Crohn's & Colitis 360, 2022, **4**, 1–8
https://doi.org/10.1093/crocol/otab082
Advance access publication 21 December 2021
Observations and Research

A Clinical Predictive Model for One-year Colectomy in Adults Hospitalized for Severe Ulcerative Colitis

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Background: Models to predict colectomy in ulcerative colitis (UC) are valuable for identification, clinical management, and follow-up of high-risk patients. Our aim was to develop a clinical predictive model based on admission data for one-year colectomy in adults hospitalized for severe UC.

Methods: We performed a retrospective analysis of patients hospitalized at a tertiary academic center for management of severe UC from 1/2013 to 4/2018. Multivariate regression was performed to identify individual predictors of one-year colectomy. Outcome probabilities of colectomy based on the prognostic score were estimated using a bootstrapping technique.

Results: Two hundred twenty-nine individuals were included in the final analytic cohort. Four independent variables were associated with one-year colectomy which were incorporated into a point scoring system: (+) 1 for single class biologic exposure prior to admission; (+) 2 for multiple classes of biologic exposure; (+) 1 for inpatient salvage therapy with cyclosporine or a TNF-alpha inhibitor; (+) 1 for age <40. The risk probabilities of colectomy within one year in patients assigned scores 1, 2, 3, and 4 were 9.4% (95% CI, 1.7–17.2), 33.7% (95% CI, 23.9–43.5), 58.5% (95% CI, 42.9–74.1), 75.0% (95% CI, 50.5–99.5). An assigned score of zero was a perfect predictor of no colectomy.

Conclusion: Risk factors most associated with one-year colectomy for severe UC included: prior biologic exposure, need for inpatient salvage therapy, and younger age. We developed a simple scoring system using these variables to identify and stratify patients during their index hospitalization.

Lay Summary

The one year risk of colectomy in patients hospitalized with ulcerative colitis increases if they are younger than 40-years-old, have used one or more biologic drugs in the past and/or receive an inpatient salvage (step-up) therapy during the hospitalization.

Key Words: severe ulcerative colitis, one-year colectomy, colectomy risk factors, clinical predictive score

Introduction

Ulcerative colitis (UC) is characterized by periods of activity or disease remission, the course of which can be difficult to predict but results in significant morbidity for patients with chronically active disease requiring escalation of medical therapy and/or colectomy.[1,2] The 5- and 10-year cumulative risk of colectomy in patients with UC is 10–15%, which may increase to 40% following one or more hospital admissions for UC in the subset of patients with severe disease phenotypes.[3,4] The introduction of anti-tumor necrosis factor (anti-TNF) therapies has altered the disease course in patients with severe disease demonstrating decreased rates of hospitalization, colectomy, and mortality.[5]

The main indications for colectomy include emergent conditions, such as fulminant or medically refractory acute severe UC, subacute and chronic complications requiring elective colectomy, most commonly development of colorectal carcinoma or high-grade dysplasia, and intolerance to medical therapy or intractable disease.[6] While colectomy is an important strategy for management of medically refractory disease, the threshold for surgery and timing varies by clinical setting. Patients expectedly prefer the avoidance of surgery given its potential impact on quality of life due from post-procedural complications, such as fecal incontinence, pouchitis/cuffitis, reduced fecundity in females, and erectile dysfunction in males.[7] Physicians may also hesitate to advise irreversible surgery as several medical therapeutic options exist. However, inappropriate delays in colectomy increase the risk of emergent surgery, which carries higher morbidity and mortality in comparison to an elective procedure.[8,9,10,11] Thus, an important aspect of managing patients presenting with severe UC is early identification of those likely to fail medical treatment.

Models to predict colectomy, particularly scoring systems from which individual scores can be calculated and assessed quickly, are valuable for identification, clinical management,

Received for publication: September 21, 2021. Editorial Decision: November 22, 2021

and follow-up of patients. Predictive models most commonly incorporate clinical, biochemical, radiologic, and endoscopic indicators of disease activity.[12] Travis et. al developed one of the earliest predictive indices for colectomy in patients with severe UC which associated stool frequency > 8/day and C-reactive protein (CRP) > 45 mg/dL on the third day of admission following treatment with intravenous (IV) corticosteroids with the risk of admission colectomy (85% positive predictive value [PPV]).[8] Subsequent models have tested various factors to improve prediction of patients who will ultimately require colectomy.[12] However, most predictive indices utilized to triage patients were developed prior to the current widespread biologic use and do not reflect the effect of these therapies on the natural disease course of patients with severe UC.[13] Therefore, appropriate application of the predictive indices to current clinical practice requires validation in updated prospective cohorts. Validation efforts have been mixed: the Fulminant Colitis Index, prospectively assessed in a randomized, placebo-controlled trial of rescue infliximab therapy, predicted early colectomy with a 47% PPV in the infliximab group in comparison to a 72% PPV in the original trial cohort, while a retrospective study of patients with moderate-to-severe UC undergoing treatment with infliximab did not find significant predictivity with use of this index.[14,15,16]

The creation of predictive indices for colectomy risk in patients with severe UC undergoing contemporary medical management is therefore a necessary area of study. Le Baut et al. most recently developed a four-point prognostic scoring system of biochemical and clinical factors in a cohort of French patients treated with immunomodulator and biologic therapies.[17] The aim of our study was to similarly assess the prognostic value of known risk factors for one-year colectomy among patients admitted for a severe UC flare.

Methods

Participants and study settings

We performed a retrospective analysis of all adult patients hospitalized at a tertiary academic center for management of UC between 1/2013 and 4/2018. Hospitalized cases of UC were identified using the ICD-9 code 556.X and ICD-10 code K51.X and separately reviewed for clinical, radiographic, histologic, and endoscopic information. Misclassified cases of UC (n = 55), those with a history of a pouch or admission for a planned surgery (n = 445), and cases of UC not admitted for colitis (n = 430) were excluded from the analysis (Supplementary Figure 1). Only the first admission for individuals with multiple hospitalizations was included to incorporate only one admission per patient. Additionally, only individuals responding to initial steroid therapy or those requiring salvage therapy were included to exclude those electing to undergo surgical management of disease.

Clinical characteristics

Baseline and outcome measures were collected via chart review or extracted from the electronic medical record (EMR). Cases with active colitis were defined as having > 3 bowel movements per day and/or frequency, rectal bleeding, cramping, or tenesmus. Severe colitis was defined as 6 or more bowel movements within a 24-hour period with one of the following: fever > 38.8 °C, heart rate > 90, hemoglobin < 10.5 g/dL, ESR > 30 or CRP > 3 mg/dL.[18] We did not record stool frequency throughout the hospitalization due to incomplete reporting in the medical record. Variables collected based on chart review included the extent of colitis, transfer from an outside institution (OSH), concomitant infections, and endoscopic procedures performed in the four weeks prior to and during hospitalization. Endoscopic disease activity was assessed utilizing the Mayo endoscopic sub-score for UC.[19] Pertinent medical history included disease duration, prior need for inpatient management of UC, smoking history, prior exposure to IV corticosteroids, and overall burden of co-morbidities as represented by the Charlson–Deyo score.[20]

Medications on admission were recorded to include systemic steroids (defined as the use of 5 mg prednisone or more daily), orally administered 5-aminosalicylic acids (5-ASA), immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), biologic anti-tumor necrosis factor (TNF) agents, and anti-integrins. Patients were considered biologic naïve if they had no prior exposure to a biologic therapy. Patients previously administered agents with an anti-TNF therapy class or an anti-integrin were assigned to a single biologic class. If multiple anti-TNF therapies were administered without transition to a second class, a single biologic class was still assigned. In addition, due to the slower onset of action with anti-integrin therapy which may take up to 10 weeks to achieve a response, individuals with recent initiation (within 60 days of admission) of anti-integrin therapy were downgraded one level, ie, individuals previously exposed to anti-TNF therapy with recent initiation of anti-integrin therapy were categorized as a single biologic class.[21] Individuals exposed to anti-TNF therapy and anti-integrin therapy (>60 days after exposure) were considered to have been exposed to multiple biologic classes.

The analysis only included admission variables to reflect data that would be available for clinical decision-making at the time of score utilization. Post-discharge variables, such as exposure to new treatments, were not included given variability in outpatient practices and missing data variables for patients not followed directly within our hospital system.

Inpatient management

Patients hospitalized for severe colitis were managed as per standard guidelines.[22] Testing for *C. difficile* infection was performed routinely on admission. In the absence of a response to intravenous corticosteroids after 3–5 days, patients were offered colectomy, calcineurin based salvage therapy, or salvage therapy with infliximab. The choice of salvage therapy was made according to the attending physician discretion. Calcineurin inhibitor therapy consisted of intravenous cyclosporine or oral tacrolimus (n = 4) as previously described.[23] Infliximab was given as a single infusion or several infusions of 5–10 mg/kg based on attending discretion. Thirty-seven individuals receiving infliximab received an initial loading dose of 5 mg/kg and twenty-three received an initial dose of 10 mg/kg.

Statistical analysis

Basic descriptive statistics were reviewed for all variables. Univariate logistics regression and multivariate logistics regression were performed to investigate the associations between the independent variables of interest and the dependent variable of one-year colectomy risk. In the multivariate

analysis, we coded continuous variables as binary variables by using the median of the variable as the cutting point. For the age variable, we coded it as a binary variable by using 40 as the cutting point as studied in prior literature – poor prognosis has been attributed to ages specifically younger than 40 in population-based studies following the natural history of UC.[24,25] A risk score was then calculated for each observation based on the observed values of the variables that were found to be statistically significant in the multivariate analysis. For each level of the risk score, the risk point estimate was derived based on the percentage of one-year colectomy among the observations with the score, and the 95% confidence interval of the risk point estimate was derived using the bootstrap method with 1000 replications. A two-sided P-value ≤ .05 was considered statistically significant. Statistical analysis was conducted using JMP 13.1.0 (SAS Institute, Inc., Cary, NC) and Stata 16 (StataCorp, LLC, College Station, TX).

Ethical Considerations

The study was approved by the University of Chicago Institutional Review Board (IRB18-0597).

Results

Patient characteristics

Two hundred eighty-five unique admissions for severe UC were identified. Among these admissions, 41 did not respond to initial intravenous corticosteroids and underwent colectomy without an attempt at salvage therapy and fifteen patients did not have 1-year outcomes available leaving 229 patients in the final analysis. When compared to the final cohort, those excluded without an attempt at salvage therapy were more likely to be older (45 years vs. 34.7 years, P = .002), transferred from an OSH (41.5% vs. 19.2%, P = .002), and more likely to be exposed to multiple classes of biologic therapies (24.4% vs. 9.2%, P = .0003). This group also presented with lower serum albumin (3.06 ± 0.68 g/dL vs. 3.38 ± 0.62 g/dL, P = .010) and no difference in CRP (48.63 ± 64.57 mg/L vs. 40.21 ± 50.96 mg/L, P = .564).

In the analytic cohort of 229 patients, baseline characteristics are presented in Table 1. The median patient age was 30.6 (IQR: 23.3–43) years and 108 (47.2%) of the patients were female. The median disease duration was 2.8 (IQR: 0.7–8.3) years and 140 (61.4%) patients had pancolitis. Endoscopic information was available in 184 (80.3%) among which 109 (59.2%) had a Mayo endoscopic sub-score of three. Severe colitis as diagnosed by Truelove and Witts criteria was present in 174 (76%) patients.

Prior to the hospitalization, 142 (62%) patients were receiving oral corticosteroids and 76 (33.2%) were on an immunomodulator. One hundred sixteen (50.7%) patients were naïve to biologic therapy while 92 (40.2%) had prior exposure to a single class of a biologic therapy and 21 (9.2%) had prior exposure to multiple biologic classes. Among patients that were biologic naïve (n = 116), one had a recent initiation of vedolizumab and was considered in the biologic naïve category. Among individuals exposed to a single biologic drug class (n = 92), four (4.3%) had treatment with an anti-integrin without exposure to anti-TNF therapy. Seven (7.6%) had a recent initiation of anti-integrin therapy with past exposure to anti-TNF therapy and were downgraded to a single biologic class. The remaining 81 patients had exposure to anti-TNF therapy among which 56 (69.1%) had exposure to one prior anti-TNF, 21 (25.9%) had exposure to two prior anti-TNFs and four (4.9%) had exposure to three prior anti-TNFs. Among the 21 patients with multiple biologic classes,

Table 1. Baseline patient characteristics.

Characteristic	n = 229	n, included[a]
Demographic parameters		
Female	108 (47.2%)	229
Age, years[b]	30.6 (23.3–43)	229
White	174 (76%)	229
Smoker	6 (2.6%)	229
Outside hospital transfer	44 (19.2%)	229
Malnutrition diagnosis	16 (7%)	229
Charlson–Deyo score[b]	0 (0–0)	226
Disease activity		
Duration of disease[b]	2.8 (0.7–8.3)	229
Prior admission for IV steroids	85 (37.1%)	229
First episode of colitis	19 (8.3%)	229
Diagnosis of severe colitis	174 (76%)	229
Extension of disease		
E1	28 (12.3%)	228
E2	60 (26.3%)	
E3	140 (61.4%)	
Mayo endoscopic score		
Score 1	14 (7.6%)	184
Score 2	61 (33.1%)	
Score 3	109 (59.2%)	
IV steroids started	223 (97.4%)	229
C. difficile infection	38 (17.1%)	222
Inpatient treatment		
Steroids alone	103 (45%)	229
Infliximab	60 (26.6%)	
Calcineurin inhibitor	66 (28.8%)	
Biological parameters[b]		
CRP, mg/L (IQR)	21 (6–52)	225
Protein, g/dL	6.7 (6–7.2)	220
Albumin, g/dL	3.4 (3–3.9)	220
Na, mmol/L	138 (136–140)	229
BUN, mg/dL	10 (7–14)	229
Creatinine, mg/dL	0.8 (0.6–0.9)	229
Hemoglobin, g/dL	11.5 (10–13.1)	229
WBC ($\times 10^9$per L)	9.9 (7.8–13.2)	229
Platelets ($\times 10^9$ per L)	360 (288–438.5)	229
Medications prior to admission		
Biologic naive	116 (50.7%)	229
Single biologic class	92 (40.2%)	
Multiple biologic classes	21 (9.2%)	
Steroids	142 (62%)	229
5-ASA	117 (51.1%)	229
Immunomodulator	76 (33.2%)	229
Opiates	21 (9.2%)	229
SSRIs	16 (7%)	229

[a]Number of patients with available data on this variable.
[b]The median and inter-quartile range (IQR) are presented.
CRP, C-reactive protein; Na, sodium; BUN, blood urea nitrogen; WBC, white blood cells; 5-ASA, aminosalicylates; SSRIs, selective serotonin reuptake inhibitors.

Table 2. Univariate logistic regression analysis.

Variable	Odds ratio	Confidence interval	*P*-value
Demographic parameters			
Female	0.78	0.44–1.37	.39
Age >40	**0.97**	**0.95–0.99**	**.01**
White	1.39	0.7–2.76	.35
Outside hospital transfer	1.77	0.9–3.5	.1
Malnutrition diagnosis	1.85	0.66–5.19	.24
Charlson–Deyo score, median (IQR)	1.06	0.76–1.47	.73
Disease activity			
Duration of disease, years, median (IQR)	1	0.96–1.04	.98
Prior admission for IV steroids	**2**	**1.13–3.55**	**.018**
First episode of colitis	0.25	0.06–1.09	.07
Diagnosis of acute severe colitis	1.79	0.88–3.66	.11
Extension of disease			
E1	Ref		
E2	2.13	0.7–6.47	.18
E3	2.25	0.8–6.3	.12
Mayo endoscopic score			
Score 1	Ref		
Score 2	1.79	0.36–8.95	.48
Score 3	3.76	0.8–17.64	.09
IV steroids started	0.43	0.08–2.18	.31
C. difficile infection	0.64	0.29–1.44	.28
Inpatient treatment			
Steroids alone	Ref		
Infliximab	2.15	0.99–4.66	.05
Calcineurin inhibitor	**6.94**	**3.37–14.27**	**<.0001**
Biological parameters			
CRP, mg/L	1	0.99–1	.61
Protein, g/dL	0.31	0.07–1.32	.11
Albumin, g/dL	0.64	0.39–1.04	.07
Na, mmol/L	0.99	0.89–1.09	.77
BUN, mg/dL	0.98	0.93–1.02	.43
Creatinine, mg/dL	0.32	0.09–1.14	.08
Hemoglobin, g/dL	**0.87**	**0.76–0.98**	**.03**
WBC (×10^{9}per L)	0.99	0.95–1.03	.61
Platelets (×10^9 per L)	1	0.99–1	.32
Medications prior to admission			
Biologic naive	Ref		
Single biologic class	**3.59**	**1.89–6.84**	**<.0001**
Multiple biologic classes	**8.3**	**3.02–22.75**	**<.0001**
Steroids	**2.72**	**1.44–5.16**	**.002**
5-ASA	**0.44**	**0.24–0.79**	**.005**
Immunomodulator	1.41	0.78–2.54	.25
Opiates	1.15	0.44–2.99	.77
SSRIs	1.03	0.35–3.	.95

Bold values represent statistically significant results.
CRP, C-reactive protein; Na, sodium; BUN, blood urea nitrogen; WBC, white blood cells; ASA, aminosalicylates; SSRIs, selective serotonin reuptake inhibitors.

all were treated with an anti-integrin initiated greater than 60 days prior to admission. In this subset, fifteen (71.4%) were exposed to one prior anti-TNF, five (23.8%) had exposure to two prior anti-TNFs and one (4.7%) had exposure to three prior anti-TNFs.

Colitis management and progression to colectomy

Most patients (223, 97.4%) were initiated on intravenous corticosteroids on hospital admission. Within the entire inclusion cohort, 103 (45%) responded to intravenous steroids and did not require escalation to a salvage therapy. Among the individuals requiring a salvage regimen, 66 (28.8%) received a calcineurin inhibitor and 60 (26.2%) received inpatient administration of infliximab. Seventy (30.6%) patients required colectomy within one year of admission. The median time to colectomy was 2 (IQR: 0–5.75) months. Both responders and non-responders to IV steroids progressed to colectomy within one year: 15.5% of patients (16/103) that responded to IV steroids required colectomy as compared to 42.8% (54/126) of non-responders requiring salvage therapy ($P < .0001$).

Univariate logistic regression

Results of the univariate logistic regression analysis for one-year colectomy are summarized in Table 2. Significant risk factors included: prior biologic exposure, either to one class (OR: 3.59, 95% CI, 1.89–6.84; $P < .0001$) or multiple classes (OR: 8.3, 95% CI, 3.02–22.75; $P < .0001$) of biologic therapy; use of oral corticosteroids prior to admission (OR: 2.72; 95% CI, 1.44–5.16; $P = .002$); 5-aminosalicylic acid (5-ASA) use prior to admission (OR: 0.44; 95% CI, 0.24–0.79; $P = .005$); previous hospitalization requiring IV corticosteroids (OR: 2; 95% CI, 1.13–2.55; $P = .018$); administration of salvage therapy during admission with cyclosporine (OR: 6.94, 95% CI, 3.37–14.27; $P < .0001$); and older age (age > 40, OR: 0.97, 95% CI, 0.95–0.99; $P = .010$). Inpatient salvage with anti-TNF therapy demonstrated borderline significance (OR: 2.15, 95% CI, 0.99–4.66; $P = .05$).

Multivariate analysis and model creation

Results of the multivariate logistic regression analysis for one-year colectomy are summarized in Table 3. In the final multivariate model, risk factors significant for one-year colectomy included: prior biologic exposure to one class (OR: 3.88, 95% CI, 1.40–10.7; $P = .009$) or multiple biologic classes (OR: 10.8, 95% CI, 2.50–47.01; $P = .001$); need for salvage therapy with cyclosporine (OR: 4.03, 95% CI, 1.57–10.30; $P = .004$) or anti-TNF (OR: 4.00, 95% CI, 1.33–12.02; $P = .014$); and age > 40 (OR: 0.32, 95% CI, 0.11–0.88; $P = .027$). Using the multivariate analysis, a

Table 3. Multivariate logistic regression analysis.

Variable	Odds ratio	Confidence interval	*P*-value
Demographic parameters			
Female	1.4	0.53–3.71	.5
Age >40	**0.32**	**0.11–0.88**	**.027**
White	0.96	0.37–2.47	.93
Outside hospital transfer	1.62	0.52–5.05	.41
Malnutrition diagnosis	1.33	0.29–6.21	.72
Charlson–Deyo score, median (IQR)	0.058	0.003–1.23	.07
Disease activity			
Duration of disease, years, median (IQR)	0.87	0.39–1.97	.75
Prior admission for IV steroids	0.34	0.036–3.18	.34
First episode of colitis	0.36	0.061–2.09	.25
Diagnosis of acute severe colitis	1.37	0.47–3.97	.56
Extension of disease			
E1	Ref		
E2	1.21	0.30–4.86	.79
E3	0.86	0.24–3.14	.82
Mayo endoscopic score			
Score 1	Ref		
Score 2	1.18	0.18–7.61	.86
Score 3	1.19	0.18–7.98	.86
IV steroids started	0.34	0.036–3.18	.34
C. difficile infection	0.7	0.23–2.14	.53
Inpatient treatment			
Steroids alone	Ref		
Infliximab	**4**	**1.33–12.02**	**.014**
Calcineurin inhibitor	**4.03**	**1.56–10.3**	**.004**
Biological parameters			
CRP, mg/L	1.48	055–3.98	.44
Protein, g/dL	1.1	0.39–3.09	.85
Albumin, g/dL	1.02	0.32–3.21	.98
Na, mmol/L	1.01	0.40–2.52	.99
BUN, mg/dL	1.28	0.55–2.98	.57
Creatinine, mg/dL	0.97	0.36–2.61	.95
Hemoglobin, g/dL	0.92	0.36–2.33	.85
WBC ($\times 10^9$ per L)	1.33	0.59–2.97	.49
Platelets ($\times 10^9$ per L)	1.58	0.69–3.60	.28
Medications prior to admission			
Biologic naive	Ref		
Single biologic class	**3.88**	**1.40–10.75**	**.009**
Multiple biologic classes	**10.8**	**2.50–47.01**	**.001**
Steroids	1.7	0.70–4.11	.24
5-ASA	0.99	0.42–2.32	.98
Immunomodulator	1.08	0.47–2.52	.85
Opiates	1.05	0.31–3.62	.94
SSRIs	0.78	0.17–3.65	.75

Bold values represent statistically significant results.
CRP, C-reactive protein; Na, sodium; BUN, blood urea nitrogen; WBC, white blood cells; ASA, aminosalicylates; SSRIs, selective serotonin reuptake inhibitors.

four-point scoring system was created: (+) 1 for single class biologic exposure, (+) 2 for multiple classes of biologic exposure. (+) 1 for inpatient salvage therapy with cyclosporine or anti-TNF, and (+) 1 for age < 40. The risk probabilities of colectomy within one year in patients assigned scores 1, 2, 3, and 4 were 9.4% (95% CI, 1.7–17.2), 33.7% (95% CI, 23.9–43.5), 58.5% (95% CI, 42.9–74.1), and 75.0% (95% CI, 50.5–99.5). An assigned score of zero was a perfect predictor of no colectomy.

Comparison and subgroup analysis

The performance of the current study score was compared against a score developed by Le Baut et al. to predict one-year colectomy in the study population. The Le Baut et al. score includes prior exposure to thiopurines or anti-TNF agents, presence of *C. difficile* infection, CRP > 30 mg/L, and albumin < 30 g/L. In the subset of patients with available data to calculate both scores (209/229), the current study score showed an improved predictive ability for one-year colectomy (AUC: 0.76 vs. 0.59; $P = .0001$). Among included patients in the highest risk group (score = 4), the observed colectomy rate with the study score was 72.7% as compared to 50% using the previously published score from Le Baut et al. (Supplementary Figure 2). The performance of the scores was also tested in two subgroups to comment on applicability to patients with acute severe UC defined strictly by Truelove and Witt's criteria ($n = 174$) and to patients with greater endoscopic disease severity (Mayo 2 or 3 disease, $n = 170$). The AUCs were in these subsets were: 0.781 (95% CI, 0.713–0.840) and 0.736 (95% CI, 0.661–0.807), respectively.

Discussion

Current medical therapies are inadequate to achieve remission in all patients with UC, particularly those with severe phenotypes characterized by high relapse rates, corticosteroid dependence, and need for escalation of medical therapy. Patients hospitalized for management of severe disease must therefore weigh the risks of surgery with those of continuing or escalating medical treatment. In these scenarios, clinical indices that predict the risk of colectomy can identify patients with higher likelihood of progression to surgery and inform shared decision-making in favor of elective surgical management over ineffective or harmful overtreatment. At the very least, indices can target high-risk patients for close outpatient follow-up. In the current analysis we define four-point risk score created using readily available, objective clinical data: prior biologic exposure, administration of salvage therapy during admission, and age.

Our clinical predictive score is based on a cohort of hospitalized patients with severe UC, the majority of whom presented

with corticosteroid-refractory disease requiring escalation to salvage therapy. In comparison to the IV steroid response rate pooled from 32 studies that included patients with both moderate and severe UC (67%), the response rate observed in our cohort (45%) is lower which is likely reflective of the greater underlying disease severity in this predominantly referral cohort.[13] However, our primary outcome of one-year colectomy was overall congruent with that observed in literature. We observed a one-year colectomy rate of 30.6% similar to that observed among the CONSTRUCT cohort (40%) which followed the outcomes of patients randomized to salvage treatment with either cyclosporine or infliximab.[26] Our findings also resemble pooled one-year colectomy rates following salvage therapy in a systematic review of 12 studies: 20.7% and 36.8% among patients receiving infliximab and cyclosporine, respectively, although it should be noted that individuals proceeding directly to colectomy were excluded from the one-year colectomy rates in this current study.[4]

Our multivariate analysis identified prior biologic exposure as a criterion that predicted one-year colectomy. A qualitative synthesis of 70 studies identifying risk factors for colectomy in patients with refractory UC associated an extensive drug history – prior exposure to systemic steroids, immunomodulators, and biologics – with risk for overall colectomy.[27] Patients with severe underlying disease are more likely to exhibit extensive drug exposure as non-response to treatment is higher. In an analysis of the Active Ulcerative Colitis (ACT) 1 and 2 clinical trials of infliximab initiation in biologic-naïve patients with UC, a baseline Mayo score ≥ 10 suggested increased non-response to infliximab and risk of colectomy.[28,29] Switching to another agent does not necessarily increase the chance of remission: a systematic review of six studies showed remission rates of 0% to 50% among UC patients after treatment with alternative anti-TNF drug following infliximab non-response.[30] Patients with severe disease are often treated with multiple class of medications, including biologics, in an effort to avoid colectomy. However, despite effectively delaying colectomy, biologic therapy may not prevent it entirely.[3]

Treatment with inpatient salvage therapy – either infliximab or cyclosporine – also predicted one-year colectomy in our multivariate analysis with a median latency of two months. High early colectomy rates have been observed in patients with severe UC despite infliximab rescue therapy. Solberg et al. observed that 64% of colectomies were carried out in the first month following infliximab rescue therapy and Jakobovitz et al. similarly observed an early incidence of surgery, a median time to colectomy of six months.[31,32] In our multivariate model and scoring system, use of CNI therapy or anti-TNF therapy was comparably associated with a risk of one-year colectomy. In the Cyclosporine versus Infliximab in Patients with Severe Ulcerative Colitis Refractory to Intravenous Steroids (CySIF) clinical trial, Laharie et al. failed to identify a significant difference in rates of treatment failure or colectomy between biologic-naïve patients receiving cyclosporine or infliximab.[33] Thus, we demonstrated that despite demonstrated efficacy of rescue therapies, patients with disease severe enough to progress to salvage treatment remain at a high risk of colectomy.

Lastly, our multivariate analysis identified young age as a significant risk factor for colectomy. Several population-based studies have associated young age at diagnosis with an increased risk of colectomy.[27,34,35,36] Using the IBSEN database of UC patients followed for ten years, Solberg et al. observed that patients younger than 40 years of age at diagnosis had higher rates of disease relapse and colectomy.[37,38] Increased disease severity in those diagnosed at an early age and inadequate treatment adherence among younger patients could contribute to high relapse rates.[39,40] Conversely, studies have suggested that patients diagnosed at an older age exhibit higher regression of inflammatory lesions and decreased frequency of exacerbations.[36] Although age cannot be modified, recognition of its predictivity for colectomy will inform which patient demographics warrant close monitoring.

We found the score derived by Le Baut et al. to be less predictive of one-year colectomy in the current study population.[17] Unlike our scoring system, Le Baut et al.'s found an association between one-year colectomy and *C. difficile* infection (CDI) and admission laboratory variables, such as CRP and serum albumin. The two studies did not find a uniform association with CDI and long-term colectomy risk potentially due to variations in testing practices.[41,42] Rates of CDI were higher in our study group when compared to the French population, 17.1% vs. 4.3%, and the variability in prevalence suggests different testing standards. Our center used polymerase chain reaction (PCR) to detect the presence of toxogenic bacteria, which are more often isolated in the stool of individuals with IBD regardless of active infection.[43] Current guidelines recommend the use of confirmatory testing for toxin production as molecular tests may convey false positive results.[44,45] Le Baut et al. did not detail their method of *C. difficile* detection, but their lower reported rate of infection suggests use of direct toxin assessment. Our analysis also did not find associations with inflammatory biomarkers, such as albumin and CRP, which were included in the French model. One explanation is that we excluded patients who underwent admission colectomy without a salvage attempt because our intent was to model risk in individuals undergoing continued medical treatment. The excluded patients had severe steroid-refractory disease and thus exhibited inflammatory biomarker derangements, such as significantly lower serum albumin levels in comparison with patients in the analytic cohort. Since CDI, CRP, and serum albumin were not associated with one-year colectomy in our cohort, it is expected that the Le Baut et al. score would be less predictive of a surgical outcome in our population (AUC: 0.76 vs. 0.59). External validation of our score will be required to establish its predictive ability.

The greatest strength of this study is the creation of a simple and updated clinical predictive score that reflects current medical management of patients with severe UC. The components of the model are entirely objective, while other models have incorporated subjective measures, such as bowel frequency or the presence of bloody stools, that may be difficult to gather during retrospective analyses. Furthermore, the concordance of significant variables in our risk score with existing data on predictive factors of colectomy supports our model. We also individually reviewed each case for inclusion in the analysis after initial identification through use of International Classification of Diseases (ICD) codes. Reliance solely on the accuracy of billing diagnostic codes, some of which have not been independently validated, may lead to inappropriate inclusion of patients and overestimation of study results.[46] Individual review of each medical chart also allowed us to adequately characterize underlying disease severity. There is inevitable inter-center variation in disease severity among

medical centers: those with a high volume of IBD referrals attend to sicker patients than non-referral centers. A high-risk referral population may overrepresent the proportion of patients who undergo colectomy. Thus, an accurate representation of our baseline population allows generalization of our findings to centers treating similar patients.

Our study has several limitations. The retrospective analysis of manually extracted data is subject to documentation errors and omissions. Due to the high referral volume at our center, we were unable to follow all patients who returned to local institutions upon discharge without a shared electronic medical record. We were thus unable to establish incidence of one-year colectomy in all patients, and exclusion of this missing variable reduced our sample size. This may have limited our ability to demonstrate a significant association between one-year colectomy and variables such as serum albumin and CRP which could have been appreciated in a larger sample size. Regardless, our cohort is of one the most sizeable for inclusion in a modeling study to develop a clinical predictive score for colectomy in patients with severe UC. Lastly, the performance of our prediction model was not evaluated using an external validation cohort, which is the strongest test as it uses independent data to validate the model.

Conclusion

We created a simple, objective score to calculate an individual patient's risk of one-year colectomy following hospitalization for a severe UC. The predictive ability of the score lends itself to clinical use – a score of 0/4 was a perfect predictor of no colectomy at one year and a score of 4/4 predicted a 75% colectomy risk. Prospective studies are needed to externally validate our clinical predictive score for colectomy in a similar cohort of patients. Validation in different populations, hospitalized patients at centers with low IBD volume or outpatient cohorts, would increase the generalizability of our score.

Supplementary Data

Supplementary data is available at *Crohn's and Colitis 360* online.

Funding

D.M. supported by an Associates Board award from the Gastrointestinal Research Foundation.

Conflicts of Interest

All authors have no expressed conflicts of interest with respect to the submitted work.

Writing Assistance

No support provided.

Data Availability

The data underlying this article cannot be shared publicly due to privacy requirements from the supporting institution. The data will be shared on reasonable request to the corresponding author.

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