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Histological Activity as A Predictor of Clinical Outcome in Ulcerative Colitis: A 1-Year Real-World Prospective Study

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1. Abstract

1.1. Background and Aims: The role of histological scores in Ulcerative Colitis (UC) is debated. The primary endpoint was to assess, in a cohort of UC patients undergoing colonoscopy, the role of histological activity as a predictor of clinical activity at 1 year. Secondary endpoint was to assess the possible correlations between the degree of clinical, endoscopic and histological UC activity as assessed by dedicated scores.

1.2. Methods: In a prospective, real-world study, UC patients were enrolled and followed-up for 1 year. Clinical, endoscopic and histological activity scores were blindly assessed by 3 investigators by using the Mayo partial score (activity≥3), Mayo endoscopic score (activity≥2) and the Geboes Simplified Score (activity≥3.1). Statistical analysis: data expressed as mean [range], Spearman's correlation coefficients, Cox proportional hazards regression model (OR [95%CI]).

1.3. Results: Seventy-seven UC patients with clinical, endoscopic and histological assessment were clinically followed-up for 1-year. At baseline, UC was clinically active in 15 (19.4%), inactive in 62 (80.6%)patients. Endoscopic activity was observed in 39 (50.6%) and histological activity in 37 (48%) patients. At baseline, significant correlations were observed between clinical and endoscopic (r=0.43; p<0.0001), clinical and histological (r=0.32; p=0.004), endoscopic and histological scores (r=0.65; p<0.0001). Univariate analysis identified clinical activity (HR 4.82 [2.15-10.82]; p<0.001) and histological activity (HR 2.59 [1.11-6.08]; p=0.02) as predictive factors for clinical activity within 1-year. Multivariate model confirmed histological activity as a predictive marker of clinical activity (HR 2.44 [1.04-5.75]; p<0.04).

1.4. Conclusions: In a real world-study, histological activity was identified as a risk factor for clinical activity within one-year, suggesting the usefulness of this parameter for proper assessment of UC.

2. Background and Aims

Ulcerative Colitis (UC) is a chronic Inflammatory Bowel Disease of unknown etiology [1]. An inappropriate mucosal immune response towards luminal antigens appears involved in the pathogenesis of the disease [2]. Highly effective immunomodulatory treatments able to induce not only clinical, but also endoscopic remission have been developed [3-5]. Mucosal Healing (MH) is associated with a long-term clinical remission, thus representing a therapeutic target in UC [3-5]. Endoscopic scores have been developed in order to quantitate the severity of UC lesions [6]. Complete resolution of the inflammatory process, at both macroscopic and microscopic level, should be searched [7]. Endoscopic healing may indeed not necessarily imply a complete resolution

of microscopic inflammation [8], as histological activity may be observed in clinically and endoscopic ally quiescent UC [9]. Thus, histological healing in UC may represent an additional endpoint in clinical trials and in daily clinical practice. While the relevance of endoscopic healing in UC has been extensively investigated [3], data regarding histologic healing are limited.

The correlation between clinical, endoscopic and histological degree of activity in UC has not been fully established, although recent studies [10] suggest that histological healing is associated with a better clinical outcome than endoscopic healing only.

The primary endpoint of the present prospective single-center, real-world study, was to determine, in a cohort of UC patients undergoing colonoscopy, the role of histological activity as a predictor of clinical activity at 1 year. Secondary endpoint was to assess the possible correlations between the degree of clinical, endoscopic and histological UC activity as assessed by dedicated scores.

3. Methods

3.1. Study Population

In a single-center prospective study, consecutive patients with an established diagnosis of UC fulfilling inclusion criteria were enrolled from February 2016 to February 2017. During the study period, all patients underwent colonoscopy or proctosigmoidoscopy according to conventional clinical criteria [11]. Inclusion criteria included: a) well defined diagnosis of UC [11]; b) age>18 and ≤80 years; c) any UC extent; d) regular follow up (≥2 visit/year) at our tertiary IBD referral center; e) clinical indication for colonoscopy [11]; f) compliance to complete the 1-year follow up. Exclusion criteria: a) missing/incomplete data in clinical records; b) severe comorbidities; c) proctocolectomy; d) severe clotting defects. Patients were recruited regardless of clinical activity and received standard care, with regular assessments (maximum interval: 6 months).

3.2. Study Design

Demographic and clinical characteristics were prospectively reported in a database including: birth date, gender, UC duration, UC extent, current/previous treatments (current treatments: therapies ≤6 months), comorbidities, clinical, endoscopic and histological activity scores. Conventional Immunosuppressive (IS) included thiopurines and methotrexate. UC extent was assessed according to the Montreal Criteria [12]. Clinical, endoscopic and histological degree of activity were assessed the day of colonoscopy.

3.3. Baseline Assessments

3.3.1 Clinical Activity

Clinical activity was assessed by one single IBD-dedicated gastroenterologist using the partial Mayo score (Grades 0-9: clinical activity≥3) [13], at both enrollment the day of colonoscopy and at each visit performed within the 1-year follow up.

3.3.2. Endoscopic Activity

Endoscopic assessment was performed according to standard criteria [11] by one single IBD- dedicated gastroenterologist, unaware of clinical activity. The following parameters were reported: complete/incomplete colonoscopy (reason for incomplete endoscopy), oedema, hyperemia, erosions, ulcers, polyps, additional findings. Bowel preparation was assessed by the Boston Index [14].

The endoscopic degree of activity was assessed using the Mayo endoscopic score [13]: 0= normal endoscopic features; 1= erythema, decreased vascular pattern, mild friability; 2= marked erythema or friability, absent vascular pattern, erosions; 3= spontaneous bleeding, ulcerations. A Mayo endoscopic score ≥2 defined endoscopic activity [13].

3.3.3. Histological Activity

In each patient, rectal biopsies (≥2) were taken, regardless of the endoscopic and clinical activity. In long-standing UC, quadrantic biopsies (n=4) were taken every 10 cm to search for dysplasia. Biopsies were oriented, fixed in formalin (10%), stained with Hematoxylin-Eosin and assessed by one single IBD-dedicated histopathologist. Routine histology included findings compatible with UC [11].

Histological activity was graded according to the Geboes Simplified Score (GSS) for UC [15]. The area more severely involved was considered. Histologically active inflammation was defined by a Geboes score ≥3.1 [15]. The pathologist was aware of the diagnosis of UC and of the endoscopic findings, but he was blinded in terms of clinical and endoscopic activity scores.

3.4. Clinical Follow Up

Clinical, endoscopic and histological assessments were performed at entrance, followed by clinical assessment at 1 year, by using the Mayo clinical sub score [13]. During the 1-year follow up, additional criteria for assessing clinical activity of UC included the need of corticosteroids, IS, biologics, hospitalization and/or disease-related surgery.

3.5. Statistical Analysis

The Wilcoxon test was used to compare characteristics across patients for continuous factors and the Chi-square or Fisher's exact test, if a cell count was <5 in a 2x2 Table, was used for categorical variables. Spearman's correlation coefficients were used to investigate the association between different activity scores. Relapse-Free Survival (RFS) was defined as the time from the date of colonoscopy to the date of clinical relapse. Patients who did not experience this event were censored at time of their last visit (1-year follow-up). Kaplan-Meier curves were used to estimate the probability of RFS. The log-rank test was used to complete the comparisons. The Cox regression model was used for both univariate and multivariate analysis to examine the independent effect of factors on RFS. For the analysis of prognostic factors, the pro-

portionality assumption was checked for each of the considered variables (age, gender, smoking habits, mean clinical, endoscopic and histological scores), by testing the dependency of their hazard ratio (HR) over time. When using a stepwise variable selection procedure to identify independent factors prognostic for RFS, variables were added using forward selection according to a selection entry criterion of 0.05 and removed using backward elimination according to a selection stay criterion of 0.05. The relevance of a prognostic factor was assessed via Wald-type test statistics, the HR and its 95% confidence interval [CI] for survival. All reported P-values were 2-sided. All data analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC, USA).

3.6. Ethical Considerations

The study was approved by the Ethic Committee of the University Hospital Policlinico "Tor Vergata" of Rome, Italy (protocol n.5697/2017). All authors approved the final version of the manuscript and approved the decision to submit the manuscript for publication.

4. Results

4.1. Study Population

During the study period, 77 UC patients completed the clinical follow up at 1-year and were therefore considered for the analysis. Demographic and clinical characteristics of the study population are summarized in Table I. According to the study protocol, additional 14 UC patients undergoing colonoscopy during the study period, but not fulfilling the inclusion criteria were excluded from the analysis.

At enrollment, treatment in the 77 UC patients included: mesalazine (2.4 gr/day) in 42 (54.5%), sulphasalazine (3 gr/day) in 29 (37.7%), systemic corticosteroids in 4 (5.2%), low absorbable steroids in 2 (2.6%) and/or enema using corticosteroids or mesalazine in 32 (41.5%) patients. A present/past history of IS was observed in 26 (33.8%) patients, including thiopurines in all 26 and methotrexate in 2 (IS duration: 52.8 [1-156] months). At enrollment, 10 (13%) patients were using thiopurines and 12 (15.6%) patients TNFα antagonists (Infliximab: n=8; adalimumab: n=1). Both thiopurines and TNFα antagonists were ongoing in 3 patients.

4.2. Clinical Activity at Baseline

At enrollment, 62/77 (80.5%) patients were in clinical remission (Mayo score: 0 n=47 [62.3%]; 1 n=7 [9.1%]; 2 n=7 [9.1%]). Differently, the remaining 15 [19.5%] patients were clinically active (Mayo score: 3 n=5 [6.5%]; 4 n=4 [5.2%]; 5 n=2 [2.6%]; 6: n=4 [5.2%]).

4.3. Colonoscopy

Indication for colonoscopy included: surveillance (n=44 [57.1%]), treatment optimization (n=18 [23.4%]), assessment before/after biologics/IS (n=15 [19.5%]). Colonoscopy was complete in 65 out of the 68 (95.5%) patients with no history of intestinal resections.

Table I: Demographic and clinical characteristics of the 77 Ulcerative Colitis patients clinically followed-up for 1 year. Clinical, endoscopic and histologic assessment performed at enrollment.

Characteristics	**Total UC patients (N=77) N (%)**
Gender	
Males	43 (55.8%)
Females	34 (44.2%)
UC extent	
Proctitis	20 (26.0%)
Left-sided colitis	24 (31.2%)
Pancolitis	33 (42.8%)
Extraintestinal manifestations	11 (14.3%)
Appendectomy	4 (5.2%)
UC-related surgery	5 (6.5%)
Conventional immunomodulators	26 (33.8%)
TNFα antagonists	12 (15.6%)
Smoking habits	
Smoker	5 (6.5%)
No smoker	46 (59.7%)
Ex-smoker	26 (33.8%)
Age, mean [range]	51.7 [24-80]
UC duration, mean [range]	14.7 [1-48]

Abbreviations: UC= Ulcerative Colitis; TNFα= Tumor necrosis Factor-α.

The coecum was not visualized in 3 (4.5%) of these 68 patients due to inadequate preparation (n=1) or diverticular stricture (n=2). In the remaining 9 out of the 77 (11.6%) patients, proctosigmoidocopy rather than colonoscopy was performed (ileo-rectal anastomosis: n=3; indication for local treatment: n=3; severe UC: n=3). No adverse events occurred during/after colonoscopy.

The overall quality of bowel cleansing was adequate in most of patients according to the Boston score [14]. Additional findings included: pseudopolyps in 14 (18.1%), adenomatous micropolyps (<1cm) in 2 (2.6%) (both tubular adenomatous polyps, low grade dysplasia), angiodysplastic lesion in 1 (1.3%), diverticulosis in 2 (2.6%) patients. No dysplasia within flat mucosa was detected.

4.4. Endoscopic Activity at Baseline

Endoscopic remission (Mayo score<2) was observed in 38 out of the 77 (49.3%) patients. The endoscopic score in these 38 patients in remission was: grade 0 in 14 (18.2%), grade 1 in 24 (31.1%) patients. Differently, endoscopic activity (Mayo ≥ 2) was detected in the remaining 39 out of the 77 (50.7%) patients: grade 2 in 16 (20.8%) and grade 3 in 23 (29.9%) patients. Figure 1 (panels a-d) shows different grades of endoscopic activity observed in 4 enrolled patients (Mayo score 0-3, respectively).

4.5. Histological Activity at Baseline

Among the 77 patients completing the 1-year follow-up, colonic biopsies at baseline showed histological remission (GSS<3.1) in

41 (53.2%) patients (G0: n=18 [23.4%]; G0.1: n=1 [1.3%]; G0.2: n=2 [2.6%]; G1.1: n=2 [2.6%]; G2A1: n=17 [22.1%]; G2A2: n=1 [1.3%]). Histological activity (GSS ≥3.1) was detected in colonic biopsies taken from the remaining 36 (48.1%) patients (G3.1: n=29 [37.7%]; G4.2: n=1 [1.3%]; G4.3: n=4 [5.2%]; G4.4: n=2 [2.6%]). Among the 36 patients with histologically active UC, endoscopic activity was observed in 31 (86.1%), while microscopically active inflammation was detected in colonic biopsies from the remaining 5 patients showing endoscopic remission. Conversely, in 8 (10.4%) patients showing endoscopic activity, histological remission was observed. Figure 2 shows microscopically active (panel a) or inactive (panel b) inflammation in colonic biopsies taken from 2 UC patients.

Figure 1a

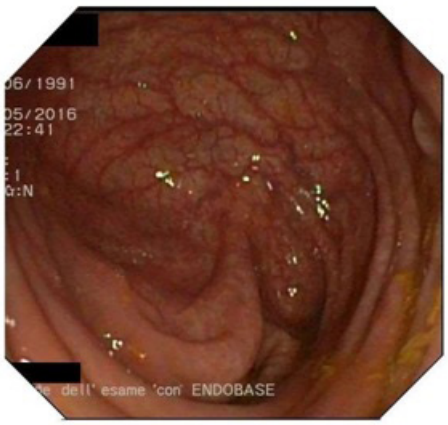

Figure 1b

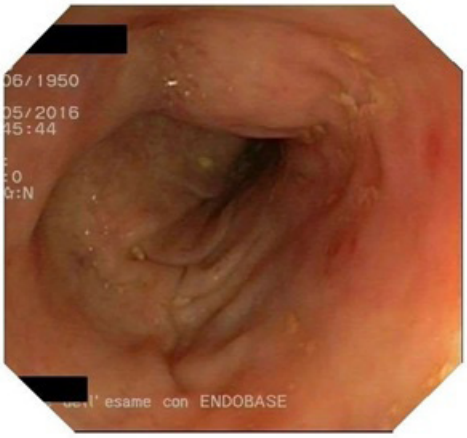

Figure 1c

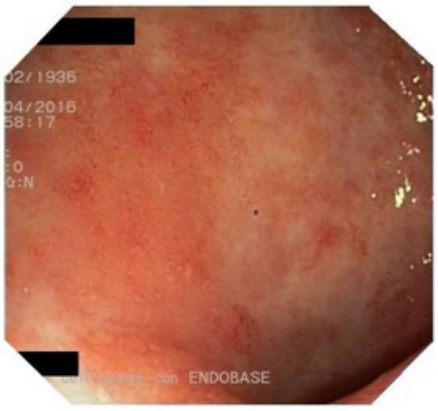

Figure 1d

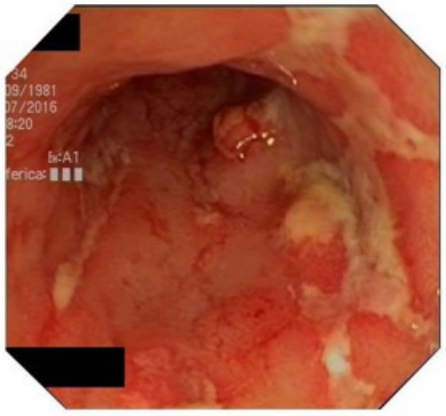

Figure 1: (panels a-d)
Endoscopic findings in 4 UC patients showing different grades of activity as assessed by the Mayo endoscopic score: grade 0 (panel a); grade 1 (panel b); grade 2 (panel c); grade 3 (panel d).

Figure 2a

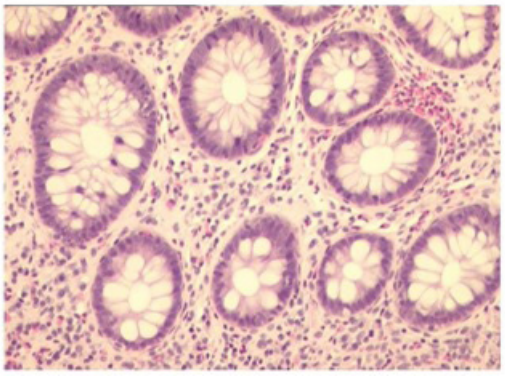

Figure 2b

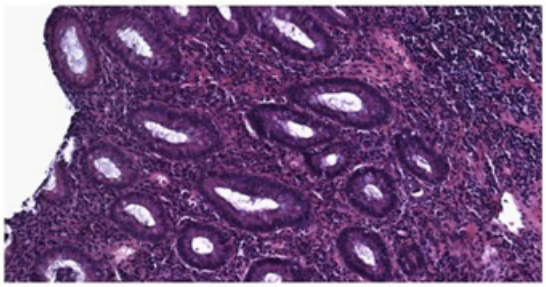

Figure 2: (panels a,b)
Histological findings in 2 UC patients assessed by the Geboes Simplified Score: histological remission (Geboes simplified score <3.1) (panel a); histological activity (Geboes simplified score ≥3.1) (panel b).

4.6. Clinical Activity During The 1-Year Follow Up

When considering the 1-year follow-up, clinically active UC after enrollment was observed in 24 out of the 77 (31%) patients. Among these 24 patients, clinical relapse required hospitalization in 5 (20.8%), systemic corticosteroids in 6 (25%), biologics in 1 (4.2%) and topical treatment in 12 (50%). No patients required surgery. At baseline, among these 24 UC patients, endoscopic activity was observed in 15 (63%) and histological activity in 16 (67%). Among the 5 patients showing endoscopic remission but concomitant histological activity at baseline, 1 patient developed clinical relapse within 12-months.

4.7. Correlation Between Clinical, Endoscopic and Histological Activity Scores

Significant correlations were observed at baseline between clinical and endoscopic scores (r=0.43; p<0.0001), clinical and histological scores (r=0.32; p=0.004), endoscopic and histological scores (r=0.65; p<0.0001). These correlations, expressed as box-plot analysis, are reported in Figure 3 (panels a-c).

Figure 3a

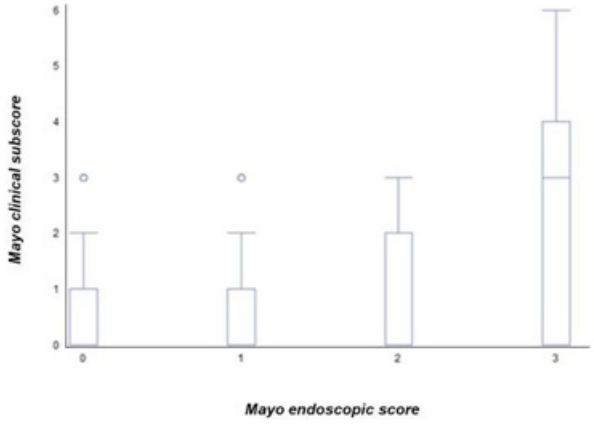

Figure 3b

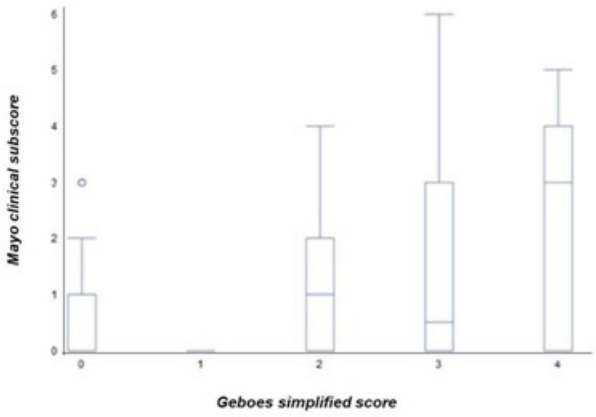

Figure 3c

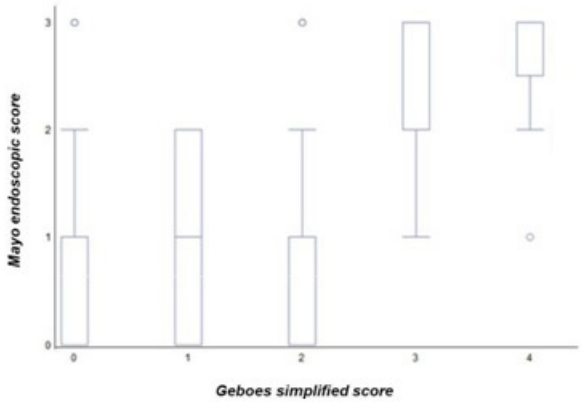

Figure 3: (panels a-c)
Box-plot analysis in the 77 UC patients with clinical, endoscopic and histological assessment at enrollment, with subsequent clinical follow up for 1 year. Panel a: Clinical partial Mayo score vs Mayo endoscopic score; panel b: Clinical partial Mayo score vs simplified histological Geboes score; panel c: Mayo Endoscopic score vs Simplified histological Geboes score.

4.8. Risk Factors for Clinical Activity During The 1 Year Follow Up

In univariate analysis, variables considered as risk factors for clinical relapse included: age, gender, smoking, clinical activity [13], endoscopic and histologic activity [13, 15]. Univariate analysis identified clinical activity (HR 4.82 [2.15-10.82]; p<0.001) and histological activity (HR 2.59 [1.11- 6.08]; p=0.02) as predictive factors for clinical relapse ≤1 year. Conversely, the endoscopic degree of activity was not identified as a predictive factor for UC relapse (HR 1.76 [0.77-4.03]; p=0.17). Gender, age and active smoking also did not represent risk factors for clinical relapse (HR 0.73 [0.33- 1.64]; p=0.45; HR 0.97 [0.94-1.00]; p=0.1 and HR 1.46 [0.65-3.26]; p=0.35, respectively).

According to these preliminary findings, a multivariate analysis was performed. In the tested population, the multivariate model identified clinical and histological activity as predictive markers of clinical relapse (HR: 4.77 [2.12-10.74]; p=0.0002 and HR: 2.44; [1.04-5.75]; p=0.04, Respectively) (Table II).

Table II: Predictive factors for clinical relapse at 12 months in the 77 Ulcerative Colitis patients prospectively followed up for one year: variables considered

PARAMETER	RELAPSE WITHIN 1 YEAR		*p*
	No, *n* (%)	Yes, *n*(%)	
Gender			
Females	22 (41.5%)	12 (50%)	0.48
Males	31 (58.5%)	12 (50%)	
Smoking habits			
Smoker	34 (64.2%)	12 (50%)	0.24
No Smoker	19 (35.8%)	12 (50%)	
Clinical activity			
Remission(Mayo partial subscore <3)	49 (92.5%)	13 (54.2%)	<0.0001
Active (Mayo partial subscore ≥3)	4 (07.5%)	11 (45.8%)	
Endoscopic activity			
Remission (Mayo partial subscore <2)	29 (54.7%)	9 (37.5%)	0.16
Active (Mayo partial subscore ≥2)	24 (45.3%)	15 (62.5%)	
Histological activity			
Remission(Geboes simplified score <3.1)	33 (62.3%)	8 (33.3%)	0.01
Active (Geboes simplified score ≥3.1)	20 (37.7%)	16 (66.7%)	

On the basis of these analysis, we estimated that, in the tested population, patients with histologically active inflammation (GSS≥3.1) [15] at baseline had a 2. 44-fold higher risk of clinical relapse ≤1 year than patients showing histological remission (GSS<3.1) at enrollment.

4.9. Clinical and Histological Degree of Activity as Predictors of Clinical Relapse

The role of clinical and, separately, histological activity as predictors of clinical relapse ≤12 months was also supported by Kaplan-Meier analyses. As shown in Figure 4 (panel a) indeed, Kaplan- Meier curves showed that survival from clinically active disease during the 12-months study was significantly lower in patients clinically active vs inactive at baseline (Mayo Partial Score:<3 vs ≥3, respectively; p=0.001).

Conversely, Kaplan-Meier curves showed that survival from clinical relapse during the 12- months study was not lower in patients showing endoscopically active vs inactive disease at baseline (p=0.16) (Figure 4; panel b).

As for clinical activity (Figure 4, panel a), Kaplan-Meier curves showed that survival from clinically active UC during the 12-months study was significantly lower in patients showing histologically active vs inactive disease at baseline, according to the GSS (p=0.02) (Figure 4, panel c).

Figure 4a

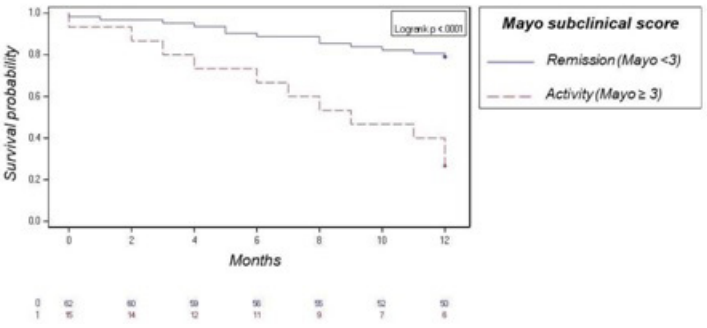

Figure 4b

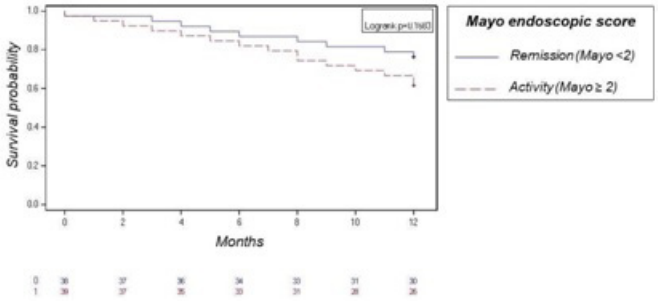

Figure 4c

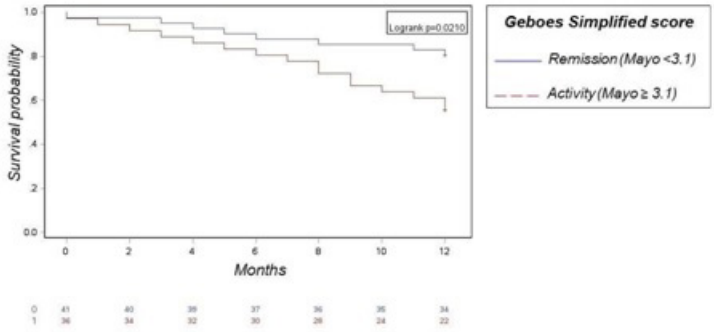

Figure 4: (panels a-c)
Kaplan-Meier curves of survival from clinically active UC within the 12-months study period, as assessed by the Mayo Partial Score (remission vs activity), according to clinical (panel a), endoscopic (panel b) or histological activity (panel c) at baseline.

5. Discussion

Mucosal healing as assessed by colonoscopy currently represents one of the main targets of UC treatment [7]. Clinical, endoscopic and histological scores of activity have been developed and are currently used in clinical trials and in daily clinical practice [16-18]. Differently from endoscopic activity, the clinical usefulness of histological activity as a therapeutic target in UC is under investigation [19].

These observations prompted us to evaluate the role of clinical, endoscopic and histological activity as assessed by quantitative scores, as predictive markers of clinical relapse in a homogeneous cohort of UC patients clinically followed up for 1-year.

Findings from our prospective single-center study support that in the tested UC population, histologically active inflammation at baseline represented a predictive marker of clinical activity within the subsequent year. The same finding was not reported when assessing the predictive value of endoscopic activity at baseline, although the observed HR was at the limit of the statistical significance. These observations suggest that the achievement of histologic remission may represent a new and more reliable therapeutic target in UC. According to present findings, histological degree of inflammation provided additional information useful for UC assessment, not necessarily concordant with the endoscopic degree of activity. This concept is also supported by a prospective study [10] reporting a different role for endoscopic and histological remission as predictors of UC course. Over a 6-years follow-up, histological remission was identified as a better predictor of lower need of corticosteroids and UC-related hospitalizations when using different clinical activity scores [20-22]. Accordingly, a retrospective study [23] reported that basal plasmacytosis may predict UC relapse in patients with complete MH. Differently from our findings, active histological inflammation was not identified as an independent predictive factor of clinical relapse [23]. However, given the high association between active inflammation and basal plasmacytosis, when pooling these 2 variables, these histological markers were highly predictive of UC clinical relapse (OR 6.63; p=0.002) [23].

The histological degree of inflammation may be useful for optimizing UC treatments inducing stable remission. Combining clinical, endoscopic and histological remission ("deep remission") may represent a stronger predictor of UC remission [3, 25].

The histological score used was the GSS [15], which is partially validated. The previous Geboes Score [24] indeed defines the degree of activity on the basis of the most severe sub score among all the specimens, regardless of the biopsy site. The GSS was chosen as it is one of the most widely used score in clinical trials [26, 27] and it also allows to grade finely the degree of inflammation. Moreover, this score showed a moderate inter observer agreement, thus suggesting its reproducibility and reliability [15]. In our study, even though moderate correlation was detected between endoscopic and histological scores, some discrepancies were observed. Although in few cases (n=8; 10.4%), histological remission was detected in endoscopically active patients, as already described [9]. The quite long UC duration in our population, and immunomodulatory treatments able to modify the distribution of microscopic inflammation may be involved in this finding.

The observed rate of UC clinical relapse within 12 months was expected [9, 23], although within the lower range. This finding was not related to UC extent, as almost two-thirds of patients showed extensive (42.2%) or left-sided (31.8%) colitis. Differently, characteristics of our population, including only outpatients in follow up, with regular clinical and endoscopic assessments may account for the relatively low frequency of clinical relapse.

Although the monocentric study design limits the strength of the results, several observations support the reliability of our findings. The study included a quite large and homogeneous cohort of UC patients followed-up for 1 year. Moreover, clinical characteristics of the tested population were comparable to those observed in the general UC population (i.e. percentage of smokers, history of appendectomy, EIM) [11], thus supporting the lack of a selection bias. Among limitations of the study, proctosigmoidoscopy rather than colonoscopy was performed in few patients (n=9), according to inclusion criteria. However, this observation should not affect our findings as most of these few patients showed endoscopic and histological activity. This is also supported by the site of biopsy sampling, always including the rectum, according to current guidelines [11]. This protocol should allow a comparable grading of microscopic inflammation among the 77 patients, including those assessed by proctosigmoidoscopy or showing MH. In more than half of patients, biopsies were taken not only from the rectum,

but also from additional colonic segments. In these patients, the most severe degree of histological activity was considered for the analysis of the data, according to the GSS [15]. Present observations also allow a proper assessment of the sample size required to investigate in a larger study the usefulness of histology as a subclinical marker of clinical outcome in patients with UC.

Additional strength of the study is the prospective design including a quite large population of patients with clinical endoscopic and histological activity blindly scored by independent IBD- dedicated investigators. The reported observations in a cohort of UC patients with clinical indication to perform colonoscopy also support the feasibility of assessing the microscopic degree of activity in clinical practice. This achievement requires both a disease-specific histological activity score and an IBD-dedicated histopathologist willing to apply it.

6. Conclusions

The reported observations in a cohort of UC patients with clinical indication to perform colonoscopy also support the feasibility of assessing the microscopic degree of activity in clinical practice. This achievement requires both a disease-specific histological activity score and an IBD- dedicated histopathologist willing to apply it. Moreover, our findings provide additional evidence supporting the role of activity scores able to quantitate the microscopic degree of inflammation in clinical management of UC.

The growing use of standardized histological activity scores in clinical practice is helping to understand whether the assessment of the severity of microscopic inflammation in UC may represent a new treatment target. In our real-world prospective study, histological activity was identified as a risk factor for clinical activity within one-year, suggesting the usefulness of this parameter for proper assessment of UC.

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