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Histologic Healing is More Strongly Associated with Clinical Outcomes in Ileal Crohn's Disease than Endoscopic Healing

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Abstract

Background & Aims: Deep remission, based on clinical remission and evidence of healing during endoscopic evaluation, are goals of medical treatments for Crohn's disease (CD). We investigated whether histologic healing is associated with outcomes of patients with CD ileitis.

Methods: We performed a retrospective study of 101 patients with CD (52% male) isolated to the terminal ileum who had a colonoscopy between September 2005 and June 2015. Our analysis included patients in clinical remission at colonoscopy who had biopsies collected from colon and ileum. The ileum was evaluated for endoscopic healing (no ulceration) and histologic evidence of healing (no active inflammation, erosions, ulceration, or neutrophil infiltration). We compared times of clinical relapse-free survival, medication escalation, corticosteroid use, or hospitalization secondary to disease activity between patients with and without histological and endoscopic

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healing, followed for a median 21 months. We identified factors associated with survival using Kaplan Meier analysis and Cox proportional hazard model.

Results: At ileo-colonoscopy, 63% of patients had endoscopic healing and 55% had histologic evidence of healing. The level of agreement between endoscopic and histologic activity was fair (62%, K=0.2250, *P*=.0064). Forty-two patients had clinical relapse, 45 had medication escalation, 30 required corticosteroids, and 17 were hospitalized (3 required surgery). On multivariate analysis, only histologic healing was associated with decreased risk of clinical relapse (hazard ratio [HR], 2.05; 95% CI, 1.07–3.94; *P*=.031), medication escalation (HR, 2.17; 95% CI, 1.2–3.96; *P*=.011), and corticosteroid use (HR, 2.44; 95% CI, 1.17–5.09; *P*=.018). No factors were associated with hospitalization.

Conclusions: In patients with ileal CD in clinical remission, histologic healing but not endoscopic healing is associated with decreased risk of clinical relapse, medication escalation, or corticosteroid use.

Keywords

inflammatory bowel disease; mucosal healing; histology; histopathology; prognostic factor

INTRODUCTION

In patients with Crohn's disease (CD), persistent inflammation leads to bowel damage. Cumulative bowel damage, described as progressing from inflammatory to stricturing and then to a penetrating phenotype, may predict long-term disability, and can lead to linical symptoms and need for surgery.[1]

Historically, treatment of CD aimed to control clinical symptoms. However, clinical symptoms poorly correlate with endoscopic mucosal disease activity, and resolution of symptoms alone fails to alter this natural progression of CD and cumulative bowel damage.[2] Mucosal healing, on the other hand, is associated with better long-term outcomes; patients who achieve mucosal healing have lower rates of hospitalization and surgery, and are less likely to have a clinical flare on follow-up.[3–6] Therefore, 'deep remission', defined as clinical remission and endoscopic healing without bowel ulceration has emerged as the recommended goal of treatment therapy.[7, 8]

Histological inflammation may persist in the setting of mucosal healing. In UC, histological inflammation is a stronger predictor of clinical flares, corticosteroids use and hospitalization for disease activity than mucosal healing.[9, 10] In addition, histological normalization has been associated with improved long-term clinical outcomes when compared to histological quiescence.[11] This has led to suggestions that histological assessment in UC should be used as an adjunct to mucosal disease assessment in standard care.[11, 12]

The role of histological assessment in CD has been poorly explored. Despite the recent appreciation for the value of endoscopic assessment in CD, there is little evidence as to whether microscopic examination of the mucosa adds any further prognostic information. Histological healing is achievable in CD[13, 14] but, due to the patchy nature of the disease, it is often felt that histological assessment is subject to too much biopsy bias and is too

difficult to study.[15] In addition, there is currently no consensus on the use of a specific scoring system when assessing histological changes in CD.

The aims of this study were to explore whether histological healing (supplementary Table 1) provides any further prognostic information in regard to clinical outcomes, hospitalization and medication escalation in patients with ileal CD when compared to endoscopic healing (EH) alone.

METHODS

An exploratory retrospective case-control study of patients with CD limited to the terminal ileum was performed and was approved by the Institutional Review Board (IRB13–1063). All patients who underwent colonoscopy for CD at the University of Chicago between September 2005 and June 2015 were identified. For patients with a confirmed diagnosis of CD based on clinical and histological information, the electronic medical record was then reviewed. Inclusion criteria comprised a colonoscopy to the terminal ileum, biopsies of both the colon and terminal ileum with disease limited to the terminal ileum both macroscopically and microscopically throughout the duration of their disease, clinical remission at the time of the colonoscopy and ≥6 months of clinical follow-up following colonoscopy. Patients with inadequate documentation, inflammation present in the colon, undergone a colectomy, or confirmed *Clostridioides difficile* infection at the time of follow-up colonoscopy were excluded.

Medical Records Abstraction

Endoscopy reports were retrieved through an electronic documentation system (Provation, Minneapolis, MN). Demographic, clinical, histologic and biochemical data were collected from the electronic medical record system (EPIC, Wisconsin, USA), including date of disease onset, disease duration, smoking history, CD phenotype according to Montreal classification (B1–inflammatory, B2–stricturing, B3–penetrative), disease location (ileal disease only included), and previous and current use of anti-inflammatory agents and/or immunosuppressant therapy (steroids, immunomodulators, anti-TNF agents) at the time colonoscopy.

Endoscopic Assessment

An academic IBD expert gastroenterologist with minimum of 5 years' experience performed all endoscopies, during which endoscopic photographs were obtained from each bowel segment, with targeted photos of the areas of endoscopic activity. As per the inclusion criteria, patients could not have evidence of past or present colonic CD. Consistent with recent large clinical trials and the STRIDE guidelines, endoscopic healing (EH) was defined as the presence of no mucosal ulceration including aphthae[12,16,17], which was confirmed by both the endoscopic report and photographic evidence.

Histologic Assessment

Within the unit, mucosal biopsies from both the ileum and colon are routinely taken targeting the area of most significant mucosal inflammation. Patients were excluded if there was histological evidence of CD in the colon.

The histopathology reports from all diagnostic, screening and surveillance endoscopic biopsies contained in the patient's electronic medical records were reviewed. Two pathologists (JRT and JH) who specialize in gastrointestinal histology and whose agreement has been previously described,[18] routinely assessed all biopsies and reported the worst affected area. There are several histological scoring schemes that have been utilized in CD, however none of these have been validated.[19–21]

In the absence of a validated histological grading score in CD, histological healing was assessed using a modified ileal global histological disease activity score (iGHAS).[14] The iGHAS is the most commonly used histological index in CD and assesses and scores two features of chronicity (architectural changes and infiltration of mononuclear cells in the lamina propria) and five features of activity (epithelial damage, polymorphonuclear cells in the lamina propria, polymorphonuclear cells in the epithelium, presence of erosions and/or ulcers, epithelial granuloma). For the purposes of the current study, histologic assessment was dichotomized to 'histologic healing', where none of the features of activity above were present, and 'histologic activity', where one or more of the features were present. Severity of inflammation was not scored, as stated in Supplementary Table 1.

Assessment of Clinical Outcomes

At every patient clinic visit at the University of Chicago, the Harvey Bradshaw Index (HBI) is calculated.[22] All patients who were in clinical remission at the time of the colonoscopy, defined as an HBI ≤ 4, and who had ≥ 6 months of follow-up were included. Clinical relapse-free survival, medication-escalation-free survival, corticosteroid-free survival and hospitalization-free survival were calculated and defined as time from colonoscopy to event. Clinical relapse was defined at clinical follow-up as HBI > 4 that resulted in alteration or addition of medical therapy, hospitalization or surgery. Escalation of medication was defined as need for a course of corticosteroid or change in medication maintenance including change of biologic agent or escalation of dose, addition or change of immunomodulator in combination therapy for CD, or escalation from immunomodulator to biologic agent. Corticosteroid use was defined as the requirement for an increase dosage or new course of oral corticosteroids including budesonide for active CD symptoms. Hospitalization was recorded if required for disease activity or refractory disease including need for surgery.

Statistical Analysis

Continuous variables were summarized using medians and interquartile ranges (IQR). Categorical variables were expressed as the percentage and number of cohort. Cohen's kappa coefficient (**κ**) was calculated to measure agreement between endoscopic and histological activity.

Kaplan-Meier analyses were performed to compare clinical relapse-free survival, medication escalation-free survival, corticosteroid-free survival and hospitalization-free survival in those with and without EH and with and without histological healing. Univariate and multivariate Cox proportional hazard regression analysis was performed to identify predictors of clinical relapse, medication escalation, corticosteroid use and hospitalization. All variables with p-values of less than or equal to 0.10 on univariate analysis were retained and integrated into the multivariable models. A two-sided p-value of 0.05 or less was considered statistically significant. All data analyses were performed using Stata 12.0 (StataCorp, College Station, TX).

RESULTS

Patients

Of 1287 patients with documented CD and a colonoscopy, 150 fulfilled entry criteria with disease limited to the terminal ileum, normal colonoscopic biopsies and evaluable biopsies from the ileum. Of these, 101 were in clinical remission at the time of colonoscopy and were included in the study (Figure 1).

The patients' demographics and clinical characteristics are shown in Table 1. 52% of patients were male with median age of diagnosis of 25 years old and median duration of disease at time of colonoscopy of 12 years. 86% of patients had two or more sets of biopsies taken of the terminal ileum. At colonoscopy, 64 patients (63%) had EH and 55% had achieved histological healing. The level of agreement between endoscopic activity and histological activity was fair at 62% (κ=0.2250; p=0.011).

Clinical Relapse-free Survival

Median follow-up time was 21 (IQR 12–40) months. Clinical relapse occurred in 42% (n=42) of patients after median time of 16 (IQR 7–26) months. As shown in Figure 2, patients with EH and histological healing were less likely to experience clinical relapse (Figure 2a–b). By univariate analysis, no other factors were associated with improved clinical relapse-free survival (Table 2). By multivariable analysis, only histological activity remained associated with clinical-relapse free survival with HR 2.05 (1.07, 3.94; p=0.031; Table 2). EH did not independently predict a lower rate of clinical relapse.

Medication Escalation-Free Survival

The medication regimen was escalated in 45% (n=45) of patients, two of whom were in clinical remission, but had moderate or severe endoscopic disease activity on colonoscopy. Thirty-two patients required a course of oral corticosteroids (budesonide or prednisolone), 19 required a new biologic agent, 1 had escalation of biologic agent dosing and 6 patients had an immunomodulator added to their biologic therapy. Patients with histological healing were less likely to have medication escalation (Figure 2c). EH was not significantly associated with a lower rate of medication escalation. (Figure 2d) The only factor associated with improved medication escalation-free survival was the achievement of histological healing compared to histological activity with HR 2.17 (1.20, 3.96; p=0.011) on univariate analysis and HR 2.08 (1.14, 3.80; p=0.017) on multivariable analysis (Table 2).

Corticosteroid-free survival

Patients with histological healing, but not EH, were less likely to have a requirement for salvage therapy with corticosteroids (Figure 3a–b). By univariate and multivariable analyses, the only factor associated with corticosteroid-free survival was the achievement of histological healing compared to histological activity (HR 2.44 (1.17, 5.09), p=0.018; Table 2).

Hospitalization-free survival

17% (n=17) of patients were hospitalized and 3 patients proceeded to ileocecectomy. Due to small numbers, predictors of surgery could not be analyzed. No factor was associated with hospitalization-free survival. EH and histological healing did not protect from hospitalization on follow-up (See figure 3c–d).

DISCUSSION

Recently there has been increased emphasis placed on objective markers of disease activity. In CD particularly, the association with clinical symptoms and bowel damage is poor.[3] This may, in part, explain why, despite the advent of many new therapies, the natural history of the disease has, up until recently, barely changed.[23] Recently, expert consensus has stated that the target of treatment for CD should be EH, as defined by lack of ulceration, in order to attempt to prevent ongoing bowel damage.[12] Unlike UC, where histological healing has been defined as an adjunct to EH[24] and the combination of both has been proposed as a new endpoint of interest[25], the role of histology in CD, beyond diagnosis, is poorly defined. In the current exploratory study, the prognostic value of histology in patients with CD restricted to the ileum has clearly shown that histological remission is associated with superior clinical-relapse free survival and reduced need for medication escalation and corticosteroids. Moreover, the results indicate the poor performance of EH alone as a prognostic predictor.

As in UC, this study demonstrates that there is a disparity between EH and histological remission. We found that the level of agreement between endoscopic activity and histological activity was only fair at 63 % (k=0.2250). Microscopic inflammation persisted in 36% of those who achieved EH. This is similar to previous reports of persistent microscopic inflammation in the setting of EH of between 25–37% [8, 26] and emphasizes the need to consider histologic outcomes separate to endoscopic measures of remission in CD.

Several studies have demonstrated the effect of medical therapy on histologic healing in patients with CD; azathioprine, methotrexate and the biologics can all result in histological healing.[13, 14, 16, 17, 27] A sub-analysis of 13 patients from the ACCENT 1 study established that histological improvement after 54 weeks of infliximab was associated with a consistent decrease in the expression of inflammatory markers including CD68 and gelatinase B in the colonic mucosa.[28] The relationship of histology to chance of relapse was explored in a study of 46 patients with Crohn’s colitis undergoing surveillance colonoscopy and histology and/or active mucosal disease did not predict chance of relapse. [20] This study also found similar lack of association in patients with UC. However, a recent paper of 62 CD patients in clinical remission demonstrated that histological inflammation was strongly associated with

an increased risk of clinical flares within 1–2 years and that endoscopic activity alone did not predict clinical flares on follow-up. [19] Two recent studies have also specifically examined the link between histological remission and outcomes in ulcerative colitis and found that histological disease activity was linked to an increased chance of clinical relapse. Bryant et al[10] demonstrated that histological remission predicted reduced corticosteroid use and episodes of acute severe colitis requiring hospitalization in a cohort of 91 patients with UC over a period of 6 years. In a large cohort of 310 patients from Chicago, histological normalization was also found to be achievable and this predicted a lower chance of clinical relapse over the ensuing 16 months.[11] Due to such studies, routine histological assessment is now recommended in UC. [12] This exploratory study on ileal CD demonstrates that histological assessment in CD patients is also clinically relevant, despite the patchy nature of the disease. Therefore, we recommend that routine ileal biopsies be obtained when patients with terminal ileal disease are being assessed.

As we strive to achieve deeper markers of disease control, histological healing may emerge as a treatment target in CD. This aspiration, however, raises several issues. Dichotomously scoring the histopathology of individual biopsies as healed versus inflamed using the criteria applied in the current study should be relatively easy, as opposed to scoring the severity of inflammation. It is the patchy nature of inflammation in CD with the implications around what should be defined as ‘healed’ that provides the uncertainty and controversy. Studies of where the biopsies should be taken and how many are needed to confidently make such a decision are required so a validated and reproducible histological index can be established. Despite this, the results of the current study have clearly demonstrated that the goal of gaining meaningful prognostic information from assessing histological healing in the terminal ileum is achievable.

Even if these guidelines existed, it is as yet unclear if it is even possible to achieve histologic healing in the majority of patients or whether treating our patients more aggressively with medical therapy will improve rates of histological healing. Hence, while histologic healing might provide prognostic information, it cannot, at this stage, be recommended as a target upon which therapeutic decisions in patients with ileal disease can be made. While those who have a healed ileum have a better clinical outlook, whether this group who achieve this level of “deeper remission” need less stringent follow-up or monitoring, or are less likely to have disease that progresses to a stricturing or penetrating phenotype requires further study.

CD causes chronic transmural inflammation of the gastrointestinal tract. There is evidence that patients who achieve transmural healing also have more favorable clinical outcomes on follow-up compared to patients who achieve EH alone.[29] It is unclear if transmural inflammation persists in the setting of histologic healing as demonstrated on mucosal biopsies or if achieving the potentially even deeper target of transmural healing could result in further improvement in clinical outcome compared to histologic healing alone but this should be looked at in future research.

There are several limitations to this study. First, this is a retrospective analysis with a relatively small sample size and there may be inaccuracies in data collection that affect results. The extensive experience of the involved clinicians and the overlapping data sources

(electronic records, endoscopy records and pathology reports) aim to minimize this limitation, but those patients in prolonged clinical remission may not be included due to not having had a colonoscopy or endoscopic biopsies. Secondly, the generalizability of the data is also uncertain; this is a single-center study based in a tertiary hospital setting where experts in the area of IBD manage patients. Thirdly, the findings are currently applicable only to patients with ileal CD. The patchiness of the disease make histologic studies in patients with colonic or ileo-colonic disease challenging. In the same way, however, the restriction to terminal ileal disease was a strength of the current study as it aimed to examine a concept with clearly positive results. It provides the impetus to expand the work to more extensive disease to determine whether normalization of histology has prognostic value as it does in ileal disease and UC. Fourthly, even though the current histologic scale was not assessing severity of inflammation, but rather the normality of biopsies, its application and reproducibility has not undergone independent validation. Because there are currently no validated histological indices in Crohn's disease, we focused on the absence of an active inflammatory infiltrate to represent the absence of histologic activity. The presence of acute inflammation, which is of clinical significance, is simple and reproducible, and is the outcome that has been reported to improve following biologic treatment in previous CD trials.[14, 16, 17] Fifthly, the use of clinical remission as an inclusion criterion for this study also has its own limitations. Patients with both histologic and EH may have clinical symptoms, so not all patients with EH would be included in this study. In addition, it is unclear what percentage of patients had an inflammatory relapse as the outcomes analyzed were clinical relapse and need for steroids or medication escalation, which may have occurred in some patients who had worsening symptoms despite no increase in inflammatory burden. Finally, it is noted that biomarker assessment at time of colonoscopy would strengthen this study and that future prospective studies should include calprotectin, C-reactive protein assessment and perhaps intestinal ultrasound to determine how they compare to histological and endoscopic assessment alone.

In conclusion, we have demonstrated in patients with CD restricted to the terminal ileum the potential for histological healing to act as a prognostic marker. It is associated with improved clinical outcomes, less chance of clinical relapse and decreased need for medication escalation. We propose that histological assessment of healing should be part of endoscopic assessment in CD. However, there is a clear need for standardized and validated histological indices in CD and the prognostic value of their application to CD affecting the colon and rectum require evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

EH	Endoscopic Healing
CD	Crohn's disease
HBI	Harvey Bradshaw Index

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Need to Know

Background:

Deep remission, based on clinical remission and evidence of healing on endoscopic evaluation are goals of medical treatments for Crohn's disease (CD).

Findings:

In patients with ileal CD in clinical remission, histologic healing, but not endoscopic healing, indicates that patients have decreased risk of clinical relapse, medication escalation, or corticosteroid use.

Implications for patient care:

Patients in remission from CD should be evaluated for histologic evidence of healing.

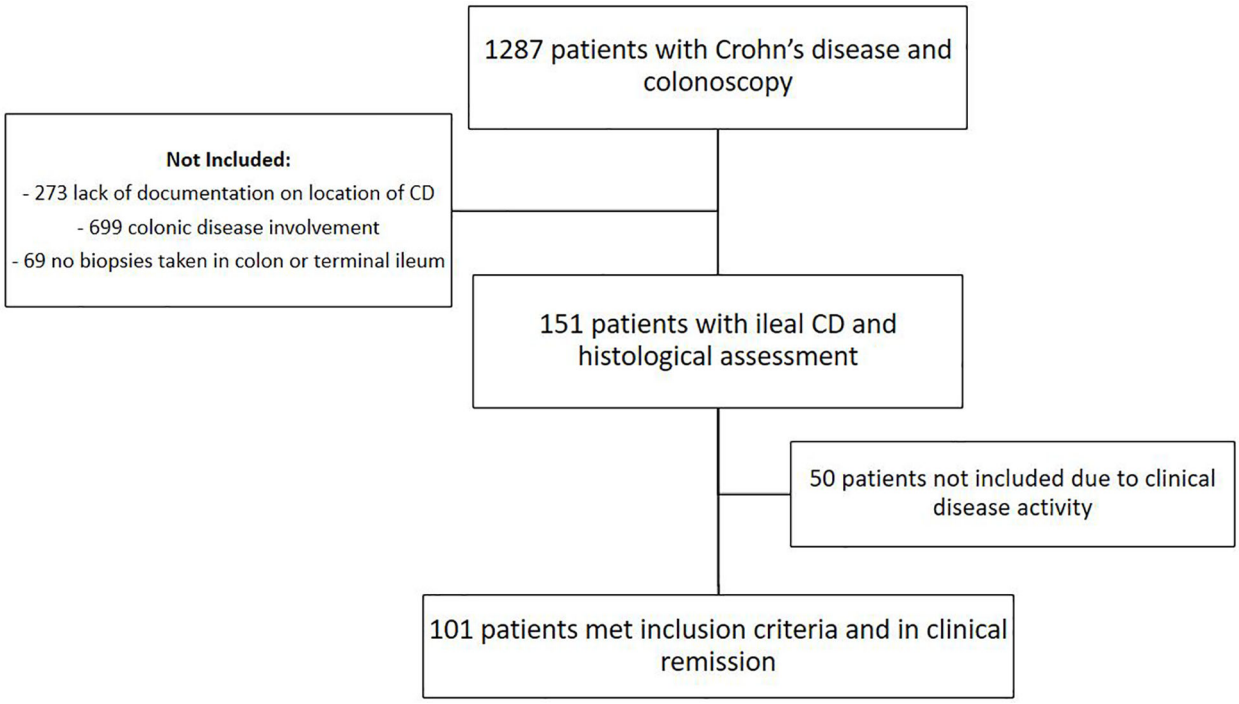

Figure 1:
Flow chart of patients included in the study

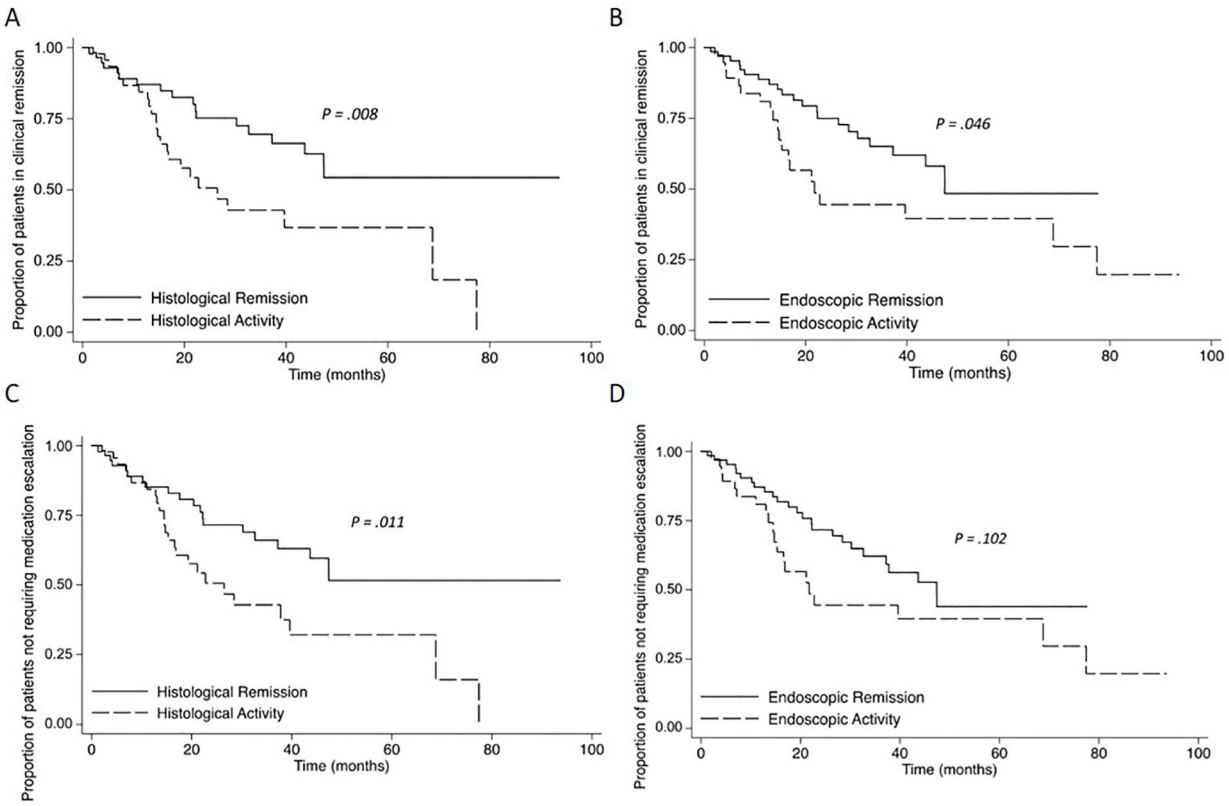

Figure 2:

Kaplan-Meier analysis of effect of endoscopic and histological activity on (A) Clinical relapse-free survival versus histological healing (B) Clinical relapse-free survival versus endoscopic healing (C) Medication escalation-free survival versus histological healing (D) Medication escalation -free survival versus endoscopic healing

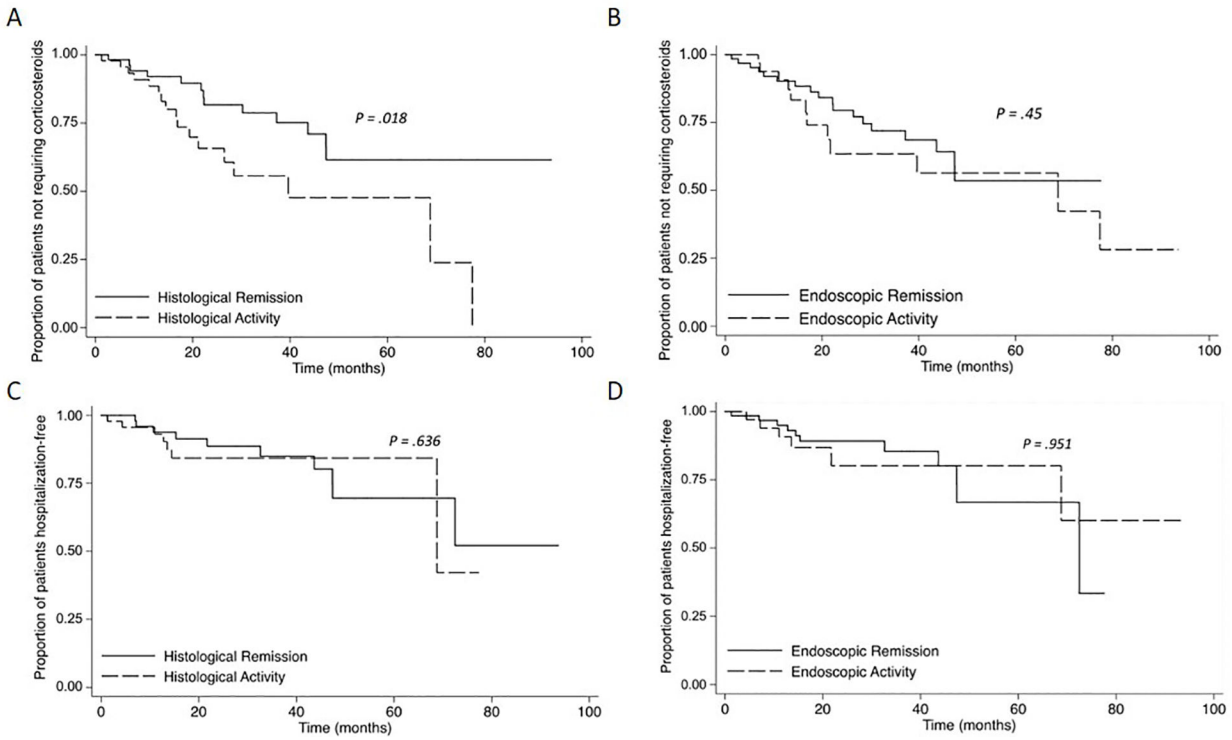

Figure 3:

Kaplan-Meier analysis of effect of endoscopic and histological activity on (A) Corticosteroid-free survival versus histological healing (B) Corticosteroid-free survival versus endoscopic healing (C) Hospitalization-free survival versus histological healing (D) Hospitalization -free survival versus endoscopic healing

Table 1:

Clinical Characteristics at Baseline

Baseline characteristics (N = 101)	Patients with histological healing n=56	Patients without histological healing N=45
	Median (IQR) or Percentage (n)	
Age at diagnosis of CD (years)	24 (16–31)	27 (19–34)
Gender (male)	48% (n=27)	58% (n=26)
Duration of disease (years)	14 (9–25)	9 (3–19)
Disease phenotype		
B1 (inflammatory)	14% (n=8)	38% (n=17)
B2 (stricturing)	61% (n=34)	40% (n=18)
B3 (penetrating)	25% (n=14)	22% (n=10)
Medications at time of colonoscopy:		
Oral prednisolone/budesonide	20% (n=11)	18% (n=8)
5-amino-salcylic acid	9% (n=5)	11% (n=5)
6-mercaptopurine/azathioprine	45% (n=25)	38% (n=17)
Methotrexate	11% (n=6)	9% (n=4)
Anti-tumor necrosis factor	32% (n=18)	31% (n=14)
Ustekinumab	2% (n=1)	0% (n=0)
Vedolizumab	7% (n=4)	4% (n=2)
Endoscopic healing	73% (n=41)	51% (n=23)

Table 2:

Univariable predictors of clinical outcome measures in patients with Crohn's Disease

Variable	Clinical Relapse n=42† HR (95% CI), p-value	Medication escalation n=45† HR (95% CI), p-value	Corticosteroid Requirement n=32† HR (95% CI), p-value	Hospitalization for severe disease n=17† HR (95% CI), p-value
Age diagnosis of CD (years)	0.98 (0.95, 1.01), p=0.196	0.98 (0.95,1.00), p=0.127	0.98 (0.95, 1.01), p=0.204	0.98 (0.94,1.03), p=0.463
Sex (male)	0.66 (0.36, 1.23), p=0.197	0.60(0.32,1.09), p=0.095	0.65 (0.32, 1.32), p=0.239	0.49 (0.18, 1.36), p=0.171
Disease duration (years from diagnosis to colonoscopy)	0.99 (0.97, 1.02), p=0.569	0.99 (0.97,1.01), p=0.656	0.99 (0.96, 1.02), p=0.637	1.00 (0.96, 1.04), p=0.980
Penetrative vs Inflammatory (B2vsB1)	0.78 (0.39, 1.58), p=0.493	0.89 (0.44,1.76), p=0.729	1.08 (0.45, 2.59), p=0.860	1.95 (0.43, 8.90), p=0.391
Stricturing vs Inflammatory (B3vsB1)	0.44 (0.16, 1.20), p=0.111	0.45(0.17, 1.22), p=0.120	0.62 (0.19, 1.99), p=0.422	1.06 (0.17, 6.56), p=0.947
Maintenance therapy				
- 5-ASA	1.21 (0.48, 3.11), p =0.682	1.13(0.44, 2.88), p=0.794	0.90 (0.27, 2.97), p=0.861	1.08 0.24, 4.76), p=0.923
- Immunomodulator	0.66 (0.35, 1.25), p=0.202	0.73(0.39, 1.36), p=0.327	0.62 (0.30, 1.27), p=0.193	0.41 (0.13, 1.25), p=0.117
On oral corticosteroids at endoscopy	1.50 (.73, 3.05), p=0.267	1.20(0.47, 3.05), p=0.703	1.34 (0.47, 3.88), p=0.578	1.29 (0.29, 5.72), p=0.737
Ongoing histological activity	2.31 (1.24, 4.31), p=0.008*	2.17(1.20, 3.96),p=0.011*	2.36 (1.16, 4.81), p=0.018*	1.27 (0.47, 3.43), p=0.636
Ongoing endoscopic activity	1.87 (1.01, 3.45), p=0.046*	1.64(0.91,2.99), p=0.102	1.39 (0.68, 2.85), p=0.369	0.97 (0.35, 2.67), p=0.951

†Cox regression univariate analyses presented.

p Value of ≤0.05 considered significant and marked by*.

5ASA, 5-aminosalicylic acid.