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Faecal Calprotectin and UCEIS Predict Short-term Outcomes in Acute Severe Colitis: Prospective Cohort Study

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Abstract

Background and Aims: Early objective markers for failure of intravenous[iv] corticosteroid for acute severe colitis [ASC] can avoid delay in rescue therapy or colectomy. We investigated faecal calprotectin [FC], C-reactive protein [CRP], and endoscopy using the ulcerative colitis endoscopic index of severity [UCEIS] as predictors of steroid failure following intensive therapy of ASC.
Methods: Consecutive patients with ASC satisfying Truelove and Witts' criteria, hospitalised at a single centre from May 2015 to November 2016, were included; all received iv corticosteroids. The primary outcome measure was steroid failure defined as colectomy and/or rescue therapy with ciclosporin or infliximab during admission. FC levels were measured at admission and on Day 3 of intensive therapy. UCEIS was scored at admission, and CRP on Day 3 of intensive therapy.
Results: Of 49 patients, 21 [43%] failed iv corticosteroids and 15 [31%] underwent surgery. FC levels were significantly higher in steroid failures (2522 [590–9654] µg/g) compared with steroid responders (1530 [352–10 278] µg/g) at admission [$p = 0.04$], as well as on Day 3 of iv corticosteroid therapy (2718 [222–9175] µg/g vs 727 [218–4062] µg/g, $p = 0.001$). Steroid failures had a higher median [range] UCEIS score than responders (6 [4–8] vs 5 [4–7] [$p = 0.001$]). CRP level did not differ significantly between steroid failures and responders. A UCEIS > 6 at admission and FC > 1000 µg/g on Day 3 were independent predictors of steroid failure and need for rescue therapy/colectomy.
Conclusions: All patients with UCEIS > 6 and Day 3 FC > 1000 µg/g failed iv corticosteroids. The UCEIS score on admission and Day 3 FC are early predictors of failure of ivcorticosteroid therapy.

Key Words: Acute severe colitis; steroid failure; prediction

1. Introduction

Acute severe colitis [ASC], defined by Truelove and Witts' criteria, is a medical emergency requiring hospitalisation and time-bound management.ASC complicates the course of ulcerative colitis [UC] in up to 25% of cases, with a third of these episodes being the presentation of UC.[1,2] Corticosteroids remain first-line therapy for ASC, with a colectomy rate of 29% that has not changed since the 1970s.[3] Delay in surgery has been associated with worse outcomes.[4,5] There is therefore a need to identify at an early stage those patients at high risk of iv corticosteroid therapy failure, thereby identifying patients in need of surgery or second-line 'rescue' therapy. Several indices have been proposed as predictors of lack of response to

corticosteroids,[6–9] with stool frequency and CRP at Day 3 [Oxford criteria] being most widely adopted.[10] They are, however, based on stool frequency which is a patient-reported outcome and a subjective clinical variable dependent on rectal inflammation, which may in turn be influenced by local therapy. There remains a need for objective markers to complement existing indices.

In this regard, faecal calprotectin[FC], a neutrophil cytosolic protein,[11] has emerged as a marker for disease activity in inflammatory bowel disease [IBD]. FC has been found to discriminate between mild, moderate, and severe endoscopic appearance of UC,[12] and a fall in FC predicts response to infliximab therapy in UC.[13,14] A prospective study of 90 patients with ASC showed that FC was significantly higher in patients undergoing colectomy during the hospital stay, with a [remarkably precise] level > 1992.5 µg/g associated with the need for colectomy within the next year.[15] In that study FC was measured between Days 0 and 4 of admission, so it was not possible to determine its value in predicting steroid response at an early stage.

Serum CRP level is a marker of systemic inflammation and can be used as marker of inflammatory burden in ASC. However results have been inconsistent, with a few studies finding CRP to be useful in predicting response to iv corticosteroid therapy in ASC,[7,8] and a few that did not.[6,9]

The Ulcerative Colitis Endoscopic Index of Severity [UCEIS], a validated index that accounts for 86–88% of intra- and inter-observer variability in the assessment of endoscopic severity,[16,17] has been shown to predict early and long-term response to anti-tumour necrosis factor alpha [TNFα] therapy[18,19] and predict steroid failure in ASC. In another retrospective study of 89 patients with ASC, the median UCEIS was significantly higher in steroid non-responders than responders [6 vs 5, $p = 0.005$] and a score of 7 or 8/8 was associated with the need for rescue therapy or colectomy in all patients.[20] The present study was designed prospectively to assess the role of FC on admission and Day 3 of intensive therapy, CRP level on Day 3, and UCEIS on admission, in predicting response to iv corticosteroid therapy in patients with ASC.

2. Methods

2.1. Patients

All patients with ASC as defined by Truelove and Witts' criteria [below], who were hospitalised at the All India Institute of Medical Sciences [AIIMS], New Delhi, from June 2015 to November 2016, were screened for inclusion. Secondary referrals, children aged < 18 years, and patients who had an emergency colectomy without receiving steroids, were excluded [ethical approval AIIMS IRB: IESC/T-277].

2.2. Definitions

Ulcerative colitis: diagnosis based on clinical, radiological and histological criteria.[21] Patients with index presentation of ASC that later turned out to be infection or Crohn's colitis were excluded.

Acute severe colitis: based on Truelove and Witts' criteria [six or more stools with blood and one or more of following: haemoglobin < 105 g/L, erythrocyte sedimentation rate > 30 mm/h, fever > 37.8°C, or tachycardia > 90/min.[10,22]

Steroid failure: use of rescue medical therapy (iv ciclosporin 2 mg/kg for up to 4 days, oral tacrolimus 0.1 to 0.2 mg/kg [adjusted to trough levels of 5–10 ng/mL], or infliximab 5 mg/kg, although cost constraints often mitigated against the latter) during hospitalisation[ie within 5–7 days of iv corticosteroid].

Disease extent: maximum macroscopic extent at colonoscopy preceding ASC according to Montreal classification.[23] For patients presenting with ASC at diagnosis, extent was determined from the first colonoscopy after discharge or the surgical specimen if they underwent colectomy.

Previous steroid use: any use of systemic corticosteroids before the index episode of ASC.

Steroid use in first year of diagnosis: corticosteroids in first year after diagnosis, including the ASC event if within the first year of diagnosis.

Charlson comorbidity index[24]: to record and stratify comorbidities.

UCEIS[17]: the sum of three descriptors: vascular pattern [scored 0–2]; bleeding [scored 0–3]; and erosions and ulcers [scored 0–3], range 0–8; assessed in the most severely affected area at flexible sigmoidoscopy [performed by SJ or SB]. Both operators had experience of grading endoscopic activity using the UCEIS in > 100 patients with ulcerative colitis, before the start of the study [Figure 1].

Faecal calprotectin: faecal samples were collected and stored at -80°C within 1 h of collection. All samples were analysed by sandwich ELISA using two antibodies to different epitopes of human calprotectin, in accordance with manufacturer's instructions [DIA source Immuno Assay SA, Belgium]. All samples were analysed at the end of the study. Laboratory personnel were blinded to the outcomes.

2.3. Study design

This was a prospective observational cohort study that collected data on baseline demographics, previous therapy for UC, plain abdominal radiograph, and endoscopic assessment of severity [UCEIS][17] by unprepared flexible sigmoidoscopy within 24 h of admission, clinical observations of pulse rate, temperature, blood pressure, and stool frequency, and laboratory parameters during the hospital stay. Serum CRP was done on Day 3 of iv corticosteroid therapy, and faecal samples were taken on admission for culture, *C. difficile* toxin assay by ELISA, and calprotectin, which was repeated on the first morning sample on Day 3 of iv corticosteroid therapy, where the day of admission was counted as Day 1. Outcome was failure to respond to iv corticosteroid therapy [use ofrescue therapy or colectomy, as above].

2.4. Management

All patients received intravenous and rectal hydrocortisone (400 mg/day [d] iv, 200 mg/d per rectum [pr]), while continuing 5-aminoxsalicylate [5ASA] therapy, according to guidelines,[25] as well as antibiotics [ciprofloxacin and metronidazole] given the

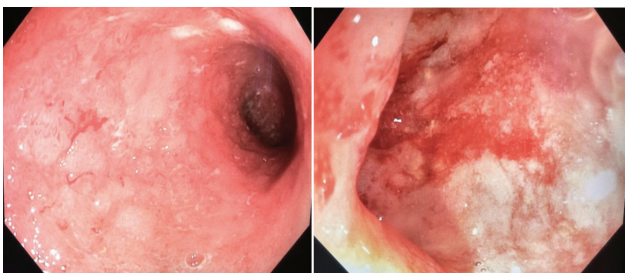

Figure 1. Flexible sigmoidoscopy image of patients showing a] Ulcerative Colitis Endoscopic Index of Severity [UCEIS] = 4 [V2/B1/U1 = 4/8]; and b] UCEIS = 7 [V2/B3/U2 = 7/8].

prevalence of gastrointestinal infection in India. Blood transfusion was given as required [haemoglobin < 80 g/L], and mucosal biopsies were taken at flexible sigmoidoscopy to exclude CMV infection. Oxford criteria[7] were used to identify patients at high risk of colectomy, and if unresponsive to 5–7 days of iv corticosteroids, rescue therapy or colectomy was advised. The choice, decision, and timing was made after joint medical-surgical review and patient counselling. Patients responding to iv corticosteroids were discharged on 40 mg/d prednisolone with a taper period of 3 to 4 months, along with azathioprine.

2.5. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation [SD] and non-Gaussian distribution as median and range. Categorical variables were summarised as frequencies with percentages. Quantitative variables at admission were compared using Student's t test or Mann-Whitney U test, and qualitative variables by chi-square test. Comparison of the means of continuous variables for two groups was based on analysis of variance or the nonparametric Kruskal-Wallis test, where indicated. Receiver operator characteristic curves were used to identify cut-off with optimal sensitivity and specificity. Clinically relevant variables with p-values < 0.1 were considered for multivariable analysis, which was performed for steroid failure as outcome variable. A subgroup analysis excluding patients with cytomegalovirus immunohistochemistry [CMV IHC] positivity was done to identify independent predictors of steroid failure in this subgroup; p- values < 0.05 were considered statistically significant. Analyses were performed using Stata software 11.2 [College Station, TX, USA]

3. Results

3.1. Patients

A total of 53 patients with 57 episodes of ASC were hospitalised during the study period; 8/53 were excluded [Figure 2], so 45 patients with 49 episodes of ASC were included in the study. Response to iv corticosteroids occurred in 28/49 episodes and failure in 21/49. Of the latter, 8/21 received rescue therapy [3 ciclosporin, 2 tacrolimus, 2 infliximab, and 1 patient received iv immunoglobulin[26,27]] and 15/21 had surgery, including 2 after rescue therapy.

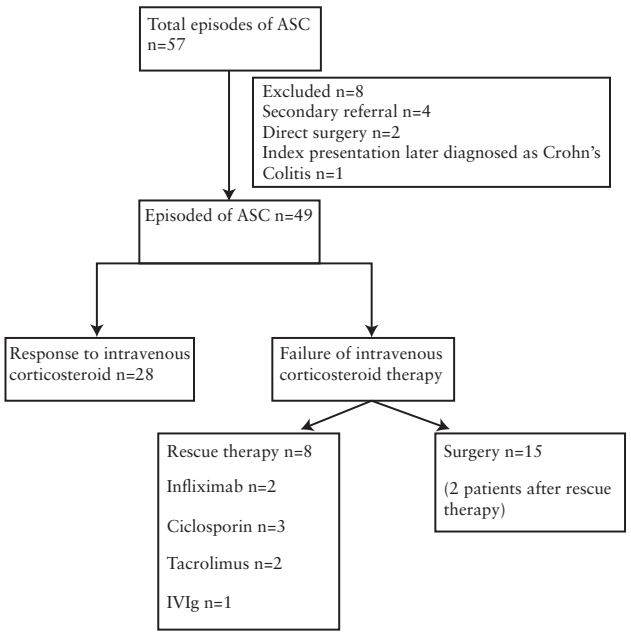

Figure 2. CONSORT diagram: study population.

3.2. Baseline demographic and clinical characteristics

Mean age on admission was 36 ± 12 years, 74% male, and 8% presented with ASC at diagnosis [see Table 1 for demographics]; 71% met two or more of Truelove and Witts' criteria on admission, and 33% had Charlson comorbidity index ≥ 1.

3.3. Clinical and laboratory parameters during hospitalisation

Median stool frequency on the day of presentation was 12 [6–20], which decreased to 7 [2–18] on Day 3 of iv corticosteroids [Table 2]. Median haemoglobin [range] was 98 [47–155] g/L and erythrocyte sedimentation rate]ESR] on admission was 45 [10–82] mm/h, and 25% received blood transfusion[s] [Table 2]. Median FC on admission was 1776 [352–10 278] µg/g and 880 [218–9175] µg/g on Day 3 [p = 0.03]. Median UCEIS was 5 [4–8]. Median CRP level on Day 3 of iv corticosteroid was 23.8 [1.4–209] mg/L. One patient was positive for *C difficile* toxin in stool and CMV IHC was positive in 10/49 [20%] episodes. Patients received iv corticosteroids for a median 5 [3–10] days, with duration of hospital stay being 11 [5–36] days. Four patients developed toxic megacolon, all of whom underwent colectomy. One patient died on postoperative Day 3 from ventricular arrhythmia due to hypokalaemia.

3.4. Comparison of clinical and laboratory parameters between corticosteroid responders and failures

Patients who failed iv corticosteroids [ie needing rescue therapy and/or colectomy] met a higher number of additional Truelove and Witts' criteria on admission (64% [3–4] vs 34% [1–2], p = 0.04) and a higher frequency of steroid use in the first year of diagnosis, although this did not quite reach significance (14/28 [76%] vs 16/21 [50%], p = 0.06). They also had a higher stool frequency on Day 3: 8 [3–18] vs 6 [2–10] [p = 0.02]. There was no difference in age of presentation, sex, extent of disease, duration of UC before ASC, previous use of azathioprine, steroids, or tobacco, comorbidities, or presence of extra-intestinal manifestations [EIMs].

3.4.1. Faecal calprotectin

FC was significantly higher in steroid failures than responders, both on admission (2522 [590–9654] µg/g vs 1530 [352–10 278] µg/g, p = 0.04]), and on Day 3 (2718 [222–9175] vs 726.5 [218–4062] µg/g, p = 0.001).There was no difference between admission and Day 3 value of FC in steroid failures ([2522 [590–9654] vs 2718 [222–9175] µg/g, p = 0.9), whereas among the responders, the Day 3 FC decreased significantly from baseline (1530 [352–10 278] to 726 [218–4062] µg/g, p = 0.001) [Table 2] [Figure 3].

There was a 21% fall in FC value [from admission to Day 3] among steroid responders as compared with 16% rise in steroid failures [p = 0.05]. A failure of FC to fall on Day 3 was associated with steroid failure in 69% [11/16] of patients as compared with 30% [10/33] when it fell on Day 3 [p = 0.01].

3.4.2. Endoscopic activity

Steroid failures had a higher median UCEIS at baseline (6 [4–8] vs 5 [4–7], p = 0.001) compared with responders [Table 2].

Table 1. Comparison of baseline demographic and clinical characteristics in steroid responders and failures among patients with acute severe colitis.

	Total, *n* = 49	Steroid responders, *n* = 28	Steroid failures, *n* = 21	*p*-Value
Age [years]	36.1 ± 11.9	37.6 ± 12.9	34.2 ± 10.4	0.3
Duration of UC preceding ASC [months]	36 [1–180]	36 [1–180]	36 [1–168]	0.4
Male [%]	36 [74]	20 [71]	16 [76]	0.7
Index presentation of UC as ASC [%]	4 [8.2]	3 [10.7]	1 [4.8]	0.6
Extent				0.8
E2 [left-sided colitis]	15 [32]	9 [33]	6 [30]	
E3 [extensive colitis]	32 [68]	18 [67]	14 [70]	
Previous azathioprine	22 [45]	12 [43]	10 [48]	0.7
Previous ASC	12 [25]	8 [28]	4[19]	0.5
Previous steroid use	39 [80]	21 [75]	18 [86]	0.5
Steroid use in 1st year of diagnosis of UC	30 [61]	14 [50]	16 [76]	0.06
Tobacco user	10 [20]	8 [29]	2 [10]	0.15
Presence of EIMs	15 [31]	7 [25]	8 [38]	0.3
Number of Truelove and Witts' criteria on admission in addition to bloody stool frequency ≥ 6				0.04
1	14 [29]	7 [25]	7 [33]	
2	21 [42]	16 [57]	5 [24]	
3 or more	14 [29]	5 [18]	9 [43]	
Charlson comorbidity index ≥ 1	16 [33]	11 [39]	5 [24]	0.3
Pulse rate on admission [/min]	100 [69–142]	100 [80–142]	100 [69–128]	0.7
Stool frequency on admission [/day]	12 [6–20]	10 [6–18]	12 [6–20]	0.08
Pulse rate beginning Day 3 [/min]	84 [60–110]	84 [60–110]	86 [64–102]	0.8
Stool frequency during Day 3[/day]	7 [2–18]	6 [2–10]	8 [3–18]	0.02

Value[s] provided as mean ± standard deviation, median [range] or *n* [%], as appropriate. Extent not available in two patients.
UC, ulcerative colitis; ASC, acute severe colitis; EIMs, extra-intestinal manifestations.

Table 2. Comparison of laboratory parameters and management in steroid responders and steroid failures among patients with acute severe colitis.

	Total, *n* = 49	Steroid responders, *n* = 28	Steroid failures, *n* = 21	*p*-Value
Haemoglobin on admission [g/L]	98 [47–155]	97 [47–155]	98 [5.3–15]	0.7
ESR on admission [mm/h]	45 [10–82]	42 [10–57]	47 [22–82]	0.3
Blood transfusion *n* [%]	12 [25]	5 [18]	7 [33]	0.2
White cell count [x 10^9/L]	8.6 [3.8–30.7]	9.5 [3.8–30.7]	7.9 [4.3–14.3]	0.2
Platelets on admission [x 10^9/L]	359 [50.9–764]	355.5 [50.9–764]	370 [132–578]	0.9
Albumin on admission [g/L]	30 [10–46]	30 [20–46]	27 [10–43]	0.14
Median faecal calprotectin on admission [µg/g, range]	1776 [352–10278]	1530 [352–10278]	2522 [590–9654]	0.04
UCEIS on admission	5 [4–8]	5 [4–7]	6 [4–8]	0.01
UCEIS > 6 *n* [%]	10 [20]	2 [7]	8 [38.1]	0.01
Haemoglobin Day 3 [g/L]	95 [61–144]	96 [61–144]	94 [64–132]	0.7
Platelets Day 3[x10^9/L]	317 [121–622]	315 [147–622]	325 [121–503]	0.4
CRP Day 3 [mg/L]	23.8 [1.4–209]	19.6 [1.4–178]	36 [2.7–209]	0.4
Albumin Day 3 [g/L]	30 [11–46]	31 [21–46]	27 [11–40]	0.09
Median faecal calprotectin Day 3 [µg/g, range]	880 [218–9175]	727 [218–4062]	2718 [222–9175]	0.001
Meeting Oxford third day criteria,* *n* [%]	23 [47]	10 [36]	13 [62]	0.06
Stool positive for *C. difficile* toxin, *n* [%]	1 [2]	0	1 [5]	
Toxic megacolon during admission, *n* [%]	4 [8]	0	4 [19]	
Median duration of iv steroid [days, range]	5 [3–10]	5 [5–8]	5 [3–10]	0.12
Median duration of admission [days, range]	11 [5–36]	8 [5–21]	20 [10–36]	0.001
Mortality *n* [%]	1 [2]	0	1 [5]	

Value[s] provided as mean ± standard deviation, median [range], or *n* [%], as appropriate. Extent was not available in 2 patients.
*Oxford third day criteria: stool frequency > 8/d or CRP > 45 mg/L and 3-8 stools on third day of iv corticosteroid therapy.
CRP, C-reactive protein; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

3.4.3. C-reactive protein

Median CRP levels on day 3 of iv corticosteroid therapy did not differ significantly between steroid- failures and –responders (36 [2.7–209] mg/L vs 19.6 [1.4–178] mg/L, $P = 0.4$) [Table 2].

3.4.4. Other parameters

Steroid failures and responders did not differ in terms of stool frequency or ESR on admission, or other parameters [Tables 1 and Table 2], including CMV-positivity in mucosal biopsies. Duration

of iv corticosteroids did not differ between steroid failures and responders, although steroid failures had a longer duration of hospital stay (20 [10–36] vs 8 [5–21] days, [p = 0.001]. Of patients satisfying Oxford criteria [stool frequency on Day 3 > 8/d or stool frequency 3-8/d with CRP > 45 mg/L], 13/23 [57%] failed iv corticosteroids compared with 8/26 [31%] patients who did not satisfy the criteria [Table 3].

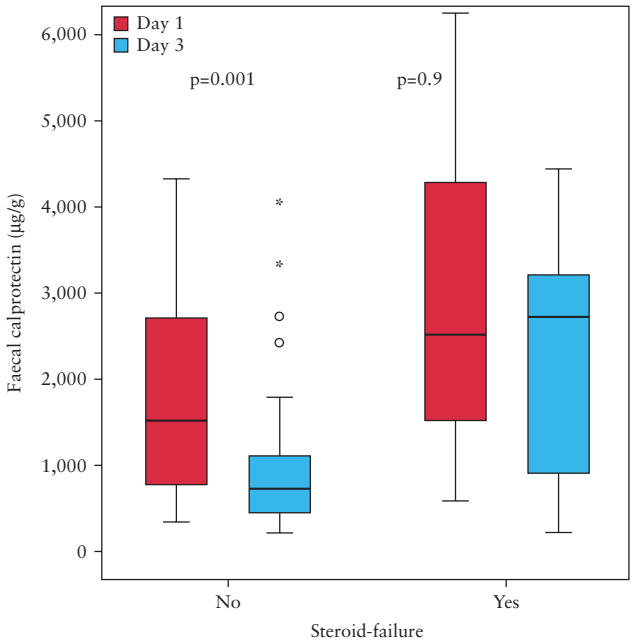

Figure 3. Box plots showing faecal calprotectin level in steroid responders and failures at admission and on Day 3. Faecal calprotectin fell in responders [(530 [352–10278] vs 726 [218–4062] µg/g, p = 0.003) and did not in non-responders (2522 [590–9654] vs 2718 [222–9175]µg/g, p = 0.9).

3.5. Multivariable analysis

On univariate analysis of steroid use in the first year, more than two additional Truelove and Witts' criteria on admission [Day 3 stool frequency > 8, Day 3 FC > 1000 µg/g, and UCEIS > 6] met the criteria for multivariable analysis between steroid failures and responders. On multivariable analysis, only UCEIS score > 6 (odds ratio [OR] 8.6 [95% confidence interval 1.3–56], p = 0.02)and FC > 1000 µg/g on Day 3 of iv corticosteroids (OR 7.9 [95% CI 2.0–31.8], p = 0.004) remained significantly associated with steroid failure [Table 4].

3.6. Faecal calprotectin and UCEIS as predictors of steroid-response

Cut-offs for FC thresholds to predict steroid failure were derived from receiver-operating characteristic [ROC] curves for FC on admission and on Day 3.

FC > 1800 µg/g on admission could discriminate between steroid failures and responders with a sensitivity of 66%, specificity 64%, and area under the curve [AUC] 67% [95% CI 51.8–82.2]. FC > 1000 µg/g on Day 3 of iv corticosteroids could discriminate steroid failure with a sensitivity of 71%, specificity 75%, and AUC 77% [95% CI 62.8–91.3, Figure 4].

UCEIS > 6 had a specificity of 93% and positive predictive value [PPV] of 80% in predicting steroid failure, but a low sensitivity of 38% and negative predicitive value [NPV] of 67% [Figure 5 and Table 3].

All patients with Day 3 FC > 1000 µg/g and UCEIS > 6 failed iv corticosteroids. If either one of these criteria was present, 17/26 [65%] failed iv corticosteroids, whereas if both were absent, only 4/23 [17%] failed iv corticosteroids [p = 0.001], with OR 8.9 [2.3–34] [Table 3].

Table 3. Comparison of Oxford third day index, faecal calprotectin, and UCEIS for prediction of steroid failure.

	Sensitivity	Specificity	PPV	NPV	OR [95% CI]
Oxford third day index[a]	62%	64%	56%	69%	2.9[0.9–9.4]
Day 3 faecal calprotectin > 1000 µg/g	71%	75%	68%	78%	7.9[2–31.8]
UCEIS > 6	38%	93%	80%	67%	8.6[1.3–56]
Either UCEIS > 6 or FC > 1000 µg/g	81%	68%	65%	83%	8.9 [2.3–34]
Both UCEIS > 6 and FC > 1000 µg/g	29%	100%	100%	65%	

Oxford third day criteria: stool frequency > 8/d or CRP > 45 mg/L *and* 3-8 stools on third day of iv corticosteroid therapy

FC, faecal calprotectin; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; PPV, positive predictive value; NPV, negative predictive value; OR [95% CI], odds ratio [95% confidence interval].

Table 4. Multivariate analysis for predictors of steroid response.

	Steroid failure			
	Univariate		Multivariable	
	OR [95% CI]	p-Value	OR [95% CI]	p-Value
Steroid use in 1st year	3.2 [0.9–11.1]	0.06		ns
Number of Truelove and Witts' criteria on admission > 2	3.4 [0.9–12.6]	0.06		ns
Oxford third day criteria[a]	2.9 [0.9–9.4]	0.06		ns
Day 3 faecal calprotectin > 1000 µg/g	7.9 [1.9–31.7]	0.004	7.9 [2–31.8]	0.004
UCEIS on admission > 6	8.6 [1.3–56]	0.02	8.6 [1.3–56]	0.02

[a]Oxford third day criteria: stool frequency > 8/d or C-reactive protein [CRP] > 45 mg/L and 3-8 stools on third day of iv corticosteroid therapy.
OR, odds ratio; CI, confidence interval; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; ns, not significant.

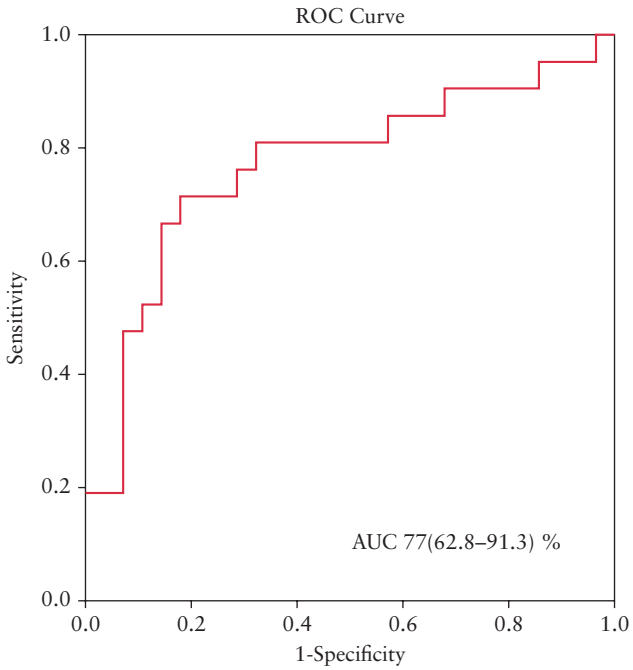

Figure 4. Receiver operator curves [ROC] of faecal calprotectin Day 3 for prediction of steroid failure (area under ROC [AUROC] 77% [62.8–91.3 %]).

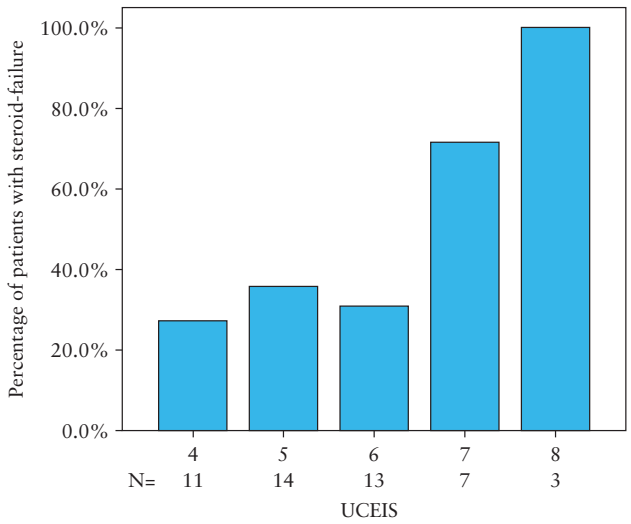

Figure 5. Bar chart representing percentage of patients with steroid failure with increasing Ulcerative Colitis Endoscopic Index of Severity [UCEIS].

Those with UCEIS ≤ 6 tended to have lower median calprotectin on Day 3 than those with UCEIS > 6 (785 [218–7427] µg/g vs 1993 [393–9175] µg/g, p = 0.07) [Figure 6].

We performed a subgroup analysis of episodes without CMV infection [n = 39] which showed similar results, with Day 3 FC > 1000 µg/g and UCEIS > 6 being the only independent predictor of steroid failure [Supplementary Appendix, available at *ECCO-JCC* online].

3.7. Prediction score

A simple predictive score was derived, based upon UCEIS score on admission and Day 3 FC. This score was defined as:

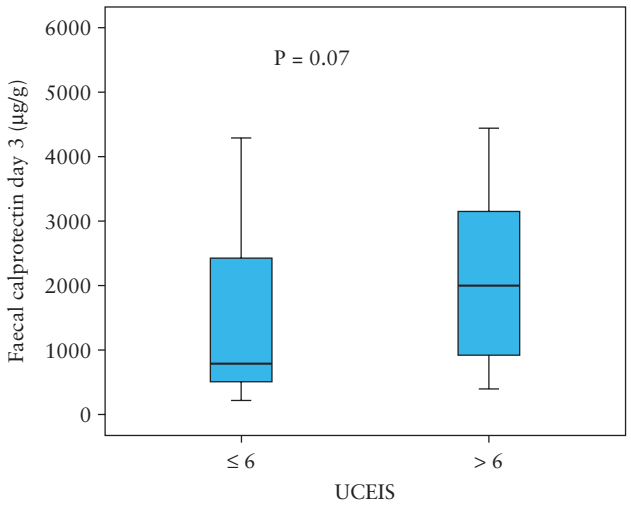

Figure 6. Boxplot representing Day 3 faecal calprotectin in patients with Ulcerative Colitis Endoscopic Index of Severity [UCEIS] ≤ 6 and > 6 [p = 0.07].

risk score : FC > 1000µg / g + UCEIS > 6, where FC > 1000µg / g = 1 and UCEIS> 6 = 1; and FC< 1000µg / g = 0 and UCEIS< 6 = 0.

This score ranged from 0 to 2, with the score of 0, 1 and 2 having PPV of 17%, 65%, and 100%, respectively for steroid failure in ASC. Also, 83% of those who had a score 0 responded to iv corticosteroids [Table 5].

4. Discussion

There is a large therapeutic gap for patients with ASC when treated conventionally with intravenous corticosteroids. This gap is bridged either by medical rescue therapy [infliximab/ciclosporin/tacrolimus] or by colectomy. Timely intervention in patients with ASC not responding to iv corticosteroids is of paramount importance, because delays in initiating rescue therapy or surgery are associated with a higher rate of complications, including death.[4,5] The third day of intensive corticosteroid therapy has become the most important juncture in the treatment of patients with ASC, since clinical [stool frequency] and laboratory parameters [CRP] on Day 3 can predict the likelihood of needing colectomy.[28] However, stool frequency is a semi-objective measure, may be affected by topical therapy, and may not reflect the true inflammatory burden of the disease. There is, therefore, a need for objective parameter[s] to identify as early as possible in the disease course those patients who will need medical rescue therapy or surgery. An earlier prospective study from India evaluated 55 episodes of ASC and found haemoglobin < 90 g/L, CRP > 18.6 mg/L, and prolongation of prothrombin time [PT] > 2 s at admission to independently predict steroid failure.[29] Another study on 30 patients with ASC, found that an admission stool frequency ≥ 9, pulse rate ≥ 120/min, temperature ≥ 38°C, and serum albumin ≤ 20 g/L, together with pancolitis, independently predicted steroid failure.[30] The present study, for the first time, has prospectively evaluated two objective markers—UCEIS and faecal calprotectin—in predicting steroid response in patients with ASC.

The rates of steroid failure rate [21/49, 43%] and colectomy [15/45, 33%] in our study at AIIMS, New Delhi, are similar to reports from Western centres.[3,31,32] We also found no difference in median age, disease duration, extent, course, previous

Table 5. Prediction score for steroid failure on basis of Day 3 faecal calprotectin and UCEIS.

Score		Sensitivity	Specificity	PPV	NPV
0	UCEIS ≤ 6 and Day 3 FC < 1000 µg/g	19%	32%	17%	34%
1	UCEIS > 6 or Day 3 FC ≥ 1000 µg/g	81%	68%	65%	83%
2	UCEIS > 6 and Day 3 FC ≥ 1000 µg/g	29%	100%	100%	65%

FC, faecal calprotectin; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; PPV, positive predictive value; NPV, negative predictive value

immunomodulator use, haemoglobin, or albumin between steroid failures and responders. As an insight into the similarities between UC in India and elsewhere,[20,28] we also found a significant association between steroid failure and steroid use in first year of disease, ≥2 Truelove and Witts' criteria on admission, and higher median stool frequency on Day 3. These all reflect a higher inflammatory burden of disease.

However, unlike other studies, median CRP levels were no different between steroid failures and responders. Consequently, the Oxford third day index was also not significantly different between the two groups. The CRP is not uniformly elevated during active UC[33] and, although some indices for predicting colectomy include CRP,[7,8,29] others do not.[6,9] This may reflect the differences between predicting steroid failure and predicting colectomy.

In contrast, median FC levels [both at admission and on Day 3] and endoscopic severity were higher in steroid failures than steroid responders. Indeed, the only independent predictors of steroid failure after adjusting for other variables were FC and UCEIS on Day 3, and the combination of the two identified all steroid failures in this prospective cohort.

A novel finding in our study was that when FC failed to fall between admission and Day 3, then this was associated with steroid failure in 69% patients. We found that FC both at admission and on Day 3 to be predictive of steroid failure, and FC level on Day 3 to be an independent predictor of steroid failure; 68% patients with Day 3 FC > 1000 µg/g had steroid failure as compared with only 22% with FC < 1000 µg/g (OR [95% CI] 8 [2–32]). FC broadly correlates with the severity of colitis,[12] and serial levels have been shown to predict response to infliximab therapy.[13,14] An earlier study showed FC to be higher in steroid-refractory patients with ASC,[15] but it lacked FC measurements on a specific day, which limited applicability of the results in clinical practice. FC predicted steroid failure better than CRP, which may mean that FC is a more direct marker of intestinal inflammation.

The median UCEIS was significantly higher [6/8 vs 5/8] in steroid failures compared with responders. This difference appears small, but confirms a retrospective study of 86 patients.[20] The UCEIS was an independent predictor of steroid failure (OR = 9 [95% CI 1.3–56]) and 8/10 patients with a UCEIS of 7 or 8/8 were steroid failures. It may be argued that the UCEIS is not objective, since the endoscopist may well be the clinician looking after the patient; however, every patient admitted with ASC has [or should have] a flexible sigmoidoscopy within 24 h of admission, not only to confirm the severity of colitis, but also to exclude complications such as CMV. As far as objectivity is concerned, the UCEIS accounts for 86–88% of inter-observer variation in multiple populations across the world.[17] A simple prediction score based on Day 3 FC > 1000 µg/g and UCEIS > 6 can be used to predict steroid failure, with 0 meaning both negative, 1 meaning either positive, and 2 meaning both positive, to give a PPV of 17%, 65%, and 100% prediction of steroid failure, respectively.

The primary outcome of the present study was steroid failure, which was defined as the need for surgery/rescue therapy. We realise that the choice of rescue therapy was not uniform, but this reflects the real world. The choice of rescue therapy was based on multiple factors including cost, availability, potential for complications, physician, and patient choice. Nevertheless, the choice of rescue therapy could not affect the primary outcome.

There are, of course, other limitations to this study. The sample size, although prospective, is small. It is similar to that which led to the Oxford criteria,[7] which changed practice. It is from a single centre in North India, but the demographics and outcomes are very similar to those from elsewhere. Access to biological or medical rescue therapy may differ in India, tending to a bias towards colectomy, but this is the real world for most, and our numbers suggest otherwise. It is, however, conceivable that higher-dose infliximab may have reduced the rate of colectomy, but not every study concurs.[34] Although the UCEIS scoring system is a quantitative and objective parameter, an external *post hoc* [based on video clip] assessment of the UCEIS by blinded investigators would have improved the study. We simply need better treatment for ASC and early predictors of the failure of conventional steroid therapy.

A combination of a faecal calprotectin > 1000 µg/g on Day 3, and UCEIS ≥ 6 on admission with ASC, is associated with all patients who will fail iv corticosteroids and need medical rescue therapy or colectomy. The sooner objective measures of early response to treatment for ASC are adopted, the fewer delays there should be in decision making between physicians and surgeons.

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Conflict of Interest

None to declare.

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Author Contributions

SJ: study design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision, and final approval of the manuscript. SK: analysis and interpretation of data, drafting of the manuscript, critical revision, and final approval of the manuscript. SV: statistical analysis, critical revision, and final approval of the manuscript. SB, VS, PS, NRD, SP, GM: acquisition of data, drafting of the manuscript, critical revision, and final approval of the manuscript. ST: analysis and interpretation of data, drafting of the manuscript, critical revision, and final approval of the manuscript. VA: study concept and design, analysis and interpretation of data, study supervision, drafting of the manuscript, critical revision, and final approval of the manuscript.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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