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The Modified Mayo Endoscopic Score (MMES): A New Index for the Assessment of Extension and Severity of Endoscopic Activity in Ulcerative Colitis Patients

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Abstract

Background and aims: Current endoscopic activity scores for ulcerative colitis (UC) do not take into account the extent of mucosal inflammation. We have developed a simple endoscopic index for UC that takes into account the severity and distribution of mucosal inflammation.

Methods: In this multicentre trial, UC patients undergoing colonoscopy were prospectively enrolled. For the Modified Score (MS), the sum of Mayo Endoscopic Subscores (MESs) for five colon segments (ascending, transverse, descending, sigmoid and rectum) was calculated. The Extended Modified Score (EMS) was obtained by multiplying the MS by the maximal extent of inflammation. The Modified Mayo Endoscopic Score (MMES) was obtained by dividing the EMS by the number of segments with active inflammation. Colon biopsies were obtained from the rectum and sigmoid, as well as from all inflamed segments, by standard methods. Clinical activity was scored according to the Partial Mayo Score (PMS). Biological activity was scored according to C-reactive protein (CRP) and faecal calprotectin (FC) levels. Histological activity was scored according to the Geboes Score (GS).

Results: One hundred and seventy-one UC patients (38% female, median age 47 years, median disease duration 13 years) were included. The MMES correlated significantly with the PMS ($r = 0.535$), CRP ($r = 0.238$), FC ($r = 0.730$) and GS ($r = 0.615$) (all $p < 0.001$). Median MMES scores were significantly higher in patients with clinical, biological or histological activity (all $p \leq 0.001$)

Conclusions: The MMES is an easy to use endoscopic index for UC that combines the severity analysis of the MES with disease extent, and correlates very well with clinical, biological and histological disease activity.

Keywords: Endoscopic scores; ulcerative colitis; disease extent

1. Introduction

Mucosal healing (MH) has become an important goal in the treatment of ulcerative colitis (UC). The presence of MH has been demonstrated to decrease the risk of relapse, hospitalizations, colorectal cancer and colectomy.[1–5] Recently, endoscopic assessment has been demonstrated to be a feasible and more beneficial strategy than clinical assessment to guide treatment optimization in UC patients.[6] However, there are several limitations with an endoscopy-based approach to treatment. Firstly, many different endoscopic scores exist. Moreover, no validated definition of MH currently exists in the literature. Although different endoscopic scores have been used to define MH,[7–13] the Mayo endoscopic subscore (MES) of 0 or 1 has been one of the most used definitions.[2,14–22] Secondly, patients may present with patchy healing (especially those on topical treatment); however, at present there are no data on the outcomes of this partial MH.

The first endoscopic scores were developed to assess the severity but not the extent of endoscopic activity in ulcerative colitis. These include the Baron score,[23] the Powell–Tuck index,[24] the MES,[25] the Sutherland index[26] and the Rachmilewitz index,[27] most of them sharing similar endoscopic variables.

In the Baron score (four-point scale),[23] the Powel–Tuck index (Saint Mark's index, three-point scale)[24] and the endoscopic subscore of the Sutherland index (UC disease activity index, four-point scale),[26] the degree of endoscopic disease activity is mainly based on the severity of mucosal friability and bleeding, while the presence of mucosal ulcerations is not included. In contrast, the modified Baron score (five-point scale)[28] and the Rachmilewitz endoscopic index (12-point scale)[27] were developed to incorporate the vascular pattern, as well as the presence of granularity, hyperaemia, friability, bleeding and ulcerations.

The MES (four-point scale) was developed in 1987 by Schroeder et al.[25] Partly due to its simplicity, the MES is the most commonly used endoscopic activity index in clinical trials for evaluating treatment efficacy in terms of endoscopic improvement.

None of the aforementioned endoscopic scores has been validated.

Recently, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS, nine-point scale) has been developed based on the intra- and inter-observer variability of 10 endoscopic descriptors.[29] This index grades three endoscopic findings, namely vascular pattern, bleeding and erosions/ulcers, into different levels of severity with precise definitions. The UCEIS, as well as the previous endoscopic scores, is based on the macroscopic evaluation of the most severely involved colon segment and does not take into account the extent of UC involvement.

So far, the only endoscopic index taking into account all the colonic segments is the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS), developed in 2013 by Samuel et al.[30] This index is calculated by a formula that includes four different variables (granularity, vascular pattern, ulceration and bleeding–friability), all of them scored in each of the five segments (rectum, sigmoid, descending, transverse and ascending). It has been validated by rigorous methodology and it has high inter-observer agreement. However, its feasibility and simplicity of use need to be demonstrated in clinical practice. Moreover, the UCCIS was not correlated to histological activity.

The MES is still the best known and most extensively used endoscopic index both in clinical trials and in clinical practice. Our aim was to develop a simple score for UC endoscopic activity, taking into account the severity and distribution of mucosal inflammation based upon the widely used MES. As secondary objectives, we aimed to correlate this new endoscopic score with clinical, biological and histological activity.

2. Methods

2.1. Patient population

This was a prospective longitudinal study in two tertiary referral hospitals: the University Hospitals Leuven (Leuven, Belgium) and McGill University Health Centre (Montreal, Canada). We included adult UC patients diagnosed according to conventional endoscopic, radiological and histological criteria[31] who underwent colonoscopy or sigmoidoscopy as part of routine clinical care between December 2012 and March 2014. Patients were allowed to take any UC treatment, including mesalamine, steroids, immunosuppressants, biologicals and all investigational agents. All patients gave written informed consent. The study was approved of by the local ethics committees of the centres in Belgium (ML8655) and in Canada (12-392-GEN).

Subjects with a history of (sub)total colectomy or those in whom the upper limit of colonic inflammation was not reached during endoscopy were excluded.

2.2. Clinical activity

Clinical activity was scored on the same day as endoscopy according to the Partial Mayo Score (PMS). Symptomatic remission was defined as a Mayo stool frequency subscore of 0 or 1 and a Mayo rectal bleeding subscore of 0.[2]

2.3. Biological activity

A blood analysis was obtained on the day of colonoscopy, including the determination of haemoglobin, leucocytes, platelets, C-reactive protein (CRP) and albumin. A stool sample that was obtained immediately before bowel preparation was provided by each patient for the analysis of faecal calprotectin (FC). The FC level was measured with the Quantum Blue kit (Bühlmann, Schonenbuch, Switzerland). A CRP <5 mg/L and a FC <250 µg/g[32,33] were considered to indicate inactive disease.

2.4. Endoscopic activity

During endoscopy, the operator scored the visualized colon for UC activity using the provided Modified Mayo Endoscopic Score (MMES) scoring sheet (Table 1). The colon was divided into five segments (ascending, transverse, descending colon, sigmoid and rectum) and for each segment the operator assessed the MES. The operator also reported the maximal extent of inflammation at the time of colonoscopy. The sum of individual MESs of all segments was calculated to obtain the Modified Score (MS) on a 15-point scale. The Extended Modified Score (EMS) was then obtained by multiplying the MS by disease extent in decimetres. The MMES was obtained by dividing the EMS by the number of segments with active inflammation. A caecal patch and pseudopolyps were not regarded as representing inflammation. See example in (Table 1).

2.5. Histological activity

Colonic biopsies were obtained from the rectum and at 25 cm in all patients and additionally at all macroscopically inflamed segments.

Histological activity was scored according to the Geboes Score (GS). This is a comprehensive grading system that evaluates for the presence of architectural changes, mononuclear cells, eosinophils, neutrophils, crypt destruction and erosions or ulcerations (Supplementary Table 1).[34] Active histological activity was defined as

GS ≥3.1 (presence of neutrophils in the epithelium).[35] One additional parameter, basal plasmacytosis, was also evaluated.[35]

Because multiple biopsies were obtained, the biopsy with the highest GS was the one included in the analysis.

2.6. Statistical analyses

We used SPSS Version 19.0 (SPSS, Chicago, Illinois, USA) for appropriate statistical methods. Descriptive statistics were calculated as percentages for discrete data and medians with interquartile ranges (IQRs) for continuous data. Spearman correlations between the endoscopic activity scores and histological activity scores, the PMS, albumin, CRP level and FC were calculated. Significance was accepted at $p < 0.05$.

3. Results

3.1. Patient characteristics

The patients' characteristics are summarized in Table 2. A total of 171 patients were included (76 from McGill University Health Centre in Montreal and 95 from University Hospitals Leuven). Forty-two out of the 171 patients underwent incomplete colonoscopies; all 42 were patients with known distal UC in whom the upper limit of endoscopic inflammation was reached.

3.2. Correlation analysis

Spearman's correlations among clinical, biological, endoscopic and histological activity are shown in Table 3. The histological activity and FC correlated best with the endoscopic scores, followed by clinical activity. In contrast, the correlation between CRP and endoscopic activity was poor regardless of endoscopic score.

3.3. Clinical, biological and histological variables and MMES

The median MMES scores were significantly higher among patients with clinical, biological and histological activity compared with patients in clinical, biological and histological remission (Figure 1).

Table 1. Example of calculation of the Modified Mayo Endoscopic Score (MMES).

Colonic segments	Evaluated[1] (0 or 1)	Inflamed[2] (0 or 1)	MES[3] (0–3)
Rectum	1	1	3
Sigmoid	1	1	2
Descending colon	1	1	2
Transverse colon	1	0	0
Ascending colon	1	0	0
Total (= Mayo score)	5	3	7

Maximal extent (dm)[a] = 5.
Mayo score = 3.
Modified Score (sum of MES values) = 7.
Extended Modified Score (EMS; MS × maximum extent) = 7 × 5 = 35.
Mayo Modified Endoscopic Score
(EMS/no. of segments with Mayo Endoscopic Subscore > 0) = 35/3 = 11.7

[1]Evaluated: 1 if this segment was (completely or partly) evaluated.
[2]Inflamed: 1 if Mayo Endoscopic Subscore for this segment was not 0.
[3]Mayo Endoscopic Subscore: evaluated for the macroscopically most severely inflamed part; score 0 for a segment with normal or inactive disease; score 1 for a segment with erythema, decreased vascular pattern, mild friability; score 2 for a segment with marked erythema, absent vascular pattern, friability, erosions; score 3 for a segment with ulcerations or spontaneous bleeding.
[a]Maximal extent: measured in decimetres during withdrawal.

Interestingly, median FC level was proportional to MMES grade (Figure 2). However, in the multivariate analysis, after adjusting for the extent and severity of endoscopic activity only the severity of endoscopic activity defined by MES remained as an independent risk factor for FC ≥250 (µg/g) [odds ratio (OR) 2.25, 95% confidence interval (CI) 1.42–3.57; $p = 0.001$]. Similar results were obtained for the MS (OR 1.78, 95% CI 1.41–2.24; $p < 0.001$).

3.4. MMES and MES

As expected, MMES medians (IQR) were different for the four grades of MES (Figure 3). Different grades of MMES were reported for each grade of MES considering the extent of endoscopic activity, demonstrating the added information provided by MMES compared with MES.

3.5. Prediction of active histological activity by MMES

Active histological activity (GS ≥3.1) was predicted by MMES >0.8 with 74% sensitivity and 79% specificity. The area under the curve (AUC) was 0.79 (95% CI 0.72–0.96; $p < 0.001$) (Figure 4). Similarly, MMES >0.8 predicted the presence of basal plasmacytosis with 83% sensitivity and 79% specificity (AUC 0.85, 95% CI 0.79–0.91; $p < 0.001$)

4. Discussion

This study assessed the MMES, a newly developed endoscopic score for UC, taking into account the total endoscopic mucosal disease extent. The score can be easily calculated by assessing the commonly used MES for five colonic segments and the total extent of mucosal inflammation. We have shown that MMES correlates well with

Table 2. Patient characteristics ($n = 171$).

Female (%)	65 (38)
Age (years), median (IQR)	47 (34–56)
Disease duration (years), median (IQR)	13 (6–20)
UC extension: E1/E2/E3[1] (%)	23/68/66 (15/43/42)
Medication at the time of endoscopy (%)	
Mesalamine	113 (66)
Corticosteroids	13 (8)
Immunosuppressive therapy[2]	32 (19)
Anti-tumour necrosis factor	44 (26)
Partial Mayo Score, median (IQR)	0 (0–2)
C-reactive protein (mg/L), median (IQR)	1.9 (0.5–5.8)
Haemoglobin (g/dL), median (IQR)	14.2 (13.2–15.1)
White blood cells ($10^{9/L}$) (IQR), median (IQR)	6.5 (5.2–8.4)
Platelets ($10^{9/L}$), median (IQR)	245.5 (207–304)
Albumin (g/L), median (IQR)	4 (40.2–45.2)
Faecal calprotectin (µg/g), median (IQR)	118 (100–486)
Disease extent (dm), median (IQR)	0.5 (0–3.5)
Mayo Endoscopic Subscore, median (IQR)	1 (0–2)
Modified Score, median (IQR)	1 (0–3)
Extended Modified Score, median (IQR)	1 (0–11)
Modified Mayo Endoscopic Score, median (IQR)	0.6 (0–5.3)
Patients with Geboes Score ≥3.1 (%)	75 (48)
Patients with diffuse/focal basal plasmacytosis (%)	36/34 (22/21)

IQR, interquartile range.
[1]UC extent according to Montréal classification: E1, proctitis; E2, left-sided colitis; E3, extensive colitis. [2]Azathioprine, 6-mercaptopurine, methotrexate, tacrolimus.

Table 3. Spearman correlations between clinical, biological, endoscopic and histological activity.

	Mayo Endoscopic Subscore	Partial Mayo Score	Fecal calprotectin (µg/g)	C-reactive protein (mg/L)	Geboes Score
Modified Score	0.945	0.622	0.725	0.266	0.657
	p <0.001	p < 0.001	p < 0.001	p = 0.001	p < 0.001
Extended Modified Score	0.866	0.534	0.714	0.226	0.605
	p < 0.001	p < 0.001	p < 0.001	p = 0.005	p < 0.001
Mayo Modified Endoscopic Score	0.887	0.535	0.730	0.238	0.615
	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
Geboes Score	0.682	0.540	0.617	0.197	
	p < 0.001	p < 0.001	p < 0.001	p = 0.017	
C-reactive protein (mg/L)	0.310	0.261	0.487		
	p < 0.001	p = 0.001	p < 0.001		
Fecal calprotectin (µg/g)	0.669	0.555			
	p < 0.001	p < 0.001			
Partial Mayo Score	0.548				
	p < 0.001				

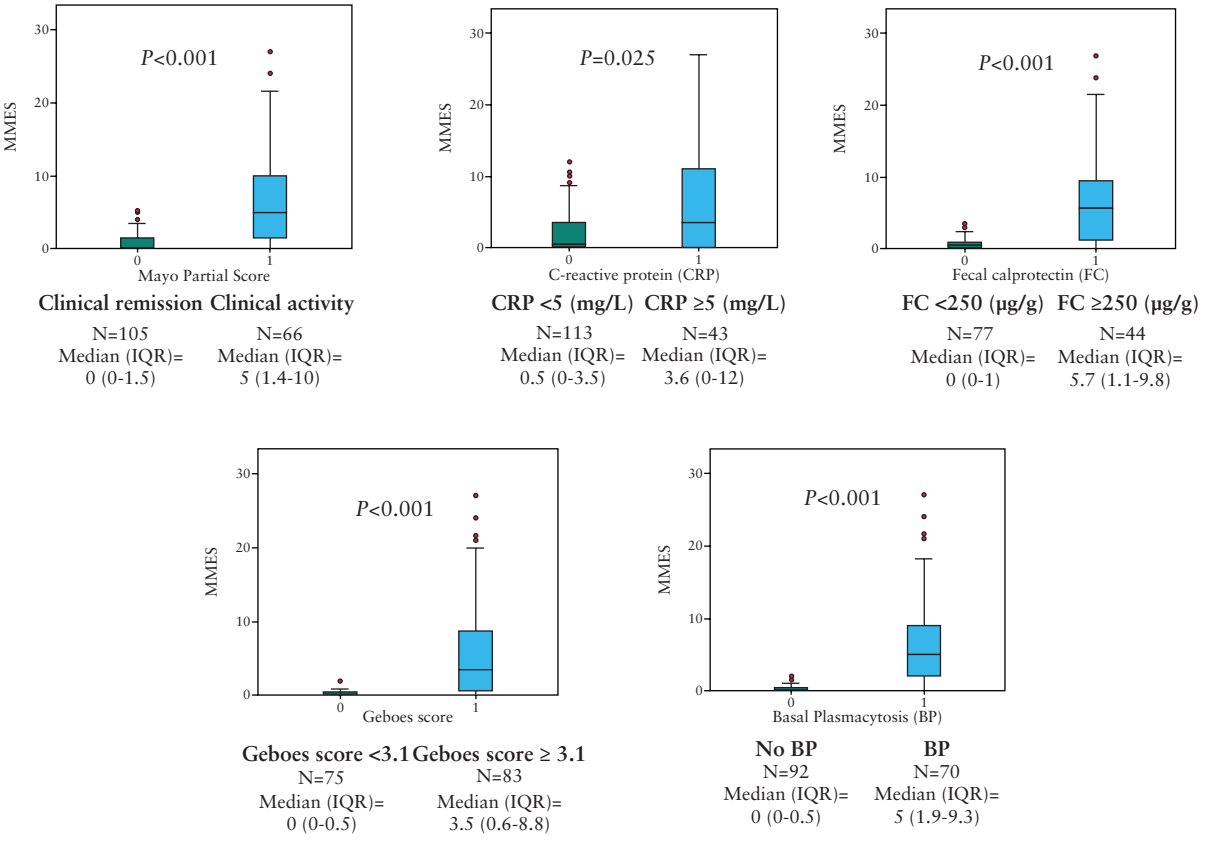

Figure 1. MMES scores in patients with/without clinical, biological and histological activity.

clinical, biological and histological variables of disease activity. The main advantage of the MMES is the fact that it takes into account disease extent and makes it possible to assess partial mucosal healing, which may influence patient management

Despite the development of many different endoscopic scores for UC,[23,24,26–28] the MES[25] remains the most commonly used one, because of its easy calculation and its use in both clinical practice and clinical trials. However, this score does not take into account the extent of endoscopic activity, which changes during both the natural and the treated course of a UC patient's disease in ~20–50% of cases[36–40] and also after medical treatment. The MES includes only four grades to classify a wide variety and distribution of endoscopic inflammation. In this context, it may not reflect accurately the endoscopic response to specific drugs in clinical trials. For example, a patient with pancolitis MES grade 2 at baseline who is treated with anti-tumour necrosis factor (anti-TNF) would be classified as a non-responder if control colonoscopy showed healing of the major part of the colon but persisting erosions in the rectum. There is a need to better characterize this therapeutic response, and taking disease extent into account can accommodate the collection of better data to clarify the role of partial healing in the outcome of UC patients.

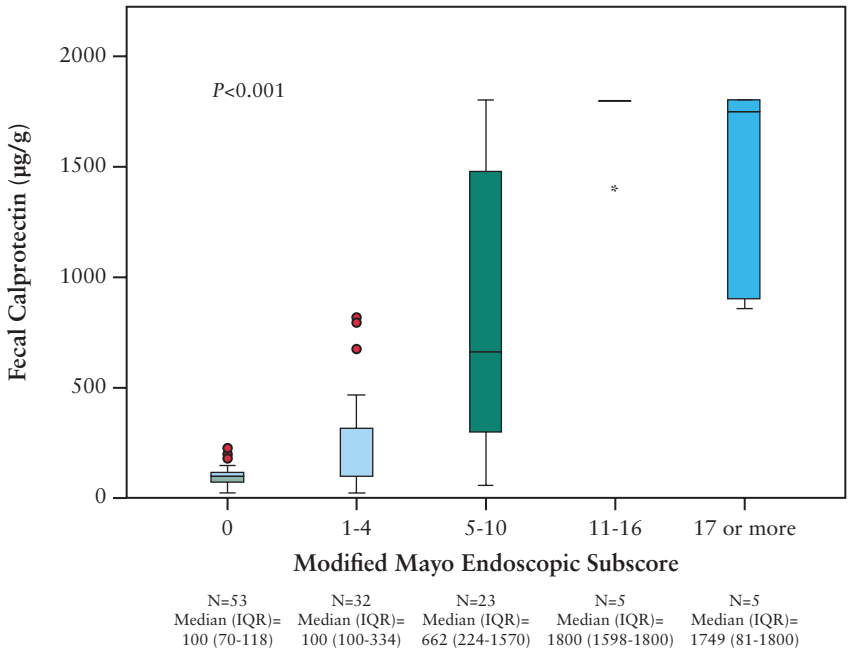

Figure 2. Median of faecal calprotectin in different grades of endoscopic activity according to the Modified Mayo Endoscopic Score.

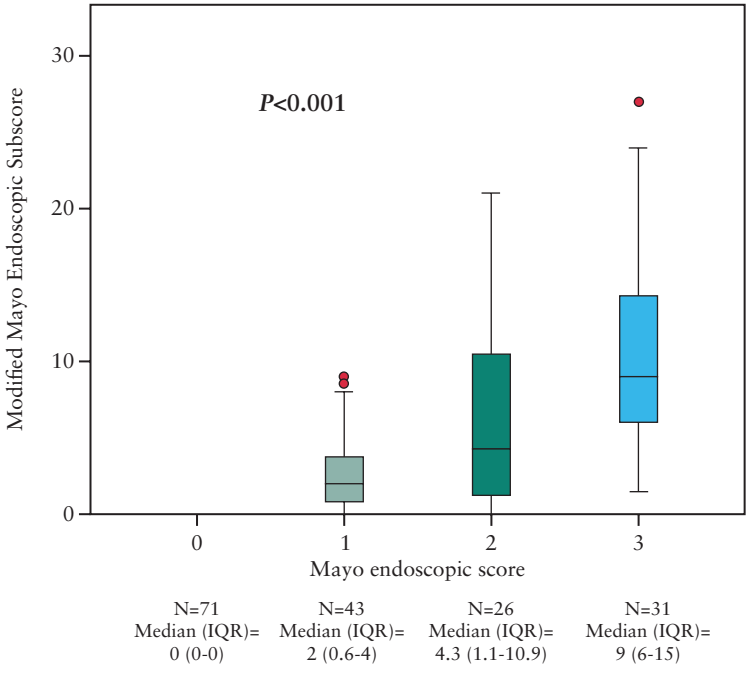

Figure 3. MMES median distribution according to Mayo Endoscopic Subscore.

Partial MH has been previously assessed in Crohn's disease (CD). In a *post hoc* analysis of the SONIC study,[41] the endoscopic response (partial MH) was defined as a decrease from baseline in the Simple Endoscopic Score for Crohn's Disease (SES-CD) or Crohn's Disease Endoscopic Index of Severity (CDEIS) of at least 50%. The presence of endoscopic response at week 26 of treatment identified those most likely to be in corticosteroid-free clinical remission at week 50. Although the definition of MH is not yet validated, the post hoc analysis of the SONIC study highlights the importance of considering also partial MH when assessing the response to any treatment. Despite the fact that, in the long term, complete MH is probably the most desirable endpoint, some treatments may result in a partial initial response, even though at a later stage a complete response may occur. Patients with such a treatment response should be recognized by careful endoscopic assessment in order not to misclassify them as non-responders as a result of using a less sensitive index to assess endoscopic activity, which may underestimate the response to the treatment.

Because of the need for a more accurate assessment of endoscopic activity in UC, two new endoscopic scores have been validated in the last 3 years. The first one is the UCEIS,[29] which is an accurate index and has been demonstrated to capture 90% of the variability in the overall assessment of endoscopic severity but does not assess the endoscopic

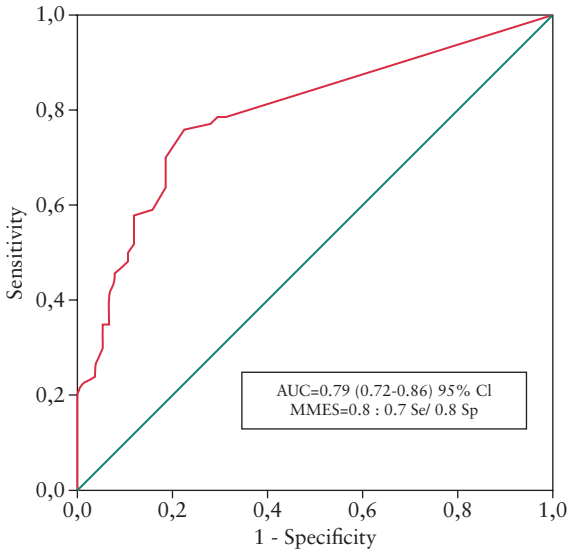

Figure 4. Area under the curve to predict active histological disease (Geboes Score ≥3.1) by MMES.

extent and therefore cannot be used to identify partial MH. Indeed, as with the MES, only the most severely affected segment is evaluated, so partial MH cannot be picked up. The more recently developed UCCIS[30] is today the only endoscopic score for UC that considers endoscopic activity in all the segments of the colon. This score accounts for 80% of the variability in the endoscopic assessment of severity. However, this score requires the assessment of four endoscopic variables in the five segments of the colon followed by a complex calculation to render the final score. Therefore, despite its accuracy, the UCCIS may not be the easiest index to use in clinical practice. Moreover, most of the endoscopic procedures in the UC assessment are sigmoidoscopies and not complete colonoscopies, and no specific recommendation is given for the use of UCCIS in this context.

One of the advantages of MMES is that it relies on the maximal extent of inflammation. Therefore, in patients with proctitis or left-sided colitis, sigmoidoscopy is normally enough to calculate the score. Moreover, its calculation is based on the widely known MES, not introducing new variables for the clinician. The fact that the MMES correlates well with clinical, biological and histological activity indexes indicates its possible clinical value in patient assessment and management.

One interesting finding of our study is the correlation of FC levels with the different grades of MMES, although in the multivariate analysis, after adjusting for the endoscopic extent, only the severity of the endoscopic activity was an independent predictor of FC levels. This has special relevance, as the literature on the utility of FC is scant and controversial. Roseth et al.[42] found similar levels of FC among UC patients, regardless of their disease extent, whereas Diamanti et al.[43] showed that levels of FC were proportional to disease extent.

One of the strengths of this study is that all colonic samples were scored according to the GS[34] and basal plasmacytosis since both have been demonstrated to have a prognostic value to predict clinical relapse in UC patients.[35] We have also demonstrated that MMES >0.8 can accurately predict active histological activity defined by GS ≥3.1 and/or the presence of basal plasmacytosis.

Of note, patients classified in a specific grade of MES are further scored differently by the MMES according to disease extent. This might be a more accurate way of following up disease activity.

Our study has some limitations. First, the endoscopies were not video-recorded and therefore inter-observer agreement was not assessed. Second, the majority of patients were selected from the outpatient clinic and therefore a high proportion were in clinical and endoscopic remission. Third, 42 out of the 171 colonoscopies were incomplete, although these were only in patients with known distal colitis where the maximal extent of endoscopic activity was reached; moreover, this reflects daily clinical practice. Fourth, MMES does not reflect the impact of segmental colitis, since its calculation is done with the maximal extent of endoscopic activity. Finally, a multicentre prospective cohort study with central reading will be necessary to validate the MMES. In addition, the accuracy of MMES in assessing response to specific treatments needs to be studied in more detail to explore its potential added value in clinical trials.

In conclusion, the MMES is a simple index to assess endoscopic activity in UC, taking into account the extent of mucosal inflammation and with an excellent correlation with clinical, biological and histological disease activity.

Further prospective studies are warranted to assess the clinical value of the MMES. Of note, a long-term trial should evaluate the predictive value of partial MH on long-term outcome.

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Conflict of Interest

Triana Lobatón, Chelsea Maedler and Victoria Marcus have no conflicts of interest; Talat Bessissow receives speaker fees from Abbvie, Janssen, Forestlab, Shire, Ferring and Takeda and does consultancy for Abbvie, Janssen, Forestlab, Shire and Takeda; Gert De Hertogh does consultancy for Genentech, Centocor, Novartis, Shire and Galapagos; Séverine Vermeire receives financial support for research from UCB Pharma, MSD and Abbvie, lecture fees from Abbvie, Merck, Ferring, UCB Pharma and Centocor, and does consultancy for UCB Pharma, AstraZeneca, Ferring, Abbvie, Merck, Ferring, Shire and Pfizer; Gert Van Assche receives financial support for research from Abbvie and Ferring, lecture fees from Janssen-Cilag, Merck and Abbvie and consultancy for PDL BioPharma, UCB Pharma, Sanofi-Aventis, Abbvie, Ferring, Novartis, Biogen Idec, Janssen Biologics, NovoNordisk, Zealand Pharma A/S, Millenium/Takeda, Shire, Novartis and BMS; Paul Rutgeerts receives financial support for research from UCB Pharma, Abbvie, Janssen Biologics, Merck and Prometheus, lecture fees from Abbvie and Merck, and does consultancy for Amgen, Merck, UCB Pharma, Genentech, BMS, Abbvie, Janssen Biologics, Millenium, Neovacs, Actogenics and Prometheus; Raf Bisschops receives speaker fees or research support from Pentax, Fujifilm, Olympus, Ferring and Ipsen; Marc Ferrante receives financial support for research from Janssen Biologics, lecture fees from Merck, Tillotts, Ferring, Abbvie and does consultancy for Abbvie, Merck and Janssen Biologics.

Author Contributions

Triana Lobatón participated in patient recruitment, collected and analysed the data and wrote the manuscript; Gert Van Assche, Séverine Vermeire and Paul Rutgeerts participated in patient recruitment and in study design; Talat Bessissow, Raf Bisschops, Alain Bitton and Waqqas Afif participated in patient recruitment; Gert De Hertogh, Bart Lemmens, Chelsea Maedler and Victoria Marcus scored the colonic biopsies; Marc Ferrante designed the study, participated in patient recruitment, revised the analysis and revised the manuscript.

Conference presentation

The complete content of this manuscript has been presented during majar IBD congresses: Belgian Gastroenterology Week, 14 February 2014; 9th ECCO congress, Copenhagen, February 2014; Digestive Disease Week, Chicago, USA, May 2014.

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