 95% confidence interval, 0.81-0.87, $p < 0.0001$). Only 12.5% of biopsied segments exhibited microscopic inflammation without endoscopic inflammation. Neo-terminal ileum (neo-TI) biopsies exhibited the highest discordance; UC colonic biopsies had the highest concordance. Postsurgical CD patients who completed the 48-month follow-up ($n = 138$) were included in the survival analysis. The probability of MAO-free survival was significantly higher in patients with a Rutgeerts score of i0 at baseline than in those with higher scores. Microscopic inflammation in the neo-TI did not predict a higher risk of MAOs ($p = 1.00$).

Conclusions: In a real-world setting, endoscopic inflammation predicted histologic inflammation with high accuracy. In patients with a Rutgeerts score of i0, microscopic inflammation in neo-TI biopsies did not predict more aggressive disease behavior over the next 4 years. These results have implications for the design of clinical trials, suggesting the use of endoscopic healing as an endpoint.

Key Words: Inflammatory bowel disease; mucosal healing; microscopic inflammation

1. Introduction

Accumulating data support the "treat-to-target" strategy for the management of inflammatory bowel disease (IBD); the goals of this strategy are to achieve the resolution of intestinal inflammation and clinical symptoms.[1] The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Working Group was the first to assess different therapeutic goals for treat-to-target strategies in a real-world scenario.[1,2] In their most recent consensus, they suggested that mucosal healing based on endoscopy should be a key goal of treatment but fell short of recommending histologic remission.[2]

Although mucosal healing is currently considered the main therapeutic goal in the management of IBD, the definition of mucosal healing varies across clinical trials and guidelines.[1–5] Conceptually, mucosal healing is characterized by the resolution of visible intestinal inflammation and mucosal ulcers as well as by a reduction in inflammatory immune cells (such as neutrophils and lymphocytes).[6–8] Mucosal healing as determined by endoscopy has been found to predict sustained remission (clinical and steroid-free remission) and survival (resection-free and hospitalization-free survival), improved quality of life, and improved long-term outcomes in patients with IBD as well as reduced incidence of penetrating complications in patients with Crohn's disease (CD).[9–14] The most compelling data that support the value of histologic remission come from cohort studies in ulcerative colitis (UC) patients,

demonstrating an increased risk of colitis-associated cancer in patients with ongoing microscopic inflammation.[15–18]

With the development of novel treatments, biologics, and small molecules, randomized controlled trials have shown that mucosal healing in IBD is an attainable goal. Not only do definitions of mucosal healing vary, but the time to achieve mucosal healing also varies among agents and mechanisms of action. Most approved medications for IBD result in mucosal healing, including anti-tumor necrosis factors (TNFs),[11,19–24] vedolizumab,[25] ustekinumab,[26–28] anti-interleukin (IL)-23 (p19) therapies[29–35], and Janus kinase (JAK) inhibitors.[36,37] However, with the development of increasingly innovative drugs, the definition of mucosal healing used as an endpoint in clinical trials has changed; recent studies aim to achieve deeper and more sustained levels of remission in patients with IBD. Indeed, while the original clinical trials of anti-TNF or vedolizumab defined the endpoint of mucosal healing as endoscopic remission (an Endoscopic Mayo Score [EMS] of 0-1 in UC and the absence of ulcerations in CD),[11,21,25] recent clinical trials of JAK inhibitors, such as upadacitinib or anti-IL-23, have used a deeper level of remission as an endpoint (endoscopic Mayo subscore of 0 and a Geboes histologic score <2.0 in UC, and the absence of mucosal neutrophils or epithelial damage in CD).[38,39]

Most researchers and clinicians apply common endoscopic indices to rate inflammation. For CD, the Simple Endoscopic Score for Crohn's Disease (SES-CD)[40] is used, complemented by the Rutgeerts score in patients with an ileocolic anastomosis.[41] In UC patients, the EMS[42,43] and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scores[44] are commonly used. These scoring systems are widely available in endoscopy reporting software and thus are available to gastroenterologists. In contrast, histologic scoring systems are primarily used in the context of clinical trials, and their use has not been validated[45,46]; thus, they are less frequently used by general pathologists.

To date, there is a paucity of data regarding the agreement between endoscopic grading and histologic assessment of intestinal inflammation in clinical practice. The added value of histology compared with endoscopic assessment alone remains unclear. Given the importance of mucosal healing in the current management of IBD, we investigated the additional value of biopsies for the assessment of intestinal inflammation. The primary aim of our study is to evaluate the concordance between endoscopic and histologic grading of intestinal inflammation in IBD patients and to identify which subset of IBD patients presents the greatest discordance between histologic and endoscopic findings. In the subset of patients with greatest discordance (postoperative [post-op] CD patients), we prospectively compared the value of isolated histologic inflammation (also referred to as microscopic inflammation) vs validated endoscopic scores for predicting long-term disease behavior. Our study sheds light on the additional information provided by histology when monitoring inflammation in IBD patients.

2. Methods

2.1. Study design and patient characteristics

In this longitudinal, prospective, observational study, we enrolled a cohort of patients with a previously established diagnosis of CD, UC, or unclassified IBD (IBD-U) based on standard endoscopic, histologic, and radiologic criteria. Patients were enrolled from October 2010 to October 2018. All patients underwent a complete colonoscopy according to standard clinical practice and provided consent for the collection of clinical data and tissue samples to include in our institutional review board-approved biorepository, the Inflammatory Bowel Disease Center Clinical Phenotype Database and Specimen collection. Our study was approved by the University of Miami Institutional Review Board and included a total of 749 patients.

We collected information on patient characteristics (age, gender, race, country of origin, ethnicity, body mass index, and type of IBD) and medical therapy at the time of colonoscopy. Intestinal biopsies for research purposes were collected from the ileum and ascending colon in all CD patients and the sigmoid colon or rectum in UC patients, with a matching biopsy for histology. Biopsies of other colonic segments were performed for clinical care as deemed necessary by the physician. Our database included the endoscopist grading of inflammation at each annotated site and the pathologist grading of inflammation according to a standardized rating of microscopic inflammation (see below for further details). The degree of endoscopic inflammation was compared with that of histologic inflammation in the same area of the colon and the terminal ileum (TI).

2.2. Endoscopic assessments

Endoscopies were performed as part of routine clinical care by 4 different IBD-experienced endoscopists; these endoscopists had performed >5000 colonoscopies and had at least 10 years of experience providing routine care for patients with IBD. From 2010 to 2015, all colonoscopies were performed with high-definition white light endoscopy (WLE) (Olympus CV-160); from 2015 to 2018, an Olympus CV-180 colonoscope was used.

Endoscopy findings were recorded in the database following a specific protocol. In UC patients, the classification of inflammation at a site was performed with the same criteria as the EMS but referred only to the specific segment of the colon that was biopsied; scoring was as follows: 0 = *no inflammation*, 1 = *mild inflammation*, 2 = *moderate inflammation*, and 3 = *severe inflammation*. In patients with CD, the intestinal inflammation of each biopsied segment was classified according to the SES-CD subscore of the specific area of the intestine that was examined: 0 = *no inflammation*, 1-4 = *mild inflammation*, 5-8 = *moderate inflammation*, and 9-12 = *severe inflammation*. For areas with no inflammation, the endoscopist noted if the area appeared to have been affected previously, for example, if there were signs of scarring. In post-op CD patients, biopsies were collected from the neo-TI and from the anastomosis if deemed necessary by the performing endoscopist. For the SES-CD scoring and selection of biopsy locations in patients with previous surgery, the ileocolic anastomosis was considered the "right colon," and the neo-TI was considered the ileum.

Examples of the macroscopic appearance of inflammation on endoscopy are shown in Figure 1. Additionally, the endoscopist recorded the total SES-CD for all patients with CD, the Rutgeerts score for CD patients with previous intestinal resection, and the EMS for UC patients.

2.3. Histologic assessment

In our study, 4 fragments of intestinal mucosa were obtained from each biopsied intestinal segment and placed in 1 jar. Two pathologists derived a single final assessment of the degree of histologic inflammation from each jar. The selection of biopsy location was determined by the endoscopist conducting the examination. Due to the multiple mucosal fragments obtained from each segment, the pathologists had sufficient tissue to

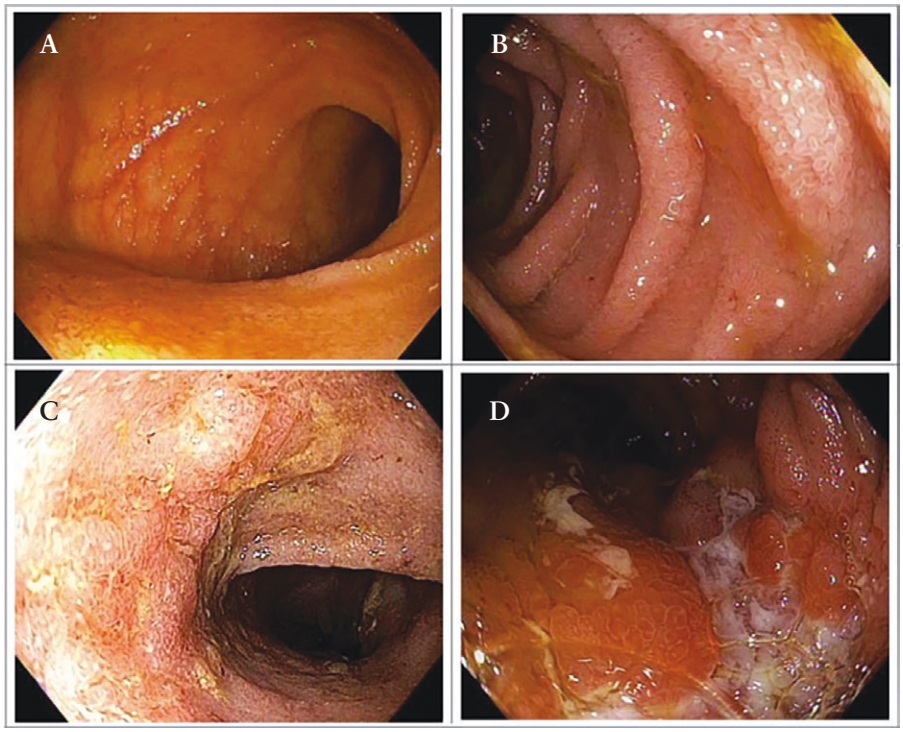

Figure 1 Representative images of the 4 levels of endoscopic inflammation: A, normal mucosa; B, mildly inflamed mucosa; C, moderately inflamed mucosa; and D, severely inflamed mucosa. Images taken from different patients.

accurately evaluate the level of inflammation.[47] The 2 experienced gastrointestinal pathologists (JP and JE) separately reviewed the 2807 biopsied segments from 749 patients; these pathologists were blinded to the endoscopic evaluations. If there was a lack of agreement between pathologists, the sample was jointly reexamined and discussed until a consensus was reached. The degree of acute inflammation on biopsied segments was classified as *no*, *mild*, *moderate*, or *severe inflammation*. Histologic findings included acute cryptitis, crypt abscesses, acute epitheliitis, surface erosion, and ulceration.

Given the absence of an ideal histological score correlating with clinical outcomes in IBD and the "real-life" nature of our study, we opted to grade disease activity based on the scoring system utilized at the University of Miami. This decision aligned with current guidelines and ensured the reliability and applicability of our results in other clinical practice settings in IBD. During the recruitment period, the Department of Anatomic Pathology of the University of Miami employed the Pattern, Activity, Interpretation, and Dysplasia (PAID) scheme for histological classification, as recommended by the British Society of Gastroenterology.[48] In this scoring system, disease activity at the histologic level was categorized as follows[49,50]: *no inflammation* (absence of intraepithelial neutrophils, foci of cryptitis, crypt abscesses, erosion, or ulcers), *mild inflammation* (cryptitis in up to 25% of crypts and/or crypt abscesses in up to 10% of crypts), *moderate inflammation* (cryptitis in more than 25% of crypts, crypt abscesses in more than 10% of crypts, and/or sparse small foci of surface erosion), and *severe inflammation* (ulceration or multiple foci of erosion) (see Figure 2 for examples).

2.4. Statistical analyses

The primary objective of this study was to assess the relationship between endoscopic inflammation and histologic inflammation. The secondary objective was to identify factors that characterize patients who are more likely to exhibit discordance between endoscopic and histologic inflammation. Clinical data were compared among 4 subgroups according to the severity of inflammation on the biopsied segments. Descriptive statistics and baseline demographic characteristics are expressed as the median and interquartile range. Categorical variables were analyzed using chi-squared tests or Fisher's exact tests. Continuous variables were analyzed using Student's *t* tests. Tetrachoric correlation analysis of the endoscopic and histologic levels of inflammation was performed using the PROC CORR and PROC FREQ procedures in SAS 9.4 (SAS Institute, Cary, NC) to obtain *p*-values and 95% confidence intervals (CIs) for the correlation.

In the second part of the study, we included only the subset of IBD patients with the highest degree of discordance between histologic and endoscopic assessments of mucosal inflammation. This cohort was composed of CD patients who previously underwent intestinal resection involving the TI; the highest degree of discordance was observed in biopsied segments collected from the neo-TI at the index colonoscopy for the current study. Therefore, in this part of the study, we only included biopsied segments from the neo-TI and not biopsied segments from the ileocolic anastomosis. Previous studies have suggested that inflammation of the neo-TI is more strongly correlated with clinical and surgical recurrence, as well as progression to severe endoscopic recurrence, in post-op CD patients.[51] This rationale underpins the subclassification of Rutgeerts i2 in the modified Rutgeerts score (mRS) into i2a and i2b, depending on whether the recurrence manifests at the anastomosis or the neo-TI.[51] The CD patients included were followed for at least 48 months after the index colonoscopy, and the occurrence of major adverse outcomes (MAOs) was recorded. MAOs included IBD-related hospitalization or

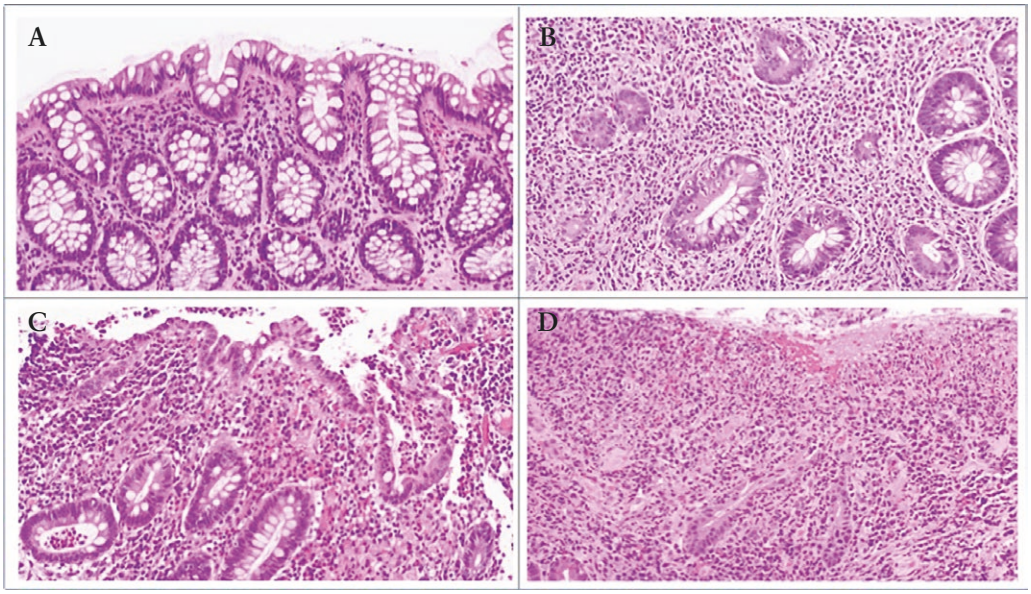

Figure 2 Representative images of the 4 levels of histologic inflammation in colon biopsies. A, Hematoxylin and eosin (H&E)-stained section showing unremarkable colonic mucosa and the absence of acute inflammation (100× magnification). B, H&E-stained section showing mild active colitis, as revealed by architectural distortion and the presence of neutrophils within colonic crypts (acute cryptitis) (100× magnification). C, H&E-stained section showing moderate colitis with few crypt abscesses (200× magnification). D, H&E-stained section showing severe active colitis, characterized by mucosal ulceration (200× magnification).

surgery, worsening of the Rutgeerts score by at least 2 points compared with that of the index colonoscopy, and the initiation or dose escalation of immunomodulators, biologic agents, or small molecules. Switching to another drug within the same class (eg, anti-TNFs) due to immunogenicity was not categorized as an MAO. Conversely, instances where a change of therapeutic class was needed due to the ineffectiveness of the previous medication were classified as MAOs.

For the purposes of this analysis, we divided the post-op CD patients into 4 groups according to their Rutgeerts score at the index colonoscopy and the presence of histologic inflammation in biopsied segments from the neo-TI: patients with no endoscopic inflammation (a Rutgeerts score of i0) and no histologic inflammation (the NE-NH group), patients with no endoscopic inflammation (a Rutgeerts score of i0) and any grade of histologic inflammation (the NE-H group), patients with mild endoscopic inflammation (a Rutgeerts score of i1 or i2) and any grade of histologic inflammation (the E-H group), and patients with severe endoscopic inflammation (a Rutgeerts score of i3 or i4) and any grade of histologic inflammation (the SE-H group). Kaplan-Meier time-to-event analysis was performed using the PROC LIFETEST procedure in SAS 9.4. The survival analysis calculated the time from study initiation to the first MAO or to censoring at the end of study (a follow-up period of 4 years). Differences among subgroups were assessed using log-rank tests with Bonferroni correction.

3. Results

3.1. Demographic characteristics of the IBD population

The study included 749 IBD patients who provided a total of 2807 research biopsied segments; 495 patients had only 1 colonoscopy during the study period, and 254 patients had 2 or more colonoscopies (Table 1). Self-identified Hispanic individuals accounted for 37.7% of the cohort. Most patients self-identified as White (92.9%). The mean age of participants was 47.9 years (median age = 45), and there were equal numbers of men and women (50.3% men). In terms of IBD type, CD was more prevalent (60.2%) than UC (38.5%) or IBD-U (1.3%). Most patients were receiving medical therapy at the time of endoscopy; 93 patients (12.4%) were not receiving any medical therapy at this time. Among those receiving medical therapy, 355 patients (47.4%) were on biologics, 156 (20.8%) were on mesalamines, 109 (14.6%) were on immunomodulators, and 36 (4.8%) were on steroids.

3.2. Endoscopic and histologic characteristics of the cohort

Of the 2807 biopsied segments, 791 (28.2%) were from the TI, 270 (9.6%) were from the neo-TI, 1031 (36.7%) were from the right colon, and 684 (24.4%) were from the left colon. Of all collected biopsied segments, 781 (27.2% of all biopsied segments) were obtained from endoscopically inflamed areas during colonoscopy. The average SES-CD was 3.69, and the average EMS was 0.66. Characteristics of the sampled tissue are presented in Table 2. Approximately one-third of the biopsied segments (30.1%, 845 biopsied segments) exhibited microscopic inflammation.

3.3. Endoscopic and histologic inflammation are strongly related

Analysis of all the endoscopy-biopsy pairings revealed a strong association between the degree of inflammation on endoscopy and the degree of inflammation in biopsied segments. Of the biopsied segments, 2026 (72.2% of all biopsied segments) were from segments without endoscopic inflammation. In this subset of biopsied segments, 1773 (87.5%) had no active inflammation, as confirmed by histologic assessment (Figure 3A). Among the 253 healthy-appearing biopsied segments that exhibited inflammation on histologic assessment, 90% showed mild inflammation, 7% showed moderate

Table 1 Patient demographic characteristics (n = 749).

Age, mean (median)	47.9 (45.0)
Gender (%)	
Female	372 (49.7)
Male	377 (50.3)
Race (%)	
White/Caucasian	696 (92.9)
Black/African American	26 (3.5)
Multiracial	15 (2.0)
Other	12 (1.6)
Ethnicity (%)	
Not Hispanic or Latino	467 (62.3)
Hispanic or Latino	282 (37.7)
Jewish descent—yes (%)	215 (28.7)
US born—yes (%)	500 (66.8)
BMI (%)	
Underweight	35 (4.7)
Normal	359 (47.9)
Overweight	240 (32.0)
Obese	115 (15.4)
Diagnosis	
Crohn's disease	451 (60.2)
Ulcerative colitis	288 (38.5)
Unclassified inflammatory bowel disease	10 (1.3)
Number of colonoscopies (%)	
1	495 (66.1)
2	157 (21.0)
3	54 (7.2)
≥4	43 (5.7)
Therapy at the time of colonoscopy (%)	
Biologics	355 (47.4)
Mesalamine	156 (20.8)
Immunomodulators	109 (14.6)
Corticosteroids	36 (4.8)
No medications	93 (12.4)

Abbreviation: BMI, body mass index.

Table 2 Characteristics of the sampled tissue (n = 2807 biopsies).

Previously affected (%)	
Yes	1398 (49.8)
No	1409 (50.2)
Area sampled (%)	
Terminal ileum	791 (28.2)
Neo-terminal ileum	270 (9.6)
Right colon	1031 (36.7)
Transverse colon	31 (1.1)
Left colon	684 (24.4)
Degree of inflammation on endoscopy (%)	
Normal	2026 (72.2)
Mild	489 (17.4)
Moderate	222 (7.9)
Severe	70 (2.5)
Degree of inflammation on biopsy (%)	
Normal	1962 (69.9)
Mild	538 (19.2)
Moderate	102 (3.6)
Severe	205 (7.3)
"Discordant" biopsy—yes (%)	253 (9.0)

inflammation, and 3% showed severe inflammation. Similarly, the majority of biopsied segments with endoscopic inflammation also exhibited histologic inflammation. Indeed, among the 781 biopsied segments (27.8% of all biopsied segments) collected from an endoscopically inflamed area, 592 were categorized as inflamed on the histologic examination. We compared the endoscopic assessment to the histologic assessment. Endoscopy correctly identified the presence of inflammation in 592 of 845 biopsied segments, yielding a sensitivity of 70.6%. In 1773 of 1962 biopsied segments, endoscopy correctly identified the absence of inflammation, yielding a specificity of 90.4%. These values correspond to a probability of 75.8% for detecting inflammation via histologic assessment when the sample is rated as inflamed via endoscopic assessment (the positive predictive value [PPV]) and a probability of 87.5% for not detecting inflammation via histologic assessment when the sample is rated as noninflamed via endoscopic assessment (the negative predictive value [NPV]).

We also calculated the tetrachoric correlation (ie, the correlation between 2 binary variables vs 2 continuous variables) between endoscopic inflammation (yes vs no) and histologic inflammation (yes vs no). The resulting correlation was 0.84 (95% CI, 0.81-0.87, $p < 0.0001$), suggesting that endoscopic assessment of the intestinal mucosa is a good predictor of microscopic inflammation in histologic assessments.

Subsequently, we analyzed the concordance between the degree of endoscopic and histologic inflammation separately according to disease type (CD, UC, or IBD-U). In UC and IBD-U patients, we observed concordance between endoscopic and histologic degrees of inflammation in 1078 biopsied segments (80.7% of all UC and IBD-U biopsied segments). Notably, only 102 biopsied segments (7.6% of all biopsied segments from UC and IBD-U patients) from noninflamed mucosa exhibited microscopic inflammation; the vast majority of these biopsied segments (87.3%, 89 biopsied segments) demonstrated only mild histologic inflammation. The probability of detecting inflammation via histologic assessment when the sample was rated as inflamed via endoscopic assessment (PPV) in UC and IBD-U patients was 79.4%, whereas the probability of not detecting inflammation via histologic assessment when the sample was rated as noninflamed on endoscopic assessment (NPV) was 90.4%. The degree of concordance between endoscopic and histologic findings across different degrees of inflammation in UC and IBD-U patients is shown in Figure 3B.

We found slightly lower concordance rates in CD patients. Overall, 986 biopsied segments exhibited concordance between endoscopic and histologic degrees of inflammation (67.0% of all biopsied segments from CD patients), with 151 biopsies (10.2% of all biopsied segments from CD patients) from noninflamed mucosa showing microscopic inflammation (Figure 3C). The probability of detecting inflammation via histologic assessment in biopsied segments that were inflamed on endoscopic assessment (PPV) in CD patients was 73.8%, while the probability of not detecting inflammation via histologic assessment when the endoscopy showed no inflammation (NPV) was 84.4%.

A **All patients, n (%)**

Endoscopy \ Histology	Normal	Mild	Moderate	Severe	Total
Normal	1773 (63.16)	224 (7.98)	19 (0.68)	10 (0.36)	2026
Mild	170 (6.06)	211 (7.52)	35 (1.25)	73 (2.6)	489
Moderate	16 (0.57)	90 (3.21)	37 (1.32)	79 (2.81)	222
Severe	3 (0.11)	13 (0.46)	11 (0.39)	43 (1.53)	70
Total	1962	538	102	205	2807

B **UC & IBDU patients, n (%)**

Endoscopy \ Histology	Normal	Mild	Moderate	Severe	Total
Normal	956 (71.61)	89 (6.67)	11 (0.82)	2 (0.15)	1058
Mild	53 (3.97)	80 (5.99)	20 (1.5)	13 (0.97)	166
Moderate	3 (0.22)	35 (2.62)	22 (1.65)	21 (1.57)	81
Severe	1 (0.07)	6 (0.45)	3 (0.22)	20 (1.5)	30
Total	1013	210	56	56	1335

C **CD patients, n (%)**

Endoscopy \ Histology	Normal	Mild	Moderate	Severe	Total
Normal	817 (55.5)	135 (9.17)	8 (0.54)	8 (0.54)	968
Mild	117 (7.95)	131 (8.9)	15 (1.02)	60 (4.08)	323
Moderate	13 (0.88)	55 (3.74)	15 (1.02)	58 (3.94)	141
Severe	2 (0.14)	7 (0.48)	8 (0.54)	23 (1.56)	40
Total	949	328	46	149	1472

Figure 3 Agreement between endoscopic and histologic assessments of the grade of inflammation. A, All patients. B, Ulcerative colitis (UC) and unclassified inflammatory bowel disease (IBD-U) patients. C, Crohn's disease (CD) patients.

3.4. Characterization of patients with discordance between endoscopic and histologic findings

We identified a subset of patients (n = 190, 25.4% of all patients) who had at least 1 biopsied segment obtained from endoscopically normal mucosa that was rated as inflamed upon histologic inspection (253 biopsied segments, 9% of all biopsied segments). In these "discordant" patients, the most common degree of histologic inflammation was *mild* (224 biopsied segments, 7.98%), followed by *moderate* (19 biopsied segments, 0.68%), and *severe* (10 biopsied segments, 0.36%). Descriptive statistics of this group of discordant patients are provided in Table 3.

Next, we further investigated the concordance rates between endoscopic and histologic assessments of intestinal inflammation by stratifying patients with CD, IBD-U, and UC according to the intestinal segment from which the biopsy was collected. Patients with UC and IBD-U showed higher average concordance rates than patients with CD in the whole colon and TI. Notably, the highest rates of concordance were observed in the TI (90.86% concordance in UC patients and 94.44% concordance in IBD-U patients), followed by the right colon and the transverse colon (89% and 100% concordance in both UC and IBD-U patients, respectively; however, there were very few biopsied segments of the transverse colon). The highest discordance rate was found in biopsied segments collected from the neo-TI in CD patients, with concordance in 76.43% of biopsied segments, followed by the ileum in CD patients, with concordance in 79.23% of biopsied segments. All percentages of agreement and disagreement, classified by disease type and intestinal site, are displayed in Table 4.

3.5. Many biopsies are needed to detect histologic inflammation in the absence of endoscopic inflammation

We also examined how many normal-appearing segments on endoscopy were found to be inflamed upon histologic assessment of biopsied segments. Of the 2026 total intestinal segments rated as normal on endoscopy, 253 (12.49%) were found to be inflamed on histologic assessment. Thus, approximately 8 normal-appearing segments were needed to find 1 sample with microscopic inflammation. We further broke this down by location. In the colon, 166 (12.95%) of the 1282 normal-appearing segments were rated as inflamed on histologic assessment. Thus, the number of normal-appearing segments needed to find an inflamed sample was 7.72 in the colon. In the ileum, only 87 (11.69%) of the 744 normal-appearing segments were found to be inflamed, corresponding to 8.55 normal-appearing ileum segments needed to find an inflamed sample.

Subsequently, we examined these values according to IBD type. Among CD patients, 151 (15.6%) of the 968 normal-appearing segments were found to have histologic

Table 3 Characteristics of the discordant patients (n = 190).

	Not discordant	Discordant	p-Value (χ^2)
Gender (%)			0.82
Female	279 (49.9)	93 (48.9)	
Male	280 (50.1)	97 (51.1)	
Race (%)			0.14
White/Caucasian	519 (92.9)	177 (93.2)	
Black/African American	21 (3.7)	5 (2.6)	
Multiracial	13 (2.3)	2 (1.1)	
Other	6 (1.1)	6 (3.1)	
Ethnicity (%)			0.34
Not Hispanic or Latino	354 (63.3)	113 (59.4)	
Hispanic or Latino	205 (36.7)	77 (40.6)	
Jewish descent—yes (%)	164 (29.3)	53 (27.9)	0.61
US born—yes (%)	375 (67.1)	125 (65.8)	0.74
BMI (%)			0.15
Underweight	27 (4.8)	7 (3.7)	
Normal	262 (46.8)	97 (51.0)	
Overweight	192 (34.3)	51 (26.9)	
Obese	78 (14.1)	35 (18.4)	
Diagnosis			0.82
Crohn's disease	332 (59.4)	117 (61.6)	
Ulcerative colitis	219 (39.2)	71 (37.3)	
Unclassified inflammatory bowel disease	8 (1.4)	2 (1.1)	
Therapy at the time of endoscopy			0.27
Biologics	261 (46.7)	104 (54.7)	
Mesalamine	120 (21.4)	36 (18.9)	
Immunomodulators	78 (14.0)	22 (11.5)	
Corticosteroids	30 (5.3)	5 (2.7)	
No medications	70 (12.5)	23 (12.1)	

Abbreviation: BMI, body mass index.

inflammation. Thus, on average, 6.41 biopsied segments of normal-appearing tissue would be needed to find an inflamed sample in these patients. Among UC patients, this estimate was higher (10.37 normal-appearing segments needed to find an inflamed sample), with only 102 (9.64%) of the 1058 normal-appearing segments showing inflammation on microscopic examination.

3.6. Microscopic inflammation does not predict MAOs in post-op CD patients

As discussed above, the neo-TI of CD patients was the most frequent site of discordance between endoscopic and histologic findings. We next explored the clinical implications for these discordant patients by conducting a survival analysis. This analysis included 138 post-op CD patients (NE-NH group = 52 patients, NE-H group = 20 patients, E-H group = 43 patients, and SE-H group = 23 patients), who were followed for 48 months. The demographic and clinical characteristics of these patients are shown in Table 5.

Among the 138 post-op CD patients, 72 (52%) experienced at least 1 MAO, and 25 (18.1%) experienced more than 1 MAO. The probability of MAO-free survival was significantly higher in patients with a Rutgeerts score of i0 at the index colonoscopy, regardless of the presence of microscopic inflammation (ie, the NE-NH and NE-H groups had a higher probability of MAO-free survival than the E-H [$p < 0.01$] or SE-H groups [$p < 0.01$]) (Figure 4). Notably, the presence of microscopic inflammation in the neo-TI in the absence of endoscopic inflammation did not lead to a higher risk of MAOs during follow-up compared with the absence of microscopic inflammation (NE-H group vs NE-NH group, $p = 1.00$). Moreover, the NE-NH and NE-H groups had a disease course characterized by fewer MAOs compared with the E-H and SE-H groups (Figure 5). These data do not support a difference in the probability of disease complications, endoscopic worsening of the disease, or escalation of treatment among patients with microscopic inflammation of normal-appearing tissue in the neo-TI compared with those without microscopic inflammation. Notably, 11 out of 52 patients (21.2%) in the NE-NH group and 4 out of 20 patients (20.0%) in the NE-H group experienced a worsening of the Rutgeerts score by at least 2 points during the 4-year follow-up. These findings highlight that the presence of microscopic inflammation, compared with its absence, in patients with endoscopic remission do not correlate with a worsening of endoscopic disease activity over the 4-year follow-up period.

3.7. Microscopic inflammation and MAOs in CD patients

We then focused on CD patients with histologic inflammation but normal endoscopic results, with the goal of performing the same survival analyses as with post-op CD patients. Specifically, we compared the occurrence of MAOs (IBD-related hospitalization; IBD-related surgery; worsening of SES-CD score by at least 3 points in a specific intestinal segment compared with that of the index colonoscopy; and the initiation or dose escalation of immunomodulators, biologics, or small molecules) between CD patients with histologic inflammation and no endoscopic inflammation vs CD patients without histologic or endoscopic inflammation. For this analysis, we excluded patients with UC because several papers have already prospectively evaluated the role of histologic inflammation in predicting the disease course of UC patients.[52–57]

Patients with CD were divided based on the location of discordance between endoscopic and histologic findings (ie, in the TI or the colon) to assess whether microscopic inflammation at these sites predicted more MAOs over a 4-year follow-up period. Thus, for ileal localization, we included patients with ileal CD (Montreal L1) exhibiting histologic inflammation on biopsied ileal segments but no endoscopic inflammation who had at least 4 years of follow-up. For colonic localization, we included patients with colonic CD (Montreal L2) displaying histologic inflammation on biopsied colonic segments but no endoscopic inflammation who had at least 4 years of follow-up. Patients with ileocolonic disease (Montreal L3) were excluded from the analyses to avoid the confounder that a patient may develop an MAO from an endoscopically/histologically inflamed segment at another intestinal site.

After applying these stringent selection criteria, we identified only 4 patients with ileal discordance and 4 patients

Table 4 Percentages of agreement and disagreement between endoscopy and histology, according to disease type and intestinal site.

		CD		IBD-U		UC	
		Agree	Disagree	Agree	Disagree	Agree	Disagree
Terminal ileum	Frequency	309	81	17	1	348	35
	%	20.99	5.5	28.81	1.69	27.27	2.74
	Row %	79.23	20.77	94.44	5.56	90.86	9.14
	Column %	25.99	28.62	32.69	14.29	30.96	23.03
Neo-terminal ileum	Frequency	201	62	0	0	7	0
	%	13.65	4.21	0	0	0.55	0
	Row %	76.43	23.57	—	—	100	0
	Column %	16.9	21.91	0	0	0.62	0
Right colon	Frequency	502	92	16	2	372	47
	%	34.1	6.25	27.12	3.39	29.15	3.68
	Row %	84.51	15.49	88.89	11.11	88.78	11.22
	Column %	42.22	32.51	30.77	28.57	33.1	30.92
Transverse colon	Frequency	15	3	1	0	12	0
	%	1.02	0.2	1.69	0	0.94	0
	Row %	83.33	16.67	100	0	100	0
	Column %	1.26	1.06	1.92	0	1.07	0
Left colon	Frequency	162	45	18	4	385	70
	%	11.01	3.06	30.51	6.78	30.17	5.49
	Row %	78.26	21.74	81.82	18.18	84.62	15.38
	Column %	13.62	15.9	34.62	57.14	34.25	46.05
Total	Frequency	1189	283	52	7	1124	152
	%	80.77	19.23	88.14	11.86	88.09	11.91

Abbreviations: CD, Crohn's disease; IBD-U = unclassified inflammatory bowel disease; UC, ulcerative colitis.

with colonic discordance. Given the small sample size, which precluded statistical analysis, we have simply described the disease course of these patients below. In the ileal discordance group, 2 patients had inflammatory-type disease (Montreal B1) and 2 had stenosing disease (Montreal B2). Of these 4 patients, 3 did not experience any MAOs during the 4-year follow-up. The fourth patient, who also had jejunal involvement, underwent a jejunal resection for stenosing disease approximately 1 year after the index colonoscopy.

In the colonic discordance group, all patients had inflammatory-type disease (Montreal B1), and 1 patient also had associated perianal disease. Three patients did not experience any MAOs throughout the 4-year follow-up, although 1 of these 3 patients started ustekinumab therapy more than 4 years after the index colonoscopy. The fourth patient was prescribed azathioprine in combination with mesalamine approximately 6 months after the index colonoscopy; however, the patient did not take this medication and remained free of MAOs during the 4-year follow-up. Thus, although this cohort comprises only 8 patients, our findings suggest that the presence of histologic inflammation without endoscopic inflammation did not lead to a more severe disease course over a 4-year follow-up period in the small subgroup with histologic inflammation and normal endoscopy.

4. Discussion

In the era of improved medical therapies, we have raised the bar on the outcomes to achieve. The updated STRIDE-II guidelines advocate for the therapeutic targets of endoscopic mucosal healing, clinical response and remission, and normalization of inflammatory markers. Yet histologic healing (in UC) and transmural healing (in CD) were not included as formal treatment targets because there was insufficient long-term evidence to justify pushing our therapies to achieve this depth of remission and thereby change clinical outcomes.[2] In this article, we address the clinically relevant question of whether histologic confirmation is necessary to corroborate endoscopic findings of inflammation in UC and CD.

In the present study, we investigated the relationship between endoscopic inflammation and histologic inflammation in a broad group of IBD patients followed in a tertiary IBD center. Most patients were in remission, as is the case in the majority of patients with IBD.[58] We found a strong correlation and a high concordance between endoscopic and histologic ratings of the degree of inflammation. The concordance was highest in the colon biopsies of UC patients; 90.4% (956 out of 1058) of biopsied segments from areas scored as *no inflammation* on the endoscopic evaluation (EMS = 0) were not microscopically inflamed. Among the remaining 102 discordant biopsied segments, the vast majority (87.3%) had only mild histologic inflammation, diverging from the endoscopic findings by only 1 grade of inflammation. Several studies have already described the predictive value of histologic inflammation in the disease course of UC patients.[52–57] Compared with persistent microscopic inflammation, histologic healing was associated with reduced rates of disease relapse, escalation of steroids or therapy, IBD-related hospitalization, and IBD-related surgery among UC patients in endoscopic remission.[52,55,59] Other studies have reported

Table 5 Characteristics of postoperative CD patients included in the survival analysis (n = 138).

Age, mean (median)	42.7 (40)
Gender (%)	
Female	60 (43.4)
Male	78 (56.6)
Race (%)	
White/Caucasian	131 (94.9)
Black/African American	2 (1.4)
Multiracial	3 (2.2)
Other	2 (1.4)
Ethnicity (%)	
Not Hispanic or Latino	89 (64.5)
Hispanic or Latino	50 (36.2)
Jewish descent—yes (%)	54 (39)
US born—yes (%)	96 (70.0)
Montreal classification: age at onset	
A1: ≤16 y	44 (31.9)
A2: 17-40 y	78 (56.6)
A3: >40 y	16 (11.6)
Montreal classification: location	
L1: terminal ileum	56 (40.6)
L2: colon	3 (2.2)
L3: ileo-colon	78 (56.6)
L4: upper gastrointestinal	12 (8.7)
Montreal classification: behavior	
B1: nonstricturing, nonpenetrating	3 (2.2)
B2: stricturing	122 (88.4)
B3: penetrating	29 (21.0)
Perianal disease—yes (%)	48 (34.8)
Number of previous intestinal resections, mean (median)	1.8 (1.0)
Therapy at the time of colonoscopy (%)	
Biologics	98 (71.0)
Mesalamine	12 (8.7)
Immunomodulators	62 (44.9)
Corticosteroids	15 (10.9)
No medications	16 (11.6)

Abbreviations: CD, Crohn's disease.

higher rates of discordance between endoscopy and histology in UC of up to 30%. However, in these prior studies, UC patients were categorized as being in endoscopic remission if they had an EMS ≤1.[60] Our study provides reassurance that a UC patient with EMS of 0 is unlikely (ie, has a ~10% chance) to have mild microscopic inflammation. As a clinician caring for a patient in clinical and endoscopic remission, one would need to decide if mild microscopic inflammation merits treatment modification.

Similarly, in CD patients, we found that 15.6% of biopsied segments from healthy-appearing mucosa exhibited inflammation according to the histologic assessment; of these discordant biopsied segments, 89.4% were discordant by only 1 degree of inflammation (*no inflammation* on endoscopy and *mild inflammation* on histology). Overall, our findings suggest that endoscopic assessment is sufficient, as discordant biopsied segments exhibit only mild histologic inflammation.

Interestingly, biopsied segments collected from the TI and neo-TI in patients with CD showed lower concordance rates. CD patients who underwent a previous TI resection exhibited the highest discordance rates in biopsied segments from the neo-TI, with normal endoscopic findings but microscopic inflammation in approximately 24%. We now recognize that colonic CD patients are more likely to respond to currently available treatments than those with ileocolonic or ileal CD, as mucosal healing appears more difficult to achieve in the ileum.[61,62]

To further investigate whether these findings are clinically meaningful for the disease course, we followed CD patients with biopsied segments from the neo-TI for at least 48 months after the index colonoscopy to ascertain the occurrence of MAOs (IBD-related hospitalization; worsening of the Rutgeerts score by at least 2 points compared with that of the index colonoscopy; IBD-related surgery; and the initiation or dose escalation of immunomodulators, biologics, or small molecules). We clearly showed that patients with a Rutgeerts score of i0 exhibited significantly fewer MAOs during the 4-year follow-up period compared with those having higher Rutgeerts scores, regardless of the presence of microscopic inflammation. Indeed, the presence of isolated histologic inflammation in the neo-TI did not predict a higher risk of MAOs during follow-up compared with the absence of microscopic inflammation. Unfortunately, we could not perform the same analysis for nonsurgical CD patients with microscopic inflammation in the ileum or colon due to the small number of patients who were in endoscopic remission but had histologic inflammation. The few patients we identified did not have significant disease progression in the examined intestine over the ensuing 4 years.

Our results are consistent with previous studies that did not find any differences in the long-term disease behavior of CD patients with and without histologic remission.[59] Recent studies have reported agreement between endoscopic and histologic outcomes of remission at 12 and 52 weeks after the initiation of mirikizumab (concordance rates of 82.7% and 71.0%, respectively) in a cohort of CD patients.[39] Similarly, 23.8% of CD patients in endoscopic remission were found to demonstrate active histologic inflammation[63]; importantly, histologic activity in patients with endoscopic remission was not associated with clinical relapse over a 2-year follow-up period. Similar percentages of CD patients were demonstrated to achieve endoscopic or histologic remission after treatment optimization, which was associated with a lower risk of treatment failure within a 2-year period.[64] These studies indicate that there is insufficient evidence to justify the escalation of immunosuppressant treatment to reach the expanded goal of histologic healing,[2] in addition to the absence of validated, representative, reliable, and accepted scoring systems for histologic assessment in CD.

Our findings have important clinical implications. First, we suggest that histology may not substantially enhance the information provided by a well-described endoscopy. Specifically, normal-appearing tissue does not need to be biopsied unless surveillance for dysplasia or pathogens (such as cytomegalovirus [CMV] in patients with acute severe UC) is indicated. These indications were not evaluated in the present study, and we did not detect any CMV cases. Even in the neo-TI (the most likely location to exhibit microscopical inflammation in the absence of endoscopic inflammation), we demonstrated

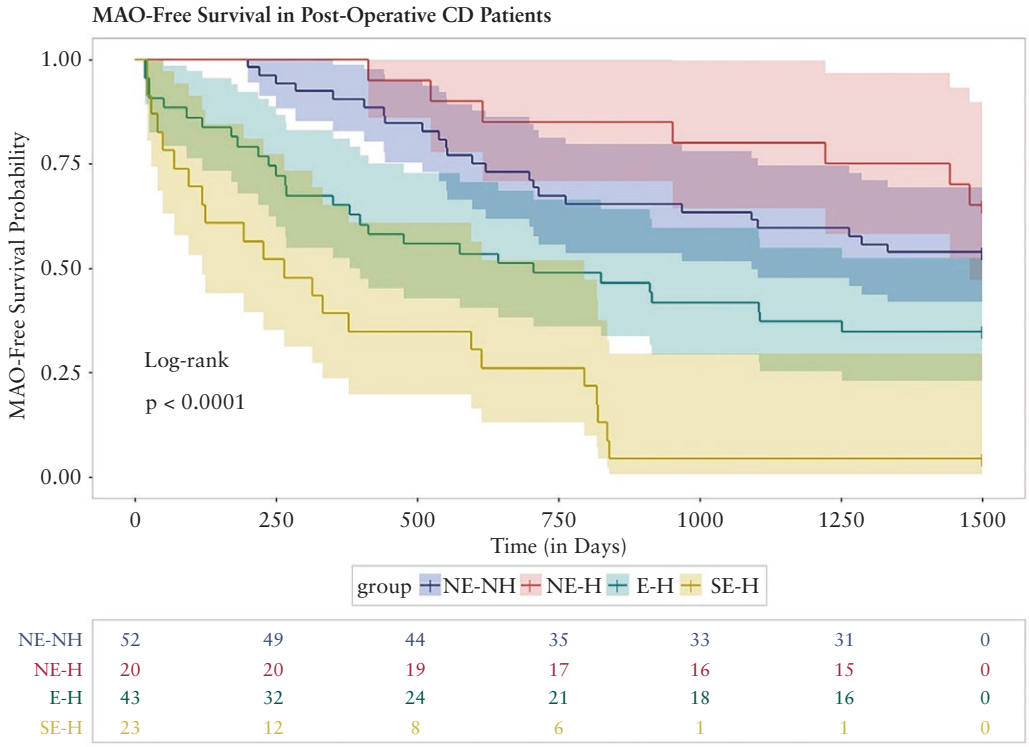

Figure 4 Time-to-event analysis for the occurrence of MAOs in post-op CD patients. NE-NH group: no endoscopic inflammation (Rutgeerts score of i0), no histologic inflammation; NE-H group: no endoscopic inflammation (Rutgeerts score of i0), any histologic inflammation; E-H group: endoscopic inflammation (Rutgeerts score of i1 and i2), any histologic inflammation; and SE-H group: severe endoscopic inflammation (Rutgeerts score of i3 and i4), any histologic inflammation. Shaded areas reflect 95% confidence intervals. The E-H and SE-H groups had a significant higher risk of at least 1 MAO during the 48-month follow-up period compared with the NE-NH and NE-H groups ($p < 0.01$). The numbers below the graph display the numbers of subjects at risk in each group. The probability of MAO-free survival during the 48-month follow-up period was significantly higher in the NE-NH and NE-H groups (ie, no endoscopic inflammation, regardless of the presence of microscopic inflammation); these 2 groups did not significantly differ in the probability of MAO-free survival ($p = 1.00$). Abbreviations: CD, Crohn's disease; MAO = major adverse outcome; post-op = postoperative.

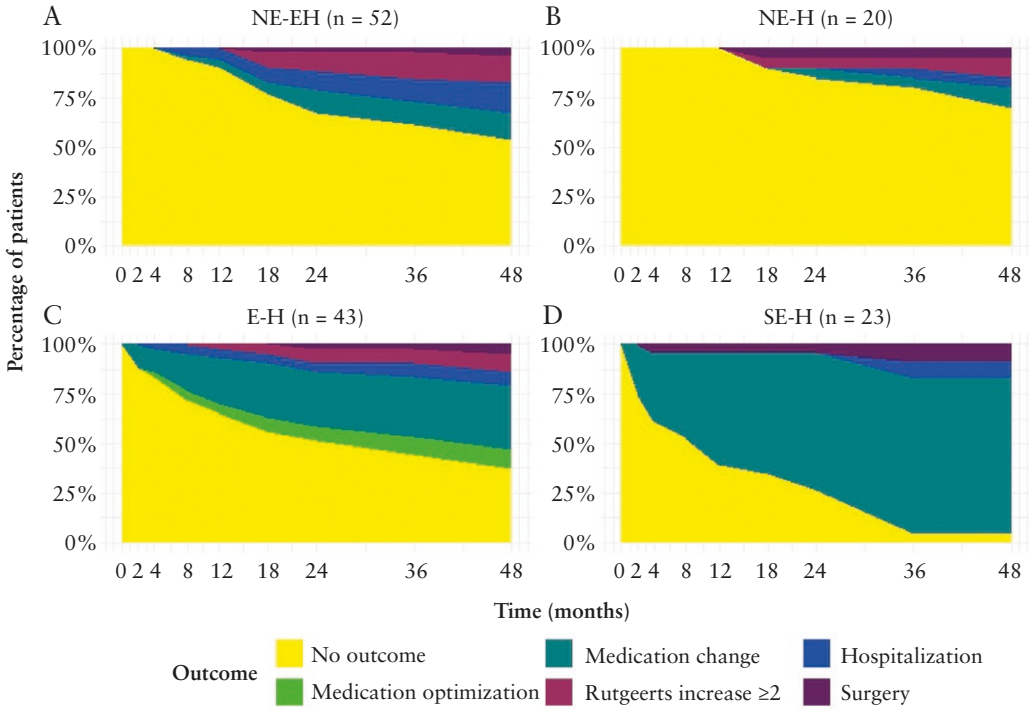

Figure 5 Stacked density plots demonstrating the most severe major adverse outcome recorded among post-op Crohn's disease (CD) patients during the follow-up period. A, The NE-NH group; B, NE-H group; C, E-H group; and D, SE-H group. NE-NH group: no endoscopic inflammation (Rutgeerts score of i0), no histologic inflammation; NE-H group: no endoscopic inflammation (Rutgeerts score of i0), any histologic inflammation; E-H group: endoscopic inflammation (Rutgeerts score of i1 and i2), any histologic inflammation; and SE-H group: severe endoscopic inflammation (Rutgeerts score of i3 and i4), any histologic inflammation. Comparisons involved the neo-terminal ileum of CD patients only.

that this discordance is not associated with more aggressive disease behavior over a 4-year period.

Our analysis has some limitations. Over 40 histological scoring systems (varying in the features included) have been developed for both CD and UC, but to our knowledge, none have been validated and shown to correlate with important patient outcomes. In the absence of an ideal histological score that is correlated with clinical outcomes in IBD and given the "real-life" nature of our study, we opted to grade histological disease activity based on the scoring system utilized at the University of Miami. This practical pathology scoring system can be reproduced in clinical practice and has been used by prior studies.[49,50] Second, endoscopic scoring was performed by experienced IBD endoscopists. Therefore, the reproducibility of these findings might be affected if endoscopies are performed by less-experienced gastroenterologists. Nevertheless, the endoscopic indices that we used are embedded in commonly used endoscopy reporting software and thus are widely accessible. Third, the majority of the patients in this study had mild inflammation or were in endoscopic remission. In contrast to clinical trial data, in which the colonoscopies are done within months or a year after the initiation of therapy, our data were from a cohort of IBD patients who were on stable medication; most underwent colonoscopy to monitor mucosal healing or to detect dysplasia. Thus, our findings apply to patients on stable medications for IBD rather than those who recently initiated therapy.

5. Conclusion

We demonstrated a strong correlation between endoscopic and histologic assessments of intestinal inflammation. The highest concordance rate was observed in UC patients. Notably, our study is the first to demonstrate that high-resolution WLE performed by IBD-experienced endoscopists can accurately identify the absence of inflammation (even at the histologic level) by rigorously applying widely validated scores such as the EMS (in UC) and the SES-CD (in CD). Therefore, we believe that endoscopic mucosal healing is a reasonable surrogate for histologic healing in IBD patients in routine clinical practice. The implications of these findings for the time and expense of biopsies are considerable, especially given the number of biopsies needed to detect inflammation in normal-appearing mucosa. We suggest that the collection of biopsies be performed only if the results would alter therapeutic decisions regardless of endoscopic findings. Future prospective studies are needed to develop a protocol for biopsy sampling and a standardized IBD histologic scoring system to evaluate the impact of histologic remission in CD patients.

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Conflict of Interest

MTA has served as a consultant or on the advisory board of the following companies: AbbVie Inc., Amgen, Bristol Myers Squibb, Celsius Therapeutics, Eli Lilly and Company, Gilead Sciences, Janssen Pharmaceuticals, Matera Prima, and Pfizer Pharmaceutical. Additionally, MTA has been a teacher, lecturer, or speaker for Alimentiv and Takeda Pharmaceuticals. All other authors declare that they have no conflicts of interest.

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Author Contributions

FDV and JMS reviewed the literature, analyzed the dataset, and wrote the manuscript. MAQ enrolled the patients, developed the dataset, and reviewed the manuscript. RMK and TK-S performed the statistical analysis. JP evaluated the pathology specimens and provided images. OD, AD, and DK enrolled the patients, developed the dataset, and reviewed the manuscript. MTA designed the study, enrolled the patients, assisted in the development of the dataset, and wrote and reviewed the final manuscript.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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