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Validation of the ACE (Albumin, CRP and Endoscopy) Index in Acute Colitis: Analysis of the CONSTRUCT dataset

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ABSTRACT

Background and Aims

In 2020 we reported the ACE Index in Acute Colitis which used biochemical and endoscopic parameters to predict steroid non-response on admission in patients with acute ulcerative colitis (UC). We aimed to validate the ACE Index in an independent cohort.

Methods

The validation cohort comprised the patients screened as eligible for inclusion in the CONSTRUCT study, a prospective, randomised, placebo-controlled trial which compared the effectiveness of treatment with infliximab versus ciclosporin in patients admitted with acute UC. The CONSTRUCT cohort database was reviewed at The Edinburgh IBD Unit and the same biochemical and endoscopic variables and cut-off values as those in the derivation cohort were applied to the validation cohort.

Results

In total, 800 patients were identified. 62.5% (55/88) of patients with a maximum ACE Index of 3 did not respond to IV steroids (positive predictive value (PPV) 62.5%, negative predictive value (NPV) 79.8%). Furthermore, 79.8% (158/198) of patients with an ACE Index of 0 responded to IV steroids (PPV 79.8%, NPV 62.5%). Receiver Operator Characteristic (ROC) curve analysis produced an Area Under the Curve (AUC) of 0.663 (p=<0.001).

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Conclusions

We have now reported and externally validated the ACE Index in Acute Colitis in a combined cohort of over 1000 patients from across the United Kingdom. The ACE Index may be used in conjunction with clinical judgement to help identify patients admitted with active UC who are at high risk of not responding to IV steroids. Further studies are required to improve objectivity and accuracy of assessment.

KEYWORDS

Inflammatory bowel disease; ulcerative colitis; IV steroids

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Introduction

The prevalence of ulcerative colitis (UC), one of the two main forms of inflammatory bowel disease (in addition to Crohn's disease), continues to rise[1]. Treatment is focused on maintenance of remission and managing flares of disease. Hospital admissions for UC, however, are common and 1589 admissions for UC have been reported in NHS Lothian between 1st January 2010 and 31st December 2019[2]. Intravenous (IV) steroids remain the first line medical therapy for patients admitted with acute severe UC (ASUC), as defined by Truelove and Witts criteria[3] , but are also frequently used to treat patients admitted acutely with active UC without systemic effects (termed hereafter as 'non-severe acute UC (NSAUC)). Almost a third[4] of patients however, may not respond to IV steroids and go on to require second line medical therapies (primarily infliximab or ciclosporin) or a colectomy.

A significant body of research in recent years has focused on predicting outcome in patients with ASUC treated with IV steroids; the Ho[5] score and Travis[6] scores, in particular, are both used to identify patients at high risk of not responding to steroids on day three of treatment[7]. Furthermore, in 2011, a Spanish study sought to identify patients with ASUC and NSAUC at risk of steroid non-response[8]. In 2020 we reported the novel ACE (Albumin, CRP and Endoscopy) Index in Acute Colitis[9], which used biochemical and endoscopic parameters to predict steroid non-response on admission ([Albumin ≤30g/l (0 or 1)] + [C-Reactive Protein (CRP) ≥50mg/l (0 or 1)] + [endoscopically severe according to physician's global assessment component of the Mayo Score) (0 or 1)]) in a combined cohort of patients with ASUC and NSAUC. In our cohort, 78.1% of patients with a day 0 score of 3 did not respond to IV steroids. We identified a high-risk subset of patients for targeted counselling and early-administration of second line therapy; this is particularly crucial as treatment delays are associated with increased mortality[10]. Other

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centres have subsequently proposed alternative admission indices to risk stratify patients admitted with ASUC[11,12].

The aim of this study was to validate the ACE Index in an independent cohort. The validation cohort comprised all patients considered eligible for inclusion in the initial phase of the CONSTRUCT trial[13] (the CONSTRUCT cohort) a prospective, randomised, placebo-controlled study which compared the effectiveness of treatment with infliximab versus ciclosporin in patients admitted with acute UC (comprising both ASUC and NSAUC). Previously published data was limited to the 270 patients who went on to be included in the randomised controlled trial (RCT). In externally validating the ACE Index, we sought to further demonstrate that earlier risk stratification of patients with acute UC was possible and may prove to have significant benefits for patient outcomes.

Materials and methods

Patients and study design

The CONSTRUCT cohort comprised all patients admitted with acute UC to 52 district general and teaching hospitals across England, Scotland and Wales between 10th June 2010 and 4th March 2013. This cohort included all screened patients who were deemed eligible for inclusion in the RCT (i.e., patients who did not respond to IV steroids) and also patients who were not eligible for the RCT as they responded to IV steroids, or progressed to colectomy without second line medical treatments being given. A full description of the CONSTRUCT study design and protocol has been previously detailed by Seagrove et al[14].

The electronic CONSTRUCT cohort database was reviewed at The Edinburgh IBD Unit and inclusion was limited to the following criteria: confirmed treatment with IV steroids, documented response or non-response to IV steroids, stool microscopy culture and sensitivity negative, *Cytomegalovirus* negative

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histology at flexible sigmoidoscopy, and *Clostridium difficile* stool culture negative, and all patients for whom the components of the ACE Index were documented (CRP, albumin and endoscopic severity on admission). As in the ACE Index manuscript, inclusion was not limited to patients who satisfied Truelove and Witts' definition[3] of acute severe ulcerative colitis (ASUC) but also comprised those with NSAUC.

Definitions

The Lennard-Jones criteria[15] were used to define a diagnosis of UC.

IV steroid dose was as per local hospital policy and the British National Formulary.

Response to IV steroids in the ACE Index study was defined as discharge from hospital without further medical or surgical treatment for UC.

Non-response in the ACE Index study was defined as a requirement for either secondary line medical therapy or surgery.

IV steroid non-response was defined in the CONSTRUCT study as failure to respond to a course of up to 5 days of IV steroids but immediate surgery was not required (assessed by Truelove and Witts criteria, a Mayo score of at least 2 on flexible sigmoidoscopy, or clinical judgement).

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ASUC was defined according to Truelove and Witts' definition.

NSAUC was defined as <6 stools/day or ≥6 stools/day without the presence of blood or without at least 1 marker of systemic disturbance (as defined by Truelove and Witts).

Acute UC was defined as comprising both ASUC and NSAUC.

Statistics

IBM SPSS Statistics Subscription (Build 1.0.0.1461) and Medcalc (2022) were used for all statistical analysis. Continuous variables are presented as median values and interquartile ranges and categorical variables are presented as frequencies with percentages. The same variables and cut-off values as those in the derivation cohort [Albumin ≤30g/l (0 or 1)] + [CRP ≥50mg/l (0 or 1)] + [endoscopic severity of three (severe according to physician's global assessment component of the Mayo Score) (0 or 1)]) were used to score the validation cohort to determine the performance of the ACE Index. Receiver Operator Characteristic (ROC) curve analysis was performed to calculate the Area Under the Curve (AUC) of the ACE Index in the validation cohort.

Ethical considerations

All eligible CONSTRUCT cohort patients provided written informed consent. The protocol, patient information sheets and consent forms, all questionnaires, and amendments were approved by the Research Ethics Committee for Wales (08/MRE09/42) and local research and development committees.

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Results

Patient demographics

In total, 800 patients were admitted with acute UC between 10th June 2010 and 4th March 2013 who satisfied the inclusion criteria. Median age on admission was 37 years (interquartile range (IQR) 31-41); 57.0% (454/796) of patients were male; UC was newly diagnosed in 30.2% (240/796) of patients. (Table 1)

Clinical outcomes

A total of 486 patients (60.8%) responded to IV steroids. Median admission albumin was 38.0 g/L (IQR 33.0-42.0), median CRP 38 mg/L (IQR 10.0-98.0) and median endoscopic severity was 2 (IQR 2-3). Endoscopic assessment was performed a median of 1 day from admission (IQR 0-3). Median ACE Index was 1 (IQR 0-2).

A further 314 patients (39.3%) did not respond to IV steroids; 83.8% (263/314) of non-responders received second line medical therapies (infliximab or ciclosporin) with the remaining 16.2% (51/314) of non-responders proceeded to colectomy without further medical treatment. In non-responders, median admission albumin was 34 g/L (IQR 28.0-39.0), median CRP 58 mg/L (IQR 20.9-124.8) and median endoscopic severity was 3 (IQR 2-3). Median ACE Index was 2 (IQR 1-2).

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Application of the ACE Index

In total, 62.5% (55/88) of patients with an ACE Index of 3 did not respond to IV steroids (positive predictive value (PPV) 62.5%, negative predictive value (NPV) 79.8%; sensitivity 57.9%, specificity 82.7%; median albumin 26 g/L (IQR 23-28), median CRP 128 mg/L (IQR 90-223), median endoscopic severity 3 (IQR 3-3)).

Furthermore, 79.8% (158/198) of patients with an ACE Index of 0 responded to IV steroids (PPV 79.8%, NPV 62.5%, sensitivity 82.7%, specificity 57.9%; median albumin 41 g/L (IQR 37-44), median CRP 10 mg/L (IQR 5-21), median endoscopic severity 2 (IQR 1-2)). (Table 2 and Figure 1)

ROC curve analysis of the ACE Index in the validation cohort produced an AUC of 0.663 (95% confidence interval (CI) 0.624 to 0.701, p=<0.001). (Figure 2)

Truelove and Witt's criteria sub-analysis

When Truelove and Witts criteria were applied to the cohort, 273 patients (34.1%) were identified as suffering from NSAUC; 527 patients (65.9%) had ASUC. Amongst those with NSAUC, 70.0% (n=191) responded to IV steroids, 30.0% (n=82) did not respond to IV steroids. Amongst those with ASUC, 56.0% (n=295) responded to IV steroids and 44.0% (n=232) did not respond to IV steroids.

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Discussion

In this external validation study we have demonstrated that the ACE Index can support clinical decision making to help predict outcome on admission for patients with acute UC. This finding adds to our existing evidence that it may facilitate earlier decisions to be made regarding treatment escalation.

While the AUC of the validation cohort was lower than that in the derivation cohort (0.663 versus 0.754), it is understandable that variation in cohort size will have influenced the results reported in the derivation (n=215) and validation (n=800) cohorts; in addition, endoscopic assessment was performed by a limited number of endoscopists in the derivation cohort, in comparison to the geographically diversity in the validation cohort. Despite this, in the validation study a maximum possible score of 3 was still found to have a high NPV (79.8%) and high specificity (82.7%). The size of the validation cohort in this study is a strength and distinguishes it from other studies that have proposed admission risk stratification indices[12]; furthermore, the cohort is not only large in size, but also comprises patients from across the United Kingdom (as opposed to being restricted to one or two centres). The inclusion of patients with NSAUC is a further strength as it is reflective of realistic clinical practice and acknowledges that this group of patients is associated with a 21.3% steroid nonresponse rate and 6.6% colectomy rate[16] – significant proportions of patients who should not be overlooked. Furthermore, at present, patients tend to stay on IV steroids for at least three days before a definitive decision is made that second line therapies or surgery are needed[17], the ACE Index offers a means to predict outcome which may be applied soon after admission and minimise treatment delays. The ACE Index is also practical in its clinical application and

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is not dependent on other scoring systems (such as Truelove and Witts and the Ulcerative Colitis Endoscopic Index of Severity) to further classify patients.

There are some limitations to acknowledge. This was a retrospective validation study, however it was felt that prospectively validating the ACE Index may be subject to confirmation bias; consequently a retrospective external validation using a rigorously derived cohort of comparable patients was deemed to be preferable. Missing data regarding components of the ACE Index (mainly endoscopic severity because contemporaneous endoscopic confirmation was not a requirement for recruitment into the CONSTRUCT study if the diagnosis had previously been proven histologically) restricted the number of patients that could be included in the validation study. This reduced the possible cohort by 126 patients but a robust total of 800 patients was still achieved. Nevertheless, the requirement for endoscopic assessment will limit the use of the score in some patients.

While the results we have reported in our validation study have, to some extent, been encouraging, the reduced AUC in the validation cohort indicate that there is still work to be done to accurately risk stratify patients on admission. Endoscopic assessment has been revealed as an important indicator of future disease course in both our paper and other research[12], however it is subjective which may impact its reliability. The use of artificial intelligence in endoscopy is a rapidly emerging and expanding field, and early studies have demonstrated that it may be used to accurately and objectively grade disease severity of UC[18]. Corticosteroid response gene signatures have also been identified[19] which may have the potential to be incorporated into risk assessment algorithms and lead to the consideration of alternative therapies to induce remission. Research is ongoing into the use of high dose tofacitinib as an alternative rescue therapy following a lack of response to IV steroids[20] and how it may safely be incorporated into the

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treatment algorithm of those suffering from acute disease, particularly those with previous anti-TNF alpha exposure. Consideration of tofacitinib or infliximab as first line therapies in place of IV steroids in patients felt to be at high risk of steroid failure is controversial and any clinical trials would have to undergo rigorous ethical review.

We have now reported and externally validated the clinical utility of the ACE Index in Acute Colitis in a combined cohort of over one thousand patients from across the United Kingdom. When used in conjunction with clinical judgement, the ACE Index is a straightforward means of assessing patients admitted with acute UC and identifying a cohort of patients who may not respond to IV steroids; this will support timely decision making. Early assessment of acute UC is a rapidly evolving field and artificial intelligence and gene sequencing may have a role in future studies of increasing accuracy in predicting patients who would benefit from treatment escalation.

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AUTHORSHIP STATEMENT

Guarantor: Dr Rebecca K Grant

All authors approved the final version of the manuscript.

RKG contributed to the conception of the work, analysis and interpretation of the data and drafting of the manuscript. HAH contributed to acquisition of the CONSTRUCT data and critical revision of the manuscript. G-RJ, NP, RWL, WMB, JGW LA, AW and CWL contributed to the critical revision of the manuscript. IDRA was thesenior author and contributed to the conception of the work, interpretation of the data and performed critical revision of the manuscript for important intellectual content.

CONFLICTS OF INTEREST

RKG, WMB, HAH, JGW, LA and AW have no conflicts of interest to declare. GRJ is funded by a Wellcome Trust Clinical Research Career Development Fellowship and has received fees for educational events from Takeda, Ferring, Fresnius, Abbvie and Janssen. NP has received consulting fees from Janssen and Abbvie and support to attend meetings from Janssen. RWL has received an NIHR Hepatology Research Partnership: SHARP, has received consulting fees from Dr Falk, payment for hosting an educational evening for Viatris, and support to attend educational meetings from Advanz

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Table 1: Validation cohort background demographics and admission results

VARIABLE		TOTAL [n=800]
Montreal Classification of disease extent at diagnosis, % (N)	*1 (proctitis)*	13.4 (66/494)
	2 (left sided colitis)	43.3 (214/494)
	3 (pancolitis)	30.6 (151/494)
	4 (unknown)	11.1 (55/494)
Male, % (N)		57.0 (454/796)
Age at admission (years), median (interquartile range (IQR))		37.0 (27.0-52.0)
Pre-existing diagnosis of ulcerative colitis, % (N)		69.8 (556/796)
Prior biologic treatment, % (N)		6.2 (44/708)
Oral steroid (prednisolone) at time of admission, % (N)		46.4 (345/744)
Bloody stool frequency/day, median (IQR)		10.0 (5.0-14.0)
Haemoglobin (g/L), median (IQR)		130.0 (112.0-147.0)
Albumin (g/L), median (IQR)		37.0 (31.0-41.0)
C-Reactive Protein (CRP) (mg/L), median (IQR)		43.6 (13.0-104.3)

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Endoscopic severity (Mayo Score), % (N)	*0*	1.3 (10)
	1	8.0 (64)
	2	35.9 (287)
	3	54.9 (439)

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Table 2 – Distribution of ACE Index in the validation cohort

ACE Index	*Total patients (N)*	*Responders, % (N)*	*Non-responders, % (N)*
0	198	79.8 (158)	20.2 (40)
1	306	64.1 (196)	35.9 (110)
2	208	47.6 (99)	52.4 (109)
3	88	37.5 (33)	62.5 (55)

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FIGURE LEGENDS

Figure 1 – ACE Index Performance: Validation cohort

Score total = albumin ≤30 g/L (scored 0 or 1) + CRP ≥50 mg/L (scored 0 or 1) + increased endoscopic severity (scored 0 or 1). Minimum score = 0; maximum score = 3.

Figure 2 – Receiver Operator Characteristic curve analysis

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Figure 1

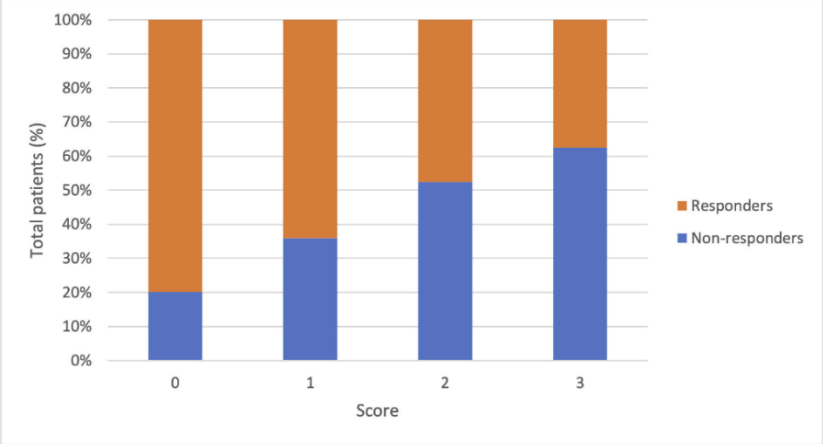

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Figure 2