

ORIGINAL PAPERS

The use of a segmental endoscopic score may improve the prediction of clinical outcomes in acute severe ulcerative colitis

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ABSTRACT

Background: Acute severe colitis (ASC) remains a challenging complication of ulcerative colitis. The early identification of patients who will not respond to optimal therapy is warranted. Increasing evidence suggests that endoscopy may play a role in predicting important outcomes in acute severe colitis.

Methods: The endoscopic activity of consecutive patients with acute severe colitis was evaluated using the Mayo endoscopic sub-score (Mayo) and the ulcerative colitis endoscopic index of severity (UCEIS). Two segmental indexes were also produced by summing the scores of the rectum and sigmoid (seg-Mayo and seg-UCEIS, respectively). Endpoints included the need for salvage therapy with infliximab or cyclosporine, refractoriness to corticosteroids, and colectomy.

Results: Of one hundred and eight patients enrolled in the study, 60 (55.6%) were male; with a median age of 34.5 years (range 15-80). All patients received intravenous steroids. Fifty-nine patients (55.6%) showed an incomplete or absent response to steroids, 35 patients (34.3%) received salvage therapy with infliximab or cyclosporine and 38 patients (33.3%) were colectomized during the index hospitalization or within the first year of follow-up. All scores were able to predict the need for surgery, but only the seg-UCEIS significantly predicted refractoriness to steroids.

Conclusions: There was a strong correlation between endoscopic severity and unfavorable outcomes. The UCEIS outperformed the Mayo endoscopic sub-score in all important outcomes. Segmental scoring further improved the performance of the UCEIS.

Key words: Endoscopy. Ulcerative colitis. Inflammatory bowel disease. Prognosis.

INTRODUCTION

About 15 to 25% of patients with ulcerative colitis will develop an episode of acute severe colitis, a medical emer-

gency requiring hospitalization and presenting a high risk for short-term colectomy (1). Mortality in acute severe colitis has significantly decreased from 24% to about 1% since the introduction of intravenous steroid therapy (2). Unfortunately, one third of patients show only partial or no response to steroids, and even with salvage therapy, one in every three patients will still require colectomy in the short-term (3). Early identification of non-responders can prevent futile and potentially hazardous therapy and avoid unnecessary delays in surgery. Available predictors include clinical parameters such as the number of bowel movements (4), laboratory markers such as serum C-reactive protein and albumin (5,6), fecal biomarkers such as fecal calprotectin and lactoferrin (7,8), and endoscopy. The presence of deep colonic ulceration has been associated with an increased likelihood of colectomy (9). More recently, two studies have shown that the ulcerative colitis endoscopic index of severity (UCEIS) can predict unfavorable outcomes in ulcerative colitis (10,11). As current guidelines recommend performing endoscopy in all patients with acute severe colitis to confirm the diagnosis and exclude underlying infection (1,12), its use as a prognostic marker is justifiable. Current endoscopic scores in ulcerative colitis grade the severity of endoscopic activity according to the most severe segment of mucosa, and do not take into account the full extent of mucosal inflammation. However, studies have shown that both rectal sparing and patchy disease may occur during the natural history of ulcerative colitis (13). Assessing only the most affected segment may therefore reflect the degree of inflammation inadequately. Scores which account for the extent of endoscopic activity have shown promising results in non-severe ulcerative colitis and may also improve prediction in acute severe colitis (14).

In this study, we compared the accuracy of the Mayo and UCEIS scores in predicting several important outcomes using a cohort of patients with acute severe ulcerative colitis. We also studied the potential advantage of

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using a simple segmental endoscopic score produced by assessing the endoscopic activity of both the rectum and sigmoid.

MATERIAL AND METHODS

Study design and patients

We performed a retrospective analysis of consecutive patients admitted to the Department of Gastroenterology of Santa Maria Hospital between January 2000 and April 2015 with acute severe ulcerative colitis. Acute severe colitis was defined according to the Truelove and Witts' criteria (≥ 6 bloody stools per day and one or more of: pulse > 90 bpm, body temperature > 37.8 °C, hemoglobin < 105 g/l, and erythrocyte sedimentation rate > 30 mm/h). These criteria are recommended by The European Crohn's and Colitis Organization (1), The American College of Gastroenterology (15), and The Association of Coloproctology of Great Britain and Ireland (ACPGBI) (16). The inclusion criteria were age 18 or over, a confirmed diagnosis of ulcerative colitis (1) and clinical and laboratory criteria of acute severe colitis. Demographic details, disease parameters and in-hospital clinical course were included in the analysis. This study was approved by our institutional board. As this was a retrospective study, formal patient consent was not collected.

Endoscopy

All patients underwent unprepared flexible sigmoidoscopy at admission. As endoscopic findings might be masked by steroid therapy, patients who underwent a sigmoidoscopy more than 48 hours after admission were excluded. All examinations were performed by experienced endoscopists or by supervised residents. Each endoscopy was evaluated according to the Mayo endoscopic sub-score and the UCEIS. The Mayo endoscopic sub-score is a part of the Mayo score that is rated 0-3 based on the presence of erythema, erosions and ulceration (17). The UCEIS is a newly developed tool ranging from 0 to 8, and includes vascular pattern, mucosal bleeding, erosions and ulcers (18). The respective segmental scores (seg-Mayo and seg-UCEIS) were produced by adding the endoscopic evaluation of the rectum and sigmoid (ranging from 0 to 6 and from 0 to 16 respectively). Three gastroenterologists were responsible for rating all endoscopic examinations (based on pictures and videos).

Management of acute severe colitis

All patients were treated with intravenous steroids (prednisolone 40-60 mg/day, methylprednisolone 60 mg, or hydrocortisone 400 mg/day). If by the third day of admission the patient had not improved significantly (defined by a stool frequency > 8 /day or between 3 and 8/day with a C-reactive protein > 45 g/l), salvage therapy was given which was either infliximab or cyclosporine. This strategy is in accordance with the current recommendations by The European Crohn's and Colitis Organization (19). Infliximab was given at 5 mg/kg at 0, 2 and 6 weeks, and then every 8 weeks for patients with clinical response. Cyclosporine was given at 2-4 mg/kg/day as

a continuous infusion for up to 14 days with close monitoring for therapeutic levels (150-250 ng/ml) and drug toxicity. Patients not showing a significant response to rescue therapy or with a worsening clinical condition were referred for prompt surgery upon the decision of a multidisciplinary group including dedicated gastroenterologists and colorectal surgeons. Patients who had previously failed salvage therapy were also referred for surgery.

Study endpoints

Each endoscopic score was correlated with clinical outcomes including the need for second-line therapy (salvage therapy), steroid refractoriness and surgery. Salvage therapy included either infliximab or cyclosporine. Our definition of steroid refractory disease included all patients who required salvage therapy and/or surgery.

Statistical analysis

We used a Kolmogorov-Smirnov test to evaluate the normality of distribution of our continuous variables. Continuous variables were expressed in mean \pm standard deviation (SD) or median + range depending on normal or non-normal distribution. Normal distribution continuous variables were compared using the Student's *t* independent samples test and non-normal continuous variables were compared using the Mann-Whitney test. Categorical variables were described using frequencies and percentages. Correlation between scores and between the rectum and sigmoid evaluation was determined using Spearman's correlation coefficient. Agreement between endoscopists was assessed using the Cohen's kappa test. The area under the receiver operating characteristics curve (AUROC) was used to assess the accuracy of each scoring system in predicting binary outcomes. Kaplan-Meier survival curves were used to assess the colectomy-free survival according to each endoscopic score and were compared using the log-rank test. The significance level for this study was 0.05. Statistical analysis was performed using SPSS v21.0.

RESULTS

General characteristics and demographics

From a cohort of 120 patients meeting the inclusion criteria, 12 cases were excluded due to insufficient or incomplete data. We included 108 patients in our final analysis, 55.6% male, with median age of 34.5 years (range 15-80). At the onset of acute severe colitis, 73 patients (67.6%) were using 5-aminosalicylates (15.1% topical therapy), 28 (25.9%) thiopurines, 17 (15.7%) infliximab, and 3 (2.8%) cyclosporine. The median follow-up time from the date of admission was 33.0 months (range 2-120). Fifty patients (46.3%) presented with acute severe colitis during the first year of disease. The median disease duration before admission was 24.0 months (range 0-420). All patients met Truelove and Witts' criteria with a median score of 4 (range 2-5). Patient's characteristics are presented in table I.

Table I. Demographic details of patients included in the study

Patients (n)	108
Male gender, n (%)	60 (55.6)
Age in years, median (range)	34.5 (15-80)
Smoking status, n (%)	9 (8.3)
ASC within 1 year of diagnosis (%)	50 (46.3)
Truelove and Witts (median \pm IQR)	4 (2-5)
<i>Disease extension</i>	
Left sided, n (%)	26 (24.1)
Extensive, n (%)	82 (75.9)
<i>Concomitant medication</i>	
Oral 5-aminosalicylates, n (%)	73 (67.6)
Topical 5-aminosalicylates, n (%)	11 (10.2)
Tiopurines, n (%)	28 (25.9)
Infliximab, n (%)	17 (15.7)
Cyclosporine, n (%)	3 (2.8)
<i>Endpoints</i>	
Steroid refractory, n (%)	59 (55.7)
Salvage therapy, n (%)	34 (31.5)
Infliximab, n (%)	25 (23.1)
Cyclosporine, n (%)	8 (7.4)
Colectomy, n (%)	34 (31.5)
Death, n (%)	4 (3.7)
<i>Endoscopic scores</i>	
UCEIS, median (range)	5 (2-8)
Segmental UCEIS, median (range)	10 (4-15)
Mayo, median (range)	3 (1-3)
Segmental Mayo, median (range)	6 (1-6)

ASC: Acute severe colitis; UCEIS: Ulcerative colitis endoscopic index of severity; Mayo: Mayo endoscopic score.

Clinical course

All patients were treated with intravenous steroids. Fifty-nine patients (55.6%) showed an incomplete or absent response to steroids. Of those, 34 patients (57.6%) received salvage therapy. The drug of choice in 25 patients was infliximab and cyclosporine in 8 patients. One patient received sequential therapy with cyclosporine and infliximab. Thirty-four patients (31.5%) underwent surgery, 26 during the current admission, and 8 during the first year of follow-up. The median time to colectomy was 27 days (range 1-320). The estimated colectomy-sparing effect of salvage therapy was 73.5%, 70.6% and 64.7% at 0, 1 year and 2 years, respectively. Finally, 4 patients (3.7%) died during admission: 3 from severe nosocomial infections leading to multi-organ failure, and 1 during emergency surgery for toxic megacolon.

Endoscopic evaluation

There were no complications associated with endoscopy. Median endoscopic scores were as follows: Mayo 3 (range 1-3), seg-Mayo 6 (range 1-6), UCEIS 5 (range 2-8) and seg-UCEIS 10 (range 3-15). There was a moderate correlation between the Mayo and UCEIS scores (Spearman's rho 0.460, $p = 0.001$) and between each original classification and its respective segmental score-Mayo and seg-Mayo (Spearman's rho 0.671, $p = 0.001$) and UCEIS and seg-UCEIS (Spearman's rho 0.878, $p = 0.001$). There was a low-moderate correlation between the rectum and sigmoid endoscopic evaluation according to the seg-Mayo (Spearman's rho 0.539, $p < 0.001$) and moderate according to the seg-UCEIS (Spearman's rho 0.694, $p < 0.001$) (Fig. 1). We did not find a correlation between the endoscopic scores and the Truelove and Witts criteria. Rectal sparing (Mayo endoscopic sub-score of 0 or 1) was present in 13 patients (12.0%), only 2 of which were under topical 5-aminosalicylates.

Study endpoints

Rescue therapy

There was no significant association between the Mayo ($p = 0.450$), seg-Mayo ($p = 0.381$), UCEIS ($p = 0.297$) and seg-UCEIS ($p = 0.715$) and the requirement of salvage therapy with either infliximab or cyclosporine.

Steroid refractoriness

The mean seg-Mayo (5.13 ± 1.30 versus 5.48 ± 1.13 , $p = 0.049$) and seg-UCEIS (8.77 ± 2.57 versus 10.14 ± 2.59 , $p = 0.008$) were significantly higher in patients who were steroid refractory. The Mayo ($p = 0.233$) and UCEIS ($p = 0.062$) were not statistically significant. Statistically significant receiver operating characteristic curve predictive of steroid refractoriness was observed only with the seg-UCEIS (AUROC 0.649, 95% CI 0.545-0.754, $p = 0.009$) and not with the Mayo ($p = 0.468$), seg-Mayo ($p = 0.113$) or UCEIS ($p = 0.071$). The proportion of steroid-refractory patients increased from 0% with a seg-UCEIS of 3/4 to 85.7% with a seg-UCEIS of 14/15 ($p = 0.045$). Patients with a seg-UCEIS score of 14 had a risk 17 times higher of developing steroid-refractory disease ($p = 0.011$).

Colectomy

Patients who required surgery had significantly higher Mayo (2.72 ± 0.59 versus 3.0 ± 0 , $p = 0.004$), seg-Mayo (5.06 ± 1.37 versus 5.88 ± 0.41 , $p = 0.001$), UCEIS (4.69 ± 1.35 versus 5.82 ± 0.97 , $p < 0.001$) and seg-UCEIS (8.75

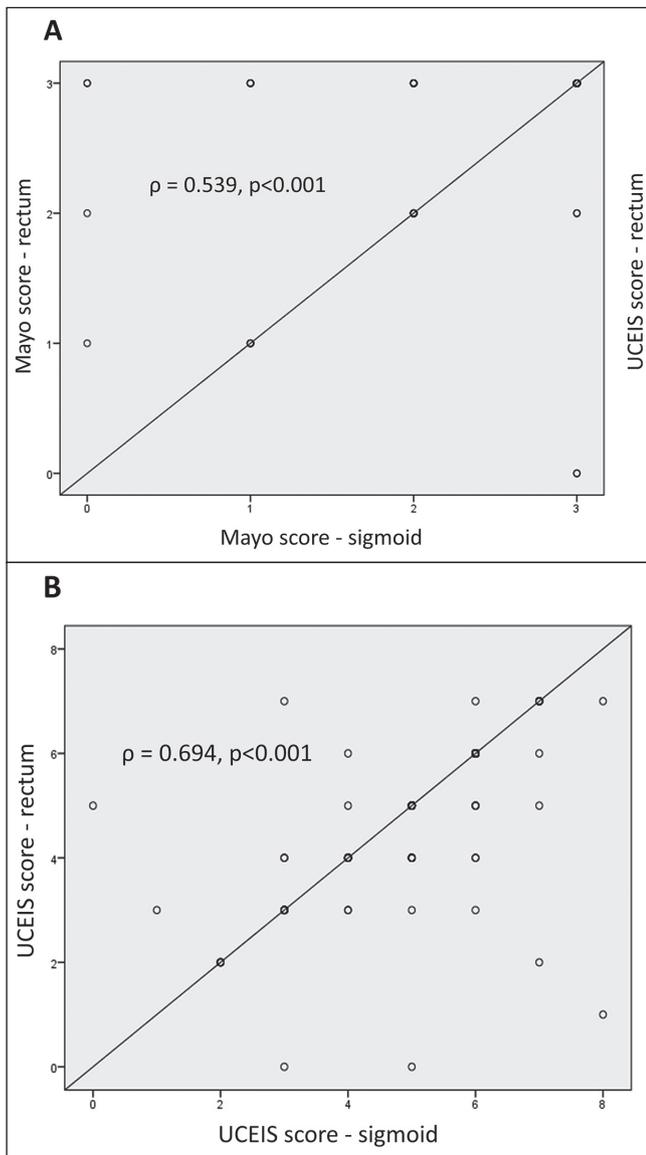


Fig 1. Scatter plot showing the correlation (Spearman's rho) between the endoscopic scores of the rectum and sigmoid, using the Mayo (A) and the UCEIS (B) scores.

± 2.66 versus 11.15 ± 1.83 , $p < 0.001$) scores (Fig. 2). The seg-Mayo (AUROC 0.663 95% CI 0.560-0.766, $p = 0.007$), UCEIS (AUROC 0.736 95% CI 0.640-0.833, $p < 0.001$) and seg-UCEIS (AUROC 0.755 95% CI 0.664-0.847, $p < 0.001$), but not the Mayo ($p = 0.081$), were significant predictors of the need for colectomy. Of note is the fact that as endoscopic severity increased so did the likelihood of requiring surgery. The proportion of patients requiring colectomy increased from 0% with a Mayo score of 1 to 37.8% with a Mayo score of 3 ($p = 0.103$); from 0% with a seg-Mayo of ≤ 2 to 40.7% with a seg-Mayo of ≥ 5 ($p = 0.03$); from 0% with an UCEIS ≤ 3 to 69.2% with UCEIS ≥ 7 ($p < 0.001$), and from 0% with a seg-UCEIS of ≤ 4 to 71.4% with a seg-UCEIS of ≥ 14 ($p = 0.01$).

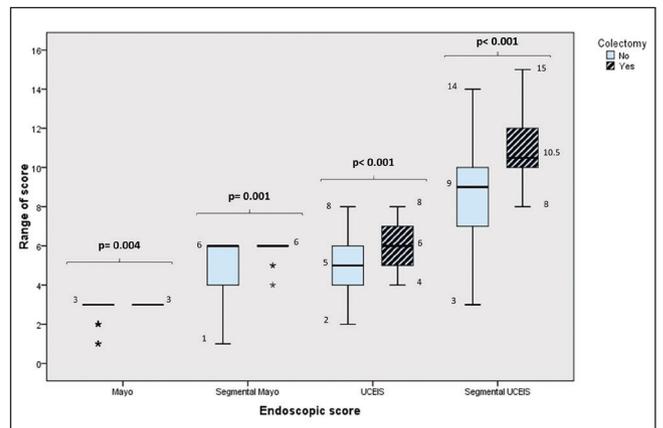


Fig 2. Box-and-whisker plot showing the difference in endoscopic severity between patients who underwent surgery compared with those that did not undergo surgery. The p value was determined by the independent samples Mann-Whitney U test.

Kaplan-Meier survival curve analysis showed a clear effect of increasing endoscopic severity on colectomy-free survival (Fig. 3). Patients with a seg-UCEIS ≥ 14 had less than a 30% chance of avoiding surgery at 1 year (long-rank test, $p < 0.001$). In a multivariate regression analysis including age, gender, disease extension, Truelove and Witts' score, C-reactive protein and endoscopic score, only the Truelove and Witts' score and UCEIS/seg-UCEIS were independently associated with colectomy (Table II). Every 1-point increase in the UCEIS and seg-UCEIS increased the likelihood of surgery by 2.78 and 1.79, respectively. Patients with a seg-UCEIS score of 14 had a risk 25 times higher of requiring colectomy. The Mayo and seg-Mayo were not independent predictors of colectomy.

DISCUSSION

Despite the recent advances in the management of acute severe ulcerative colitis, the disease still carries a poor prognosis, requiring prompt recognition and initiation of medical therapy. Only 50-70% of patients with acute severe colitis will show a significant response to intravenous steroids (4), and even with salvage therapy with infliximab or cyclosporine, at best, half of them will be saved from immediate surgery (20). Delayed surgery has been associated with increased postoperative complications (21). Early and reliable predictors of treatment response are warranted. A recent study has shown that the UCEIS score was able to predict the need for salvage therapy and colectomy in the setting of acute severe ulcerative colitis (10). To our knowledge, our study is the first comparing the Mayo and the UCEIS in this setting. Our results show a clear superiority of the UCEIS over the Mayo endoscopic sub-score in assessing the need for surgical treatment. Steroid-refractory disease is defined by a lack of a meaningful clinical response to steroids with doses of up to 40 to

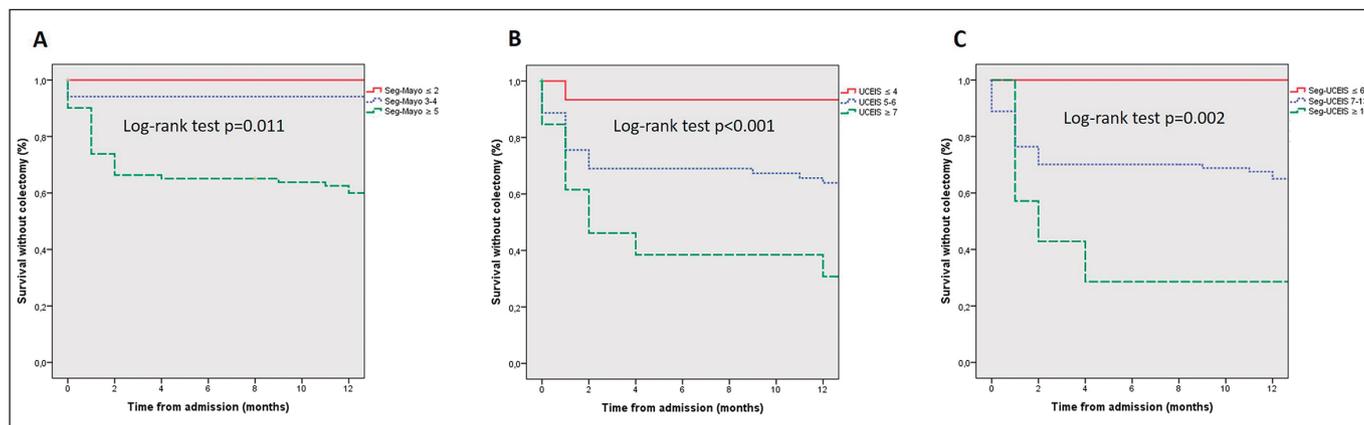


Fig 3. Kaplan-Meier survival curves showing the colectomy-free survival at 1 year according to the segmental Mayo (A), UCEIS (B) and segmental UCEIS (C). The p value was determined using the log-rank test.

Table II. Multivariate logistic regression analysis of colectomy. Age, gender, disease extension, Truelove and Witts' score, C-reactive protein and each endoscopic score were included in the analysis. Data is shown only for significant values

	Endoscopic score	Female gender	Truelove and Witts score
Mayo	NC, $p = 0.998$	0.22 (0.05-0.89), $p = 0.034$	2.45 (1.20-5.03), $p = 0.014$
Seg-Mayo	5.82 (0.940-36.043), $p = 0.058$	0.19 (0.04-0.87), $p = 0.032$	2.52 (1.19-5.35), $p = 0.016$
UCEIS	2.78 (1.48-6.77), $p = 0.003$	-	2.38 (1.11-5.07), $p = 0.025$
Seg-UCEIS	1.79 (1.23-2.61), $p = 0.003$	-	2.23 (1.05-4.76), $p = 0.038$

Mayo: Mayo endoscopic score; Seg-Mayo: Mayo segmental endoscopic score; UCEIS: Ulcerative colitis endoscopic index of severity; Seg-UCEIS: Segmental ulcerative colitis endoscopic index of severity; NC: Not statistically computable. Values are expressed as odds ratio (95% confidence interval), p value.

60 mg/day (or equivalent) of prednisone by the third day of admission. As the rates of salvage therapy and colectomy significantly increase in the presence of steroid refractoriness, a method capable of predicting this outcome is of the utmost importance. However, neither the Mayo nor UCEIS were capable of assessing this endpoint. Unusual endoscopic patterns have long been recognized in ulcerative colitis. Rectal sparing, for example, is reported in up to 13% of patients with fulminant colitis, but its prognostic value remains unknown (22). Of note, 12% of our patients presented rectal sparing, but only 15.4% were treated with topical aminosaliclates, reinforcing that fact that different expressions of ulcerative colitis exist. We have demonstrated that the pattern of endoscopic severity significantly differed between the rectum and sigmoid using both the Mayo and UCEIS scores. Based on this observation, we hypothesized that segmental scoring, combining disease severity and the extent of inflammation, would significantly improve our previous results. The resulting segmental scores proved to be superior to their original versions, accurately predicting both the need for surgery and the occurrence of steroid refractoriness. Nevertheless, the segmental Mayo score produced only marginally significant results ($p = 0.06$). As a result, the segmental UCEIS probably represents the most reliable segmental score. However, our results need to be interpreted with caution. First of all,

segmental endoscopic scoring was performed retrospectively. While the agreement between raters was good, our results need to be confirmed in a prospective study with central validation. Unfortunately, the number of patients admitted with this condition even in high-volume centers is small, making prospective studies in acute severe colitis very difficult to perform. In spite of this, our sample size is robust, representing one of the largest published studies on this topic. Unlike the Oxford study (10), we could not predict the need for salvage therapy irrespective of the score. Nevertheless, our endpoint of steroid refractoriness is probably more important as it truly reflects the pool of patients who will not respond to steroids and will require salvage therapy with infliximab, cyclosporine or surgery. Furthermore, we have confirmed our hypothesis that not only the severity of inflammation but also the extension of inflammation is determinant for the outcome of acute severe colitis.

In conclusion, in spite of some limitations of our study, we clearly show that the UCEIS is superior to the Mayo endoscopic score in predicting the need for surgery. A simple modification of the UCEIS (including the information provided by assessing both the rectum and sigmoid) appears to be more accurate in assessing the severity of the episode of acute severe colitis, being able to identify steroid non-responders. The early and adequate use of the

information provided by the flexible endoscopy may further assist clinicians in managing difficult patients with severe ulcerative colitis.

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