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HISTOLOGIC NORMALIZATION OCCURS IN ULCERATIVE COLITIS AND IS ASSOCIATED WITH IMPROVED CLINICAL OUTCOMES

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Abstract

Background & Aims—Mucosal healing, determined by histologic analysis, is a potential therapeutic target for patients with ulcerative colitis (UC). However, the histologic features of tissue normalization, as an outcome of treatment, have not been well described. We examined the prevalence and predictive values of normalization of the colonic mucosa, based on histologic analysis (histologic normalization) in patients with UC, and determined its association with risk of clinical relapse, compared with histologic disease quiescence and endoscopic mucosal healing.

Methods—We performed a retrospective study of 646 patients with confirmed UC who underwent colonoscopy at a tertiary medical center from August 2005 through October 2013. We reviewed reports from pathology analyses of random mucosal biopsies from each colon segment, and categorized them into 3 groups based on histology findings: (1) normalization (completely normal mucosa with no features of chronicity present), (2) quiescence (crypt atrophy or branching without signs of active inflammation including erosions, abscesses, or focal neutrophil infiltration), or (3) active disease (epithelial infiltration by neutrophils, crypt abscesses, erosions, or ulceration). Histology findings were compared with clinical and endoscopic findings. We

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Jon Erich: Acquisition of data and drafting of the manuscript

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assessed variables associated with histology findings and, in patients in clinical remission (Simple Clinical Colitis Activity Index score ≥ 2 and subscore of ≥ 1 for stool frequency or rectal bleeding), predictive values for clinical relapse at follow-up evaluations 6 months later or more were calculated.

Results—Of the 646 patients included in the study, 60% had endoscopic mucosal healing, 40% had histologic quiescence, and 10% had histologic normalization. The level of agreement between mucosal and histologic activity was moderate (agreement for 68% of samples; $k = 0.50$; $P < .001$). On multivariate analysis, only proctitis associated with histologic normalization ($P = .002$). Of 310 patients in clinical remission at initial review, 25% had a clinical relapse, after a median time of 16 months (interquartile range, 10–23 months). Histologic normalization was independently associated with increased odds of relapse-free survival compared with histologic quiescence (hazard ratio, 4.31; 95% confidence interval, 1.48–12.46; $P = .007$) and histologic activity (hazard ratio, 6.69; 95% confidence interval, 2.16–20.62; $P = .001$); mucosal healing was not associated with increased odds of relapse-free survival compared with no mucosal healing (hazard ratio, 1.02; 95% confidence interval, 0.56–1.85; $P = .954$).

Conclusions—Histologic normalization of colonic mucosa can be used as a clinical endpoint for patients with UC. We associated histologic normalization with increased odds of relapse-free survival compared to endoscopic healing or histologic quiescence. Further studies are needed to determine whether histologic normalization should be a goal of treatment for patients with UC.

Keywords

histopathology; mucosal healing; inflammatory bowel disease; normalization

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease characterized by periods of disease activity alternating with periods of quiescence. The primary treatment goal in UC has been to limit these periods of activity and maintain clinical remission, traditionally defined as cessation of rectal bleeding and normalization of stool frequency.¹ In recent years endoscopic mucosal healing (MH) in UC has been associated with improved clinical outcomes compared to achieving clinical remission alone.^{2–5} In fact, MH has been associated with prolonged remission, fewer hospitalizations and colectomies and an improved quality of life.^{2–8}

Despite such improved outcomes associated with MH, up to 40% of patients with MH have persistent histologic inflammatory activity.^{3,9–12} Therefore, there is interest in the significance of histologic remission, as a “deeper” marker of disease control compared with MH. Although more research is needed into the practicality and validity of histologic assessment, it is known that reduced histologic activity is associated with decreased risks of relapse, hospitalization, corticosteroid use, colectomy, and colorectal neoplasia.^{3,9–18}

It has been a common understanding that, following a diagnosis of UC, histologic abnormalities of the mucosa persist. This idea has been so established that when histologic grading has been described in UC, normalization has not generally been defined as an

outcome that is distinct from quiescence; and histologic healing is generally described simply as absence of active inflammation.^{3,9,14,19} Furthermore, in 2 recently described histologic indices, the focus has been on short-term treatment responsiveness and architectural abnormalities have been excluded in their assessment.^{20,21}

Although there are infrequent descriptions of histologic normalization in the literature,²² it remains incompletely defined in the context of clinical outcomes. In addition, patient, disease, and treatment characteristics associated with histologic normalization have not been studied, and it had not been determined if complete histologic normalization (CHN) is associated with improved clinical outcomes compared to histologic remission or endoscopic MH alone.

The aims of this study were to examine the prevalence and predictors of histologic normalization in patients with confirmed UC, and to determine if normalization is associated with improved clinical outcomes compared with ongoing histologic activity, histologic quiescence, and endoscopic MH.

METHODS

A retrospective case-control study was performed and approved by the institutional review board (13-1063). All patients who underwent colonoscopy at University of Chicago between August 2005 and October 2013 for UC were identified by 1 or more of the International Classification of Diseases, Ninth revision, Clinical Modification codes for UC (556.0, 556.2, 556.3, 556.5, 556.6, 556.8, 556.9). Patients were eligible for inclusion if they had an established diagnosis of UC at the time of this “follow-up” colonoscopy and documentation of previous complete colonoscopy and segmental biopsies obtained in at least the rectum, left colon, and right colon that showed chronic changes (with or without acute changes) consistent with a histologic diagnosis of UC more than 1 year prior. Patients who had inadequate documentation, had undergone a colectomy, or had confirmed *Clostridium difficile* infection at time of follow-up colonoscopy were excluded.

Medical Records Abstraction

Endoscopy reports were retrieved through the electronic documentation system for endoscopic reports (Provation, Minneapolis, MN). Demographic, clinical, histologic, and biochemical data were collected from our electronic medical record system (EPIC, Verona, WI), including age at diagnosis, disease duration, smoking history, and previous and current use of anti-inflammatory agents and/or immunosuppressant therapy (steroids, immunomodulators, anti-tumor necrosis factor agents) at time of follow-up colonoscopy.

Endoscopic and Histologic Assessment

The bowel was divided into 3 segments as per the Montreal classification for UC²³: (1) proctitis (E1, rectum only), (2) left-sided (E2, rectum to splenic flexure), or (3) extensive colitis (E3, disease proximal to splenic flexure). Disease extent was determined using a modified Montreal classification in that, rather than endoscopic appearance, histology was used on most proximal biopsy showing evidence of disease, whether acute or chronic inflammation, or chronic architectural changes (ie, crypt branching/shortening, decreased

crypt densities, and irregular mucosal surfaces). Maximal disease extent was determined at any colonoscopy performed over the patient's history. The endoscopic and histologic severity and number of biopsies taken from each segment at follow-up endoscopy were recorded.

Endoscopic Mucosal Assessment—An academic inflammatory bowel disease (IBD) expert gastroenterologist with minimum 5 years' experience performed all endoscopies, during which endoscopic photographs were obtained from each segment of bowel, with targeted photographs of areas of mucosal activity. An independent reviewer classified patients into 3 distinct groups of endoscopic grade of inflammation using the endoscopic subscore of the Modified Mayo Disease Activity Index.²⁴ A score of 0 (no friability, granularity, and intact vascular pattern) was classified as normal, 1 (mild erythema or decreased vascular pattern) as quiescent mucosa, and a score of 2 (any of moderate or marked erythema, absent vascular pattern, friability, erosions, ulceration, or contact/spontaneous bleeding) as mucosal activity. Endoscopic MH was defined by either completely normal or quiescent mucosa (Modified Mayo Disease Activity Index endoscopic subscore 1).

Histologic Assessment—As is routine in this unit, random mucosal biopsies were obtained from each colon segment, targeting the area of most significant mucosal disease activity. Two pathologists who specialize in gastrointestinal histology routinely assess all biopsies and report histology using a standardized scale that includes histologically normal, quiescent, mild, moderate, or severe disease. We reviewed these pathologic reports and categorized histology specimens into 3 distinct groups using the modified Riley score as described by Bryant et al¹⁶, but with the subcategorization of histologic remission into histologic normalization and histologic quiescence based on the absence or presence of architectural changes, respectively. Based on the maximum inflammation score at each segment, patients were categorized as (1) histologic normalization: completely normal mucosa with no features of chronicity present; (2) histologic quiescence: features of chronicity including crypt atrophy or branching but no active inflammation, such as erosions, crypt abscesses, or focal neutrophil infiltration; and (3) histologic activity: presence of any epithelial infiltration by neutrophils, crypt abscesses, erosions or ulceration.

As previously reported, the inter-observer agreement for interpretation of UC histology between our pathologists using a 6-point scale that classifies varying severities of inflammatory activity (including normal) was very good (kappa=0.6).¹³ In this study, an additional 150 samples were re-graded by one of the expert pathologists (JH) who was blinded to the prior official reads of these specimens; 50 were histologically normal, 50 quiescent and 50 had active histology. All 150 samples were interpreted correctly (kappa=1.0).

The primary outcome of CHN was defined by normalization of mucosa without histologic features of chronicity in all bowel segments on follow-up colonoscopy in a patient with previous structural changes on biopsy consistent with UC.

Assessment of Clinical Relapse-Free Survival

Patients in clinical remission at follow-up colonoscopy with 6 months of follow-up at the University of Chicago from this colonoscopy until September 2014 were included in a separate analysis of clinical relapse-free survival. At each patient clinic visit, the Simple Clinical Colitis Activity Index was calculated.²⁵ Clinical remission was defined as Simple Clinical Colitis Activity Index 2 and subscore of 1 for stool frequency or rectal bleeding as determined from physician records. Clinical relapse-free survival was defined as time from colonoscopy to period of clinical relapse, with clinical relapse defined at clinical follow-up as Simple Clinical Colitis Activity Index >2, subscore >1 for stool frequency or rectal bleeding, or medication escalation for symptoms, hospitalization for UC relapse, or colectomy for refractory UC.

Statistical Analysis

Continuous variables were summarized using medians and interquartile ranges. Categorical variables were expressed as percentage and number of cohort. Cohen kappa coefficient (k) was calculated to measure agreement between mucosal and histologic activity.

Univariate analysis of baseline characteristics was performed to identify predictive factors for CHN. The Mann-Whitney U test and analysis of variance were used to compare continuous variables, and Pearson's chi-squared test was used to compare categorical variables. Multivariate analysis to identify independent factors associated with histological outcomes was performed using logistic regression.

Kaplan-Meier analysis was performed to compare clinical relapse-free survival in those with and without CHN and MH and log-rank statistics were performed to compare sub-groups of interest. Cox proportional hazard regression analysis was performed to identify independent predictors of clinical regression.

All variables with $P < .20$ on univariate analysis were retained and integrated into the multivariate models. A 2-sided $P < .05$ was considered statistically significant. All data analyses were performed using Stata 12.0 (StataCorp, College Station, TX).

RESULTS

Patients

A total of 646 patients fulfilled the entry criteria and were included in the analysis. Baseline characteristics at time of follow-up colonoscopy are shown in Table 1. Using endoscopic criteria, 40% ($n = 261$) had endoscopic mucosal activity, 35% ($n = 228$) mucosal quiescence, and 24% ($n = 157$) mucosal normalization on follow-up colonoscopy. Using histologic criteria, 50% ($n = 321$) had ongoing activity, 40% ($n = 260$) histologic quiescence, and 10% ($n = 65$) had CHN.

The level of agreement between mucosal and histologic activity was moderate (68%; $k = 0.50$; $P < .001$). A total of 12% (19 of 157) of patients with mucosal normalization had histologic activity and 27% (61 of 228) of patients with mucosal quiescence had histologic

activity. No patient (0 of 65) with histologic normalization had mucosal activity but 8% (20 of 260) of patients with histologic quiescence had mucosal activity.

Complete Histologic Normalization

A total of 10% (n = 65) of patients had complete normalization of their histology in all segments that had previously shown changes (ie, CHN). The mean number of biopsies taken at each endoscopy was 20 (standard deviation, 9.5) and the number of biopsies taken was not significantly different in patients achieving CHN and in those who did not (Supplementary Table 1).

CHN was identified in 9% (n = 35) of patients with extensive colitis, 8% (n = 15) with left-sided disease, and 23% (n = 15) with proctitis alone. By univariate analysis, CHN was associated with less extensive disease at baseline (P = .001), disease duration >10 years (P = .029), and negatively associated with previous steroid (P = .041) and anti-tumor necrosis factor therapy (P = .031) (Table 2). On multivariate analysis, a diagnosis of proctitis compared with left-sided (E2) (adjusted odds ratio, 3.63; 95% confidence interval, 1.56–8.46; P = .003) and extensive (E3) colitis (adjusted odds ratio, 2.81; 95% confidence interval, 1.32–5.96; P = .007) remained significantly and independently associated with CHN. There was a trend for patients with disease duration of more than 10 years to achieve CHN (adjusted odds ratio, 1.81; 95% confidence interval, 0.98–3.35; P = .058).

Clinical Relapse-Free Survival

A total of 310 patients who were in clinical remission at follow-up colonoscopy were assessed for clinical relapse-free survival. Baseline characteristics are shown in Table 3. Using endoscopic criteria, 25% (n = 80) had ongoing endoscopic mucosal activity, 41% (n = 127) quiescence, and 33% (n = 103) mucosal normalization. Using histologic criteria, 35% (n = 108) had histologic activity, 51% (n = 157) quiescence, and 15% (n = 45) CHN.

Median follow-up was 22 (interquartile range, 14–34) months and 25% (n = 77) patients experienced clinical relapse at median time 16 (interquartile range, 10–23) months. Patients with CHN had lower rates of clinical relapse compared with those with histologic quiescence and activity (Figure 1A) and patients with endoscopic MH had lower rates of clinical relapse rates compared with those with mucosal activity (Figure 1B). In patients who had MH and were in clinical remission, histologic normalization remained protective against clinical relapse (Figure 1C).

By univariate analysis, the only factors associated with improved clinical relapse-free survival were the achievement of endoscopic MH compared with no MH, and CHN compared with both histologic quiescence and histologic activity (Table 4). By multivariate analysis, only CHN compared with histologic quiescence (hazard ratio, 4.31 [1.48–12.46]; P = .007), CHN compared with histologic activity (hazard ratio, 6.69 [2.16–20.62]; P = .001), and no previous exposure to cyclosporine (P = .034) predicted clinical relapse-free survival (Table 4). MH was not independently associated with lower rate of clinical relapse.

DISCUSSION

We have demonstrated that histologic normalization of the colon in UC is possible and is characterized by statistically superior clinical relapse-free survival. A total of 1 in 10 of our cohort achieved CHN.

This is the first study to describe complete normalization of histology in UC. A study by Kleer and Appelman²⁶ did demonstrate that areas of histologic chronic colitis became normal at some point in 22 of 41 patients (54%). However, this study only described the rate of normalization of a single point in the bowel, and did not look at complete normalization of the bowel or examine patient characteristics that predicted this normalization.

Most descriptions of histologic normalization have been reported as rectal sparing. Levine et al²⁷ found that, of 24 asymptomatic patients with UC, 2 (8%) normalized their rectal biopsy on follow-up. Odze et al²² looked at 14 patients treated with either mesalamine or placebo enemas and found that, in patients on mesalamine rectal therapy, 36% of rectal biopsies normalized (defined as “complete absence” of any of the characteristic features of chronic UC). However, only 1 patient (7%) normalized all their rectal biopsies. Finally, Bernstein et al²⁸ showed that 2 of 39 (5%) patients with UC have histologic evidence of absolute rectal sparing at some point during their disease. None of these studies looked at proximal colon histologic normalization or patient or disease characteristics associated with histologic normalization.

We found that CHN was associated with less extensive disease. It has previously been described that extensive colitis is a risk factor for more complicated disease outcomes with the rate of colectomy in these patients of about 19% at 10 years compared to 5% of those who have proctitis.²⁹

Our study demonstrates that histologic normalization is associated with improved clinical outcomes when compared with histologic quiescence and activity, and is more predictive of improved outcomes than endoscopic MH alone or histologic quiescence alone. Several studies have now confirmed the value of histologic features of colitis predicting clinical relapse in UC.^{9,11,12,16,18} Riley et al⁹ found in 82 patients with UC that an acute inflammatory cell infiltrate, crypt abscess, and mucin depletion were significantly higher in those who subsequently relapsed within 12 months. Bitton et al¹¹ reported on 74 patients in clinical and endoscopic remission with rectal biopsy specimens and demonstrated that basal plasmacytosis was associated with UC relapse with a hazard rate of 4.5. In addition, Feagins et al¹⁸ described 51 patients in clinical remission and reported that basal lymphoplasmacytosis, erosions/ulceration of the epithelial, or moderate to marked architectural distortion significantly predicted clinical flares by 6 and 12 months and was more accurate at predicting flares compared with endoscopic assessment alone. Finally, Bryant et al¹⁶ demonstrated that histologic remission predicted corticosteroid use and acute severe colitis requiring hospitalization over 6 years and, similar to our study, endoscopic MH did not. Although our data confirm the importance of histologic healing in improving clinical outcomes in patients with UC over and beyond that of endoscopic MH, it is novel in

that we identify histologic normalization as a stronger predictor of a decreased risk of relapse in patients with either quiescent endoscopic mucosal or histologic UC.

Despite our findings, one must be guarded in translating these associations into clinical practice. The findings cannot yet justify increasing therapy for the sole purpose of achieving histologic normalization. It is important, however, to acknowledge that this level of “deeper remission” is associated with improved outcomes. Patients who achieve histologic normalization can be informed of their improved prognosis and may represent a cohort requiring less stringent clinical surveillance and follow-up. Furthermore, whether this is a subgroup of patients that may benefit from stable de-escalation of medical therapy or require less intensive cancer surveillance remains to be determined. Finally, similar to other recent reports,^{12,16} a total of 27% of patients in this study with mucosal quiescence had persistent microscopic inflammation. Because histologic assessment seems superior to endoscopic assessment in predicting clinical outcomes, this disparity between histologic and endoscopic outcomes indicates that one should consider incorporating histologic surveillance into clinical practice.

This study lends further evidence to the importance of histologic assessment in prognosticating a patient’s future disease course, and has implications for the design of future clinical trials. In fact, the United States Food and Drug Administration has pointed to the possibility of requiring documentation of histologic disease activity at inclusion and as an outcome measure in future clinical trials.³⁰ Clarification of a standardized and validated reporting system for histologic disease severity is needed in UC. There are current international efforts being undertaken to develop such an index.^{20,21} This study suggests any such index should include histologic normalization as a separate and independent grade.

There are several notable strengths and several limitations to this study. As with any retrospective analysis, there may be inaccuracies in data collection. However, the extensive experience of the involved clinicians and overlapping data sources (electronic records, endoscopy, and pathology reports) should minimize this limitation. The generalizability of the data is also uncertain, because this is a single-center study based in a tertiary hospital setting where experts in the area of IBD manage patients. It is unclear whether this selection issue would make normalization of histology more or less likely; although patients may be treated for their disease more aggressively, they also most likely represent a more complex range of patients with more severe disease phenotypes compared with the general community. The tertiary nature of the setting is also in part its strength, because there is standardized reporting for endoscopy and pathology at the center. In addition, although we do use a standardized approach to sampling the mucosa in our patients with UC, it is possible that these results may represent a sampling bias. We believe this limitation was minimized based on the fact that there was no significant difference in biopsy number per patient when comparing cases and control subjects (histologic normalization compared with no normalization). There is also minimal variability between biopsies within each colonic segment with the same percentage of intrasegment biopsies with the same histologic inflammatory activity score being 80% or greater across all segments of the large bowel.³¹ Furthermore, although our histologic activity and quiescence definitions are similar to those previously described by others,^{3,14,16,32} the histologic scale used here to assess histologic

normalization has not undergone independent validation. Finally, given the limitations of this retrospective review, dose and duration of medication exposures were not obtained. Although understanding more about therapies and how they may achieve histologic normalization is of interest, we suggest that this should be assessed in future trials, along with the potential for controlled de-escalation of therapies in patients who achieve CHN.

In conclusion, we demonstrate that histologic normalization is an outcome in patients with UC and have found that it occurs more often in association with less extensive disease. We demonstrate for the first time that CHN in UC is associated with improved clinical outcomes and provide further evidence that, despite the introduction and search for other predictive biomarkers in IBD, traditional histopathology may well be the most reliable. We propose that histologic assessment of disease activity should be part of endoscopic assessment in IBD. In addition, future standardized and validated histologic indices include histologic normalization as a unique outcome and encourage these findings to be incorporated into future clinical trials and clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CHN	Complete Histologic Normalization
MH	Mucosal Healing
SCCAI	Simple Clinical Colitis Activity Index

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A

B

C

Figure 1. Kaplan-Meier analysis of effect of endoscopic mucosal and histologic activity on clinical relapse-free survival

(A) Clinical relapse-free survival versus histologic healing. (B) Clinical relapse-free survival versus endoscopic mucosal healing. (C) Clinical relapse-free survival versus histologic healing in patients with endoscopic mucosal healing.

Table 1

Clinical Characteristics at Baseline

Baseline characteristics (n = 646)	Median (IQR) or Percentage (n)	
Age at diagnosis of UC (years)	29 (22–41)	
Gender (male)	50.2% (n=324)	
Greatest disease extent seen:		
Proctitis	10.1% (n=65)	
Left-Sided	30.5% (n=197)	
Pancolitis	59.4% (n=384)	
Duration of disease (years)	13 (7–22)	
Smoking status (current smoker)	6.6% (n=41)	
Endoscopic mucosal disease:		
Mucosal normalization	157 (24.3%)	Mucosal healing:385 (59.6%)
Mucosal quiescence	228 (35.3%)	
Mucosal activity	261 (40.4%)	
Histologic disease:		
Histologic normalization	65 (10.1%)	Histologic healing: 325 (50.3%)
Histologic quiescence	260 (40.2%)	
Histologic activity	321 (49.7%)	
Medications, n(%)		
Oral steroid exposure	394 (66.8%)	
Current oral steroid	54 (98.6%)	
5-ASA exposure	637 (99.5%)	
Current 5-ASA	517 (81.6%)	
Immunomodulator exposure	294 (48.1%)	
Current immunomodulator	190 (30.1%)	
Previous cyclosporine salvage	25 (4.2%)	
Anti-TNF exposure	109 (18.1%)	
Current anti-TNF	82 (13.0%)	

Table 2

Univariate Analysis of Predictors of Complete Histologic Healing in UC

Characteristic (n= 646)	CHN (n=65)	No CHN (n=581)	P value
Age, y, n (%)			
16 y	11 (17%)	49 (9%)	0.071 *
17–39 y	39 (61%)	357 (63%)	
40 y	14 (22%)	160 (28%)	
Gender, m, n(%)	40 (46%)	294 (51%)	0.496
Current smoker, n (%)	5 (8%)	36 (6%)	0.666
Disease extent at baseline, n (%)			
E1	15 (23%)	50 (9%)	0.001 **
E2	15 (23%)	182 (31%)	
E3	35 (54%)	349 (60%)	
Disease > 10 y, n (%)	47 (73%)	336 (59%)	0.029 **
Oral steroid Exposure, n (%)	33 (55%)	361 (68%)	0.041 **
5-ASA monotherapy, n (%)	40 (63%)	291 (51%)	0.082
Previous immunomodulator, n (%)	22 (36%)	272 (50%)	0.033 **
Current immunomodulator, n (%)	15 (23%)	175 (31%)	0.220
Previous cyclosporine salvage, n (%)	4 (7%)	21 (4%)	0.340
Previous anti-TNF, n (%)	5 (8%)	104 (19%)	0.031 **
Current anti-TNF Rx, n (%)	5 (8%)	77 (14%)	0.192 *
Current immunomodulator and anti-TNF, n (%)	4 (6%)	26 (5%)	0.555

* Incorporated into multivariate analysis as p-value < 0.2

** Significant p-value < 0.05

Table 3

Baseline Characteristics of Those in Clinical Remission at Baseline

Patients	N=310
Sex, n (%), male	159 (51.3%)
Age, median (IQR), y	48.4 y (36.6–58.8)
Age of diagnosis, median (IQR), y	29 y (22–41)
Active smoking status, n (%)	21 (6.8%)
Duration of disease, median (IQR), y	14 y (1–52 or 8–49)
Disease extent, n (%)	
E1	34 (11.0%)
E2	89 (28.7%)
E3	187 (60.3%)
Endoscopic mucosal disease activity, n(%)	
Endoscopic mucosal activity	80 (25.0%)
Endoscopic mucosal quiescence	127 (41.0%)
Endoscopic mucosal normalization	103 (33.2%)
Histologic disease activity, n(%)	
Histologic activity	108 (34.8%)
Histologic quiescence	157 (50.7%)
Complete Histologic normalization	45 (14.5%)
Medications, n (%)	
Past oral steroid exposure	185 (66.3%)
Current oral steroids	15 (4.9%)
Past 5-ASA exposure	303 (99.3%)
Current 5-ASA therapy	242 (79.3%)
Past IMM therapy exposure	156 (52.9%)
Current Immunomodulator (IMM) therapy	110 (36.2%)
Past anti-TNF therapy exposure	57 (19.5%)
Current Anti-TNF therapy	49 (16.2%)
Past cyclosporine salvage therapy	12 (4.1%)

Table 4

Univariate and Multivariate Analysis For Factors Associated With Clinical- Relapse Free Survival

Risk Factor	Univariate analysis: HR ^a (95% CI)	P value ^b	Multivariate analysis: HR ^a (95% CI)	P value ^b
Sex (Female)	1.15 (0.74–1.81)	0.533		
Older age at colonoscopy	0.99 (0.97–1.00)	0.152 *	0.99 (0.98–1.01)	0.408
Older age of diagnosis	0.99 (0.98–1.01)	0.436		
Current smoker	1.19 (0.51 – 2.75)	0.687		
Longer duration of disease	0.99 (0.96–1.01)	0.301		
Disease extent:				
E2 vs E1	1.33 (0.59–2.98)	0.487		
E3 vs E1	1.41 (0.66–3.01)	0.369		
Endoscopic Mucosal Healing:				
-Quiescent disease vs Normalization	1.56 (0.87–2.76)	0.131		
-Active disease vs Normalization	2.44 (1.37–4.36)	0.002		
No endoscopic mucosal healing	1.93 (1.21 – 3.07)	0.006 **	1.02 [0.56–1.85]	0.954
Histologic healing:				
-Quiescent disease vs Normalization	3.79 (1.34 – 10.68)	0.012 **	4.31 [1.48–12.46]	0.007 **
-Active disease vs Normalization	6.76 (2.39 – 19.14)	< 0.001 **	6.69 [2.16–20.62]	0.001 **
oral steroids	0.72 (0.23–2.30)	0.582		
5-ASA therapy	1.19 (0.67–2.14)	0.555		
anti-TNF therapy	0.88 (0.44–1.78)	0.724		
Dual therapy (IMM + anti-TNF)	1.42 (0.61–3.27)	0.416		
IMM therapy	1.37 (0.86–2.17)	0.183 *	1.21 (0.72–2.04)	0.469
Past anti-TNF therapy exposure	0.81 (0.42–1.54)	0.522		
Past IMM therapy exposure	1.32 (0.83–2.09)	0.236		
Past cyclosporine salvage therapy	2.34 (0.99–5.52)	0.052 *	2.71 [1.07–6.82]	0.034 **
Past oral steroid exposure	1.08 (0.67–1.74)	0.749		

^aHazard ratio for each risk factor in Cox model (estimate and 95% CI)^bSignificance level

** significant P-value < 0.05)

* Incorporated into multivariate analysis as P-value < 0.2

CI, confidence interval