This article has been accepted for publication in FLGASTRO following peer review.
The definitive copyedited, typeset version is available online at
10.1136/flgastro-2025-103253

ABSTRACT

Endoscopic severity and C-reactive protein predict initial and twelve-month outcomes of patients with acute severe ulcerative colitis receiving medical rescue therapy: the RESCUE-ASC Study

Objective: Medical rescue therapy (MRT) is effective in intravenous corticosteroid refractory acute severe ulcerative colitis (ASUC). Our aim was to identify predictors of response to MRT and avoid colectomy in the index admission or within 12 months.

Methods: Two cohorts were studied retrospectively. Analysis of 49 adults receiving MRT between 2015-19 at two tertiary Australian hospitals was first performed. Clinical, endoscopic and laboratory data were collected. Response was defined as avoiding colectomy during the same admission. Univariable and multivariable logistic regression were employed to identify predictors of response. The predictors were validated in 88 patients receiving MRT between 2020-23.

Results: In the development cohort, 40/49(81.6%) patients responded to MRT. On multivariable analysis, UCEIS score at admission [Coef-0.105(-0.19 to–0.007),p=0.03] and CRP on day 3 of post commencement of MRT (CRP-R+3)[Coef-0.004(-0.0008 to-0.0004),p=0.03] identified response to MRT. All patients (n=17) with a UCEIS score < 6 (UCEIS<6) and 100 % (n=28) patients with a CRP-R+3 < 22mg/L responded to MRT. In the validation cohort, 82/88 (93.1%) patients responded to MRT; 90.5% (19/21) with UCEIS<6 and 100% (70/70) patients with CRP-R+3 < 22mg/L responded to MRT. At 12 months after hospitalization for ASUC, in the development cohort, 16/17 (94%) patients with a UCEIS<6 and 23/28 (82.1%) patients with CRP-R+3 < 22mg/L avoided colectomy. In the validation cohort, 18/21 (85.7%) with UCEIS<6 and 64/70 (91.4%) patients with CRP-R+3 < 22mg/L avoided colectomy at 12 months.

Conclusions: UCEIS<6 and CRP-R+3 < 22mg/L identify responders to MRT and colectomy is extremely unlikely either on the index admission or within 12 months.

Keywords: Acute severe ulcerative colitis, rescue therapy, colectomy, Infliximab, Ciclosporin, Tofacitinib

KEY MESSAGES

- **What is already known?**
    - About half to two-thirds of patients with ASUC respond to first-line medical therapy with intravenous corticosteroids
    - IFX and CsA are equally effective as second-line medical therapy in patients with ASUC not responding to IV corticosteroids
    - Parameters that determine response to second-line medical rescue therapy and optimal timing of measurement of these parameters are unknown
- **What is new here?**
    - The RESCUE-ASC study has identified endoscopic severity as defined by the UCEIS score and CRP on day 3 after commencement of medical rescue therapy identify response to medical rescue therapy
    - UCEIS score < 6 at admission identifies response to medical rescue therapy and patients who are likely to avoid colectomy in the index admission and within 12 months

- A decrease of CRP on day 3 after commencing rescue therapy to < 22mg/L identifies patients who are also unlikely to require colectomy during the index admission and within 12 months

- **How can this study help patient care**?
    - Application of these objective criteria will allow definitive decision-making, patient counselling and avoid the morbidity associated with delayed colectomy

INTRODUCTION

Acute severe ulcerative colitis (ASUC) as defined by the Truelove and Witts Criteria [1] occurs in 10%-25% at diagnosis and in 20%-30% during the disease course of ulcerative colitis[2,3]. Intravenous corticosteroids (IVCS) remain the cornerstone of first-line therapy for ASUC[4]. However, data show that around 30-40% of patients do not respond to intravenous corticosteroids[5].

Indices aimed at identifying patients who will require medical rescue therapy (MRT) after 3–5 days of admission on intravenous steroids have been used in practice for more than two decades[6,7]. The ADMIT-ASC score and ACE index identify patients on admission at high risk of steroid non-response[89,10]. Endoscopic severity as assessed by the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) Score[11] and faecal calprotectin[12–14] have been shown to be predictors of need for rescue therapy. Once rescue therapy has been administered, CRP[15,16], serum albumin[171819], band neutrophil count[19], and endoscopic severity[17-18] have been used to assess risk of colectomy. There is no validated index to define response to MRT.

In recent years, exclusive enteral nutrition with a semi-elemental diet and tofacitinib have been shown to augment steroid responsiveness in ASUC[20,21]. In patients who are refractory to IVCS, ciclosporin (CsA), Infliximab (IFX) and recently JAK-inhibitors have been used as medical rescue therapy (MRT)[22–29]. IFX and CsA have been shown to have comparable efficacy in the management of steroid-refractory ASUC, however the therapeutic response rate of each drug is only about 40%[30–32]. A randomised controlled trial, examining two IFX dosing strategies in ASUC patients not responding to IVCS, demonstrated that intensified, accelerated, and standard induction regimens did not result in a significant difference in clinical response by day 14 or in remission or colectomy rates by month 3[33]. A third-line salvage therapy could be considered for highly selected patients with steroid-refractory ASUC, in whom one rescue therapy (mainly IFX or CsA) has been unsuccessful, but the standard management of patients not responding to these patients remains colectomy[34–36].

In a UK cohort, the reported colectomy rates for the ASUC patients during the same admission was around 15% and about 21% had undergone a colectomy within 12 months of their ASUC admission[8]. Delayed surgery for patients with ASUC is associated with an increased risk of post-operative complications and mortality[37–39]. It is paramount to identify patients with ASUC who are unlikely to respond to MRT to transition early to colectomy. In patients who receive MRT, there is a lack of consensus for definitions of treatment response and non-response, and in these hospitalised patients there is a lack of discharge criteria[36]. The primary aim of our study was to identify predictors of response to medical rescue therapy, **R**esponse **E**valuation to medical re**SCUE** therapy in **A**cute **S**evere ulcerative **C**olitis **(RESCUE-ASC),** and patients who are likely to avoid colectomy.

MATERIALS AND METHODS

Study design and participants

Admissions with a diagnosis of UC containing international classification of disease (ICD-10) codes (K51) at two tertiary Australian Hospitals in Southeast Queensland, Australia (Gold Coast University Hospital and Logan Hospital) between 1st January 2015 to 31st December 2019 were retrospectively identified and all patients (≥ 18 years of age) patients with ASUC, as defined by Truelove and Witts' criteria were analysed. Patients who did not respond to IVCS and received MRT were included**.** For the validation cohort, all adult ASUC admissions between 1st January 2020, to 31st May 2023 at Gold Coast University Hospital and Sunshine Coast University Hospital, Queensland, Australia were retrospectively analysed, and IVCS refractory ASUC patients who received MRT were included. The study was approved by the Gold Coast Health Service Human Research Ethics Committee (Ref: LNR/2020/QGC/67173) and by Metro North Health Human Research Ethics Committee (Project ID: 100546; EX/2023/MNHB/100546). To ensure consistency and accuracy of data extraction, all patient case records were reviewed by two IBD clinicians (PKR and DS).

Inclusion was limited to patients with ASUC as per Truelove and Witts' criteria who received medical rescue therapy (IFX or CsA) after not responding to at least 3-5 days of IVCS, either hydrocortisone 400mg/day or methylprednisolone 60mg/day. Patients not fulfilling the definition of ASUC, patients with a diagnosis of Crohn's disease, positive stool cultures for other enteric pathogens were excluded.

In all three centres, demographic (sex, age), clinical (UC history, disease duration, medication history, extra-intestinal manifestations), admission clinical parameters (stool frequency in preceding 24 hours, heart rate, temperature, haemoglobin, platelet count, CRP), admission

radiographic findings (presence of toxic megacolon on abdominal X-ray), and laboratory results were collected from day 1, day 3 of admission and on the day of medical rescue therapy. After administration of MRT, clinical and laboratory results were collected on day 1 and day 3. Endoscopic data were collected from reports and images from endoscopies performed after admission and scored based on the ulcerative colitis endoscopic index of severity (UCEIS) Score[40].

Therapeutic management

Inpatient management followed the established international guidelines, using IVCS, intravenous fluids and thromboprophylaxis with low molecular weight heparin. The Oxford criteria was used to determine non-response to IVCS therapy after 3-5 days[6] . The choice of drug for rescue therapy was as per the treating physician's preference. The standard IFX induction strategy utilised was 5mg/kg at Week 0, 2 and 6. Accelerated dose was defined as IFX at 10mg/kg on day 0 followed by 5mg/kg at weeks 2 and 6. The dose of IFX was determined by the treating Gastroenterologist based on clinical assessment of disease severity. Following successful treatment with IFX, need for maintenance IFX was based on disease severity and previous treatment history as per the treating physician's discretion. Intravenous CsA was dosed at 2mg/kg body weight with a target trough level of 200-300ng/ml at 48 hours after CsA commencement. Patients who received intravenous CsA were switched to oral CsA at discharge and commenced on a thiopurine (in between the years 2015 to 2019) or Vedolizumab (from 2020-2023).

Definitions

Ulcerative colitis: The diagnosis of UC was based on standard clinical, endoscopic and histological criteria[41].

Acute severe ulcerative colitis: Diagnosis was based on Truelove and Witts' criteria, meaning six or more stools with blood and one or more of following, haemoglobin < 10.5g/dL, erythrocyte sedimentation rate ≥ 30mm/h or CRP ≥ 30mg/L, fever ≥ 37.8ºC or tachycardia ≥ 90/min[1].

Oxford Criteria: non-response to IVCS was defined as a stool frequency of >8 or a stool frequency between 3-8 and CRP level of more than 45mg/l on day 3 of admission[6].

Disease extent was defined as the maximum endoscopic extent at index colonoscopy according to the Montreal classification[42]. In patients with their first presentation of disease as ASUC, the extent was determined from first available colonoscopy after discharge, or the surgical specimen if they underwent colectomy.

Endoscopic severity was defined by the ulcerative colitis endoscopic index of severity (UCEIS). The score (0-8) is calculated by the sum of three descriptors, including vascular pattern [scored 0-2], bleeding [scored 0-3] and erosions and ulcers [scored 0-3] assessed at the most severely affected area on flexible sigmoidoscopy[40]. UCEIS was scored based on review of images stored in the endoscopic reporting software by two authors (PKR and DS), who were not blinded to the outcome of the patient.

Steroid response was defined as the patient being discharged from the hospital without initiation for further treatment for active UC, medical or surgical. Steroid non-response was defined as requirement for second-line medical therapy or surgery.

Response to medical rescue therapy was defined as the patient being discharged from the hospital with medical therapy (or without the need for colectomy during the same admission).

Non-response to medical rescue therapy was defined as requirement for colectomy during the same admission for ASUC.

Objectives

The primary aim of our study was to identify and validate predictors of response to medical rescue therapy and avoid colectomy during the hospitalisation for ASUC. The secondary outcomes were to identify performance of these predictors in identifying patients who are likely to avoid colectomy at 30 days, 3-months and 12-months after hospitalisation for ASUC.

Statistical Analysis

Descriptive statistics were used to describe the study cohort and results reported as median with interquartile range (IQR) for continuous variables and frequencies with percentages for categorical variables. For comparison of variables, Fisher's exact or Chi-square tests were used for categorical variables and Wilcoxon Ranksum test for continuous variables. Continuous data were tested for normality using the Shapiro-Wilk test. To evaluate predictors of same admission colectomy we initially performed univariable logistic regression analysis to identify variables with a p value < 0.05, which were included in the multivariable analysis. Multivariable logistic regression analysis was performed until only variables with a p value of < 0.05 were left. Receiver operative characteristic (ROC) analysis was carried out to identify best numerical cut-offs for predictors of response to medical rescue therapy. We estimated a sample size of 45 patients to have a power of 95% and probability of exposure among responders is 90%. The thresholds identified were validated with a patient cohort from Sunshine Coast and Gold Coast, from a different time period. Patients for whom incomplete significant variable data were available were excluded from numerical scoring. A two-tailed p value of < 0.05 was considered statistically

significant for all analyses. All analyses were performed using Stata17 (StataCorp LLC, College Station, Texas).

RESULTS

Development Cohort

In the development cohort, out of 149 patients of ASUC, 66 (44.3%) patients received MRT, of which 49 patients with all relevant data were included in the analysis. Median age at admission was 34 years (IQR: 25-46), 22.57% (11/49) had a new diagnosis of UC, median disease duration was 1.5 years (IQR: 0-6), and the median time to endoscopy was 2 days from admission (IQR:1-3). Patient demographic, clinical details are provided in Table 1.

There were 85.7% (42 out of 49) of patients who received IFX and 14.3% (7 out of 49) received intravenous CsA. None of the patients received sequential rescue therapy. The median duration of IVCS prior to initiating MRT was 4 days (IQR: 4-7). In patients receiving MRT, 18.4% (9 out of 49) underwent colectomy during same admission. There were 28.6% (2/7) of patients treated with CsA and 16.7% (7 out of 42) of patients treated with IFX did not respond to MRT and underwent colectomy during the same admission, p=0.38. Median UCEIS was 6 (IQR 5-7) overall, 7 (6-7) for non-responders, and 6 (5-7) for responders, p=0.009. Stool frequency on the day of commencing MRT and CRP on day 3 after MRT commencement were significantly different between the two groups. There were 14.3% (7 out of 49) of patients on an anti-TNF agent, and 12.2% (6 out of 49) of patients who were on vedolizumab at the time of hospitalisation for ASUC. Comparison of endoscopic and biochemical parameters is provided in Table 1.

Comparison of clinical and laboratory parameters between responders and non-responders to medical rescue therapy

Non-responders had a higher stool frequency on the day of MRT [10 (IQR: 10-12) vs 8 (5-10), p=0.01]. The stool frequency on days 1 and 3 after MRT was similar between the two groups. Non-responders had a higher UCEIS [7(IQR: 6-7)] at baseline when compared to responders [6 (IQR: 5-7)], p=0.009. Median albumin at admission, on the day of MRT, on day 1 after MRT, and on day 3 of MRT was similar in the two groups. Median CRP at admission, median CRP on day of MRT, day after MRT were similar between the two groups. CRP on day 3 after MRT was significantly higher in non-responders [45 (31-51) vs 7 (2-34) mg/L, p=0.001]. This is highlighted in Table 2.

Predictors of response to medical rescue therapy: Response **E**valuation to re**SCUE** therapy in **A**cute **S**evere **C**olitis **(RESCUE-ASC)**

Development cohort

Univariable analysis identified number of Truelove Witts Criteria at admission, haemoglobin on day 3 of admission, UCEIS score at admission and CRP on day 3 post commencement of MRT (CRP on day R+3) as predictors (Table 2). On univariable analysis, current biologic use, oral steroid use at admission, admission calprotectin, dose of infliximab used, and endoscopic severity as assessed by the Mayo Endoscopic score were not significant for predicting colectomy during the same admission. On multivariable analysis, UCEIS score at admission [Coef - 0.105 (-0.19 to – 0.007), p=0.03] and CRP on day R+3 [Coef -0.004 (-0.0008 to -0.0004), p=0.03] remained significant for identifying response to MRT.

All patients with a UCEIS score < 6 (n=17) were responders to MRT [Sensitivity 42.5% (95% CI 27-59), Specificity 100% (95% CI 66.4-100), PPV 100% (95% CI 80.5-100), NPV 28.1% (95% CI 13.7-46.7)], supplementary table 1A. There were 28.1% (9 out of 32) of patients with a UCEIS score ≥ 6 who underwent a colectomy during the same admission (Supplementary Figure 1A). On further analysis of the UCEIS sub-score, all patients with the "erosions and ulcers" sub-score of <2 (n=12) avoided colectomy during the same admission. Of the patients with a "erosions and ulcers" sub-score of ≥ 2, 24.3% (9 out of 37) underwent colectomy during the same admission. All patients scored 2 points in the "vascular pattern" sub-score. In the bleeding sub-score, 92.9% (13 out of 14) patients with a score <2 avoided colectomy during the same admission and 77.1% (27 out of 35) patients with a bleeding sub-score ≥ 2 avoided colectomy.

The median CRP day R+3 was significantly higher in patients who underwent a colectomy during the same admission [44 (IQR 27-51) mg/L vs 8 (IQR 2-29) mg/L, p=0.002]. ROC analysis identified a cut-off CRP < 22mg/L on day 3 after commencing MRT [Sensitivity 70% (95% CI 53.5-83.4), Specificity 100% (95% CI 66.4-100%), PPV 100% (95% CI 87.7- 100), NPV 42.9% (95% CI 21.8-6.6)], supplementary table 1B. All 28 patients with CRP on day R+3 < 22mg/L responded to MRT and avoided colectomy during the same admission, table 4. There were 42.9% (9 out of 21) patients with CRP on day R+3 ≥ 22mg/L who did not respond to MRT (Supplementary Figure 1C). The performance of UCEIS and CRP on day R+3 thresholds in patients who received IFX as MRT is presented in supplementary table 2.

All patients (n=15) with both UCEIS <6 and CRP on day R+3 < 22mg/L avoided colectomy during the same admission [Sensitivity 37.5% (95% CI 22.7-54.2), Specificity 100% (95% CI 66.4-100), PPV 100% (95% CI 78.2-100), NPV 26.5% (95% CI 12.9-44.4)], table 3,

supplementary figure 2A. In the patients who did not achieve both UCEIS <6 and CRP on day R+3 < 22mg/L, 26.5% (9 out of 34) underwent colectomy during the same admission.

Validation Cohort

Of 179 ASUC admissions at Gold Coast and Sunshine Coast University Hospitals between 1st January 2020 and 31st May 2023, 99 (55.3%) received MRT [86 (86.9%) IFX, 10 (10.1%) CsA, 3 (3%) Tofacitinib]. The 3 patients who received Tofacitinib were excluded from the analysis. UCEIS and CRP data were available in 88 patients, in whom the thresholds were applied.

Demographics and baseline parameters are given in Supplementary Tables 3 and 4, respectively. There were six (6.8%) patients underwent colectomy during the same admission due to non-response to MRT. In this cohort, 90.5% (19 out of 21) of patients with a UCEIS <6 responded to MRT [Sensitivity 23.2% (95% CI 14.6-33.8), Specificity 66.7% (95% CI 22.3-95.7), PPV 90.5% (95% CI 69.64-99), NPV 5.96% (95% CI 1.65-14.8)], table 3 and supplementary table 1A. In patients with a UCEIS ≥ 6, 94% (63 out of 67) avoided colectomy during the same admission. All patients (n=70) with a CRP on day R+3 < 22mg/L responded to MRT [Sensitivity 85.4% (95% CI 75.8-92.2), Specificity 100% (95% CI 54.1-100), PPV 100% (95% CI 95-100), NPV 33.3% (95% CI 13.3-59)], table 4. Of patients with a CRP on day R+3 ≥ 22 mg/L, 66.7% (12 out of 18) avoided colectomy.

All patients (n=17) with both UCEIS <6 and CRP on day R+3 < 22mg/L avoided colectomy during the same admission [Sensitivity 20.7% (95% CI 12.6-31.1), Specificity 100% (95% CI 54.1-100), PPV 100% (95% CI 80.5-100), NPV 8.45% (95% CI 3.16-17.5)], table3 and supplementary table 1B, supplementary figure 2B. In the patients who did not achieve both UCEIS <6 and CRP on day R+3 < 22mg/L (n=71), 13 (18.3%) underwent colectomy during the same admission.

On combining the two cohorts, 89.1% (122 out of 137) of patients responded to MRT. In the two cohorts combined, 94.7% (36 out of 38) of patients with a UCEIS <6 at admission [Sensitivity 29.5% (95% CI 21.6-38.4), Specificity 86.7% (95% CI 59.5-98.3), PPV 94.7% (95% CI 82.3- 99.4), NPV 13.1% (95% CI 7.2-201.4)] and all patients (n=98) with a CRP on day R+3 < 22mg/L [Sensitivity 80.3% (95% CI 72.5-86.9), Specificity 100% (95% CI 78.2-100), PPV 100% (95% CI 96.3-100), NPV 38.5% (95% CI 23.4-55.4)] responded to MRT and avoided colectomy during the same admission.

All patients (n=32) with both UCEIS <6 and CRP on day R+3 < 22mg/L avoided colectomy during the same admission [Sensitivity 26.2% (95% CI 18.7-35), Specificity 100% (95% CI 78.2-100), PPV 100% (95% CI 89.1-100), NPV 14.3% (95% CI 8.22-22.5)], table 4.

RESCUE-ASC: Avoiding colectomy at 30-days, 3-months, 12-months

In the development cohort (n=49), 11 (22.5%), 13 (26.5%) and 17 (34.7%) patients had undergone colectomy by 30 days, 3-months and 12-months respectively since hospitalisation for ASUC. All patients with a UCEIS score < 6 (n=17) avoided colectomy at 30 days and 3-months, and 94.1% (16 out of 17) avoided a colectomy by 12 months. In patients with CRP on day R+3 < 22mg/L (n=28), 27 (96.4%), 26 (92.9%), 23 (82.14%) avoided colectomy at 30 days, 3-months and 12-months respectively (Table 4 and Supplementary table 1A, supplementary figures 1B and D). In patients with both UCEIS <6 and CRP on day R+3 < 22mg/L (n=15), all patients avoided colectomy at 30-days and 3-months, and 93.3% (14 out of 15) avoided colectomy by 12 months since hospitalisation for ASUC [Sensitivity 43.8 (95% CI 26.4-62.3), Specificity 94.1% (95% CI 71.3-99.9), PPV 93.3% (95% CI 68.1-99.8), NPV 47.1% (95% CI 29.8-64.9)], table 4 and supplementary table 1A.

In the validation cohort (n=88), 7 (7.95%), 12 (12.5%) and 14 (15.9%) patients had undergone colectomy by 30 days, 3-months and 12-months respectively since hospitalisation for ASUC. Of patients with a UCEIS score < 6 (n=21), 19 (90.5%), 18 (85.7%) and 18 (85.7%) had avoided colectomy at 30 days and 3-months, and 12-months respectively. In patients with CRP on day R+3 < 22mg/L (n=70), 69 (98.6%), 66 (94.3%) and 64 (91.4%) had avoided colectomy at 30 days, 3-months and 12-months respectively, tables 3 and 4. In patients with both UCEIS <6 and CRP on day R+3 < 22mg/L (n=17), all patients avoided colectomy at 30-days and 94.1% (16 out of 17) avoided colectomy at 3-months and 12-months since hospitalisation for ASUC [Sensitivity 21.6% (95% CI 12.9-32.7), Specificity 92.9% (95% CI 66.1- 99.8), PPV 94.1% (95% CI 71.3- 99.9), NPV 18.3% (95% CI 10.1-29.3)], Table 4.

DISCUSSION

In the current study, across two cohorts comprising 137 patients who received MRT, only 10% underwent colectomy in the same admission, demonstrating the effectiveness of MRT in patients with ASUC. This is similar to the recently published data, wherein the same admission colectomy rates for hospitalized ASUC patients were about 15%[8]. In the RESCUE-ASC study cohort, we have identified two parameters as predictors of response to MRT. Endoscopic severity (as defined by the UCEIS score at presentation) was identified as an early predictor of response to MRT. A UCEIS score < 6 was a key identifier of patients who are likely to avoid colectomy during hospitalisation for ASUC. Once MRT is commenced, CRP on day 3 post MRT identified responders. A fall in CRP on day R+3 < 22mg/L was the best threshold to identify responders. In these two cohorts, all patients who fulfill both thresholds avoided colectomy in the same admission. Importantly, we have demonstrated that the same threshold values

for UCEIS and CRP identify patients who are likely to avoid colectomy at 3-months and 12-months post hospitalisation for ASUC.

Previous studies have shown the presence of severe endoscopic lesions to be a predictor for short and long-term colectomy[43], and worsening or persistent endoscopic disease as assessed at a second-look sigmoidoscopy identified patients who underwent in-hospital colectomy[44] . Endoscopic severity as defined by the UCEIS score has been shown to be a marker for poor outcomes in ASUC patients[13,45]. The current study is the first study to demonstrate that UCEIS score is a predictor for identifying response to MRT in ASUC patients. As demonstrated in a previous multi-centre international cohort, UCEIS score at presentation is an early predictor of non-response to IVCS[8]. Herein, we demonstrate that it is also an early identifier of response to MRT. The identification of UCEIS score < 6 as a threshold to identify patients who are likely to respond to MRT is clinically useful and reiterates the need for early and accurate endoscopic assessment in patients with ASUC. Furthermore, in the current study, in patients with a UCEIS score < 6, 94% in the development cohort and 86% in the validation cohort had avoided colectomy at 12-months.

The importance of CRP as a biomarker in monitoring patients with ASUC is well established and this data reinforces that continued monitoring of CRP is essential in patients with ASUC. A previous study explored CRP in combination with albumin as biomarker for predicting non-response to IFX rescue therapy, however they were not specific about the timing of biomarker measurement[15]. Con et al have demonstrated that CRP-lymphocyte ratio and CRP-albumin ratio measured on day 3 after infliximab rescue therapy are useful in predicting colectomy[46]. Sninsky et al identified that CRP on day 3 after rescue therapy was a predictor of colectomy at 12 months. However, that study did not define a CRP cut-off which could accurately predict

colectomy[47]. An absolute CRP value on day 3, in those with a high CRP on admission, has been shown to be predictor for 90-day colectomy, however there was no association in those with a low CRP at admission[48]. In the current study, CRP on day 3 after initiation of MRT was a predictor of non-response to MRT and we have identified a CRP of < 22 mg/L as the optimal cut-off for identifying response to MRT. In the current study, some of the decisions to refer for colectomy may have been based on persistent CRP elevation; however, we have identified a CRP threshold which could aid day-to-day decision-making. Moreover, this threshold is predictive of the success of medical therapy not only in the acute admission, but beyond this, to 12 months. Of the patients with a CRP on day R+3 < 22 mg/L, at 3 months more than 90% of them and at 12 months more than 80% of them had avoided colectomy. Whilst there may inevitably be concern regarding an element of circularity in the association between immediate colectomy and CRP levels on day R+3, the fact that this threshold predicts response at 3 and 12 months post hospitalisation is important, and evidence to reduce the concern regarding reverse causation in decision-making.

Understanding biomarker dynamics in patients receiving MRT is an evolving field. Serum albumin has been suggested to predict non-response to infliximab rescue therapy and also colectomy within 12 months of admission[15,19,49]. In the current study serum albumin was lower across multiple time points in patients who underwent colectomy. However, on univariable analysis serum albumin at presentation, on Day R+1 and Day R+3 were not predictors of colectomy during the same hospitalisation. Clinical parameters including stool frequency[6], increasing number of Truelove and Witts' criteria[45], presence of C. difficile, prior immunomodulator or anti-TNF exposure have been shown to predict colectomy risk in patients with ASUC[50]. In the current study, increasing number of Truelove and Witts criteria did not remain as a significant predictor of response on multivariable analysis. Interestingly,

stool frequency was not a predictor of response to MRT in our cohort. Stool frequency is a subjective marker and could be affected by a multitude of factors. In the current era, therapeutic decisions should be based on more objective markers and the findings of the current study support that.

In our study, in the development cohort, all patients who received IFX dosing at 10mg/kg (n=15) avoided colectomy in the same admission and 74.1% (20 out of 27) of patients who received IFX at 5mg/kg had avoided colectomy in the same admission. In the validation cohort, 95.8% (45 out of 47) of patients who received IFX 10mg/kg and all patients (n=31) who received IFX 5mg/kg avoided colectomy during the same admission. However, our study was not powered to analyse the effect of IFX dosing. In a recent trial, in patients with a high CRP and very low albumin there was a numerically higher response rate in patients who received higher IFX doses, however the study was under-powered for sub-group analysis[33].

The study has identified and validated 2 simple variables, which can be used to identify responders to MRT in the short and long-term. Though the study included retrospective data from three centres, the clinical management in the sites was as per international guidelines. Our study also has a few limitations, mainly associated with the retrospective analysis. The lack of data on CsA or IFX levels is worthy of note and could be addressed in a prospective validation. In this context, decisions on IFX dosing were clinician dependant, rather than protocol-driven and it is possible that a higher IFX dose was used more often in patients with a higher inflammatory burden. Finally, as is increasingly the practice in many centres, most patients received infliximab and consequently the current study was underpowered to analyse CsA subgroup alone.

In conclusion, the RESCUE-ASC study has identified and validated factors which identify response to MRT in patients with ASUC, and also determined an appropriate time-point to measure them. UCEIS score at admission and CRP on day 3 after commencing rescue therapy identify patients who are likely to respond to MRT and avoid colectomy during the hospitalisation for ASUC, but also identify patients who are likely to avoid colectomy within 12 months of hospitalisation for ASUC. The application of objective criteria at this stage of admission will allow definitive decision-making and avoid the morbidity associated with delayed colectomy.

FUNDING: None

CONFLICT OF INTEREST: PKR, DeS, WM, JS, LW, LSW, DP, AS, JE, DhS, NI, MB, AD, TC declare no competing interests. JS – enclosed

ACKNOWLEDGEMENTS: We are grateful to the IBD nursing service and Gastroenterology Pharmacists who support our IBD service.

CONTRIBUTORSHIP STATEMENT:

Concept and design of study: PKR, WM, DeS, JS

Acquisition and analysis of data: DeS, PKR, JS, WM

Interpretation of data: PKR, DeS, WM, JS, TC

Drafting and revision of manuscript: PKR, DeS, WM, JS, TC

Critical revision of manuscript: PKR, DeS, WM, JS, TC, LW, LSW, DP, AS, JE, DhS, NI, MB, AD

Final approval of manuscript: PKR, DeS, WM, JS, TC, LW, LSW, DP, AS, JE, DhS, NI, MB, AD

DATA SHARING STATEMENT: The data can be shared upon reasonable request

ETHICS STATEMENT: The study was approved by the Gold Coast Health Service Human Research Ethics Committee (Ref: LNR/2020/QGC/67173) and by Metro North Health Human Research Ethics Committee (Project ID: 100546; EX/2023/MNHB/100546).

REFERENCES

1. Truelove, S. C. Cortisone in Ulcerative Colitis Final Report on a Therapeutic Trial. *Br Med J* **2**, 1041–1048 (1955).
2. Burisch, J. *et al.* Natural Disease Course of Ulcerative Colitis during the First Five Years of Follow-up in a European Population-based Inception Cohort - An Epi-IBD Study. *J Crohns Colitis* **13**, 198–208 (2019).
3. Domènech, E., Mañosa, M. & Cabré, E. An Overview of the Natural History of Inflammatory Bowel Diseases. *Digestive Diseases* **32**, 320–327 (2014).
4. Truelove, S. C. & Jewell, D. P. INTENSIVE INTRAVENOUS REGIMEN FOR SEVERE ATTACKS OF ULCERATIVE COLITIS. *The Lancet* **303**, 1067–1070 (1974).
5. Turner, D., Walsh, C. M., Steinhart, A. H. & Griffiths, A. M. Response to Corticosteroids in Severe Ulcerative Colitis: A Systematic Review of the Literature and a Meta-Regression. *Clinical Gastroenterology and Hepatology* **5**, 103–110 (2007).
6. Travis, S. P. L. *et al.* Predicting outcome in severe ulcerative colitis. *Gut* **38**, 905–910 (1996).
7. Ho, G. T. *et al.* Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther* **19**, 1079–1087 (2004).
8. Adams, A. *et al.* Inflammatory bowel disease Early management of acute severe UC in the biologics era: development and international validation of a prognostic clinical index to predict steroid response. *Gut* **72**, 433–442 (2023).

9. Grant, R. K. *et al.* The ACE (Albumin, CRP and Endoscopy) Index in Acute Colitis: A Simple Clinical Index on Admission that Predicts Outcome in Patients With Acute Ulcerative Colitis. *Inflamm Bowel Dis* **27**, 451–457 (2021).

10. Grant, R. K. *et al.* Validation of the ACE (Albumin, CRP and Endoscopy) Index in Acute Colitis: Analysis of the CONSTRUCT dataset. *J Crohns Colitis* (2023) doi:10.1093/ECCO-JCC/JJAD148.

11. Travis, S. P. L. *et al.* Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology* **145**, 987–995 (2013).

12. Ho, G. T. *et al.* Fecal calprotectin predicts the clinical course of acute severe ulcerative colitis. *American Journal of Gastroenterology* **104**, 673–678 (2009).

13. Jain, S. *et al.* Faecal calprotectin and UCEIS predict short-term outcomes in acute severe colitis: Prospective cohort study. *J Crohns Colitis* **11**, 1309–1316 (2017).

14. Sasidharan, S., Sasson, A. N., Shannon, K. M. & Ananthakrishnan, A. N. Fecal Calprotectin Is a Predictor of Need for Rescue Therapy in Hospitalized Severe Colitis. *Inflamm Bowel Dis* (2022) doi:10.1093/IBD/IZAC011.

15. Choy, M. C. *et al.* Predicting response after infliximab salvage in acute severe ulcerative colitis. *Journal of Gastroenterology and Hepatology (Australia)* **33**, 1347–1352 (2018).

16. Li Wai Suen, C. F. D., Seah, D., Choy, M. C. & De Cruz, P. Factors Associated with Response to Rescue Therapy in Acute Severe Ulcerative Colitis. *Inflammatory Bowel Diseases* vol. 30 1389–1405 Preprint at https://doi.org/10.1093/ibd/izad183 (2024).

17. Nalagatla, N. *et al.* Effect of Accelerated Infliximab Induction on Short- and Long-term Outcomes of Acute Severe Ulcerative Colitis: A Retrospective Multicenter Study and Meta-analysis. *Clinical Gastroenterology and Hepatology* **17**, 502-509.e1 (2019).

18. Gibson, D. J. *et al.* CRP/Albumin Ratio: An Early Predictor of Steroid Responsiveness in Acute Severe Ulcerative Colitis. *Journal of Clinical Gastroenterology* vol. 52 e48–e52 Preprint at https://doi.org/10.1097/MCG.0000000000000884 (2018).

19. Syal, G. *et al.* Hypoalbuminemia and Bandemia Predict Failure of Infliximab Rescue Therapy in Acute Severe Ulcerative Colitis. *Dig Dis Sci* (2020) doi:10.1007/s10620-020-06177-7.

20. Sahu, P. *et al.* Randomised clinical trial: exclusive enteral nutrition versus standard of care for acute severe ulcerative colitis. *Aliment Pharmacol Ther* **53**, 568–576 (2021).

21. Singh, A. *et al.* Tofacitinib in Acute Severe Ulcerative Colitis (TACOS): A Randomized Controlled Trial. *Am J Gastroenterol* (2024) doi:10.14309/AJG.0000000000002635.

22. Lichtiger, S. *et al.* Cyclosporine in Severe Ulcerative Colitis Refractory to Steroid Therapy. *New England Journal of Medicine* **330**, 1841–1845 (1994).

23. Järnerot, G. *et al.* Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: A randomized, placebo-controlled study. *Gastroenterology* **128**, 1805–1811 (2005).

24. Van Assche, G. *et al.* Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* **125**, 1025–1031 (2003).

25. Steenholdt, C., Dige Ovesen, P., Brynskov, J. & Benedict Seidelin, J. Tofacitinib for Acute Severe Ulcerative Colitis: A Systematic Review. *J Crohns Colitis* **17**, 1354–1363 (2023).

26. Huang, C.-W., Yen, H.-H. & Chen, Y.-Y. Rescue Therapies for Steroid-refractory Acute Severe Ulcerative Colitis: A Systematic Review and Network Meta-analysis. *J Crohns Colitis* (2024) doi:10.1093/ECCO-JCC/JJAE111.

27. Honap, S. *et al.* Acute Severe Ulcerative Colitis: An International Delphi Consensus on Clinical Trial Design and Endpoints. *Clin Gastroenterol Hepatol* (2024) doi:10.1016/j.cgh.2024.10.029.

28. Gisbert, J. P., García, M. J. & Chaparro, M. Rescue Therapies for Steroid-refractory Acute Severe Ulcerative Colitis: A Review. *Journal of Crohn's and Colitis* vol. 17 972–994 Preprint at https://doi.org/10.1093/ecco-jcc/jjad004 (2023).

29. Gilmore, R., Tan, W. L., Fernandes, R., An, Y.-K. & Begun, J. Upadacitinib Salvage Therapy for Infliximab-Experienced Patients with Acute Severe Ulcerative Colitis. doi:10.1093/ecco-jcc/jjad115.

30. Laharie, D. *et al.* Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: A parallel, open-label randomised controlled trial. *The Lancet* **380**, 1909–1915 (2012).

31. Williams, J. G. *et al.* Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. *Lancet Gastroenterol Hepatol* **1**, 15–24 (2016).

32. Narula, N. *et al.* Systematic review and meta-analysis: Infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. *American Journal of Gastroenterology* vol. 111 477–491 Preprint at https://doi.org/10.1038/ajg.2016.7 (2016).

33. Choy, M. C. *et al.* Intensified versus standard dose infliximab induction therapy for steroid-refractory acute severe ulcerative colitis (PREDICT-UC): an open-label, multicentre, randomised controlled trial. *Lancet Gastroenterol Hepatol* **0**, (2024).

34. Rivière, P. *et al.* Acute severe ulcerative colitis management: unanswered questions and latest insights. *Lancet Gastroenterol Hepatol* **9**, 251–262 (2024).

35. Etchegaray, A. *et al.* Sequential rescue therapy with JAK inhibitors in corticosteroid and infliximab-refractory acute severe ulcerative colitis: a case series. *Therap Adv Gastroenterol* **18**, (2025).

36. Honap, S. *et al.* Acute severe ulcerative colitis trials: the past, the present and the future. *Gut* (2024) doi:10.1136/gutjnl-2024-332489.

37. Leeds, I. L. *et al.* Outcomes for ulcerative colitis with delayed emergency colectomy are worse when controlling for preoperative risk factors. doi:10.1097/DCR.0000000000001276.

38. Randall, J. *et al.* Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *British Journal of Surgery* **97**, 404–409 (2010).

39. Dong, C., Metzger, M., Holsbø, E., Perduca, V. & Carbonnel, F. Systematic review with meta-analysis: mortality in acute severe ulcerative colitis. *Aliment Pharmacol Ther* **51**, 8–33 (2020).

40. Travis, S. P. L. *et al.* Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology* **145**, 987–995 (2013).

41. Dignass ⁎, A. *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 1: Definitions and diagnosis. (2012) doi:10.1016/j.crohns.2012.09.003.

42. Satsangi, J., Silverberg, M. S., Vermeire, S. & Colombel, J. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* **55**, 749 (2006).

43. Monterubbianesi, R. *et al.* Infliximab three-dose induction regimen in severe corticosteroid-refractory ulcerative colitis: Early and late outcome and predictors of colectomy. *J Crohns Colitis* **8**, 852–858 (2014).

44. Borren, N. Z. *et al.* Second-look endoscopy in hospitalized severe ulcerative colitis: A retrospective cohort study. *Inflamm Bowel Dis* **25**, 751–755 (2019).

45. Corte, C. *et al.* Association Between the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and Outcomes in Acute Severe Ulcerative Colitis. *J Crohns Colitis* **9**, 376–381 (2015).

46. Con, D., Andrew, B., Nicolaides, S., van Langenberg, D. R. & Vasudevan, A. Biomarker dynamics during infliximab salvage for acute severe ulcerative colitis: C-reactive protein (CRP)-lymphocyte ratio and CRP-albumin ratio are useful in predicting colectomy. *Intest Res* (2021) doi:10.5217/ir.2020.00146.

47. Sninsky, J. A., Staicu, A.-M. & Barnes, E. L. In Acute Severe Ulcerative Colitis Patients Who Receive Rescue Therapy, Prior Maintenance Therapy and Day 3 C-Reactive Protein After Rescue Therapy Are Associated With 12-Month Colectomy Risk. *Inflamm Bowel Dis* (2023) doi:10.1093/IBD/IZAD215.

48. Omar, Y. A. *et al.* USING LONGITUDINAL C-REACTIVE PROTEIN MEASUREMENTS THROUGHOUT HOSPITALIZATION TO ASSESS COLECTOMY RISK IN PATIENTS WITH ACUTE SEVERE ULCERATIVE COLITIS. *Gastroenterology* **168**, S61 (2025).

49. Lim, S. J. M. *et al.* Early predictors of rescue therapy and colectomy in acute severe ulcerative colitis. *Singapore Med J* **66**, 449–456 (2025).

50. Le Baut, G. *et al.* A Scoring System to Determine Patients' Risk of Colectomy Within 1 Year After Hospital Admission for Acute Severe Ulcerative Colitis. *Clinical Gastroenterology and Hepatology* (2020) doi:10.1016/j.cgh.2019.12.036.

Table 1: Clinical, demographic, endoscopic and biochemical characteristics

	Total Admissions (n= 49)	**Rescue non-responders (n =9)**	**Rescue Responders (n=40)**	**p value**
Female, n (%)	21 (42.9)	5 (55.5)	16 (40)	0.31*
Median age, years (IQR)	34 (25-46)	31 (23-34)	34.5 (25.5-50)	0.39**
Median disease duration, years (IQR)	1.5 (0-6)	3(0-9)	1.25 (0.5 – 5.5)	0.49**
First presentation of UC as ASUC, n (%)	11 (22.5)	2 (22.2)	9 (22.5)	0.68*
Disease Extent, n (%)				
Left sided colitis	12 (24.5)	2 (22.2)	10 (25)	1*
Pancolitis	37 (75.5)	7 (77.8)	30 (75)	
Smoking status, n (%)				
Never	35 (71.4)	9 (100)	26 (65)	0.16*
Former	4 (8.1)	0	4 (10)	
Current	10 (20.5)	0	10 (25)	
Drug used for rescue therapy, n (%)				
Infliximab				0.132*
5mg/kg	27 (55.1)	7 (77.8)	20 (50)	
10mg/kg	15 (30.6)	0	15 (37.5)	
CsA	7 (14.3)	2 (22.2)	5 (12.5)	0.59*
Median time to rescue therapy, days (IQR)	4 (4-7)	6 (5-7)	4 (4-7.5)	0.41**

Presence of EIMs, n (%)	6 (12.2)	1 (11.1)	5 (12.5)	1*
Number of additional Truelove and Witts' criteria at admission				
1	14 (28.6)	0	14 (35)	0.11*
2	15 (30.6)	3 (33.3)	12 (30)	
3	16 (32.6)	5 (55.6)	11 (27.5)	
4	4 (8.2)	1 (11.1)	3 (7.5)	
Superimposed *C. difficile* infection, n (%)	2 (4)	0	2 (5%)	1*
Superimposed CMV infection, n (%)	4 (8.16)	1 (11.1)	3 (7.5)	0.57*
5-ASA, n (%)				
Current	30 (61.2)	5 (55.6)	25 (62.5)	0.89*
Never	10 (20.4)	2 (22.2)	8 (20)	
Intolerant/ceased	9 (18.4)	2 (22.2)	7 (17.5)	
IMM: methotrexate or thiopurine, n (%)				
Current	11 (22.4)	1 (11.1)	10 (25)	0.45*
Never	29 (59.2)	5 (55.6)	24 (60)	
Intolerant/ceased	9 (18.4)	3 (33.3)	6 (15)	
Anti-TNF, n (%)				
Current	7 (14.3)	1 (11.1)	6 (15)	0.5*
Never	36 (73.5)	6 (66.7)	30 (75)	
Intolerant	0			
Primary non-response	1 (2)		1 (2.5)	
Secondary loss of response	5 (10.2)	2 (22.2)	3 (7.5)	
Vedolizumab, n (%)				
Current	6 (12.2)	1 (1.1)	5 (12.5)	1*
Never	41 (83.7)	8 (88.9)	33 (82.5)	
Intolerant	0	0	0	
Primary non-response	2 (4.1)	0	2 (5)	
Secondary loss of response	0	0	0	
More than 1 biologic exposure, n (%)	6 (12.2)	1 (11.1)	5 (12.5)	1*

Median UCEIS	6 (5-7)	7 (6-7)	6 (5-7)	0.009**
Median stool frequency at admission, n (IQR)	10 (9-15)	10 (10-13)	10 (8-15)	0.92**
Median stool frequency on day of rescue therapy, n (IQR)	8 (6-11)	10 (10-12)	8 (5-10)	0.01**
Median stool frequency on day 1 after rescue therapy, n (IQR)	6 (3-8)	7 (5-8)	5 (3-8)	0.26**
Median stool frequency on day 3 after rescue therapy, n (IQR)	4 (3-7)	5 (3-12)	4 (3-7)	0.33**
Median CRP at admission, n mg/L (IQR)	76 (48-117)	101.5 (88-151)	65.5 (45-114)	0.13**
Median CRP on day of rescue therapy, n mg/L (IQR)	26 (14-84)	71.5 (15-128.5)	23 (10-67)	0.17**
Median CRP on day 1 after rescue therapy, n mg/L (IQR)	21 (5.7-74)	68 (17-111)	14 (5-60)	0.09**
Median CRP on day 3 after rescue therapy, n mg/L (IQR)	16 (2-3-41)	45 (31-51)	7 (2-34)	0.001**
Median serum albumin at admission, n g/L (IQR)	32 (26-34)	31 (23-33)	32 (26-35)	0.30**
Median serum albumin on day of rescue therapy, n g/L (IQR)	25.5 (23-30)	23.5 (21-27)	26 (23-30)	0.22**
Median serum albumin on day 1 after rescue therapy, n g/L (IQR)	26.5 (24-29)	24 (23-27)	27 (24-30)	0.22**
Median serum albumin on day 3 after rescue therapy, n g/L (IQR)	27 (23.5-30.5)	27 (22-28)	27 (24-31)	0.27**
Median hemoglobin on day of admission, n g/L (IQR)	119(108-137)	107 (90-120)	122 (108.5-137.5)	0.72**
Median hemoglobin on day of rescue therapy, n g/L (IQR)	111 (95-122)	106 (85.5-114.5)	113 (96-126)	0.21**
Median hemoglobin on day 3 after rescue therapy, n g/L (IQR)	114 (96-120)	100 (90-115)	115 (103-123)	0.07**
Median admission Calprotectin, n mcg/g (IQR)	2200 (1300-5800)	3300 (3300-5800)	1950 (1050-6500)	0.17**

*Fischer Exact test

** Wilcoxon Ranksum test

#UCEIS: scored during the flexible performed at admission, prior to rescue therapy

UC: ulcerative colitis; ASUC: acute severe ulcerative colitis; IQR: interquartile range; CsA: ciclosporin; EIM: extra-intestinal manifestations; Anti-TNF: anti-tumour necrosis factor alpha; ASA: aminosalicylic acid; IMM: immunomodulator; CMV: cytomegalovirus

UCEIS: ulcerative colitis endoscopic index of severity; CRP: C-reactive protein; IQR interquartile range

Table 2: **Logistic regression analysis for predictors of response to medical rescue therapy**

	Univariable Analysis			**Multivariable Analysis**		
	OR	**95% CI**	**P**	**Coefficient**	**95% CI**	**P**
Number of additional Truelove and Witts' criteria at admission	0.42	0.23-0.74	0.003	-0.04	- 0.17to 0.07	0.44
Hemoglobin on day 3 of admission	1.04	1.00-1.07	0.03	0.001	-0.005 to 0.008	0.69
Albumin on day 3 of admission	1.06	0.96-1.16	0.23			
CRP on day 3 of admission	0.99	0.98-1.01	0.83			
Stool frequency on day 3 of admission	1.02	0.92-1.13	0.67			
Mayo Endoscopic score at admission	0.67	0.21-2.15	0.50			
UCEIS at admission	**0.33**	**0.16-0.68**	**0.003**	**-0.10**	**-0.19 to -0.007**	**0.035**
Hemoglobin on day of rescue therapy	1.03	0.99-1.06	0.07			
CRP on day of rescue therapy	0.99	0.98-1.00	0.11			
Albumin on day of rescue therapy	1.12	0.96-1.32	0.16			
Stool frequency on day of rescue therapy	0.91	0.81-1.03	0.16			
CRP on day 1 after rescue therapy	0.99	0.98-1.00	0.18			
Albumin on day 1 after rescue therapy	1.13	0.98-1.29	0.08			
Stool frequency on day 1 after rescue therapy	0.96	0.86-1.07	0.51			
Hemoglobin on day 3 after rescue therapy	1.03	0.99-1.06	0.06			
CRP on day 3 after rescue therapy	**0.97**	**0.95-0.99**	**0.015**	**- 0.004**	**- 0.008 to – 0.0004**	**0.03**
Albumin on day 3 after rescue therapy	1.16	0.97-1.39	0.01	-0.004	-0.031 to 0.023	0.75

Stool frequency on day 3 after rescue therapy	0.91	0.77-1.07	0.26			

CRP: C-reactive protein; UCEIS: ulcerative colitis endoscopic index of severity

Table 3: **Individual thresholds of UCEIS and CRP* in identifying patients who are likely to avoid colectomy and performance of RESCUE-ASC CRITERIA**

A) DEVELOPMENT COHORT				
	Avoiding same admission colectomy, n (%)	**Colectomy-free at 30 days, n (%)**	**Colectomy-free at 3 months, n (%)**	**Colectomy-free at 12 months, n (%)**
UCEIS < 6	17/17 (100)	17/17 (100)	17/17 (100)	16/17 (94.1)
UCEIS ≥ 6	23/32 (71.9)	21/32 (65.6)	19/32 (59.4)	16/32 (50)
CRP Day R + 3 < 22 mg/L	28/28 (100)	27/28 (96.4)	26/28 (92.9)	23/28 (82.1)
CRP Day R + 3 ≥ 22 mg/L	12/21 (57.1)	11/21 (52.4)	10/21 (47.6)	9/21 (42.9)
Performance of RESCUE-ASC Criteria				
	Avoiding same admission colectomy, n (%)	**Colectomy-free at 30 days, n (%)**	**Colectomy-free at 3 months, n (%)**	**Colectomy-free at 12 months, n (%)**
0 (n=19)	10/19 (52.6)	9/19 (47.4)	8/19 (42.1)	7/19 (36.9)
1 (n=15)	15/15 (100)	14/15 (93.3)	13/15 (86.7)	11/15 (73.3)
2 (n=15)	15/15 (100)	15/15 (100)	15/15 (100)	14/15 (93.3)
OR	18 (2-122) p=0.001	17.75 (2.5-125.8) p=0.004	11.3 (2.83-45.45) p=0.001	4.8 (1.79-13.07) p=0.002
AUROC	0.8750 (0.8070-0.9429)	0.8541 (0.7641-0.9440)	0.8440 (0.7479-0.9400)	0.7849 (0.6618-0.9080)
B) VALIDATION COHORT				
	Avoiding same admission colectomy, n (%)	**Colectomy-free at 30 days, n (%)**	**Colectomy-free at 3 months, n (%)**	**Colectomy-free at 12 months, n (%)**
UCEIS < 6	19/21 (90.5)	19/21 (90.5)	18/21 (85.7)	18/21 (85.7)
UCEIS ≥ 6	63/67 (94.6)	62/67 (92.5)	59/67 (88.1)	56/67 (83.6)
CRP Day R + 3 < 22 mg/L	70/70 (100)	69/70 (98.6)	66/70 (94.3)	64/70 (91.4)
CRP Day R + 3 ≥ 22 mg/L	12/18 (66.7)	12/18 (66.7)	11/18 (61.1)	10/18 (55.6)
Performance of RESCUE-ASC Criteria				
	Avoiding same admission colectomy, n (%)	**Colectomy-free at 30 days, n (%)**	**Colectomy-free at 3 months, n (%)**	**Colectomy-free at 12 months, n (%)**
0 (n=14)	10/14 (71.4)	10/14 (71.4)	9/14 (64.3)	8/14 (57.1)
1 (n=57)	55/57 (96.5)	54/57 (94.7)	52/57 (91.2)	50/57 (87.7)
2 (n=17)	17/17 (100)	17/17 (100)	16/17 (94.1)	16/17 (94.1)
OR	11.8 (2.16-64.2)	8.08 (1.9-34.33)	3.99 (1.03-15.35)	4.23 (1.28-13.9)

	p=0.004	p=0.005	p=0.044	p=0.017
AUROC	0.8069 (0.6381-0.9757)	0.7690 (0.6065-0.9314)	0.6854 (0.5155-0.8547)	0.6902 (0.5476-0.8327)

Variables in the criteria: 1 point for presence of each of the variables (UCEIS < 6, CRP on day 3 after rescue therapy < 22 mg/L). Minimum score = 0, maximum score = 2

AUROC: area under receiver operating characteristic curve; OR: odd's ratio

Table 4:Performance of both UCEIS <6 and CRP* in identifying patients who are likely to avoid colectomy

	DEVELOPMENT COHORT (n=15)				**VALIDATION COHORT (n=17)**			
	Avoiding same admission colectomy	**Colectomy-free at 30 days**	**Colectomy-free at 3 months**	**Colectomy-free at 12 months**	**Avoiding same admission colectomy**	**Colectomy-free at 30 days**	**Colectomy-free at 3 months**	**Colectomy-free at 12 months**
Sensitivity, % (95% CI)	37.5 (22.7-54.2)	39.5 (24-56.6)	41.7 (25.5-59.2)	43.8 (26.4-62.3)	20.7 (12.6-31.1)	21 (12.7-13.5)	20.8 (12.4-31.5)	21.6 (12.9-32.7)
Specificity, % (95% CI)	100 (66.4-100)	100 (71.5-100)	100 (75.3-100)	94.1 (71.3-99.9)	100 (54.1-100)	100 (59-100)	90.9 (58.7-99.8)	92.9 (66.1-99.8)
NPV, % (95% CI)	26.5 (12.9-44.4)	32.4 (17.4-50.5)	38.2 (22.2-56.4)	47.1 (29.8-64.9)	8.45 (3.12-17.5)	9.86 (4-19.3)	14.1 (6.97-24.4)	18.3 (10.1-29.3)
PPV, % (95% CI)	100 (78.2-100)	100 (78.2-100)	100 (78.2-100)	93.3 (68.1-99.8)	100 (80.5-100)	100 (80.5-100)	94.1 (71.3-99.9)	94.1 (71.3-99.9)
PLR	.	-	-	7.44 (1.07-51.8)	-	-	2.29 (0.335-15.6)	3.03 (0.436-21)
NLR	0.625 (0.492-0.795)	0.605 (0.468-0.782)	0.583 (0.443-0.769)	0.598 (0.431-0.83)	0.793 (0.71-0.885)	0.79 (0.706-0.884)	0.871 (0.7-1.08)	0.844 (0.699-1.02)
AUROC	0.688 (0.612-0.763)	0.697 (0.619-0.776)	0.708 (0.627-0.79)	0.689 (0.585-0.794)	0.604 (0.56-0.648)	0.605 (0.564-0.653)	0.558 (0.458-0.659)	0.572 (0.488-0.657)

* CRP on day 3 of post commencement of medical rescue therapy < 22mg/L

PPV/NPV: positive/negative predictive value; PLR/NLR: positive/ negative likelihood ratio; AUROC: Area under receiver operating curve; CRP: C-reactive protein; UCEIS: ulcerative colitis endoscopic index of severity

ABBREVIATIONS

ASUC: Acute severe ulcerative colitis

MRT: Medical Rescue Therapy

UC: Ulcerative colitis

IFX: Infliximab

CsA: Ciclosporin

IBD: Inflammatory bowel diseases

UCEIS: Ulcerative colitis index of severity

CRP: C-reactive protein

EIMs: Extra-intestinal manifestations

Anti-TNF: Anti-tumour necrosis factor alpha

ASA: Aminosalicylic acid

IM: Immunomodulator

Hb: Haemoglobin

TLW: Truelove and Witts' criteria

PPV: Positive predictive value

NPV: Negative predictive value

OR: Odd's ratio

PLR: Positive likelihood ratio

NLR: Negative likelihood ratio

IQR: inter-quartile range

AUROC: Area under receiver-operating curve