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Alimentary Tract

# Acute histological inflammatory activity is associated with clinical relapse in patients with ulcerative colitis in clinical and endoscopic remission

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ABSTRACT

*Background:* It has been suggested that acute histological activity has a prognostic value in the outcome of ulcerative colitis (UC) patients in clinical and endoscopic remission. Our aim was to assess the role of histology as a risk factor for clinical relapse (CR) in patients in both clinical and endoscopic remission.
*Methods:* Patients with left-sided or extensive UC in clinical and endoscopic remission (Mayo endoscopic subscore ≤1) undergoing colonoscopy for dysplasia surveillance with random colonic biopsies between 2005–2015 were included. Basal plasmacytosis, acute (AHA), and the chronic (CHA) histological inflammatory activity of all biopsy sets were evaluated.
*Results:* One hundred and thirteen patients were included. Median time in clinical remission at inclusion was 27 months (IQR 15–56). Eight percent of patients relapsed within the first year and 33% during the whole follow-up period. In the univariate analysis, the presence of AHA, alone (P = 0.048) or together with a past flare within the previous 12 months (P = 0.01), was associated with CR within the first year of follow-up. In the multivariate analysis, AHA, together with a flare within the previous 12 months, remained the only risk factor for relapse (RR = 7.5; IC95%; 1.8–29.9; P = 0.005).
*Conclusions:* In UC patients in clinical and endoscopic remission, the presence of AHA is a risk factor for clinical relapse.


## 1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory colonic disorder characterized by persistent bloody diarrhea, rectal bleeding and cramping abdominal pain. The disease course alternates between periods of clinical remission and periods of clinical relapse (CR) [1].

For many decades, the treatment goal in UC has been clinical remission, defined as a complete resolution of symptoms [2]. Since the absence of clinical activity is not always well correlated with the absence of endoscopic activity [3–8], and patients achieving mucosal healing have better outcomes with a lower number of relapses, complications and surgeries [9–11], in recent years, medical treatment has also been focused on mucosal healing as an important endpoint, together with clinical remission [12].

However, it has been reported that up to 40% of patients persist with histological inflammatory activity despite achieving clinical and endoscopic remission [13,14]. Histological inflammatory activity has been associated with a higher risk of CR, colectomy and dysplasia [16–18]. Nonetheless, the parameters used for assessing histological activity vary between studies [7,8,19]. Although several histological scores have been proposed, most have not been validated and a clear definition of histological remission has yet to be established. Almost 20 histologic scores have been developed after Truelove and Richards published the first scoring system for UC histological activity in 1956 [20]. Among them, Riley's [15] and Geboes' scores [21] are probably the most widely used. Geboes' score is one of the most detailed, though its complexity (6 different grades each divided into 4 subcategories) could limit its use in clinical practice. Moreover, this score does not include basal plasmacytosis, a fea-

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ture that has been independently related to a higher risk of CR in patients in clinical and endoscopic remission [8]. In this line, a new score developed by the same group was published recently. The so-called simplified Geboes' score simplifies the original and includes basal plasmacytosis as a histological variable [22]. Despite the differences between all of these histological scores, there are two main histological features that have demonstrated some degree of prognostic value: the presence of intraepithelial neutrophils and basal plasmacytosis [6–8].

Fecal calprotectin is the only biomarker that has shown good accuracy in predicting CR, probably because of its good correlation with both endoscopic activity and with histologic inflammation in patients in clinical and endoscopic remission [5,23].

In addition to histological activity, a very small number of epidemiological and clinical factors, such as the rate of previous flares or seasonal factors, have been associated with a higher risk of CR [6,24]. Nonetheless, none of these factors are used in clinical practice in order to escalate therapy and prevent further relapses, mainly due to a scarcity of evidence.

Our aim was to assess the role of histological activity and other epidemiological and clinical variables as possible risk factors for CR in UC patients in clinical and endoscopic remission.

## 2. Methods

This was a retrospective observational study performed at a tertiary referral center (Hospital Universitari Germans Trias i Pujol, Badalona, Catalonia, Spain).

### 2.1. Patient population

We included in our study adult patients (≥18 years old) with UC in clinical remission undergoing dysplasia surveillance colonoscopy between January 2005 and October 2015. Patients were identified from local data in the *ENEIDA* database (*Estudio Nacional en Enfermedad Inflamatoria Intestinal sobre Determinantes genéticos y Ambientales*, a nationwide database managed by the Spanish Working Group in IBD — GETECCU). Exclusion criteria were clinical activity and/or the need for steroids in the three months previous to inclusion, clinical remission for more than 10 years, a Mayo endoscopic subscore (MES) ≥2 in any segment of the colon, UC limited to the rectum, previous colonic surgical resections, or the unavailability of biopsies. *Clinical remission* was defined as a partial Mayo score of 0-1 without rectal bleeding and no requirement of steroid therapy in the previous three months. *Endoscopic remission* was defined as a completely normal colonic mucosa and/or decreased vascular pattern, erythema and/or mild friability (MES ≤1). *Clinical relapse* (CR) was defined as the presence of symptoms, together with the need for treatment optimization.

Patients were followed from the baseline colonoscopy until CR, loss to follow-up, or the end of the study period (October 2015). Only patients with a potential follow-up of 12 months were included. Demographic data, phenotypic disease characteristics, disease duration, time in clinical remission, biological activity (defined by C-reactive protein levels above the upper normal limit), and treatment at the time of colonoscopy were recorded.

### 2.2. Histological assessment

Random endoscopic biopsies were taken from different colonic segments for dysplasia surveillance in line with the recommendations existing at that time. Biopsies were fixed in formaldehyde, and processed. Sections were stained with haematoxilin and eosin. At the study inclusion, two different pathologists reviewed the sections and performed an accurated histological assessment. The most severely inflamed area, (even if it was present only in one biopsy) was considered for the analysis.

In agreement with our pathologists, histological activity was classified as normal or quiescent histological activity (NQHA) if only architectural alterations but not cellularity changes were observed (irregular surface and crypt abnormalities); as chronic histological activity (CHA) in the case of architectural alterations and increased mononuclear infiltrate in *lamina propria*, and as acute histological activity (AHA) the unequivocal damage of the epithelium with the presence of neutrophils. In addition, basal plasmacytosis (defined as the presence of basal plasma cells at the base of the crypts or in the *lamina propria*) was also evaluated.

### 2.3. Ethical considerations

The Ethics Committee of our centre approved the ENEIDA Registry on December the 22th 2006, (reference EO-06-031). All patients provided informed written consent for their participation. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.

### 2.4. Statistical analysis

The statistical descriptive analysis was performed using the SPSS version 20.0 statistical package (SPSS, Inc, Chicago, IL). For the descriptive analysis, results are expressed in frequencies, or median (interquartile range, IQR). Kolmogorov–Smirnov (K–S) was assessed for quantitative variables for normality assumption. Kaplan–Meier survival curves were also performed to assess the probability of CR. Univariate analysis was carried out with a log rank test. Multivariate analysis was performed using the Cox regression model, including the variables with a $P \leq 0.1$ in the univariate analysis and also the most relevant variables previously described in the literature as independent predictors of CR. Statistical significance was accepted for P values of less than 0.05.

## 3. Results

A total of 113 UC patients were included in the study. Patients' characteristics are summarized in Table 1. As expected, patients presented a long disease duration (median, 18 years — IQR, 14–23.5) and a median time in clinical remission (without steroid requirement) of 27 months (IQR, 15–56). Of note, 76% of patients had required steroids at any time within disease course prior to inclusion, 47% were on immunosuppressants at the time of inclusion and 88% had C-reactive protein levels within the normal range. Only 16 patients presented a MES of 1 (44% segmental, 25% distal, and 31% extensive affection), whereas the remaining 86% of

**Table 1**
Patient characteristics at inclusion.

| | |
|---|---|
| Female, n (%) | 39 (34) |
| Age (years), median (IQR) | 54 (43–65) |
| Disease duration (years), median (IQR) | 18 (14–23.5) |
| Time in clinical remission (months), median (IQR) | 27 (15–56) |
| Disease flare within previous 12 months, n (%) | 26 (23) |
| Left-sided/extensive disease, n (%) | 35/78 (31/69) |
| Active smoking, n (%) | 22 (19) |
| Primary Sclerosing Cholangitis, n (%) | 0 (0) |
| Extra-intestinal manifestation ever, n (%) | 13 (11) |
| C-reactive protein <5 mg/dL, n (%) | 98 (88) |
| Treatment, n (%) | |
| Oral or topical mesalazine | 87 (77)/4 (3) |
| Immunosuppressants | 47 (41) |
| Anti-TNF | 3 (2) |

Anti-TNF: anti-tumor necrosis factor.

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