

**Title:**

**Performance of existing predictive scores of response in patients with moderately active ulcerative colitis treated with oral corticosteroids.**

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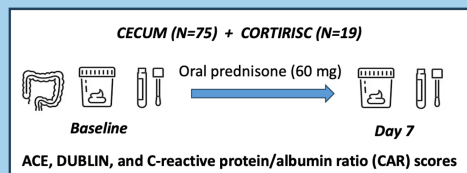
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## Performance of existing predictive scores of response in patients with moderately active ulcerative colitis treated with oral corticosteroids.

**Background:** The prediction of response to corticosteroids (CTS) in ulcerative colitis (UC) might allow for early introduction of advanced therapies.

**Aim:** To evaluate the performance of established indexes for the prediction of early response to CTS in patients with moderately active UC treated with oral prednisone and identify baseline predictors of response.

**Methods:** Data from two prospective clinical studies in patients with moderate UC treated with oral prednisone were analysed.

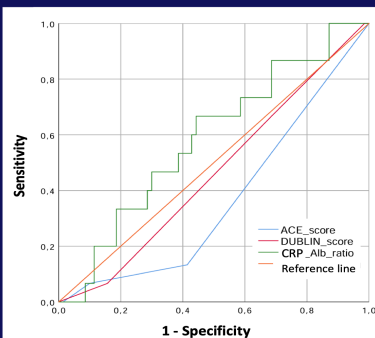


**Non-response at day 7:** rectal bleeding in >50% of bowel movements and >3 additional bowel movements from baseline.

**Conclusions:** The existing clinical-biological scores developed for therapeutic response in severe UC lack predictive accuracy for moderate UC flares treated with oral corticosteroids. Novel, tailored prediction tools are needed in this clinical setting.

**Results** N= 94; 51% extensive UC; 17% non-responders

Most patients met high-risk scores for the DUBLIN score, 17% for CAR index, whereas only one patient met the high-risk ACE score.



• None of the evaluated indexes showed a good predictive accuracy for lack of response.

• Younger age at baseline ( $p = 0.04$ ) and shorter disease duration at admission ( $p = 0.012$ ) were the only variables associated with lack of response.

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## Performance of existing predictive scores of response in patients with moderately active ulcerative colitis treated with oral corticosteroids

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*Abbreviations list*

UC: ulcerative colitis

CAR: C-reactive protein/albumin ratio

ACE: Albumin, C-reactive protein, and Endoscopy score

DUBLIN: Degree of Ulcerative colitis Burden of Luminal INflammation score

ASUC: acute severe ulcerative colitis

TNF: tumor necrosis factor

IBD: inflammatory bowel disease

MES: Mayo endoscopic subscore

ADMIT-ASC: Acute severe colitis score including Albumin, CRP, and Endoscopy

CECUM: Corticosteroid Efficacy in moderately active Ulcerative colitis trial

GETECCU: Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa

CIBEREHD: Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas

CI: confidence interval

IQR: interquartile range

**ABSTRACT**

*Background:* The prediction of response to corticosteroids in ulcerative colitis (UC) might allow early introduction of advanced therapies. Predictive scores have been proposed for severe UC, but their performance in moderate flares is unknown.

*Aim:* To evaluate the performance of established indexes to predict early corticosteroid response in moderately active UC patients treated with oral prednisone and identify baseline predictors of response.

*Methods:* Data from two prospective clinical studies in patients with moderate UC treated with oral prednisone were analysed. All patients underwent a colonoscopy before starting corticosteroids and clinical and biological assessments at baseline and after seven days. Non-response was defined as the persistence of rectal bleeding in >50% of bowel movements and >3 additional bowel movements from baseline after seven days of therapy or if rescue therapy was prescribed. ACE, DUBLIN, and C-reactive protein/albumin ratio (CAR) scores were calculated.

*Results:* Among 94 patients (51% extensive colitis), 44 achieved clinical remission and 16 were classified as non-responders at day 7. Most patients met high-risk scores for the DUBLIN score, 17% for CAR index, whereas only one patient met the high-risk ACE score. No index reliably predicted non-response. In the univariate analysis, younger age at baseline ( $p = 0.04$ ) and shorter disease duration at admission ( $p = 0.012$ ) were the only variables associated with lack of response.

*Conclusions:* The existing clinical-biological scores developed for therapeutic response in severe UC lack predictive accuracy for moderate UC flares treated with oral corticosteroids. Novel, tailored prediction tools are needed in this clinical setting.

**Keywords:** Ulcerative colitis. Corticosteroids. Lack of response. Prediction.

## INTRODUCTION

Ulcerative colitis (UC) is a relapsing-remitting, chronic, immune-mediated disease. In population-based studies, half of the patients with UC achieve disease control with mesalazine, while the other half require at least one course of systemic corticosteroids in their lifetime [1]. To date, an inadequate response to corticosteroids (i.e. refractoriness or dependency) remains the main reason for the introduction of advanced therapies in UC. Although some factors, such as extensive disease, smoking status, the proximal spread of distal forms of the disease and the presence of systemic manifestations, have been associated with a worse prognosis of UC [2], the available evidence does not support the early introduction of advanced therapies in patients with UC [3,4].

Recently, two randomized controlled trials have prompted a shift towards a more intensive therapeutic approach in patients suffering an acute severe flare of UC (ASUC), a clinical scenario that occurs in up to 25% of patients with UC and is associated with a high rate of colectomy in the short and midterm [5]. Singh et al demonstrated that the addition of tofacitinib to intravenous corticosteroids was more effective than using corticosteroids alone (the gold standard in this clinical setting) [6]. Amiot et al, exploring a different strategy for ASUC, showed that anti-TNF maintenance treatment is more effective than azathioprine in patients responding to intravenous corticosteroids for ASUC [7]. Therefore, for the first time, advanced therapies seem to be indicated in cases of ASUC, regardless of response to intravenous corticosteroids.

Moderately active UC remains a grey zone. In this clinical setting, remission rates after a conventional course of oral corticosteroids range between 40% and 50% [8,9], which is similar to intravenous corticosteroids in ASUC. In those patients with moderate flares in whom oral corticosteroids achieve clinical remission and can be successfully discontinued, the need for immunosuppressive therapies at five years exceeds 50% [10]. The identification of those patients who will not respond to oral corticosteroids would allow for the early introduction of advanced therapies in moderately active UC.

In recent years, several scores have been developed and validated to predict clinical response and outcomes, mainly in ASUC, using simple clinical and laboratory

parameters [11,12,13,14]. However, their usefulness has not been assessed in moderate flares treated with oral corticosteroids.

This study aims to assess the performance of existing predictive scores and identify factors associated with a lack of response to oral corticosteroids in patients treated for moderately active UC.

## METHODS

This is a retrospective analysis of the individual data from two prospective, controlled studies that included patients with moderately active UC who were treated with oral corticosteroids. The CECUM trial was a prospective, open, multicentre, randomised, controlled study in patients with moderately active UC conducted at 28 Spanish inflammatory bowel disease (IBD) units, which aimed to assess the efficacy of adding high-dose corticosteroid pulses to a conventional course of oral corticosteroids in patients with moderately active UC [9]. The CORTIRISC study was a prospective, single-centre study that aimed to assess the incidence of adrenal insufficiency in patients with IBD treated with a conventional course of oral corticosteroids [15]. In both studies, patients were excluded if they met criteria for steroid-dependency at any time, if they had received systemic corticosteroids for UC in the last six months before inclusion or if disease extent was limited to the rectum. In both studies, at the time of inclusion, patients had to have moderate disease activity as defined by a complete Mayo score between 6 and 10 points. Both study protocols were approved by the corresponding Clinical Research Ethics Committees and written informed consent was obtained from all patients. In both studies, patients underwent a complete clinical, biological and endoscopic assessment at baseline. Once included in the study, patients were treated with oral prednisone 60 mg/day for one week followed by a pre-established tapering schedule. Both studies conducted a clinical and blood laboratory assessment after seven days of corticosteroid treatment.

The main outcome of the present study was the *lack of clinical response* at day seven as defined by rectal bleeding in more than 50% of bowel movements, together with three or more bowel movements than usual. As secondary outcomes, we defined *partial clinical response* as a partial Mayo score  $<4$  with no rectal bleeding, and *clinical remission* as a stool frequency score  $<2$  with no rectal bleeding, both of which were also assessed at day seven.

For study purposes, the C-reactive protein (CRP)/albumin ratio (CAR) [13], the Degree of Ulcerative colitis Burden of Luminal Inflammation (DUBLIN) score (product of the Mayo endoscopic score [0-3] and disease extent [proctitis 1 point, left-sided UC 2 points and extensive UC 3 points]) [11] and the ACE score (the addition of 1 point for CRP  $>50$  mg/L, 1 point for albumin  $<30$  g/L and 1 point in case of severe Mayo endoscopic subscore -MES-) [12] were calculated at baseline. The high-risk cut-off points for lack of response or bad outcomes reported for these scores are  $>3$  points for the DUBLIN score, 3 points for the ACE index, CAR index  $>0.85$ .

All the patients included in both trials were included in the analysis. Those patients not reaching the clinical assessment at day seven because of clinical worsening, lack of clinical improvement or need for earlier rescue therapy were considered to have lack of clinical response.

### *Statistical analysis*

Qualitative variables are presented as frequencies with 95% confidence intervals (CI), while quantitative variables are presented as mean and standard deviations (normal distribution) or median and interquartile ranges (IQR) (non-normal distribution). Categorical variables were compared using the Chi-square test, and quantitative variables by the Student's *t*-test. Those variables with a *p* value lower than 0.1 were included in a multivariate logistic regression analysis to identify those factors associated with the lack of response at day 7.

Receiving operating curves (ROC), sensitivity and specificity, negative predictive value (NPV) and positive predictive value (PPV) were measured for each predictive score.



Accepted Article

## RESULTS

### *Baseline characteristics of the whole cohort*

A total of 94 patients were included, with a median age of 48 years ( $\pm 15$ ; IC95% 44.9-51.3), of whom 43% were female, 49% had left-sided colitis and 51% extensive disease. The median duration of UC was 53 months (IQR 14–133; IC95% 63.8-111.6) and 20% of cases were included at UC onset (first flare). A total of 29% of patients had previously been exposed to corticosteroids (>6 months before inclusion).

Regarding disease activity, the mean modified Mayo score was 4.3 points ( $\pm 1.2$ ). Sixty-nine percent of patients had moderate endoscopic activity (MES = 2) and 30% severe endoscopic activity. Median CRP level was 11 mg/L (IQR 3.8–21.8; IC95% 12.3-26), median faecal calprotectin (FC) was 1,530  $\mu\text{g/g}$  (IQR 542–3,015; IC95% 1,484.2-2,193.4), and mean serum albumin was 39.25 g/L ( $\pm 5.4$ ; IC95% 38.2-40.5). The mean DUBLIN score was 1 ( $\pm 1.67$ ) and the median ACE and CAR indexes were 0 (IQR 0-1) and 0.27 (IQR 0.09-0.58), respectively. Regarding the existing high-risk cut-off points for the predictive scores, 98% of patients had a DUBLIN score >3, one patient (1%) a high-risk ACE index (3 points), and 16% a CAR index >0.85.

No differences regarding baseline characteristics of the patients were observed according to the cohort of origin (**supplementary Table 1**).

### *Early response to oral corticosteroids*

After one week, 17% of patients met the criteria for lack of response to oral corticosteroids, 47% for clinical remission and 36% for partial response.

**Figure 1** shows the distribution of values of each of the evaluated indexes. Most of the patients had a high DUBLIN score and one a high ACE score. Regarding the CAR index, 17% of patients were scored as at risk. None of the evaluated indexes showed a good predictive accuracy for lack of response. The receiving operating curves, sensitivity,

specificity, and negative and positive predictive values are shown in **Figure 2** and **Table 1**.

In the univariate analysis, younger age at baseline ( $41.6 \pm 14.5$  years vs.  $49.9 \pm 14.4$  years;  $p = 0.04$ ) and shorter disease duration at admission ( $25.5$  (12.7-97.3) months vs.  $68.4$  (13.2-146.5) months;  $p = 0.012$ ) were the only variables associated with lack of response. No significant differences were found in relation to surrogate markers of severity such as MES, baseline CRP, albumin and faecal calprotectin levels (**Table 2**). In the multivariate logistic regression analysis only younger age was an independent risk factor for lack of response (OR 0.96, IC 95% 0.92-0.99;  $p=0.045$ ).

Given the results obtained, we performed a further analysis searching for clinical and laboratory factors associated with early clinical remission (at day seven). However, in the univariate analysis, only a baseline Mayo stool frequency  $<2$  points was associated with a higher likelihood of early remission ( $p = 0.002$ ). A baseline Mayo stool frequency  $<2$  points and a shorter disease duration were also significantly associated with a higher likelihood of partial clinical response at day seven ( $p=0.004$  and  $p=0.003$ , respectively).

## DISCUSSION

Patients with UC who require a conventional course of oral corticosteroids will most likely require immunosuppressants and advanced therapies. In fact, 50% of these patients do not achieve clinical remission with oral corticosteroids [9] and 25% relapse within the following five years despite being good responders to corticosteroids [10]. Our group demonstrated that simple clinical and biologic parameters after three days of corticosteroid treatment are useful for predicting early response to oral corticosteroids [16], as demonstrated by Travis et al in ASUC [17]. However, the present study shows that most of the available predictive indexes of response before starting treatment for severe flares did not perform accurately for moderately active UC treated with oral corticosteroids.

We aimed to assess the predictive performance of two of these indexes, the ACE and CAR, which were developed for ASUC. They include few parameters, which are easily obtainable in clinical practice, such as CRP, albuminaemia and endoscopic activity, and which reflect disease severity. A cut-off for non-response prediction was provided for both indexes. However, only a small proportion of patients in our cohort received high-risk scores, and this was the main reason for their unreliability in moderate disease. We also analysed other cut-off points for these indexes, unsuccessfully. Due to the data gathered in the two databases used, we were unable to assess the performance of a similar index, the ADMIT-ASC [18], which is essentially the same as the ACE but uses a different endoscopic assessment. However, the cut-off points for CRP and albuminaemia in the ADMIT-ASC entail a much more severe form of disease, and it is therefore unlikely to have performed better than ACE in our cohort. Similarly, other surrogate markers of inflammation such as neutrophil-to-lymphocyte ratio were not available and could not be assessed in this study. Finally, we also assessed the DUBLIN score because it was not specifically developed for severe UC and it has a wider scoring range. Unlike the other indexes, most of the patients in our cohort had high DUBLIN scores. However, this index did not adequately predict non-response to oral corticosteroids.

In addition to the performance of some of the available indexes, we assessed the factors associated with the lack of early response to oral corticosteroids. We found that younger age and a shorter disease duration were associated with the lack of response to oral corticosteroids. Requiring corticosteroids soon after UC diagnosis has been repeatedly reported as a risk factor for non-response [19], colectomy and steroid-dependency [20,21]. However, although one fifth of patients in our cohort were included at disease onset, the median disease duration among non-responders was almost five years, markedly longer than the 6-12 months reported in the aforementioned studies. Regarding age, it has also been reported that younger age at disease onset may be associated with a more frequent use of advanced therapies and colectomy [22]. Therefore, although there are no well-established thresholds for age and disease duration, young patients requiring oral corticosteroids for moderately

active UC within the first months after diagnosis should be closely monitored. Whether this justifies the early introduction of advanced therapies alongside or instead of oral corticosteroids remains to be established.

We chose non-response as the main endpoint in our study because this is a clinical scenario in which advanced therapies are clearly indicated and it can be clearly identified within days after starting corticosteroids. However, as expected, only 17% of the patients met our non-response criteria. In order to find additional predictive tools in moderately active UC, we also included early clinical remission at day seven as a secondary endpoint and a surrogate of “excellent responders”. However, only a low score for stool frequency at baseline was associated with this endpoint. Finally, we also included partial clinical response. This is not uncommon and accounted for almost half of our patients after seven days of corticosteroid treatment. Although this situation might be considered of little relevance, it has been reported that partial clinical response is associated with significantly higher rates of clinical relapse, re-admission and chronically active disease at one year [17] and colectomy in the long-term [23], in patients with ASUC. However, mid and long-term outcomes of partial responders to oral corticosteroids in moderately active UC has never been assessed. Moreover, a widely accepted definition of partial response is still lacking and the most appropriate time for the evaluation of partial response has not been proposed as yet [24].

We are aware of certain limitations of our study. First, endoscopic assessments at baseline were performed by the local investigators (no central reading was available) and this introduces a potential source of variability in baseline endoscopic severity. Second, early response assessment included clinical and biological but not endoscopic parameters, leading to a more subjective evaluation of outcomes. Third, faecal calprotectin measurements were not available at day seven. This precluded the use of faecal calprotectin reduction or even normalization as a surrogate marker of mucosal (endoscopic) improvement. In spite of these limitations, this is the first study evaluating the prediction of response to oral corticosteroids in moderately active UC.

The use of individual data from two prospective, controlled trials sharing selection criteria, treatment schedules and baseline and early response assessments are the greatest strengths of our study.

In conclusion, the existing clinical-biological scores developed for the prediction of therapeutic response in severe UC do not perform suitably for moderate UC flares treated with oral corticosteroids. The ACE index showed an AUC lower than chance, the DUBLIN index showed a complete absence of discriminative ability and, although the CAR reached the highest AUC value, it had a moderate sensitivity and limited specificity. These findings suggest that indices developed for severe UC are not applicable in the context of a moderate flare treated with oral corticosteroids, possibly due to differences in pathophysiology, inflammatory burden, and therapeutic response kinetics. Our results warrant future research into novel, tailored prediction tools in this clinical setting, maybe including factors related to systems biology instead of inflammatory severity.

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**Data transparency statement.** The deidentified data underlying this article will be shared on reasonable request to the corresponding author.

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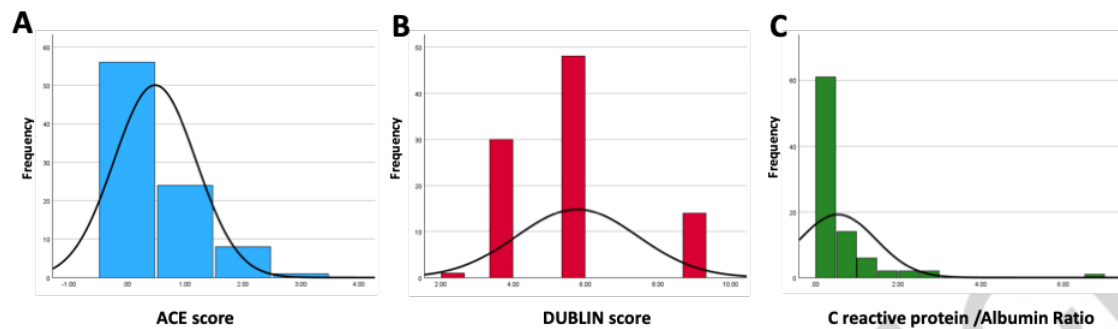
**Table 1.** Predictive accuracy for lack of response of the different indexes. CAR= C-reactive protein/albumin ratio; AUC= area under the curve; IC95%= interval confidence 95%; PPV= positive predictive value; NPV= negative predictive value.

| Index  | AUC (IC95%)        | p     | Cut-off point<br>(Youden) | Youden's<br>index | Sensitivity<br>(%) | Specificity<br>(%) | PPV<br>(%) | NPV<br>(%) |
|--------|--------------------|-------|---------------------------|-------------------|--------------------|--------------------|------------|------------|
| ACE    | 0.39 (0.22 - 0.51) | 0.105 | —                         | 0.000             | 18.8               | 59.2               | —          | —          |
| DUBLIN | 0.49 (0.31 - 0.62) | 0.657 | 5.0                       | 0.021             | 68.8               | 33.3               | —          | —          |
| CAR    | 0.58 (0.43 - 0.74) | 0.305 | 0.2856                    | 0.216             | 66.7               | 54.9               | 25         | 75         |

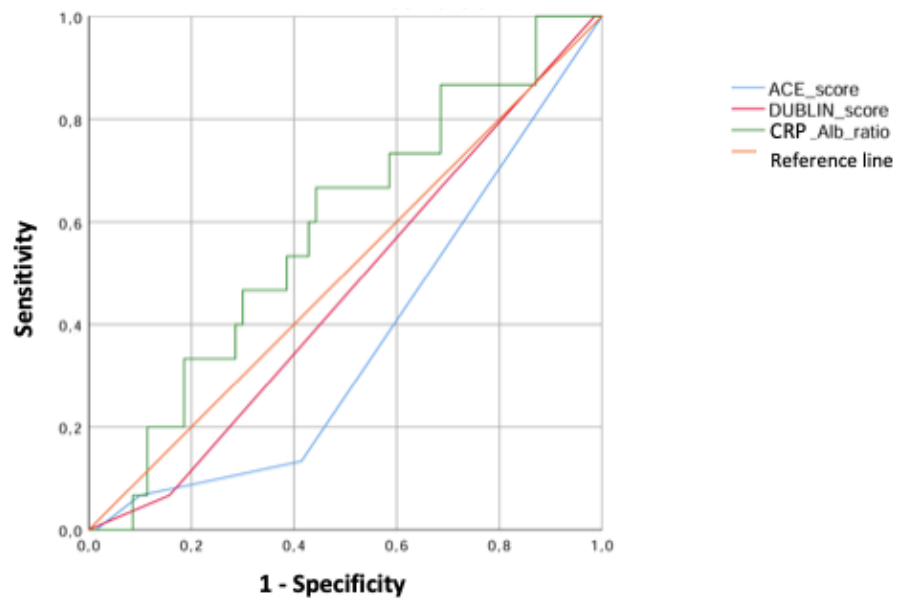
**Table 2.** Variables associated with lack of response to oral corticosteroids at day seven (univariate analysis). UC= ulcerative colitis; CAR = C-reactive protein / albumin ratio.

| Variable                            | Non-responders          | Responders          | p-value |
|-------------------------------------|-------------------------|---------------------|---------|
| Age (years)                         | 41.6 ± 14.5             | 49.9 ± 14.4         | 0.040   |
| Female sex (%)                      | 62.5                    | 39.5                | 0.091   |
| UC at onset (%)                     | 12.5                    | 22.4                | 0.375   |
| Duration of UC (months)             | 25.5 (12.7-97.3)        | 68.4 (13.2-146.5)   | 0.012   |
| UC duration <6 months (%)           | 6.3                     | 19.7                | 0.196   |
| Extensive UC (%)                    | 68.8                    | 49.3                | 0.158   |
| Previous corticosteroid use (%)     | 43.8                    | 26.3                | 0.164   |
| Baseline C-reactive protein (mg/L)  | 11.9 (4.1-26.2)         | 9.3 (3.6-18.6)      | 0.971   |
| Baseline faecal calprotectin (µg/g) | 2,042 (1,157.5-3,477.5) | 1,335 (489.8-2,905) | 0.395   |
| Baseline albumin (g/L)              | 37.9 ± 4.9              | 39.5 ± 5.4          | 0.792   |
| C-reactive protein >5 mg/L (%)      | 68.8                    | 68.5                | 0.984   |
| Albumin <30 g/L (%)                 | 6.3                     | 9.8                 | 0.683   |
| Mayo endoscopic subscore = 3 (%)    | 12.5                    | 32.9                | 0.103   |
| CAR                                 | 1 (1-1)                 | 1 (1-1)             | 0.949   |
| CAR >0.85 (%)                       | 20                      | 15.5                | 0.667   |

## Figure legends



**Figure 1.** Distribution of the values in the different scores in the overall study cohort.



**Figure 2.** Receiver operating characteristic curves for ACE, DUBLIN, and C- Reactive protein/Albumin ratio indices in the overall cohort.