

# Ileal or Colonic Histologic Activity Is Not Associated With Clinical Relapse in Patients With Crohn's Disease in Endoscopic Remission



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**BACKGROUND & AIMS:** Goals of treatment for Crohn's disease (CD) are clinical and endoscopic remission. It is not clear whether histologic markers of healing associate with endoscopic remission in patients with CD.

**METHODS:** We identified patients with CD from a single institutional registry, and collected data from 129 patients (46.5% female; mean age 25 y; mean CD duration 14.5 y) who underwent colonoscopy evaluation and had simple endoscopic scores for CD below 3 (the definition of endoscopic remission). Histologic signs of CD activity were graded in 192 biopsies (90 ileum and 102 colon), and disease was classified as active (presence of crypt destruction, neutrophils, erosions or ulcerations), quiescent (presence of architectural distortion and chronic inflammatory infiltrate), or normal histology (none of these). The primary outcome was clinical relapse within 2 y (dose escalation, change in therapy, need for systemic steroids, or CD-related hospitalization or surgery). We performed multivariable regression adjusting for relevant confounders to examine the independent predictive value of histologic activity.

**RESULTS:** Within 2 y of endoscopic evaluation, 42 patients (32.6%) had a clinical relapse. There were no significant differences in proportions of patients with active ileal CD (23.8%), quiescent CD (28.6%), or normal histology (37%) between those who relapsed and those remaining in remission ( $P = .43$ ). There were no significant differences in proportions of relapses among patients with active colonic disease (38.1%), quiescent disease (35.0%), or normal histology (27.9%,  $P = .73$ ). A linear regression analysis found no association between histologic features of active disease in ileal histology biopsies and symptom scores (Harvey Bradshaw index and simple inflammatory bowel disease questionnaire scores).

**CONCLUSIONS:** In an analysis of biopsies from patients with CD who had achieved clinical and endoscopic remission, histologic remission was not associated with clinical relapse within 2 years.

**Keywords:** IBD; Prognostic Factor; Outcome; Biomarker.

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract that affects more than 1 million individuals in the United States and thousands more worldwide.<sup>1</sup> It is characterized by typical onset at a young age and a protracted, relapsing course with progressive irreversible bowel damage including development of strictures and penetrating complications. The availability of effective biologic therapies including tumor necrosis factor  $\alpha$  antagonist (anti-TNF $\alpha$ ), anti-integrin, and anti-interleukin 12/23 antibodies have revolutionized our ability to achieve remission and prevent disease complications. In parallel with the emergence of these therapies, the treatment targets have also evolved.<sup>2–6</sup> Traditionally, the goal of treatment was clinical remission, defined by the resolution of abdominal pain and normalization of bowel habits.<sup>7</sup>

However, considerable evidence suggests that symptoms correlate poorly with objective endoscopic evidence of active inflammation,<sup>8,9</sup> and that resolution of the latter (ie, endoscopic healing) is associated with a greater reduction of CD-related hospitalizations, need for corticosteroids, and clinical relapse.<sup>7,10,11</sup> Consequently, current treatment guidelines and expert consensus

**Abbreviations used in this text:** AZA, azathioprine; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; 6-MP, 6-mercaptopurine; MTX, methotrexate; SES-CD, Simple Endoscopic Score for Crohn's Disease; SIBDQ, short inflammatory bowel disease questionnaire; TNF, tumor necrosis factor; UC, ulcerative colitis.

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statements recommend a therapeutic approach targeting the combination of clinical remission and endoscopic healing.<sup>10,12–17</sup>

It is increasingly recognized that patients with inflammatory bowel disease (IBD) who achieve clinical and endoscopic remission might not have complete histologic normalization of their intestinal mucosa.<sup>10,12–15</sup> In patients with ulcerative colitis (UC), persistence of histologic inflammation has been associated with disease relapse, therapy escalation, need for surgery, hospitalization, and risk of colorectal neoplasia. Studies of unselected populations of patients undergoing colonoscopy with absent symptoms or those targeting patients with endoscopic healing (Mayo score 0 or 1) have demonstrated persistent neutrophilic infiltration or architectural distortion in UC to be associated with future risk of clinical relapse,<sup>12,18</sup> leading to the inclusion of histologic healing as a therapeutic endpoint in clinical trials of UC.<sup>19–21</sup>

However, the importance of histologic remission in CD remains unclear. In contrast to UC where the disease is restricted to the mucosa and submucosa and the inflammation is contiguous, extending proximally from the rectum and restricted to the colon, inflammation in CD is often discontinuous and segmental. In addition, it is frequently transmural, and consequently the predictive value of randomly sampled mucosal histology may be more limited than in UC. There are few studies that have examined whether histologic activity predicts long-term prognosis in CD, and such studies had several limitations.<sup>10,22,23</sup> Apart from small sample sizes, an important limitation of prior studies on this topic is inclusion of a heterogeneous cohort of patients with varying endoscopic activity. Because of the current recommendations of treating to endoscopic remission, it is most pertinent to examine the incremental utility of histologic remission in the population that has already achieved this endpoint.

The aim of the present study was to ascertain whether persistent histologic activity was associated with clinical relapse, defined as CD-related hospitalizations, need for corticosteroids, dose escalation, or treatment failure in patients with CD who have achieved endoscopic remission. In our secondary analysis, we examined the relative predictive utility of ileal and colonic biopsies and analyzed whether persistent histologic activity impacted symptoms or health-related quality of life.

## Methods

### Study Design

This is a single center retrospective study that included patients receiving care at the Massachusetts General Hospital Crohn's and Colitis center, a referral IBD center serving the greater Boston metropolitan area. Eligible patients consisted of those who were recruited for a prospective institutional registry (PRISM) and

## What You Need to Know

### Background

Patients with Crohn's disease (CD) in endoscopic remission might still have histologic features of disease activity. It is not clear whether histologic activity can be used as an endpoint of treatment.

### Findings

In ileal and colon biopsies from patients with CD in remission, histologic features of disease activity were not associated with risk of relapse. Histologic activity did not correlate with Harvey-Bradshaw index or simple inflammatory bowel disease questionnaire scores.

### Implications for patient care

Further studies are needed to standardize a histologic scoring system for patients with CD and determine whether scores associate with outcomes.

underwent a colonoscopy with prospectively scored endoscopic severity paired with assessment of symptoms by using the Harvey-Bradshaw index (HBI)<sup>24</sup> and quality of life by using the short inflammatory bowel disease questionnaire (SIBDQ).<sup>25</sup> Eligible patients met the following criteria: (1) established diagnosis of CD (excluding isolated upper gastrointestinal disease), (2) endoscopic remission defined as a Simple Endoscopic Score for Crohn's disease (SES-CD) between 0 and 2, (3) availability of at least 1 ileal or colonic biopsy for histology, and (4) clinical follow-up for at least 2 years to ensure completeness of ascertainment of outcomes. For patients with multiple colonoscopies meeting the above criteria, the earliest procedure was used in the analysis.

### Assessment of Histologic Activity

Index pathology reports were generated by subspecialized gastrointestinal pathologists and classified as normal, inactive/quiescent, or active disease. Active disease was defined by presence of cryptitis, crypt abscesses, erosions, and/or ulcerations. Quiescent disease was defined by presence of architectural distortion, Paneth cell metaplasia, and increased number of lymphocytes and/or plasma cells. Normal or histologic healing was defined by the absence of the above and normalization of intestinal mucosa. In contrast to UC where there exists validated histologic activity scores such as the Robarts and Nancy Histologic Index,<sup>26</sup> there is no widely accepted validated scoring system in CD, and the quality of evidence of any individual scoring system is poor.<sup>27</sup> However, the components of histology that were used in classifying patients in our study exhibit significant overlap with the individual components of the other scoring systems that have been used.<sup>27</sup> For patients with biopsies from multiple colonic segments, the one with the most active disease was used in the analysis.

## Study Outcome

The primary outcome was clinical relapse within 2 years. This was defined as any CD-related hospitalization, surgery, need for rescue corticosteroids, treatment dose escalation, or change when performed for lack of disease activity response. Routine use of markers such as fecal calprotectin was not widely available during the study period.

## Covariates

Baseline demographic characteristics were recorded, including age at diagnosis, age at visit, disease duration, smoking status, location of disease, behavior of disease, medication use, symptomatic disease activity scores using the HBI, and disease-related quality of life using the SIBDQ. At the time of the index colonoscopy, the SES-CD was documented by the performing gastroenterologist. Endoscopic remission was defined as SES-CD  $< 3$ .<sup>7,28,29</sup> Current biologic use was classified as anti-TNF $\alpha$  (infliximab, adalimumab, golimumab) or other biologic therapy. Current immunomodulator use was classified as azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX).

## Statistical Analysis

This study was approved by the Institutional Review Board of Partners Healthcare. All patients provided informed consent. Categorical variables were presented as counts and percentages, and continuous variables were presented as means with standard deviations. The  $\chi^2$  test was used to compare the categorical variables. The Student *t* test was used to compare continuous variables. Univariate logistic regression was used to study the relationship between each covariate and clinical relapse. Variables significant in this model at  $P < .10$  were included in a final multivariable model to examine independent association between histology and clinical relapse. We repeated the analysis restricting the cohort to patients with SES-CD score of 0. We also constructed Kaplan-Meier curves to examine association between histologic activity and time to relapse. Linear regression models were used to assess relationship between histologic activity and disease activity indices and quality of life. All analysis was performed in Stata 15.0 (StataCorp, College Station, TX).<sup>30–32</sup>

## Results

### Study Cohort

A total of 461 patients with CD were identified by using the prospective institutional registry. After excluding those who did not have disease location data and those who did not have terminal ileum, ileocolonic,

or colonic disease ( $n = 41$ ), with incomplete SIBDQ scores ( $n = 135$ ), with incomplete follow-up ( $n = 55$ ), with incomplete colonoscopies ( $n = 7$ ), not in endoscopic remission at inclusion ( $n = 44$ ), had no biopsies obtained for histology ( $n = 27$ ), or with duplicate colonoscopies for the same patient ( $n = 23$ ), a total of 129 patients with CD were identified, totaling 90 ileal biopsies and 102 colonic biopsies. Just less than half ( $n = 60$ , 46.5%) were women. The mean age and duration of disease were 25.7 and 14.5 years, respectively. There were 54 patients on immunomodulators, 75 patients on biologics (69 patients on anti-TNF $\alpha$  therapy), and 29 patients on corticosteroids at the time of the index colonoscopy. Most patients ( $n = 115$ ) had SES-CD score of 0. Among the patients with ileal biopsies, 55 patients (61.1%) had histologic normalization, 14 patients (15.6%) had quiescent histologic activity, and 21 (23.3%) had histologically active disease. Among the patients with colonic biopsies, 61 patients (59.8%) had normal histologic activity, 20 (19.6%) had quiescent histologic activity, and 21 (20.6%) had histologically active disease. There was no association between medication use at the time of colonoscopy (immunomodulator or biologic) and achievement of histologic healing. Out of the 129 patients, there were 19 patients with baseline radiologic imaging (16 patients had no active disease and 3 patients with bowel wall thickening).

During the 2-year follow-up, the primary outcome (clinical relapse) occurred in 42 patients (33%). Among the patients who relapsed, 18 patients (43%) needed rescue corticosteroids, 15 patients (36%) needed dose escalation, 13 patients (31%) needed change in therapy, 9 patients (21%) had CD-related hospitalization where 4 patients required CD-related surgery, and 13 patients (31%) had objective radiologic imaging confirming relapse. Just less than one-fourth of patients ( $n = 29$ , 22.5%) had clinical symptoms (HBI  $> 4$ ) at the time of the index colonoscopy despite endoscopic remission. There was no difference between age at diagnosis ( $P = .875$ ), disease duration ( $P = .719$ ), smoking status ( $P = .313$ ), location of disease ( $P = .462$ ), and behavior of disease ( $P = .830$ ) when comparing patients who experienced clinical relapse with those who did not experience clinical relapse. There was no difference comparing patients being treated by MTX ( $P = .395$ ) and AZA ( $P = .842$ ), but there were more patients on baseline 6-MP ( $P = .006$ ) who did not experience clinical relapse. There was no difference in clinical relapse when comparing those on biologic therapy with those who were not ( $P = .825$ ) (Table 1).

Among patients with ileal biopsies, there was no difference in the rate of relapse between patients with normal (36.4%), quiescent (28.6%), or active histology (23.8%;  $P = .434$ ). Similarly, in patients with colonic biopsies, there was no difference in the rate of clinical relapse among patients with normal (27.9%), quiescent (35.0%), or histologically active disease (38.1%;  $P = .73$ ) (Figure 1). Two separate Kaplan-Meier survival curves

**Table 1.** Characteristics of Patients With Crohn's Disease in Endoscopic Remission Included in the Study

|                                    | Clinical relapse, N (%)     | No clinical relapse, N (%)  | P value |
|------------------------------------|-----------------------------|-----------------------------|---------|
| N                                  | 42                          | 87                          |         |
| Age at diagnosis (y)               | 25.47 ± 11.25               | 25.8 ± 11.03                | .875    |
| Age at visit (y)                   | 40.14 ± 13.23               | 40.48 ± 12.78               | .68     |
| Gender                             |                             |                             | .34     |
| Male                               | 25 (36.23)                  | 44 (63.77)                  |         |
| Female                             | 17 (28.33)                  | 43 (71.67)                  |         |
| Smoking status                     |                             |                             | .313    |
| Never                              | 27 (29.03)                  | 66 (70.97)                  |         |
| Former                             | 10 (38.46)                  | 16 (61.54)                  |         |
| Current                            | 5 (50.00)                   | 5 (50.00)                   |         |
| Location                           |                             |                             | .462    |
| L1                                 | 8 (44.44)                   | 10 (55.56)                  |         |
| L2                                 | 13 (33.33)                  | 26 (66.67)                  |         |
| L3                                 | 21 (29.17)                  | 51 (70.83)                  |         |
| Behavior                           |                             |                             | .83     |
| B1                                 | 20 (29.41)                  | 48 (70.59)                  |         |
| B2                                 | 8 (34.78)                   | 15 (65.21)                  |         |
| B3                                 | 14 (36.84)                  | 24 (63.16)                  |         |
| Perianal disease                   |                             |                             | .687    |
| Yes                                | 10 (35.71)                  | 18 (64.29)                  |         |
| No                                 | 32 (31.68)                  | 69 (68.32)                  |         |
| Disease duration (y)               | 13.98 (95% CI, 10.32–17.63) | 14.68 (95% CI, 12.62–16.74) | .719    |
| Current immunomodulator            |                             |                             | .395    |
| Methotrexate                       |                             |                             |         |
| Yes                                | 1 (16.67)                   | 5 (83.33)                   |         |
| No                                 | 41 (33.33)                  | 82 (66.67)                  |         |
| Azathioprine                       |                             |                             | .842    |
| Yes                                | 9 (31.03)                   | 20 (68.97)                  |         |
| No                                 | 33 (33.00)                  | 67 (67.00)                  |         |
| 6-Mercaptopurine                   |                             |                             | .006    |
| Yes                                | 1 (5.26)                    | 18 (94.74)                  |         |
| No                                 | 41 (37.27)                  | 69 (62.73)                  |         |
| Current biologic                   |                             |                             | .825    |
| Yes                                | 25 (33.33)                  | 50 (66.67)                  |         |
| No                                 | 17 (31.48)                  | 37 (68.52)                  |         |
| Current anti-tumor necrosis factor |                             |                             | .84     |
| Yes                                | 23 (33.33)                  | 46 (66.67)                  |         |
| No                                 | 19 (31.67)                  | 41 (68.33)                  |         |
| Current steroid                    |                             |                             | .012    |
| Yes                                | 15 (51.72)                  | 14 (48.28)                  |         |
| No                                 | 27 (27.00)                  | 73 (73.00)                  |         |

CI, confidence interval.

for ileal and colonic biopsies demonstrated similar times-to-disease relapse when comparing between patients with complete histologic normalization, quiescent histologic activity, and active histologic activity (ileal and colonic histology, log-rank  $P = .50$  and log-rank  $P = .84$ , respectively) (Figure 2).

The findings were similar when restricting the analysis to those with isolated ileal disease ( $n = 30$ ), ileocolonic ( $n = 44$ ), or colonic disease ( $n = 55$ ). In the cohort of patients with complete normalization of endoscopy (SES-CD = 0), histologic activity in either the ileum or colon was similarly not associated with future risk of relapse (Supplementary Figure 1).

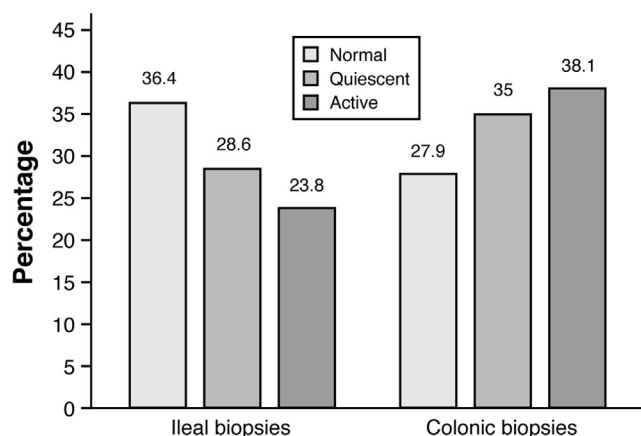
We also found no difference between histologic activity and presence of gastrointestinal symptoms and quality of life. The mean HBI and SIBDQ in patients

stratified by histologic activity in the ileum and colon are presented in Table 2.

## Discussion

It is recognized that patients with IBDs who have a normal endoscopy may have persistent histologic activity, leading to a debate on the benefit of treating to histologic normalization as a target. In a study of 129 patients with CD in endoscopic remission (SES-CD <3), we found no correlation between ileal or colonic histologic activity and future risk of relapse during the subsequent 2 years. Furthermore, histologic activity did not predict concurrent gastrointestinal symptoms or disease-related quality of life. Our findings suggest that more





**Figure 1.** Association between histologic activity and clinical relapse in patients with Crohn's disease in endoscopic remission.

work is needed to establish whether histologic healing is a relevant therapeutic target in CD.

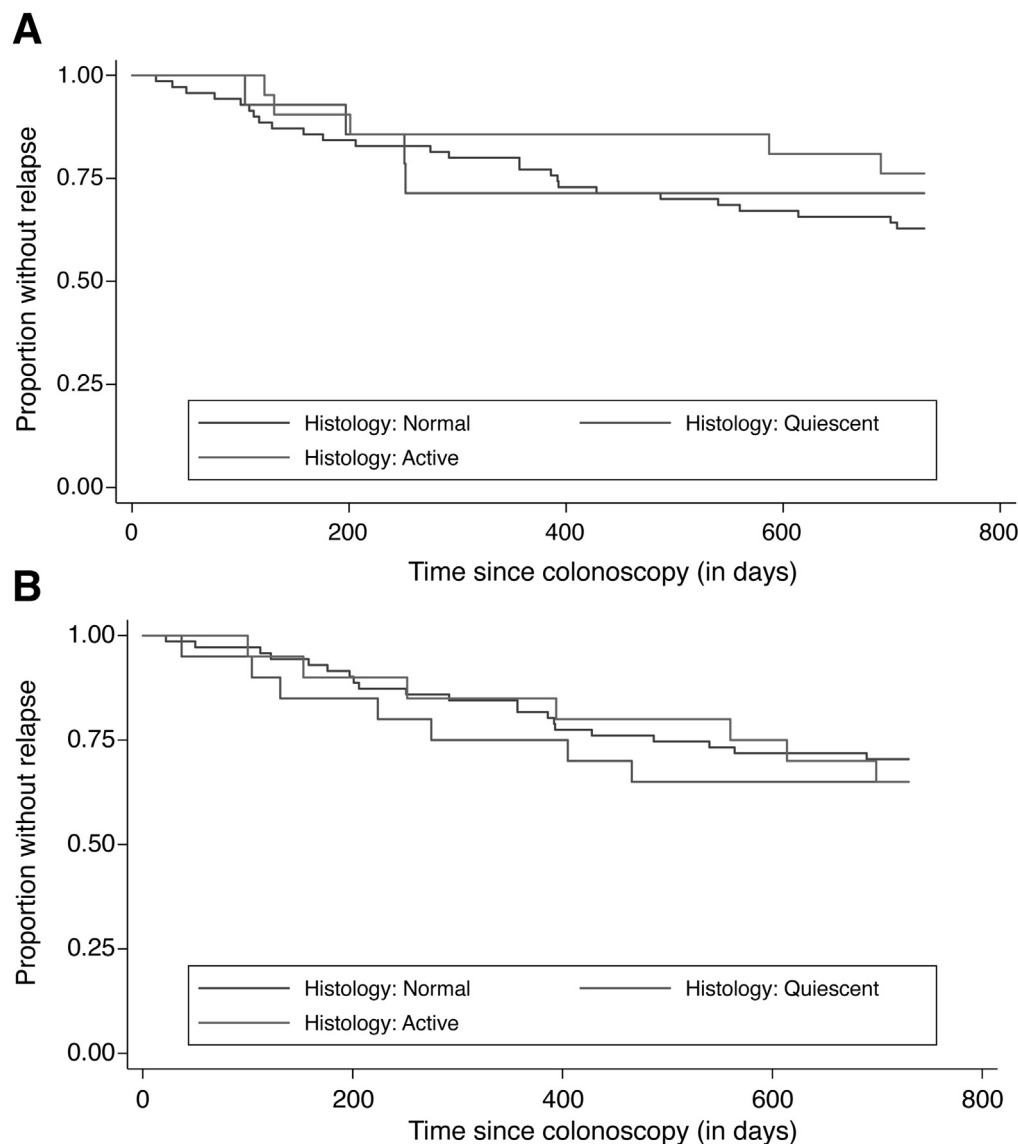
Several studies have now demonstrated that histologic healing is associated with superior outcomes in patients with UC. Christensen et al,<sup>4</sup> who performed a retrospective study of 646 patients with UC, demonstrated histologic normalization was associated with relapse-free survival. In a systematic review and meta-analysis histologic remission was associated with reduced rate of clinical relapse.<sup>3</sup> However, UC differs pathologically from CD in certain key aspects that suggest the benefit of histologic activity assessment may be less prominent in the latter. First, UC is characterized by inflammation only in the mucosa and submucosa, and consequently mucosal biopsy sampling may be an accurate reflection of inflammation in the tissue contributing to relapse in UC. In contrast, inflammation in CD may extend transmurally, and elegant studies have demonstrated that a subset of patients may have persistent mural inflammatory activity even with normal endoscopic examination.<sup>33</sup> Consequently, the value of mucosal sampling may be more modest than in UC. Second, inflammation in UC is contiguous and extending proximally, making a random biopsy sample more representative. In contrast, inflammation is more patchy and segmental in CD, thereby reducing the predictive value of any given biopsy.

A few studies have looked at the role of histologic remission in CD. Baars et al<sup>10</sup> included 152 patients with either UC or CD, where 32 patients with CD were in endoscopic remission but had either histologic activity or normalization. They concluded there was no prognostic difference between patients with solely endoscopic remission compared with those with both histologic and endoscopic remission. Brennan et al<sup>22</sup> evaluated 62 patients with CD who were in clinical remission and had index colonoscopies. Of the 103 colonoscopies, only 55 index colonoscopies revealed complete endoscopic remission as defined by SES-CD of 0. They identified that

patients with histologic activity (presence of erosions, cryptitis, crypt abscess, increased neutrophils, or increased eosinophils in the lamina propria) were more likely to have clinical flares than patients without these changes. Most recently, Christensen et al<sup>23</sup> included 101 patients with isolated terminal ileum CD who were in clinical remission, where 63% of patients had endoscopic healing at the index ileocolonoscopy. They found that histologic healing was associated with decreased clinical relapse, medication escalation, and corticosteroid use. However, in all these studies, patients with both endoscopic remission and endoscopic disease activity were included in the analysis. Our study stratified patients on the basis of the biopsy location and demonstrated that in patients with endoscopic remission, histologic activity or histologic normalization did not predict clinical relapse over a 2-year follow-up. Other histologic studies examined ileocolonic resections to determine specific histologic features that can predict development of clinical relapse. There has been conflicting evidence for the potential that myenteric plexitis is associated with early clinical relapse.<sup>34–37</sup> Most recently in 2017, Lemmens et al<sup>34</sup> demonstrated that lymphocytes within the submucosal plexus are associated with endoscopic relapse, whereas other studies have identified other inflammatory cells, mast cells, and/or eosinophils. Thus, it is possible that cellular architecture deeper to the mucosal layer is more influential in determining disease activity in CD.

There are several strengths to this study. First, patients were registered in a prospective registry, and endoscopic scoring was performed at the time of the procedure by a board-certified gastroenterologist specializing in IBD. Second, this is the largest study to date to look at a cohort of patients with CD who were in endoscopic remission and examine the association of histologic activity with clinical relapse. Third, we compiled patients with CD who were in endoscopic remission rather than those with clinical remission, because endoscopic remission is better at representing ongoing inflammation and predicting long-term prognosis. Furthermore, because of the correlation between endoscopic and histologic activity, it is most pertinent to focus studies of histologic healing on those who have already achieved endoscopic remission to study its incremental value. Grouping patients with endoscopically active disease would bias toward demonstrating a greater predictive value of histologic activity because a large subset of those with histologic active disease would have mild endoscopic activity, which, in retrospective cohorts, has been associated with worse outcomes.<sup>11,38</sup> Finally, because of the size of the cohort, we were able to analyze important factors such as complete endoscopic remission (SES-CD of 0), location of disease, and biopsy location (ileal vs colonic).

We readily acknowledge some limitations in our study. Despite our relatively large cohort of patients, our sample size may still be insufficient to ascertain value of



**Figure 2.** Kaplan-Meier survival curve for histologic activity in ileal and colonic biopsies and time to disease relapse in patients with Crohn's disease in endoscopic remission. (A) Ileal biopsies. (B) Colonic biopsies.

histology. Larger sample sizes with a prospectively studied cohort might be beneficial to examine the influence of certain medications on histologic changes and clinical relapse. Second, cross-sectional imaging (computed tomography or magnetic resonance) was available in only a very small number of patients, and consequently, we could not assess the combined utility of histologic and transmural healing. Third, on the basis of the retrospective nature of our study we were unable to determine the number of biopsies taken. However, there is not a standardized protocol for obtaining biopsies for CD or a known impact of biopsy numbers on detecting histologic activity. We classified histologic activity on the basis of pathology reports and did not use a histologic scoring system such as that of Nandi and Cortina<sup>39</sup> or the Global Histologic Disease Activity Score.<sup>40</sup> However, none of the above scoring systems have been validated, and there is no robust consensus on which system to use in contrast to UC. In addition, there

is substantial overlap between the features used to stratify disease activity in this study and the components of the above scoring systems.<sup>39,40</sup> There is an important need to develop standardized protocols for assessment

**Table 2.** Association Between Histologic Activity Symptom-based Disease Activity Scores and Health-related Quality of Life

|       | Active        | Quiescent    | Normal       | P value |
|-------|---------------|--------------|--------------|---------|
| Ileum |               |              |              |         |
| HBI   | 2.52 ± 3.30   | 2.29 ± 2.23  | 2.71 ± 2.96  | .874    |
| SIBDQ | 56.43 ± 11.31 | 59.21 ± 6.27 | 56.85 ± 9.95 | .678    |
| Colon |               |              |              |         |
| HBI   | 3.67 ± 4.79   | 2.30 ± 2.60  | 2.54 ± 2.64  | .289    |
| SIBDQ | 57.19 ± 8.28  | 58.4 ± 12.13 | 56.11 ± 9.63 | .641    |

HBI, Harvey-Bradshaw index; SIBDQ, short inflammatory bowel disease questionnaire.

of histology in CD including optimal site of sampling (to minimize variability) across patients and within a patient that is based on prior endoscopic severity, number of biopsies, and scale used for histologic assessment. Finally, we did not ascertain adherence to therapy during the follow-up period, which may have impacted relapse.

In conclusion, histologic activity in the setting of endoscopic remission is not associated with clinical relapse, defined by CD-related hospitalization, rescue steroids, escalation, or changes to therapy over 2-year follow-up. Although endoscopic and clinical remissions remain treatment goals, therapeutic studies are evolving to look at achieving histologic remission. Future prospective studies are needed to identify a protocol for biopsy sampling, standardized histologic scoring system, and evaluate the benefit of histologic remission in CD.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at <https://doi.org/10.1016/j.cgh.2020.04.050>.

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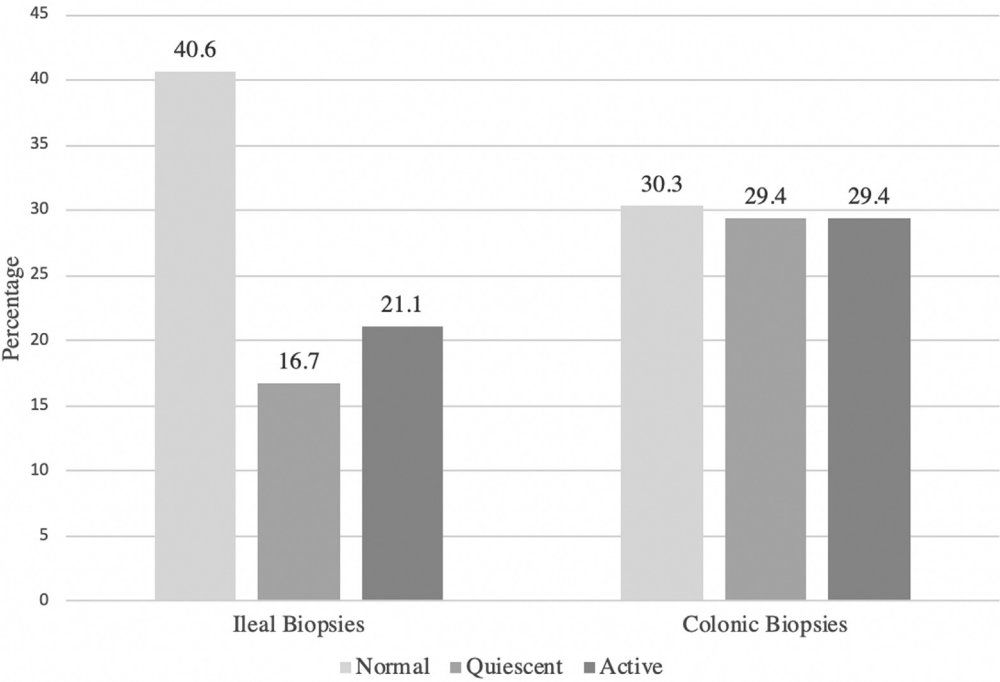
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**Supplementary Figure 1.** Association between histologic activity and clinical relapse in patients with Crohn's disease in endoscopic remission (Simple Endoscopic Score for Crohn's Disease = 0).