European Review for Medical and Pharmacological Sciences 2015; 19: 3674-3681

Application of clinical indexes in ulcerative colitis patients in regular follow-up visit: correlation with endoscopic 'mucosal healing' and implication for management. Preliminary results

C. PAGNINI[1], F. MENASCI[1], S. FESTA[1], G. RIZZATTI[1], V.D. CORLETO[2], M.M. DELLE FAVE[1], G. D'AMBRA[2], E. DI GIULIO[2], G. DELLE FAVE[1]

[1]Faculty of Medicine and Psychology, "Sapienza" University of Rome, S. Andrea Hospital, Rome, Italy
[2]Endoscopy Unit, S. Andrea Hospital, Rome, Italy

Abstract. – OBJECTIVE: Ulcerative Colitis (UC) is a chronic inflammatory disease of the colon of unknown etiology. Several clinical indexes have been proposed for UC disease activity evaluation, but none have been properly validated. Moreover, the reference parameter for the scores and their prognostic value is not clear. Mucosal healing has been recently proposed as an important end-point. Aim of the present study was to evaluate the correlation of four clinical indexes with objective diagnostic tools for UC evaluation, the discriminative ability in identifying patients with endoscopic mucosal healing, and to analyze the possible prognostic indication for disease course in 1 year of follow-up.

PATIENTS AND METHODS: We analyzed data of 75 patients recorded in regular follow-up visit in IBD clinic at S. Andrea Hospital, Rome, between 2007-2011. We recorded clinical data and lab tests at the time of the visit, and endoscopic/histological reports performed within 1 month. Clinical indexes (Seo' activity index, Simple Clinical Colitis Activity Index, partial Mayo score and Endoscopic-Clinical Correlation Index) were calculated and correlation to endoscopic and histologic activity, and to C-reactive protein increment, was assessed by mean of Spearman's rank correlation. Discriminative ability of the indexes for patients with and without endoscopic mucosal healing was tested by calculation of area under ROC curve (AUC). Patients with low and high clinical scores were compared for number of flares and increment of therapy during 1 year of follow-up.

RESULTS: Clinical indexes had a good correlation with endoscopic activity (mean r = 0.73 ± 0.06), a fair correlation with CRP-increment (mean r = 0.55 ± 0.01) and a poor one with histologic activity (mean r = 0.35 ± 0.01). The discriminatory ability of the indexes for endoscopic mucosal healing was good for all the indexes (mean AUC = 0.87 ± 0.05). Patients with high clinical score had more flares and required more frequently increase of therapy at 1 year of follow up compared with patients with low score.

CONCLUSIONS: Clinical indexes have a good correlation with endoscopic activity and can discriminate patients with and without mucosal healing. Patients with low and high score have different risk of disease flare and of need to increase therapy at 1 year. Clinical indexes may represent a useful tool for disease assessment in clinical practice in UC outpatients with mild-moderate disease.

Key Words:
Ulcerative colitis, Clinical index, Disease activity, Prognosis.

Introduction

Ulcerative Colitis (UC) is a chronic inflammatory bowel disease (IBD), involving the colon, of unknown etiology and immune pathogenesis, clinically characterized by the alternation of periods of remission and flares of the disease[1]. Despite constant progress in the basic and clinical research, UC still presents several challenges for the physician. One crucial issue in the clinical management of UC patients is the evaluation of the disease activity. In fact, UC may be characterized by different grade of bowel inflammation, in terms of severity and extension, that in turn may lead to alteration of macro- and microscopic pattern of colonic mucosa, as well as presence and severity of clinical symptoms (i.e. diarrhea, bloody stools, abdominal pain, fever). Since clinical symptoms, lab tests, endoscopic appearance and histological examination may be discordant, it is not yet clear which parameter should be the reference for the evaluation of the real activity of

Corresponding Author: Cristiano Pagnini, Ph.D; e-mail: cristiano.pagnini@uniroma1.it

the disease[2]. In recent years, the endoscopic 'mucosal healing', has been more and more indicated as an important end-point for the management of UC patients, for its association with a better short and long-term prognosis[3], although several aspects of that issue are far from being clarified[4]. Besides, endoscopy should represents the 'gold standard' for disease activity evaluation in UC, for it provides a direct evaluation of the colon, which is the target organ of the disease. Unfortunately, endoscopic examination is costly, not easily accepted by patients and not available in short time in many centers, so that routinely repetition of colonoscopy is not feasible nor appropriate.

In order to help physicians in clinical practice and to simplify and objectify the evaluation of UC activity in clinical trials, several clinical indexes have been developed[5]. The main limitation of all those indexes is the lack of an adequate validation in large and independent cohorts of patients. Moreover, the reference parameter whom the numeric score is referred to is often not completely clear, so that the prognostic utility of such indexes remains to be clarified. Nonetheless, a clinical score strongly correlated to endoscopy and predictable of the disease course would be useful for several purposes. First, it would provide an easy useful tool for patients and physicians to evaluate and monitor UC activity even in not referral centers. This would be of particular relevance especially for the management of mild-moderate UC outpatients, in which the clinical score would help in discriminating patients who need further investigation (i.e. colonoscopy), shorter follow-up visits, and/or intensification of the current treatment, and patients in which regular follow-up is sufficient, in order to optimize resources with evident economic and clinical benefits. Second, it would provide an objective and reproducible tool to evaluate patients in clinical trials, both for baseline evaluation and for the response to therapy.

Aim of our study was to evaluate, in a cohort of UC patients in our hospital, the correlation of four clinical indexes (Seo's clinical index, Walmsley's Simple Clinical Colitis Activity Index – SCCAI, Endoscopic Clinical Correlation Index – ECCI, and partial Mayo score), with objective parameters of evaluation of disease activity (endoscopic examination, histology and C-reactive protein – CRP), with particular regard to the accuracy in identifying patients with endoscopic mucosal healing. Moreover, we intended to explore the possible prognostic indications of the clinical scores evaluating the disease course of the patients (disease flare and therapeutic increment) at 1 year of follow-up.

Patients and Methods

Patients

Clinical charts of patients of the IBD Outpatients Clinic (Digestive and Liver Disease Unit) at S. Andrea Hospital in Rome, Italy, are collected in an electronic database. We analyzed patients with an established diagnosis of UC (obtained by clinical, endoscopic and histologic compatible with UC) who performed a regular follow-up visit from 2007 and 2011. Inclusion criteria were: patients who performed a regular scheduled visit and who had clinical examination, laboratory tests and a complete colonoscopy performed within an interval of time no longer than 1 month, who had a complete record of the clinical and laboratoristic parameters necessary for the calculation of the clinical scores, and who have a documented 1-year follow-up from the time of the visit. In particular, the clinical features necessary for the calculation of the scores were the following: general condition evaluation, number of bowel movements per day, number of nocturnal bowel movement, number of evacuation with blood and quantity of the blood in stools, presence of urgency, extra-intestinal disease manifestations and fever. The lab tests required were the following complete blood count, erythrocytes sedimentation rate (ESR), serum albumin level and C-reactive protein (CRP). Exclusion criteria were: patients with an uncertain diagnosis of UC, patients at their first visit or with a severe flare of disease, patients who did not have a documented report of any of the parameters necessary for the calculation of the clinical scores (i.e. clinical examination and lab tests), or with an incomplete endoscopic examination and patients without 1-year of documented follow-up. Finally, 75 patients fulfilled the inclusion criteria for the study. In all but 8 patients (11%), clinical examination and lab tests were done before colonoscopy.

Clinical Indexes Evaluation

We utilized four clinical index (i.e. SEO activity index, Walmsley's SCCAI, partial Mayo score, and ECCI) among the most commonly used in the literature for UC patients, and we calculated them according to the original articles[6-9].

For every index it was calculated the correlation with the endoscopic activity, the histologic activity and the increment of CRP. The endoscopic activity was evaluated by a modified Baron score, composed by the sum of the single score of the five colonic segments (rectum, sigma, descending, transverse and ascending colon/caecum)[10,11]. The histologic activity was evaluated by Sandborn's score, with the total score resulting from the sum of every single colonic segment[12]. Baron and Sandborn's scores, calculated from the endoscopic and histological reports, and clinical indexes were independently calculated by different operators in a blind fashion. The CRP was expressed by a relative ratio to the highest normal value. Thus, the diagnostic capacity of every single clinical score in discriminating patients with endoscopic mucosal healing (defined by a Baron endoscopic score ≤ 1) was evaluated. Finally, the capacity of the indexes in predicting the necessity of an increase of therapy and the occurrence of flare, in a period of 1 year of follow up from the initial evaluation, was evaluated. The increment of therapy was defined by increment of dose of current therapies and/or addition of new drugs. The flare was generally defined by the onset or exacerbation of symptoms (i.e. abdominal pain, increased bowel movements, blood in stools, urgency) that required the prompt access to a medical consultation (general practitioner, specialist or emergency room).

Statistical Analysis

The correlation between clinical indexes and endoscopic score, histologic score and CRP increment was evaluated by Spearman's rank correlation. Discriminative ability of every single index for mucosal healing was calculated by quantification of the area under receiver operator characteristic (ROC) curve and compared to other indexes' ROC curve. Sensitivity and specificity of every clinical index in detecting endoscopic mucosal healing were calculated. Finally, we identified two groups of patients (low and high score), according to the cut-off value already described in literature for every clinical index. The number of patients, in the two groups, who needed an increase of therapy and who experienced a flare of disease was recorded and compared by chi-squared test. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. A value of $p < 0.05$ was considered statistically significant. Med Calc statistical software version 12.5 was used for statistical calculation.

Results

The characteristics of the 75 patients finally included in the study are summarized in Table I.

All the clinical indexes tested displayed a good correlation with endoscopic activity (Mayo: r = 0.77, SCCAI: r = 0.75, ECCI: r = 0.77, SEO: r = 0.64; $p < 0.0001$) (Figure 1 A). Correlation of the indexes with the histologic score was poor (Mayo: r = 0.35, SCCAI: r = 0.33, ECCI: r = 0.36, SEO: r = 0.36; $p < 0.005$) (Figure 1 B). Considering the CRP increment, the correlation with the indexes was fair (Mayo: r = 0.54, SCCAI: r = 0.55, ECCI: r = 0.55, SEO: r = 0.57; $p < 0.0001$) (Figure 1 C).

We then calculated the ability of the indexes to discriminate patients with and without endoscopic mucosal healing (Baron endoscopic score ≤1). All the tested score displayed a very good discriminative ability with a comparable area under the ROC curve (AUC) (mean AUC = 0.87±0.05) (Figure 2). The AUC values, together with sensitivity and specificity of every single score, are reported in Table II.

According to the cut-off levels for "severe" disease of every single index already described in lit-

Table I. Characteristics of the 75 patients included in the study.

Characteristics	N (%)
Age (y)	49.7 ± 17.8*
Gender (M)	38 (51%)
Disease Localization:	
• Proctitis	8 (11%)
• Left colitis	21 (28%)
• Extensive colitis	46 (61%)
Disease activity (clinical indexes):	
• Mayo	3.7 ± 3*
• SCCAI	4.5 ± 3.3*
• ECCI	64.4 ± 55.5*
• SEO	160.9 ± 50.7*
Disease duration (years)	8.62 (1-32)**
Therapy:	
• Oral salicylates	38 (50.7%)
• Topical salicylates	6 (8%)
• Oral + topical salicylates	23 (30.7%)
• Corticosteroids	0 (0%)
• Tiopurines	1 (1.3%)
• Biologics	1 (1.3%)
• None	6 (8%)
Endoscopic mucosal healing	17 (23%)
Flare at 1 yr	27 (36%)
Increase of therapy at 1 yr	51 (68%)

* = mean ± SD, ** = years range

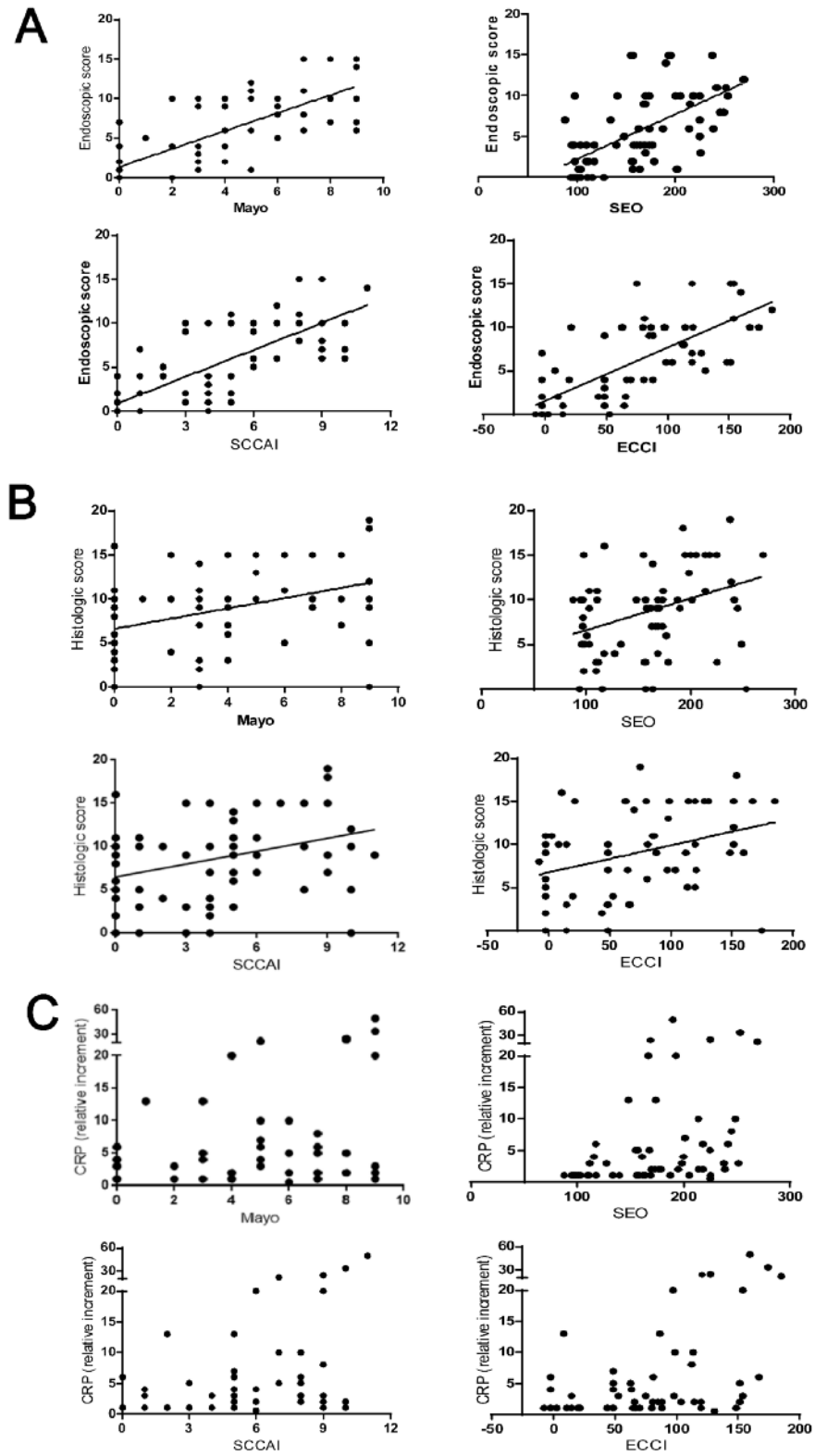

Figure 1. Correlation between clinical indexes and endoscopic score ***(A)***, histologic score ***(B)*** and CRP increment ***(C)***. Spearman's correlation of the indexes was very good with endoscopic score (mean r = 0.73 ± 0.06; $p < 0.0001$) ***(A)***, while it was not satisfactory with histologic score (mean r = 0.35 ± 0.01; $p < 0.005$) ***(B)***, and fairly good with the CRP increment (mean r = 0.55 ± 0.01; $p < 0.0001$) ***(C)***. Regression line in represented in A and B, but not in C, since CRP has been evaluated as ratio to the normal value and its increment is not linear.

Table II. Accuracy of discrimination of clinical scores for endoscopic mucosal healing.

Score	AUC ± SE	95% CI	*p*	Sensitivity	Specificity
ECCI	0.89 ± 0.04	0.80 – 0.95	<0.0001	86.2	82.4
Partial Mayo	0.86 ± 0.05	0.76 – 0.93	<0.0001	81	82.4
SEO	0.84 ± 0.05	0.74 – 0.92	<0.0001	79.3	82.4
SCCAI	0.89 ± 0.04	0.79 – 0.95	<0.0001	87.9	76.5

AUC = Area Under ROC Curve, CI = confidence interval.

erature (partial Mayo ≥ 2, SCCAI ≥ 3, ECCI ≥ 55, SEO ≥ 120 points), we identified two groups of patients (low and high-score group). Thus, number of patients who had disease flare and who required therapy modifications, in the two groups of patients, was compared. Considering flares, patients with a low score had reduced relapse of disease at 1 year comparing to patients with high score (Figure 3 A). In particular, the difference was statistically significant for ECCI [9/38 (30% of patients) vs. 18/37 (49%) of flares in low- and high-score group, respectively, $p < 0.05$]. Considering number of patients who required increment of therapy at 1 year, all the scores displayed a consistent difference between low and high score groups [ECCI: 21/38 (55%) vs. 30/37 (81%), $p < 0.05$; SEO: 12/26 (46%) vs. 39/49 (79%), $p < 0.01$; SCCAI: 13/25 (52%) vs. 38/50 (76%), $p = 0.07$; Mayo: 9/20 (45%) vs. 42/55 (76%), $p < 0.05$] (Figure 3B). For all the indexes, the group of patients with high score had higher risk of flare and of increase of therapy at 1 year (Table II).

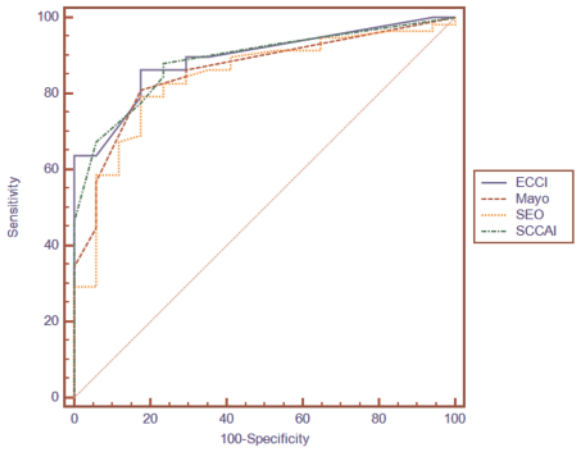

Figure 2. Comparison of ROC curves of clinical indexes for discrimination of endoscopic 'mucosal healing'. All the indexes displayed a good discriminative ability (mean AUC = 0.87 ± 0.05).

Discussion

In the present work, we tested four clinical indexes in UC patients. We first evaluated the correlation with recognized objective parameter of disease assessment, and in particular with endoscopic 'mucosal healing', and then we explore the possible indication for the practical management of the patients, by means of the assessment of the relation with the scores and the disease course in one year of follow-up. Since to date there is not a single index universally accepted and validated, different clinical scores are variably used in literature, and their utilization in daily clinical practice is not encouraged by specific designed studies. We chose four simple clinical

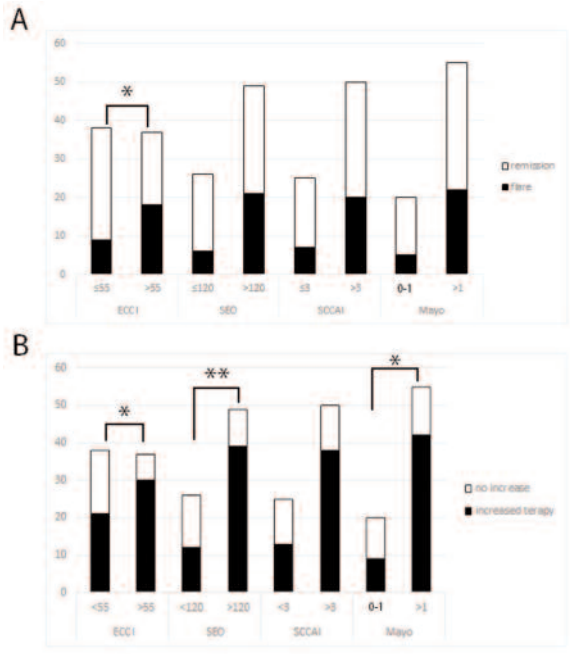

Figure 3. Comparison of number of patients with flare of disease ***(A)*** and who required an increase of therapy ***(B)***, in high- and low- score groups, at 1 year of follow-up. Patients with high score experienced more flares and required more increase of therapy comparing with patients with low clinical score.

Table III. Increase of risk of flare and of increase of therapy in high vs. low score patients.

	Flare		Increased therapy	
Score	OR	95%CI	OR	95%CI
Partial Mayo	2	0.64-6.3	3.95	1.34-11.61
Seo	2.5	0.85-7.31	4.55	1.61-12.85
SCCAI	1.71	0.61-4.85	2.92	1.06-8.09
ECCI	3.05	1.14-8.19	3.47	1.22-9.84

AUC = Area Under ROC Curve, CI = confidence interval.

indexes among the most commonly used in the literature, and we focused their utilization of UC patients with mild disease in regular follow-up visit. In this setting, clinical indexes may identify a low-risk group of patients with a probable favorable course of disease, at least at 1 year, in which aggressive follow-up and/or treatment is unnecessary. On the other side, they may suggest further diagnostic procedures and/or close re-evaluation in patients with still mild disease but with a high clinical score, suggestive of active disease. Moreover, a simple and not time-consuming score may help to monitor patients' response to therapy in trials and clinical practice.

Few studies directly compared different scores in the same set of patients. Turner et al[13] prospectively evaluated nine clinical indexes in 86 UC patients. Validity of the scores was tested by correlational analysis with different parameters (i.e. colonoscopy score, physician and patient global assessment, Mayo score and lab tests). In accord with the present study, the clinical indexes displayed very good correlation with the endoscopic score and good correlation with CRP level. The authors conclude that SCCAI and the pediatric ulcerative colitis activity index (PUCAI) showed the better results among the tested index and may be of help in clinical practice. Hirai et al[14] evaluated the performance of both clinical and endoscopic index in patients prior to treatment, at 2, 4 and 8 weeks of treatment. The authors observed a significant decrease in clinical and endoscopic scores after treatment and a good correlation among clinical indexes and between those and the endoscopic scores. Interestingly, the correlation was higher after treatment comparing with the baseline, suggesting that the clinical scores are related to the endoscopic activity in particular in mild disease, such as in the setting of patients of the present study (patients with mild disease in regular follow-up).

One major problem of clinical scores is the lack of a single reference parameter for the disease assessment. In the present work, we evaluated correlation between clinical indexes and objective diagnostic tools of particular relevance for UC patients evaluation and follow-up. Indeed, the clinical scores displayed a good correlation with endoscopy appearance, and to a lesser degree, to CRP increment. As already mentioned, endoscopy should represent the 'gold standard' for disease evaluation, for the direct observation of the mucosa. Its importance have even more emphasized by recent investigations underlining the relevance and the prognostic value of 'mucosal healing', proposed as fundamental therapeutical end-point[15,16]. Since endoscopic appearance and clinical symptoms are sometimes divergent, and considering the possible confounding role of the sole symptoms in the management of UC patients[17], the good correlation of the scores to the endoscopy is encouraging. The present study evaluates for the first time the accuracy of clinical indexes for the identification of patients with 'mucosal healing'. Considering the prognostic value of a healed mucosa in UC patients, the good accuracy of the indexes for mucosal healing may confirm their potential role in discriminating outpatients with higher or lower risk of unfavorable outcome.

We used for a comparison with lab activity of disease the CRP level increment, for its large use and availability in many centers. A novel biomarker of disease, namely fecal calprotectin, have been proven to strongly correlate with inflammatory activity[18], and testing the correlation of the scores with that parameter would be interesting. Some authors[19,20] have suggested a possible prognostic role for histological assessment, beside the macroscopic appearance, and the correlation with macroscopic and microscopic activity has been debated[21]. Bessissow et al[22] reported

a higher flare occurrence in patients with endoscopic macroscopic remission and histologic activity (in particular the presence of basal plasmacytosis) comparing with patients with complete macro- and microscopic remission. To date, routinely evaluation of bioptic samples in UC patients is not suggested by guidelines nor commonly used in clinical practice, and further researches are needed to better investigate the role of histologic activity in the management of UC patients. In our set of patients, histology poorly correlated with the clinical scores, despite a fair correlation with the endoscopic index ($r = 0.55$, $p < 0.0001$). Nonetheless, that result has to be interpreted with caution, considering that the histologic score was evaluated from the reports and not expressly calculated by the anatomopathologist.

Indeed, the prognostic value of the clinical scores have been scarcely investigated. However, we intended to explore that issue by evaluation of disease course after 1 year from the first clinical evaluation, in order to test the possible predictive suggestion of each score on the course of the disease. It is to note that we defined flare of disease as any general onset or exacerbation of symptoms suggestive of bowel inflammation, and that we consider any increment of the therapy that have been prescribed, regardless of a significant worsening of the underlying clinical condition. Consequently, in our retrospective casistic of patients in a regular follow-up visit, the clinical scores identified particularly patients with consistent favorable course of disease, since about 75% of patients with low score did not recorded any flare of disease and about 50% did not modify their therapy at 1 year of follow-up. In order to test possible prognostic value of clinical scores, specific prospectic studies in large setting of patients are needed.

The main limitation of the present work is determined by the retrospective analysis of the data, which would have influenced the results in several ways. First, although we include only patients with a complete set of clinical, lab and endoscopic data available, some clinical data may have been misinterpreted, and that would have altered the performance of the scores that require a more precise clinical assessment (i.e. Mayo and SCCAI). In fact, the assessment of patients' general condition strictly depends on a face-to-face visit, with direct interview and physical examination. This could in part explain the relative less striking performance of Mayo and SCCAI, and the good results of ECCI, comparing with previous comparative studies[13]. In fact, since ECCI include only objective parameters and not the general assessment of the patients, it may have minor problems in the retrospective calculation, in contrast to what could have happened for Mayo and SCCAI. Another explanation for the good results of the ECCI score is the fact that this is the only index expressly developed on endoscopic activity[9]. Nonetheless, the design of the study and the relative low number of patients do not allow an accurate comparison between the scores.

A further potential flaw is the fact that the endoscopic and histologic score have been retrospectively calculated. We used the modified Baron score since it is widely used in literature and it is simple and easily calculable even from the colonoscopy reports. Clinical trials usually indicate as endoscopic "mucosal healing" an endoscopic Mayo score ≤ 1. Similarly, in the present paper, we defined 'mucosal healing' a Baron score ≤ 1. Histological scores are less used, but several reports indicate that histology evaluation may add important information for the clinical management to the sole macroscopic observation[23], so that some numeric scores have been described[20]. Among the latter, we used the Sandborn's score, for it represents a simple and useful tool for histologic assessment[12]. For the relatively low number of patients, we did not stratify patients according to the kind of therapy followed at the time of the visit, so that we cannot exclude variation in clinical score calculation and in the flare rate for the different therapies. Therefore, the results of the present study need to be taken with caution and further confirmed in large prospective studies. Nonetheless, the present report confirms the usefulness of clinical score for UC activity evaluation, for the good correlation with endoscopy. For that reason, utilization of clinical indexes may be of help in the practical management of UC patients, in particular in outpatients with mild-moderate disease, with potential implication for resources optimization.

Conclusions

Clinical indexes may represent a useful tool in the daily practice for UC patients' management, for the good correlation with endoscopic activity and the accuracy in identifying patients with mu-

cosal healing. Prospective multicentric investigations in large sets of patients are necessary in order to better examine the prognostic value of the clinical score and to further implement their utilization.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet 2012; 380: 1606-1619.
2) Zallot C, Peyrin-Biroulet L. Deep remission in inflammatory bowel disease: looking beyond symptoms. Curr Gastroenterol Rep 2013; 15: 315.
3) Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut 2012; 61: 1619-1635.
4) Pagnini C, Menasci F, Festa S, Rizzatti G, Delle Fave G. "Mucosal healing" in ulcerative colitis: between clinical evidence and market suggestion. World J Gastrointest Pathophysiol 2014; 5: 54-62.
5) D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, Lemann M, Marteau P, Rutgeerts P, Scholmerich J, Sutherland LR. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology 2007; 132: 763-786.
6) Seo M, Okada M, Yao T, Ueki M, Arima S, Okumura M. An index of disease activity in patients with ulcerative colitis. Am J Gastroenterol 1992; 87: 971-976.
7) Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut 1998; 43: 29-32.
8) Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis 2008; 14: 1660-1666.
9) Azzolini F, Pagnini C, Camellini L, Scarcelli A, Merighi A, Primerano AM, Bertani A, Antonioli A, Manenti F, Rigo GP. Proposal of a new clinical index predictive of endoscopic severity in ulcerative colitis. Dig Dis Sci 2005; 50: 246-251.
10) Beattie RM, Nicholls SW, Domizio P, Williams CB, Walker-Smith JA. Endoscopic assessment of the colonic response to corticosteroids in children with ulcerative colitis. J Pediatr Gastroenterol Nut 1996; 22: 373-379.
11) Gomes P, du Boulay C, Smith CL, Holdstock G. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut 1986; 27: 92-95.
12) Sandborn WJ, Tremaine WJ, Schroeder KW, Batts KP, Lawson GM, Steiner BL, Harrison JM, Zinsmeister AR. A placebo-controlled trial of cyclosporine enemas for mildly to moderately active left-sided ulcerative colitis. Gastroenterology 1994; 106: 1429-1435.
13) Turner D, Seow CH, Greenberg GR, Griffiths AM, Silverberg MS, Steinhart AH. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. Clin Gastroenterol Hepat 2009; 7: 1081-1088.
14) Hirai F, Matsui T, Aoyagi K, Inoue N, Hibi T, Oshitani N, Fujii H, Kobayashi K, Suzuki Y, Tanaka S. Validity of activity indices in ulcerative colitis: comparison of clinical and endoscopic indices. Dig Endosc 2010; 22: 39-44.
15) Colombel JF, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011; 141: 1194-1201.
16) Lichtenstein GR, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. Inflamm Bowel Dis 2010; 16: 338-346.
17) Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2012; 107: 1474-1482.
18) D'Haens G, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, Geens P, Iwens D, Aerden I, Van Assche G, Van Olmen G, Rutgeerts P. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis 2012; 18: 2218-2224.
19) Bitton A, Peppercorn MA, Antonioli DA, Niles JL, Shah S, Bousvaros A, Ransil B, Wild G, Cohen A, Edwardes MD, Stevens AC. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology 2001; 120: 13-20.
20) Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clin Gastroenterol Hepatol 2014; 12: 929-934.
21) Lemmens B, Arijs I, Van Assche G, Sagaert X, Geboes K, Ferrante M, Rutgeerts P, Vermeire S, De Hertogh G. Correlation between the endoscopic and histologic score in assessing the activity of ulcerative colitis. Inflamm Bowel Dis 2013; 19: 1194-1201.
22) Bessissow T, Lemmens B, Ferrante M, Bisschops R, Van Steen K, Geboes K, Van Assche G, Vermeire S, Rutgeerts P, De Hertogh G. Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. Am J Gastroenterol 2012; 107: 1684-1692.
23) Feakins RM. Inflammatory bowel disease biopsies: updated British Society of Gastroenterology reporting guidelines. J Clin Pathol 2013; 66: 1005-1026.