Optimising Early Management of Acute Severe Ulcerative Colitis in the Biologics Era: Development and Validation of a Prognostic Clinical Index to Predict Steroid Response

Management of Acute Severe Ulcerative Colitis in the Biologics Era: Outcome Analysis and Development of a Prognostic Clinical Index to Predict Outcome on Admission

Short title: Predicting steroid response in ASC

Alex Adams[1*†], **Vipin Gupta**[1,2*], **Waled Mohsen**[1,3*], Thomas P Chapman[1,4], Deloshaan Subhaharan[3], Pradeep Kakkadasam Ramaswamy[3], Sudheer Kumar Vuyyuru[5], Saurabh Kedia[5], Colleen GC McGregor[1], Tim Ambrose[1], Bruce D George[1], Rebecca Palmer[1], Oliver Brain[1], Alissa Walsh[1], Vineet Ahuja[5], Simon Travis[1], and Jack Satsangi[1†]

* Joint first author, † Corresponding author
[1]Translational Gastroenterology Unit, NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[2]Department Of Gastroenterology , Cardiff University Health Board, UK
[3]Digestive Diseases Unit, Gold Coast University Hospital, Queensland, Australia
[4]Department of Gastroenterology, Western Sussex NHS Foundation Trust
[5]Department of Gastroenterology, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Grant support: This work is funded by the Oxford NIHR Biomedical Research Centre - Gastroenterology and Mucosal Immunology Theme. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Abbreviations: ASC - Acute severe colitis; **AUC** - Area under the ROC; **CRP** - C-reactive protein; **FDR** - False discovery rate; **IQR** – interquartile range (given as values of the first and third quartiles); **KNN** - K-nearest neighbours; **MARS** - Multivariate adaptive regression spline; **OR** - Odds ratio; **PPV** - positive predictive value; **ROC** - Receiver operating characteristic; **TNF** - Tumour Necrosis Factor; **UCEIS** - Ulcerative Colitis Endoscopic Index of Severity

Correspondence: John Radcliffe Hospital (Level 5), Headley Way, Headington, Oxford, OX3 9DU. Email: alex.adams@ndm.ox.ac.uk / jack.satsangi@ndm.ox.ac.uk

Disclosures: AA, **VG**, **WM**, **TC**, **DS**, **PR**, **SKV**, **SK**, **CM**, **TA**, **BG**, **RP**, **OB**, and **VA** declare no competing interests. **AW** reports personal fees outside the submitted work from Ferring Pharmaceuticals, Janssen, and Takeda. **ST** reports outside the submitted work receipt of grants/research support from AbbVie, Buhlmann, Celgene, IOIBD, Janssen, Lilly, Pfizer, Takeda, UCB, Vifor, and Norman Collisson Foundation; consulting fees from AbbVie, Allergan, Amgen, Arena, Asahi, Astellas, Biocare, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Buhlmann, Celgene, Chemocentryx, Cosmo, Enterome, Ferring, Giuliani SpA, GSK, Genentech, Immunocore, Immunometabolism, Indigo, Janssen, Lexicon, Lilly, Merck, MSD, Neovacs, Novartis, NovoNordisk, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Roche, Sensyne, Shire, Sigmoid Pharma, SynDermix, Takeda, Theravance, Tillotts, Topivert, UCB, VHsquared, Vifor, and Zeria; speaker fees from AbbVie, Amgen, Biogen, Ferring, Janssen, Lilly, Pfizer, Shire, and Takeda; no stocks or share options. **JS** has received lecture fees from Takeda and from the Falk Foundation.

Author Contributions: JS proposed the study. **WM**, **VG**, **DS**, **PRK**, **SKV**, and **SK** collected the clinical data. **AA** and **PKR** performed the analysis. **AA**, **JS**, **VG**, **WM** & **TC** contributed to study design and prepared the first draft, and all authors interpreted the results, and reviewed and contributed to the final manuscript.

Data Transparency Statement: Please contact the corresponding authors for access to anonymised data.

A preprint of this paper is hosted by medRxiv at https://doi.org/10.1101/2021.07.14.21260477

ABSTRACT

Background & aims: We aimed to determine whether changes in acute severe colitis (ASC) management have translated to improved outcomes, and to develop a simple model predicting steroid non-response on admission.

Methods: Outcomes of 131 adult ASC admissions (117 patients) in Oxford, UK between 2015-19 were compared with prospectively collected data from 1992-3. All patients received standard treatment with intravenous corticosteroids and endoscopic disease activity scoring (UCEIS). Steroid non-response was defined as receiving rescue medical therapy or surgery. A predictive model developed in the Oxford cohort was validated in Australia and India (110 hospitalised patients Gold Coast University Hospital 2015-20; 62 hospitalised patients AIIMS, New Delhi 2018-20).

Results: In the 2015-19 Oxford cohort, only 15% required colectomy during admission vs 29% in 1992-3 (p=0.033), whilst 71 (54%) patients received medical rescue therapy (27% ciclosporin, 27% anti-TNF), compared to 27% ciclosporin in 1992-3, p=0.0015. Admission CRP, albumin, and UCEIS scores predicted steroid non-response (FDR p=0.00066, 0.0066 and 0.015). A four-point model was developed involving CRP ≥100mg/L (1 point), albumin ≤25g/L (1 point), UCEIS ≥4 (1 point) or ≥7 (2 points). Scoring 0 or 4 was 100% predictive of steroid response and non-response, respectively, in all three cohorts. Patients scoring 3-4 had 83% risk of steroid non-response in Oxford and 84% (0.70-0.98) in the validation cohorts – OR 11.9 (10.8-13). Colectomy rates were 8-11% in validation cohorts in India and Australia.

Conclusion: Emergency colectomy rates for ASC have halved in 25 years, to 8-15% worldwide. Patients who will not respond to corticosteroids alone are readily identified on admission, and may be prioritised for early intensification of therapy.

Keywords: Acute severe colitis; prediction; outcome

SIGNIFICANCE OF THIS STUDY

What is already known about this subject?

• Acute severe colitis (ASC) is an important cause of morbidity and mortality in ulcerative colitis, requiring hospitalisation and, frequently, colectomy

• Biological agents, initially anti-TNF therapies, and later vedolizumab and ustekinumab, are now routinely used in maintenance strategies.

• For over 20 years, the accepted management of ASC has involved three days' treatment with intravenous (IV) corticosteroids, followed by use of accepted protocols to assess response.

What are the new findings?

• By performing a historical comparison within the same unit, we provide insight into how outcomes of ASC have changed in the age of biologics

• We identify and validate threshold values of CRP, albumin, and a validated endoscopic activity index as predictors of steroid non-response in ASC in the biologics' era

• We show that a simple clinical score based on these parameters - the "ADmission Model for Intensification of Therapy in acute severe colitis" (ADMIT–ASC) - accurately identifies patients who are unlikely to benefit from initial management with corticosteroid monotherapy

• Two further cohorts from Australia and India enabled validation of these findings, making this the first replicated prognostic score for ASC which does not rely on waiting to assess steroid response after three days. It is the only score derived and validated in patients exposed to biologics.

How might it impact on clinical practice in the foreseeable future?

• We demonstrate that the outcome of ASC has altered dramatically. Innovations in management, notably the introduction of protocol-driven management algorithms , have halved rates of emergency surgery

• On admission, prediction of the effectiveness of initial management with parenteral corticosteroids is now possible using a simple clinical scoring system based on routine blood tests, and endoscopic appearances.

• This offers an opportunity for early escalation of treatment - introducing second-line therapy or surgery, potentially avoiding futile steroid exposure and reducing the duration of hospitalisation.

• We confirm that patients with a suboptimal response to steroids remain at increased risk of re-admission and colectomy in the year following discharge, providing potential for further improvement in outcomes by identifying patients for early escalation of medical therapy.

INTRODUCTION

Ulcerative colitis (UC) is a common, chronic, immune-mediated illness, now affecting approximately 1 in 200 of the UK population and increasing in prevalence world-wide.[1,2] Approximately 25% of patients will develop an episode of acute severe colitis[3] (ASC), defined as frequent bloody diarrhoea with evidence of significant systemic biological disturbance (fever, tachycardia, anaemia, elevated inflammatory biomarkers): this complication necessitates hospitalisation for intensive medical management or surgery.[4] Landmark trials in the 20th century demonstrated the efficacy of corticosteroids as first-line medical therapy.[4] The subsequent success of ciclosporin or infliximab as rescue therapy in a proportion of patients with no response to corticosteroids[5-8] led to protocol-driven algorithms of management that have reduced mortality and colectomy rates.[9-14] Nevertheless, consistent data suggest that in the region of 40% of patients with ASC fail to respond to intravenous corticosteroids.[9,10,14] Predictive models to guide the introduction of medical rescue therapy based on early response to corticosteroids, typically by day three, are in widespread use, and have been adopted into national and international guidelines for management.[9,10] It remains unclear to what extent this has improved outcomes, or whether earlier identification of steroid non-responders is possible.

We therefore examined outcomes of patients admitted to the Translational Gastroenterology Unit in Oxford, UK, between 2015-9 and compared these with prospective historical data available from the same centre in the pre-biologics' era (1992-3),[10] and with outcomes in specialist units in India and Australia.

Our further aim was to develop and validate a model on admission to predict which patients were unlikely to respond to steroids, so that rescue therapy or surgery could be expedited. We define and validate in the Oxford population a simple index for risk stratification on the day of admission, involving serum albumin and C-reactive protein (CRP) concentrations, with endoscopic severity, as assessed by the Ulcerative Colitis Endoscopic Index of Severity (UCEIS).[15,16,17] This model, the ADMIT-ASC index (Admission Model for the Intensification of Therapy in Acute Severe Colitis),

was then successfully validated in independent cohorts in Queensland, Australia and New Delhi, India.

METHODS

Study design

A systematic retrospective study of all patients (≥16 years) admitted with ASC in Oxford between 1 May 2015 and 31 October 2019 was performed. Patients were identified from a prospectively maintained endoscopy database (Endobase, Olympus) at Oxford University Hospitals NHS Foundation Trust which comprises two hospitals, John Radcliffe and Horton General Hospital, serving a catchment area population of 700,000. Per local protocol, all patients admitted with suspected ASC underwent flexible sigmoidoscopy on admission, with UCEIS[15,16] recorded in all patients since 2015. This was cross-referenced against the Oxford BRC IBD Biobank database (InfoFlex) to assess completeness of capture. Admission records and corresponding patient case records were then reviewed to confirm patients admitted with ASC during the study period. To ensure consistency and accuracy of data extraction, all patient case records were reviewed by two IBD clinicians (VG and WM). Sample sizes were targeted to exceed those used in previous studies, such as Travis el al, 1996 (n=51), on which the current day 3 criteria are based.

Definitions

The diagnosis of UC was confirmed for each patient using established criteria.[18] ASC was defined according to modified Truelove and Witts' criteria as six or more bloody stools per day with one or more markers of systemic disturbance (heart rate >90, temperature >37.8°C, haemoglobin <105g/L, or CRP >30mg/L).[12] Steroid non-response was defined as administration of medical rescue therapy (ciclosporin or anti-TNF), or colectomy during the same admission. The 1996 Oxford criteria were used to define need for escalation of medical therapy (stool frequency of more than 8 daily, or a stool frequency of 3–8 daily and CRP of more than 45mg/L on the third day after initiating intravenous hydrocortisone).[10]

Management

Inpatient management followed established Oxford protocol and international guidelines, using intravenous hydrocortisone (100mg four times daily), rectal hydrocortisone (100mg twice daily), intravenous fluids and thromboprophylaxis with low molecular weight heparin.[11,19] Response was assessed on the third day, using the Oxford criteria to determine indications for medical rescue therapy or colectomy.[10] If required, rescue therapy followed hospital protocol (ciclosporin 2mg/kg intravenously until response, then 5mg/kg orally for 3 months; or infliximab 5mg/kg at 0, 2 and 6 weeks, rarely with a higher dose), with the choice based on previous therapy and the judgement of the treating consultant gastroenterologists (Oxford n=3, Gold Coast n=5, Delhi, n=2), if necessary after multidisciplinary discussion. Diagnosis and inpatient management in both validation centres followed the same established guidelines as detailed above, and as in Oxford, in both Australian and Indian centres, protocolised management in ASC was overseen in specialist units, and involved endoscopic assessment on admission, and Day three re-assessment of need for escalation of therapy.[10]

Outcomes

The primary outcome was steroid non-response during admission with ASC. We separately assessed need for biological therapy, ciclosporin, or colectomy during admission. Re-admission rates with ASC and colectomy rates at 12 months and within the total follow-up period were also assessed. All outcome measures were pre-specified.

Data collection

In all centres, data were collected on demographic details (gender, age), UC history (disease duration, medication history, extra-intestinal manifestations), admission clinical parameters (stool frequency in preceding 24 hours, heart rate, temperature, haemoglobin, platelet count, white cell count, CRP), admission radiographic findings (presence of toxic megacolon on abdominal radiograph defined by a transverse colon diameter >5.5cm), and endoscopic findings (UCEIS score). Data on use and duration of intravenous steroids, use of medical rescue therapy or need for colectomy during

admission were also collected. Following admission, data on re-admission rates with ASC, subsequent requirement for advanced therapy (biologic therapy or tofacitinib) or colectomy, both at 12 months and over the total follow-up period were also collected. Readmissions with ASC were treated as separate events.

Predictive index development

A predictive index was created using only UK patient data, with only the finally selected model being validated in the Australian and Indian cohorts. Our aim was to create an index which is simple and memorable, which could be used without any additional calculation or requiring a software tool. Initial modelling was performed using a variety of classification techniques (Supplemental Table 4 & Supplemental Figure 2) to identify a performance baseline against which the simple index could be compared to ensure that the simplification did not overly effect performance.

Models included a range of up to ten untransformed parameters available on admission (age, albumin, CRP, current biologic treatment, disease duration, haemoglobin, platelets, sex, stool frequency, and UCEIS). One value for CRP and 4 values for albumin were missing, only patients with complete data were used, no imputation was undertaken and outcome data was complete for all patients.

Models were tested which included a subset of the ten parameters above, with one or more thresholds at memorable values for each parameter, and with both even and weighted valuation of each parameter passing it's threshold. These models were ranked by Akaike information criterion, to identify the top 10 with the final index being chosen from these taking into account simplicity, and ease of implementation (e.g. weighing the practical difficulties of adding accurate stool frequency measurement against a very marginal increase in performance in the discovery cohort). The performance measures calculated to assess and compare models are shown in Table 6.

Predictive index validation

For validation of the day one predictive index developed in Oxford, outcomes in two independent cohorts were analysed. Firstly, a systematic retrospective study identified all adult patients meeting Truelove and Witts' criteria coded with ulcerative colitis as the primary indication for admission in electronic patient records admitted from 1 January 2015 to 30 April 2020 to Gold Coast University Hospital, Queensland, Australia, serving a catchment area population of approximately 600,000. Secondly, all patients admitted to the All India Institute of Medical Sciences (AIIMS), New Delhi, India, with ASC meeting Truelove and Witts' criteria between August 2018 and May 2020 (excluding secondary referrals, patients less than 18 years old, and patients who did not receive parenteral steroid treatment) were included. In both these cohorts the index was applied and correlated with outcomes – thereby including 110/128 Australian patients who had a UCEIS score available (all with complete albumin and CRP data), and 62 Indian patients (all with complete albumin, CRP and UCEIS data).

Statistical analysis

Analysis was performed in R (v3.6). Univariable analysis was performed with Fisher's exact test for binary variables, and logistic regression for all other variables, and for multivariable logistic regression. P values are given as corrected false discovery rates (FDR).[20] Odds ratios for univariable and multivariable logistic regression are given with confidence intervals calculated using the profile likelihood method[21] and binomial proportion confidence intervals are given for summary statistics of the final model. Preliminary statistical modelling of steroid non-response in the discovery cohort was performed using caret[22] to perform 100 repeats of 10-fold cross-validation. Blinding during analysis was not possible, but the definition of steroid response was based on pre-specified criteria and determined prior to modelling, and selection of a final predictive index in the discovery cohort was completed before data from either validation cohort was accessed.

Ethical approval

Ethical approval in Oxford was granted through the National Health Service Health Research Authority REC 16/YH/0247 and 09/H1204/30, in Gold Coast by Health Service Human Research

Ethics Committee (Ref: LNR/2020/QGC/67173), and in Delhi AIIMS by ethics committee (Ref: IEC-261/04.05.2018)

Patient and public involvement statement

As this work is a retrospective audit involving examination of routine clinical examinations and clinical outcomes patient and public involvement was not included in the design and conduct of the research.

RESULTS

Discovery cohort

In the discovery cohort, 131 admission events in 117 patients were analysed (42% male, median age 41.2years), including 38 index presentations. No demographic features predicted ASC recurrence (Supplemental Table 1). Demographic and clinical details are given in Tables 1-2.

Response to corticosteroids without need for medical rescue therapy or surgery was seen in only 52/131 ASC episodes (40%). No demographic parameters were associated with steroid response (Table 1) or ASC recurrence (Supplemental Table 1). Clinical parameters on admission were compared between steroid-responders and non-responders. Median UCEIS was 6 (IQR 5-7) overall, 6 (5-7) for non-responders, and 5.5 (5-6) for responders. Baseline CRP differed between non-responders and responders (median 43mg/L vs 101mg/L, $p=2.7 \times 10^{-6}$), but albumin, haemoglobin, stool frequency, and platelet count did not (Table 2).

In total, 71 ASC episodes (54%) involved medical rescue therapy, of whom 36 (51%) were given anti-TNF therapy (including 2 who received adalimumab, due to reasons of longer-term intravenous access) and 35 (49%) ciclosporin. At the end of follow-up 60/117 (51%) of patients were receiving advanced therapy (24 infliximab, 9 adalimumab, 21 vedolizumab, 4 tofacitinib, and 2 in clinical trials).

Overall, 19 (15%) patients required colectomy during admission, eight without receiving rescue therapy (2 patient preference, 1 readmission a month following a previous ASC episode, 1 toxic megacolon, and four patients admitted on vedolizumab therapy). Over a median follow-up of 22 (1-49) months, 14 (12%) patients required re-admission with a further episode of ASC.

In 26/131 events (20%) the patient had prior exposure to anti-TNF or vedolizumab (26/93 (28%), excluding index presentations), with 17/131 (13%) events occuring in patients currently on advanced therapy (3 infliximab, 3 adalimumab, 11 vedolizumab). One infliximab-treated patient responded to steroids and continued on infliximab; two received accelerated anti-TNF rescue therapy, neither of whom required surgery. Two of three adalimumab patients responded to intravenous steroids (subsequently discharged on vedolizumab and tofacitinib respectively); the other had surgery without rescue therapy. Of the 11 patients admitted on vedolizumab, 4 responded to intravenous steroids (1 continued vedolizumab, 2 changed to tofacitinib), 3 received rescue therapy (1 ciclosporin, 2 infliximab), and 5 had surgery during the admission (1 after unsuccessful infliximab rescue therapy).

Comparison of outcomes with pre-biological cohort in Oxford

In comparison to 1992-3[10] (Table 3) the proportion of episodes treated with ciclosporin as rescue therapy was unchanged at 27%, but the proportion of episodes resulting in any medical rescue therapy during admission doubled to 54%, as a result of the use of infliximab in 26% of episodes in the later time period. This coincides with a reduction in colectomy rates during admission from 29% to 15% (p=0.033), and a reduction in readmission with ASC from 35% to 12% (p=0.0017), despite a significantly longer median duration of follow-up, 12 (1992-93) vs 22 months (2015-19, p<0.007).

In both cohorts the rate of response to intravenous steroids was similar (41% vs 40%, p=0.87). Colectomy rates in the year following admission were approximately eight-fold lower in those who responded to steroid treatment than in those receiving medical rescue therapy (5 vs 40% p=0.013, and 2 vs 17% p=0.010). The overall rate of colectomy for patients within a year fell from 43% to 21% (21/49 in 1993-93 vs 24/117 in 2015-19, p=0.0044).

Predictive analyses of outcome in the discovery cohort

On univariable analysis, baseline CRP (FDR corrected p=0.00066, OR for a one-unit increase 1.02), albumin (p=0.0066, OR 0.89), UCEIS (p=0.015, OR 1.62), and number of Truelove and Witts' criteria (p=0.0066, OR 2.43) were significantly associated with steroid non-response (Supplementary Figure 1). Of the individual Truelove and Witts' criteria, only CRP was independently significant.

Of the components of the UCEIS score, the 'erosion and ulceration' component was independently significant (p=0.0066, OR 2.68), and stronger than the overall score. Details of univariable regressions for steroid non-response and rescue therapy are given in Table 4, with further results in Supplemental Table 2.

In multivariable logistic regression, only CRP was independently significant for steroid non-response (p=0.0076, OR 1.02). Any biologic treatment on admission was associated with the use of rescue therapy with infliximab (p=0.0049, OR 5.65), and not with ciclosporin (p=0.016, OR 0.13). Significant results from multivariable analysis are shown in Supplemental Table 3.

Predictive models of steroid non-response in the discovery cohort

Steroid non-response was modelled in the discovery cohort with 21 different classification approaches (Supplemental table 4 & supplemental figure 2). Assessment of the importance of each variable in these models revealed CRP to be the most informative variable, followed by UCEIS – in particular the erosion and ulceration component (Supplemental Figure 3). Average prediction accuracy in left out samples from cross-validation ranged from 57% (95% CI 47-66) for K-nearest neighbour (KNN) to 68% (59-77) for multivariate adaptive regression splines (MARS), though across all models accuracy was high for those predicted to be at high or low risk of steroid non-response, and worse for those of intermediate risk. ROC curve for these predictions are shown in Supplemental Figure 4, with mean AUC values ranging from 0.59 for KNN and AdaBoost to 0.75 for MARS, naive Bayes, and sparse partial least squares models. This modelling demonstrates that prediction of steroid

response and non-response is possible, but that identifying extremes of risk is more feasible than accurately predicting risk in all patients.

Selection of a predictive index

Indices were tested in the discovery cohort with a range of thresholds and with both evenly weighted and variably weighted criteria. The final index consists of four points, one each for albumin ≤ 25g/L (19% of patients), and CRP ≥ 100mg/L (34%), with UCEIS ≥ 4 (96%) scoring one point, or two points for UCEIS ≥ 7 (29%). These selected features were all significant in univariable regression (above) and correlations between them are shown in Supplemental Table 5. Of potential fifth components (in decreasing order of utility: stool frequency ≥ 14, haemoglobin ≤ 90g/L, current biologics, platelets ≥500×10^9/L, and male sex) only stool frequency made a nominal improvement, but this was not selected for the final model on the basis of the consideration that the added complexity and difficulty of accurately measuring stool frequency outweighed the minor difference in performance (7% improvement in sensitivity at a cost of 4% loss of specificity). The best performing model where UCEIS on admission endoscopy is not available is shown in Supplemental Table 6.

Scores of 3 (14% of patients) and 4 (8%) identified patients with rates of non-response to steroids of 83% and 100% (Table 5). Use of a score threshold ≥3 to identify high risk patients therefore yields a positive predictive value (PPV) of 0.89 (95% CI 0.78-1.00), with an odds ratio (OR) for steroid non-response of 7.6 (6.3-8.8) (Table 6). In comparison positive predictive values for steroid non-response using single-component models of CRP ≥ 100 and albumin ≤ 25 are 0.46 and 0.53 respectively. No significant association exists between current biologic treatment on admission and score (p=0.82), and no correlation was observed between score and non-response to medical rescue therapy.

Validation Cohorts

At the Gold Coast University Hospital, a total of 128 patients (50% male, median age 35 years) presented with ASC between January 1st, 2015 and April 30th, 2020. Demographics and clinical parameters are given in Supplemental Tables 9 & 10. At presentation, 12 (9%) patients were on biological therapy (8 anti-TNF, 4 vedolizumab), and for 41 patients (32%) the admission was their index presentation of UC.

Medical rescue therapy was given to 51 (40%) patients (4 ciclosporin, 47 infliximab). Ten (8%) patients had a colectomy during admission, with one direct colectomy. As in the discovery cohort, all features selected for the final index were significant in univariable regression (Supplemental Table 11). Validation of the index was performed in the 110 (86%) patients with a UCEIS score recorded (all with CRP and albumin results). There were no significant differences between this subset and the complete Gold Coast cohort (Supplemental Table 12).

At the All India Institute of Medical Science, 62 patients (40% male, median age 35.5 years) presented with ASC between August 2018 and May 2020. Demographics and clinical parameters are given in supplemental tables 13 & 14. Medical rescue therapy was given to 17 (27%) patients (2 ciclosporin, 15 anti-TNF) and 7 (11%) patients had a colectomy during admission.

When the final model was applied to the Australian cohort with available UCEIS scores (n=110), a similar proportion of patients scored ≥3 (18% vs 21%, p=0.63); in the Indian cohort this was significantly lower (8%, $p=4.6\times10^{-7}$). However steroid response rates for each score were similar across all three cohorts (Table 5), apart from patients with the intermediate scores of 1 or 2 who were more likely to receive rescue therapy or surgery in the UK cohort (p=0.10 & 0.002 respectively). A score of 0 was100% predictive of steroid response and a score of 4 100% predictive of steroid non-response across all three cohorts.

Proposed implementation from pooled results

Although a score of 4 was 100% predictive of steroid non-response, only 13 patients (4.3%) scored 4. Extending the threshold to a score of 3 increased the proportion of patients to 17.5%. In the combined validation cohorts this threshold is highly specific (0.96, 95% CI 0.93-1.00), with a PPV of 0.84 (0.70-0.98) and OR of 11.9 (10.8-13.0). Use of this threshold to advance treatment would prevent one delayed treatment for every 8.2 (5.8-13.7) patients assessed. Summary statistics in the discovery cohort and both validation cohorts separately and combined are shown in Table 6.

DISCUSSION

This study provides new insights into the management and outcome of severe ulcerative colitis with relevance to current clinical practice. We demonstrate that urgent colectomy rates have halved from 29% to 15% in 2015-19, in comparison with the 1992-3 series from Oxford,[10] which is supported by other studies within our unit showing a consistent rate of 25-30% until the mid 1990s and a subsequent fall.[10,23-28] Elsewhere there are recent studies with a consistent acute colectomy rate from the UK (14.9-21.4%),[29-31] Ireland (18%),[32] USA (12.4%),[33] Australia (13.3%),[34] and Portugal (13.4%).[35] However, overall rates vary widely from 2.8% (6/217) in a Finnish study[36] to 75.9% (41/54) in a French study[37], and within countries there can be substantial variability such as 7-76% in France[37-38], making the historical comparison within Oxford particularly valuable.

Re-admission and colectomy rates after discharge have also fallen by two-thirds and a half respectively. The risks of colectomy in those without a clear steroid response remain 8-fold elevated in the year following discharge.[10,39] The early identification of this group with initiation and maintenance of longer-term effective treatment therefore remains a priority beyond management of the episode of ASC.

The study also identifies a predictive index for steroid non-response that can be applied on the day of admission, validated in two independent cohorts from separate continents. A combination of CRP $\geq$ 100mg/L, albumin $\leq$ 25g/L, and a UCEIS score of 7-8 (2 points) on day 1 results in a score of 4 and certain likelihood of steroid non-response (100% in both discovery and two validation cohorts), regardless of whether the patient is already established on biologics. A score of 3-4 is associated with an 84% chance of non-response to steroids and we propose a score of 3 or greater in a biological-naïve patient is an indication for early medical rescue therapy. In a patient admitted on biological therapy a score of 3 mandates surgical discussion early in admission. The case for early medical rescue therapy is clear, but the question of whether steroid treatment should continue concomitantly needs future study.

The historical perspective from the same centre is informative, as are the contemporary data from Australia and India. A key difference between the 1992-93 study from Oxford and the present study is the precise doubling of the number receiving rescue medical therapy. In both datasets, an equal proportion of patients received ciclosporin (27%). In the current Australian dataset, where approximately 40% of patients received rescue therapy with ciclosporin or infliximab, we report an acute colectomy rate of <10%. In the Indian cohort, the colectomy rate was 11%, with 27% given rescue therapy. This provides compelling evidence that alterations in treatment strategy in the modern era, including - but not exclusively - intervention with biological therapies, have improved clinical outcome in ASC, compared with historical outcomes. Standardised protocols for assessing response, guiding care and emphasis on multi-disciplinary team involvement appear fundamentally important to set standards for care, inform patient discussion and as a basis for further audit.

The current study confirms previous observations from ourselves and others that the biological severity on admission, as defined by Truelove and Witts, predicts resistance to therapy.[27,39-43] Our data suggest that CRP is the key parameter associated with predicting non-response to steroids.

By careful modelling a simple clinical index, ADMIT-ASC, assessed on admission was derived from the CRP, albumin and a validated index of endoscopic severity (UCEIS). The index reliably identifies a subset of approximately 1 in 5 patients with highly active disease, who will fail to show response to parenteral corticosteroid therapy[11] and require consideration of escalation of therapy or surgery. These data provide a rationale to refine the paradigm for management, which is currently predicated on treating all patients with parenteral steroids and assessing steroid response on day 3.

As a counterpoint, those patients with a score of 2 or less may be managed by conventional approach, with reassessment of steroid response, and need for escalation at day 3. A score of 0 may be

particularly reassuring, since we found complete concordance with steroid response across the cohorts.

Defining risk on the day of admission carries advantages in decision-making, contingency planning, and patient counselling, especially in those at high-risk of steroid non-response. The ADMIT-ASC index is reproducible and defines high-risk patients accurately. The index is simple and implementable without other changes in practice. All the parameters are readily and reproducibly defined, without the awkward need for assessment of stool frequency. Our data break new ground by involving contemporary discovery and validation cohorts who have been managed using biologics in induction or maintenance and by taking advantage of a validated endoscopic scoring system, notwithstanding geographical, and ethnic differences between all three populations.

There are, of course, limitations. The study is retrospective in design and did not allow reliable assessment of pre-admission therapy in the discovery cohort. Nonetheless, patient identification appeared complete and painstaking searches of available databases and paper case notes were performed to avoid ascertainment bias. The validity of the discovery dataset was confirmed by independent replication in two datasets from different continents. This is the first time a predictive index in ASC has been so validated.

We did not formally capture disease morbidity or complications of treatment, other than in the context of colectomy rates or re-admission. These are subject to regular audit and there is no signal of complication rates associated either with drug therapy or colectomy.[44] We also recognise that although the proposed index accurately identifies patients at a very high or low likelihood of response to steroid treatment, there remains a significant proportion who score 1 or 2 and in whom steroid responsiveness is difficult to predict. The study was performed in three specialist centres, where management was the responsibility of IBD-focused clinicians, who followed protocols to optimise outcomes developed

in Oxford and adopted internationally. Nevertheless, most (80%) of patients came from the local population, as in any secondary care hospital. The replication in two cohorts from different genetic backgrounds, previous treatment, environmental exposures, age and disease duration is a particular strength of our study.

The present findings are highly relevant to daily practice by clinicians involved in the care of patients with acute severe colitis. The validation of an index that relies on two routine blood tests and assessment of endoscopic severity on admission is a guide to early stage decision-making. We believe that this predictive model can appropriately be applied to trials and clinical practice.

Acknowledgements
The authors acknowledge the clinical and academic contributions made to this work by Professor Satish Keshav, who sadly passed away before the study was completed.

We acknowledge the contribution of the Oxford IBD cohort study BRC, which is supported by the NIHR Oxford Biomedical Research Centre, University of Oxford. The authors thank Sister and staff of the specialist wards, IBD Specialist Nurses and administrative staff, as well as our patients. The authors are also grateful to the other Oxford IBD Cohort Investigators: Carolina V. Arancibia-Cárcamo, Adam Bailey, Ellie Barnes, Elizabeth Bird-Lieberman, Barbara Braden, Jane Collier, James East, Alessandra Geremia, Lucy Howarth, Satish Keshav, Paul Klenerman, Simon Leedham, Fiona Powrie, Astor Rodrigues, Peter Sullivan and Holm Uhlig.

REFERENCES
[1]Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. *Lancet* 2017;**389**:1756–70. doi:10.1016/S0140-6736(16)32126-2

[2]Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017;**390**:2769–78. doi:10.1016/S0140-6736(17)32448-0

[3]Travis S, Satsangi J, Lémann M. Predicting the need for colectomy in severe ulcerative colitis: A critical appraisal of clinical parameters and currently available biomarkers. *Gut* 2011;**60**:3–9. doi:10.1136/gut.2010.216895

[4]Truelove SC, Witts LJ. Cortisone in Ulcerative Colitis. *BMJ* 1955;**2**:1041–8. doi:10.1136/bmj.2.4947.1041

[5]Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in Severe Ulcerative Colitis Refractory to Steroid Therapy. *N Engl J Med* 1994;**330**:1841–5. doi:10.1056/NEJM199406303302601

[6]Järnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: A randomized, placebo-controlled study. *Gastroenterology* 2005;**128**:1805–11. doi:10.1053/j.gastro.2005.03.003

[7]Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. *Lancet Gastroenterol Hepatol* 2016; **1**: 15–24. doi:10.1016/S2468-1253(16)30003-6

[8]Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: A parallel, open-label randomised controlled trial. *Lancet* 2012;**380**:1909–15. doi:10.1016/S0140-6736(12)61084-8

[9]Ho GT, Mowat C, Goddard CJR, 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* 2004; **19**: 1079–87. doi:10.1111/j.1365-2036.2004.01945.x

[10]Travis SPL, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut* 1996;**38**:905–10. doi:10.1136/gut.38.6.905

[11]Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;**68**:s1–106. doi:10.1136/gutjnl-2019-318484

[12]Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: Current management. *J Crohn's Colitis* 2017;**11**:769–84. doi:10.1093/ecco-jcc/jjx009

[13]**Singh S**, **Allegretti JR**, Siddique SM, Terdiman JP. AGA Technical Review on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology* 2020;**158**:1465-1496. doi:10.1053/j.gastro.2020.01.007

[14]Grant RK, Jones G-R, Plevris N, 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* 2021;**27**:451–7. doi:10.1093/ibd/izaa088

[15]Travis SPL, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: The Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* 2012;**61**:535–42. doi:10.1136/gutjnl-2011-300486

[16]Travis SPL, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology* 2013;**145**:987–95. doi:10.1053/j.gastro.2013.07.024

[17]**Gupta V**, **Mohsen W**, **Chapman TP**, Satsangi J. Predicting Outcome in Acute Severe Colitis—Controversies in Clinical Practice in 2021. *J Crohn's Colitis* 2021;**15**:1211–21. doi:10.1093/ecco-jcc/jjaa265

[18]Lennard-Jones JE. Classification of Inflammatory Bowel Disease. *Scand J Gastroenterol* 1989;**24**:2–6. doi:10.3109/00365528909091339

[19]Jakobovits SL, Travis SPL. Management of acute severe colitis. *Br Med Bull* 2005;**75–76**:131–44. doi:10.1093/bmb/ldl001

[20]Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B* 1995;**57**:289–300. https://www.jstor.org/stable/2346101

[21]Venzon DJ, Moolgavkar SH. A Method for Computing Profile-Likelihood-Based Confidence Intervals. *Appl Stat* 1988;**37**:87. doi:10.2307/2347496

[22]Kuhn M. Building predictive models in R using the caret package. *J Stat Softw* 2008;**28**:1–26. doi:10.18637/jss.v028.i05

23. Truelove SC, Jewell DP. Intensive Intravenous Regimen for Severe Attacks of Ulcerative Colitis. Lancet 1974;303:1067–1070.

24. Truelove SC, Lee EG, Willoughby CP, et al. Further Experience in the Treatment of Severe Attacks of Ulcerative Colitis. Lancet 1978;312:1086–1088.

25. Chapman RW, Selby WS, Jewell DP. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. Gut 1986;27:1210–1212.

26. Hyde GM, Thillainayagam A V, Jewell DP. hyde1998.pdf. Eur J Gastroenterol Hepatol 1998;10:411–413.

[27]Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. *J Crohn's Colitis* 2010;**4**:431–7. doi:10.1016/j.crohns.2010.02.001
28. Corte C, Fernandopulle N, Catuneanu AM ari., et al. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. J Crohns Colitis 2015;9:376–381.

###

29. Sebastian S, Walker GJ, Kennedy NA, et al. Assessment, endoscopy, and treatment in patients with acute severe ulcerative colitis during the COVID-19 pandemic (PROTECT-ASUC): a multicentre, observational, case-control study. Lancet Gastroenterol Hepatol 2021;6:271–281.

30. Lynch RW, Lowe D, Protheroe A, et al. Outcomes of rescue therapy in acute severe ulcerative colitis: Data from the United Kingdom inflammatory bowel disease audit. Aliment Pharmacol Ther 2013;38:935–945.

31. Lynch RW, Churchhouse AMD, Protheroe A, et al. Predicting outcome in acute severe ulcerative colitis: Comparison of the Travis and Ho scores using UK IBD audit data. Aliment Pharmacol Ther 2016;43:1132–1141.

32. Gibson DJ, Hartery K, Doherty J, et al. CRP/Albumin Ratio: An Early Predictor of Steroid Responsiveness in Acute Severe Ulcerative Colitis. J Clin Gastroenterol 2018;52:e48–e52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28737646.

33. Cushing KC, Kordbacheh H, Gee MS, et al. Sarcopenia is a novel predictor of the need for rescue therapy in hospitalized ulcerative colitis patients. J Crohn's Colitis 2018;12:1036–1041.

34. Lim AH, Grafton R, Hetzel DJ, et al. Clinical audit: Recent practice in caring for patients with acute severe colitis compared with published guidelines - is there a problem? Intern Med J 2013;43:803–809.

35. Bernardo S, Fernandes SR, Gonçalves AR, et al. Predicting the Course of Disease in Hospitalized Patients with Acute Severe Ulcerative Colitis. Inflamm Bowel Dis 2019;25:541–546.

36. Eronen H, Ilus T, Jussila A, et al. Long-term outcome of patients with acute ulcerative colitis after first course of intravenous corticosteroids. Scand J Gastroenterol 2021;56:234–238. Available at: https://doi.org/10.1080/00365521.2020.1867892.

37. Mege D, Monsinjon M, Zappa M, et al. Is abdominal CT useful for the management of patients with severe acute colitis complicating inflammatory bowel disease? A study in 54 consecutive patients. Color Dis 2017;19:O97–O102.

38. Baut G Le, Kirchgesner J, Amiot A, et al. A Scoring System to Determine Patients' Risk of Colectomy Within 1 Year After Hospital Admission for Acute Severe Ulcerative Colitis. Clin Gastroenterol Hepatol 2021;19:1602-1610.e1. Available at: https://doi.org/10.1016/j.cgh.2019.12.036.

###

[39]Bojic D, Radojicic Z, Nedeljkovic-Protic M, et al. Long-term outcome after admission for acute severe ulcerative colitis in Oxford: The 1992-1993 cohort. *Inflamm Bowel Dis* 2009;**15**:823–8. doi:10.1002/ibd.20843

[40]Lynch RW, Lowe D, Protheroe A, et al. Outcomes of rescue therapy in acute severe ulcerative colitis: data from the United Kingdom inflammatory bowel disease audit. *Aliment Pharmacol Ther* 2013;**38**:935-45. doi:10.1111/apt.12473

[41]Henriksen M, Jahnsen J, Lygren I, et al. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. *Gut* 2008;**57**:1518-23. doi:10.1136/gut.2007.146357

[42]Stallmach A, Nickel A, Lehmann T, et al. Parameters of a severe disease course in ulcerative colitis. *World J Gastroenterol* 2014;**20**:12754-80. doi:10.3748/wjg.v20.i35.12574

[43]Jain S, Kedia S, Bopanna S, et al. Are Truelove and Witts criteria for diagnosing acute severe colitis relevant for the Indian population? A prospective study. *Intest Res* 2018;**16**:69–74. doi:10.5217/ir.2018.16.1.69

[44]Hyde GM, Jewell DP, Kettlewell MGW, Mc. C. Mortensen NJ. Cyclosporin for severe ulcerative colitis does not increase the rate of perioperative complications. *Dis Colon Rectum* 2001;**44**:1436–40. doi:10.1007/BF02234594

Author names in bold designate shared co-first authorship

Table 1 *Admission demographics in the current Oxford cohort. P values for steroid response vs non-response groups from Wilcoxon rank sum test, or Fisher's exact test where marked [F]. 5-ASA – 5-aminosalicylate; anti-TNF – anti-tumour necrosis factor; EIM – extra-intestinal manifestations of inflammatory bowel disease; IM – immunomodulator.*

	Steroid non- response (n=79)	Steroid response (n=52)
Gender		
Male	34 (43%)	21 (40%)
Female	45 (57%)	31 (60%)
Median age (range), years	44.6 (16.4-79.6)	40.6 (16.7-74.3)
Age ≥ 60 years	16 (20%)	9 (17%)
Median age at diagnosis (range), years	29.5 (12.5-79.6)	30.9 (14.7-73.7)
Median disease duration (IQR), years	1.5 (0.05-7.0)	0.8 (0.0-7.0)
Index presentation as ASC	20 (25%)	18 (35%)
Median follow up (range), weeks	98.8 (5-213)	75.4 (10-203)
EIM	11 (14%)	3 (6%)
5-ASA (n, %)		
Current	37 (47%)	23 (44%)
Never	23 (29%)	21 (40%)
Intolerant/ceased	19 (24%)	8 (15%)
IM: methotrexate or thiopurine		
Current	11 (14%)	5 (10%)
Never	49 (62%)	40 (77%)
Intolerant/ceased	19 (24%)	7 (13%)
Anti-TNF		
Current	3 (4%)	3 (6%)
Never	67 (85%)	45 (87%)
Intolerant	4 (5%)	1 (2%)
Primary non-response	3 (4%)	1 (2%)
Secondary loss of response	2 (3%)	1 (2%)
Vedolizumab		
Current	7 (9%)	4 (8%)
Never	69 (87%)	45 (87%)
Intolerant	0 (0%)	1 (2%)
Primary non-response	1 (1%)	0 (0%)
Secondary loss of response	2 (3%)	2 (4%)
Tofacitinib		
Current	0 (0%)	0 (0%)
Never	78 (99%)	52 (100%)
Intolerant	0 (0%)	0 (0%)
Primary non-response	1 (1%)	0 (0%)
Secondary loss of response	0 (0%)	0 (0%)
Previous clinical trial exposure	1 (1%)	1 (2%)
More than 1 advanced therapy exposure	8 (10%)	2 (4)

Table 2 *Day 1 admission clinical, laboratory and endoscopic data in 131 admissions for Oxford cohort. P values from Wilcoxon rank sum test, or Fisher's exact test where marked [F]. bpm – beats per minute.*

	Steroid non responder (n=79)	Steroid responder (n=52)	p value
Tachycardia >90 bpm	63 (80%)	35 (67%)	0.15[F]
Median stool frequency (IQR)	11 (10-14.5)	10 (8-13)	0.19
Median haemoglobin (IQR), g/L	123 (111.5-134)	129.5 (108.8-138.3)	0.33
Median CRP (IQR), mg/L	101 (55.7-147.7)	43.4 (23.8-72.9)	2.7×10^{-6}
Median albumin (IQR), g/L	29 (25-32)	33 (29-35)	0.33
Median platelet count (IQR), $x10^9$/L	387 (323-468)	379 (300-441)	0.50
Toxic megacolon	2 (2.5%)	0 (0%)	0.52[F]
Truelove and Witts' criteria			0.006[F]
1	18 (23%)	22 (48%)	
2	40 (51%)	25 (42%)	
3	20 (25%)	5 (10%)	
4	1 (1%)	0 (0%)	
UCEIS score			0.049[F]
3	1 (1%)	4 (8%)	
4	6 (8%)	5 (10%)	
5	20 (25%)	17 (33%)	
6	21 (27%)	19 (37%)	
7	24 (30%)	6 (12%)	
8	7 (9%)	1 (2%)	

Table 3 *Historical comparison of outcomes in Oxford: P values from Fisher's exact test, except for follow-up duration which is from a Wilcoxon rank sum test against a worst-case simulated data producing the median and range observed by Travis et al.[10] Colectomy rates for the 1992-3 cohort are from the published follow-up (median 12 months) vs 12 months following discharge in 2015-2019, the difference in follow-up durations is not considered when comparing readmission rates.*

Outcome	1992-1993 (n=51)	2015-2019 (n=131)	p value
Steroid Response			
Response by day 3	21 (41%)	52 (40%)	0.87
Response by day 6	8 (16%)	-	-
Non-responder	22 (43%)	79 (60%)	-
Rescue therapy			
Anti-TNF	0 (0%)	36 (27%)	1.9×10^{-6}
Ciclosporin	14 (27%)	35 (27%)	1.0
All	14 (27%)	71 (54%)	0.0015
Colectomy during admission	15(29%)	19 (15%)	0.033
Colectomy in 12 months after ASC episode			
Steroid response day 3	1/21 (5%)	1/52 (2%)	0.50
Medical rescue therapy	6/15 (40%)	10/60 (17%)	0.075
Total	7/36 (19%)	11/112 (10%)	0.15
Patient colectomies during 12 months	21/49 (43%)	24/117 (21%)	0.0044
Readmission	17/49 (35%)	14/117 (12%)	<0.0017
Mortality			
Admission	0 (0%)	0 (0%)	1.0
Within 1 year	1 (2%)	0 (0%)	0.28
Months follow-up Median (range)	12 (3.5-21)	21.6 (1.2-49)	<0.007

Table 4 *Results of univariable analysis in the discovery cohort. Shown as FDR corrected p value (OR, 95% confidence interval), FDR correction was performed for 21 parameters (subcomponents of Truelove & Witts' score and UCEIS apart from erosion and ulceration not shown). P values derived from generalized linear models apart from parameters marked with F which were derived from Fisher's exact test. Steroid non-response denotes rescue therapy or surgery during the admission, rescue therapy includes both anti-TNF treatment and ciclosporin. TW – Truelove and Witts'.*

	Steroid Non-response	Rescue Therapy
Age	0.86 (1.00, 0.98-1.02)	0.26 (1.00, 0.98-1.02)
Sex (Male)[F]	0.86 (1.12, 0.55-2.29)	0.47 (1.50, 0.75-3.05)
Disease Duration	0.62 (1.01, 0.98-1.05)	0.81 (0.99, 0.96-1.03)
First Admission[F]	0.70 (0.58, 0.15-1.83)	0.82 (1.21, 0.39-3.74)
Current biologic[F]	0.82 (1.21, 0.57-2.63)	0.48 (1.49, 0.71-3.21)
Albumin	**0.0066 (0.89, 0.83-0.95)**	**0.029 (0.91, 0.85-0.97)**
CRP	**0.00066 (1.02, 1.01-1.03)**	**0.0091 (1.01, 1.01-1.02)**
Haemoglobin	0.60 (0.99, 0.98-1.01)	0.76 (1.00, 0.98-1.03)
Platelets	0.55 (1.00, 1.00-1.00)	0.47 (1.00, 1.00-1.01)
Stool frequency	0.53 (1.05, 0.97-1.05)	0.31 (1.08, 0.99-1.18)
TW score	**0.0066 (2.43, 1.45-4.29)**	0.094 (1.78, 1.10-2.97)
TW without CRP	0.19 (1.75, 0.98-3.23)	0.46 (1.43, 0.82-2.55)
UCEIS score	**0.015 (1.62, 1.18-2.27)**	**0.029 (1.57, 1.15-2.18)**
UCEIS erosion & ulceration	**0.0066 (2.68, 1.53-5.00)**	**0.029 (2.13, 1.34-4.17)**

Table 5 *Breakdown of steroid response in discovery, and validation cohorts by ADMIT-ASC score involving CRP ≥ 100mg/L (1 point), Albumin ≤ 25g/L (1 point), UCEIS ≥7 (2 points), or ≥ 4 (1 point).*

	Discovery (Oxford)		Validation (Gold Coast)		Validation (India)		Combined Validation		Total	
Score	N	Response %	N	Response %	N	Response %	N	Response %	N	Response %
0	3 (2.3%)	100%	7 (6.4%)	100%	1 (1.6%)	100%	8 (4.6%)	100%	11 (3.6%)	100%
1	60 (45.8%)	61.7%	53 (48.2%)	73.6%	35 (56.5%)	77.1%	88 (50.1%)	75.0%	148 (48.8%)	70.0%
2	40 (30.5%)	22.5%	30 (27.3)	53.3%	21 (33.9%)	57.1%	51 (29.5%)	54.9%	91 (30.0%)	33.0%
3	18 (13.7%)	16.7%	17 (15.5%)	17.6%	5 (8.1%)	20.0%	23 (13.3%)	15.8%	40 (13.2%)	17.5%
4	10 (7.6%)	0%	3 (2.7%)	0.0%	0	0.0%	3 (1.7%)	0.0%	13 (4.3%)	0.0%

Table 6 *Summary statistics for final model performance predicting steroid non-response using ADMIT-ASC scores of 2-4 as thresholds in the discovery, validation, and combined validation cohorts. Score– threshold score for a prediction of steroid non-response, Prop – proportion of patients at or above threshold, sens – sensitivity, spec – specificity, Acc – accuracy, PPV/NPV – positive/negative predictive value, OR – odds ratio, NNS – number needed to test to prevent one delayed treatment, AUC – area under the receiver operating characteristic curve. All statistics show 95% confidence intervals in parentheses. Equivalent results for prediction of steroid response below score 0-2 are shown in Supplemental Table 7, and bootstrapped validation results in Supplemental Table 8.*

	Discovery (Oxford)			Validation (Gold Coast)			Validation (India)			Combined validation		
Score	≥2	≥3	4	≥2	≥3	4	≥2	≥3	4	≥2	≥3	4
Prop	51.9%	21.4%	7.6%	45.5%	18.2%	2.7%	41.9%	8.1%	0.0%	44.2%	14.5%	1.7%
Sens	0.71 (0.61-0.81)	0.32 (0.21-0.42)	0.13 (0.05-0.20)	0.69 (0.55-0.82)	0.38 (0.24-0.52)	0.07 (0.00-0.14)	0.62 (0.41-0.83)	0.19 (0.02-0.36)	-	0.67 (0.55-0.78)	0.32 (0.21-0.43)	0.05 (0.00-0.10)
Spec	0.77 (0.65-0.88)	0.94 (0.88-1.00)	1.00 (1.00-1.00)	0.71 (0.60-0.82)	0.95 (0.90-1.00)	1.00 (1.00-1.00)	0.68 (0.54-0.83)	0.98 (0.93-1.00)	-	0.70 (0.61-0.79)	0.96 (0.93-1.00)	1.00 (1.00-1.00)
Acc	0.73 (0.66-0.81)	0.56 (0.48-0.65)	0.47 (0.39-0.56)	0.70 (0.61-0.79)	0.72 (0.63-0.80)	0.62 (0.53-0.71)	0.66 (0.41-0.83)	0.71 (0.60-0.82)	-	0.69 (0.62-0.76)	0.72 (0.65-0.78)	0.63 (0.56-0.71)
PPV	0.82 (0.73-0.91)	0.89 (0.78-1.00)	1.00 (1.00-1.00)	0.62 (0.49-0.75)	0.85 (0.69-1.00)	1.00 (1.00-1.00)	0.50 (0.31-0.69)	0.80 (0.45-1.00)	-	0.58 (0.47-0.69)	0.84 (0.70-0.98)	1.00 (1.00-1.00)
NPV	0.63 (0.52-0.75)	0.48 (0.38-0.57)	0.43 (0.34-0.52)	0.77 (0.66-0.87)	0.69 (0.59-0.78)	0.61 (0.51-0.70)	0.78 (0.64-0.91)	0.70 (0.58-0.82)	-	0.77 (0.69-0.85)	0.69 (0.62-0.77)	0.63 (0.55-0.70)
OR	8.1 (7.3-8.9)	7.6 (6.3-8.8)	Inf	5.4 (4.5-6.2)	12.5 (11.2-13.9)	Inf	3.5 (2.4-4.6)	9.4 (7.1-11.7)	-	4.6 (4.0-5.3)	11.9 (10.8-13.0)	Inf
NNS	2.3 (2.0-2.9)	5.2 (3.9-8.1)	13.1 (8.2-32.4)	3.5 (2.7-5.1)	6.5 (4.5-11.5)	36.7 (17.3-315.9)	4.8 (3.2-9.2)	15.5 (8.0-297.3)	-	3.9 (3.1-5.2)	8.2 (5.8-13.7)	57.3 (27.0-471.1)
AUC	0.74 (0.65-0.83)	0.63 (0.53-0.73)	0.56 (0.46-0.66)	0.70 (0.60-0.80)	0.67 (0.57-0.77)	0.53 (0.42-0.64)	0.65 (0.51-0.79)	0.58 (0.44-0.73)	-	0.68 (0.60-0.76)	0.64 (0.56-0.72)	0.52 (0.43-0.61)