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Clinical Predictors of Early and Late Endoscopic Recurrence Following Ileocolonic Resection in Crohn's Disease

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Abstract

Background and Aims: Multiple factors are suggested to place Crohn's disease patients at risk of recurrence after ileocolic resection with conflicting associations. We aimed to identify clinical predictors of recurrence at first [early] and further [late] postoperative colonoscopy.

Methods: Crohn's disease patients undergoing ileocolic resection were prospectively recruited at six North American centres. Clinical data were collected and endoscopic recurrence was defined as Rutgeerts score ≥i2. A multivariable model was fitted to analyse variables independently associated with recurrence.

Results: A total of 365 patients undergoing 674 postoperative colonoscopies were included with a median age of 32 years, 189 [51.8%] were male, and 37 [10.1%] were non-Whites. Postoperatively, 133 [36.4%] used anti-tumour necrosis factor [anti-TNF] and 30 [8.2%] were smokers. At first colonoscopy, 109 [29.9%] had recurrence. Male gender (odds ratio [OR] = 1.95, 95% confidence interval [CI] 1.12–3.40), non-White ethnicity [OR = 2.48, 95% CI 1.09–5.63], longer interval between surgery and colonoscopy [OR = 1.09, 95% CI 1.002–1.18], and postoperative smoking [OR = 2.78, 95% CI 1.16–6.67] were associated with recurrence, while prophylactic anti-TNF reduced the risk [OR = 0.28, 95% CI 0.14–0.55]. Postoperative anti-TNF prophylaxis had a protective effect on anti-TNF experienced patients but not on anti-TNF naïve patients. Among patients without recurrence at first colonoscopy, Rutgeerts score i1 was associated with subsequent recurrence [OR = 4.43, 95% CI 1.73–11.35].

Conclusions: We identified independent clinical predictors of early and late Crohn's disease postoperative endoscopic recurrence. Clinical factors traditionally used for risk stratification failed to predict recurrence and need to be revised.

Key Words: Crohn's disease; risk factors; postoperative recurrence

1. Introduction

Crohn's disease is a chronic and progressive inflammatory condition of uncertain aetiology. The natural course of Crohn's disease entails recurrent episodes of transmural inflammation which can cause fibrostenotic and penetrating complications necessitating intestinal resection.[1] Whilst it can affect any portion of the gastrointestinal tract, the terminal ileum is most frequently involved and therefore the most commonly performed surgery is an ileocecal or ileocolonic resection. Although widespread use of anti-inflammatory medical treatment has contributed to reduce the risk of surgery,[2–6] surgery rates remain high among Crohn's disease patients diagnosed in the 21st century with more than one-quarter of them requiring intestinal resection within 10 years after diagnosis.[2,6] Unfortunately, intestinal resection is not curative, and disease recurrence resulting in further intestinal resection occurs in up to 18% of patients by 5 years and 31% of patients by 10 years after initial surgery.[6] Symptomatic and surgical recurrence is

preceded by asymptomatic endoscopically detected mucosal lesions that occur in the neoterminal ileum and at the level of the ileocolic anastomosis. Importantly, the presence and severity of these endoscopic lesions can predict the subsequent clinical course.[7–10] Effective pharmacological therapy to reduce the risk of endoscopic postoperative recurrence include thiopurines [i.e. azathioprine and 6-mercaptopurine] and anti-tumour necrosis factor [anti-TNF] monoclonal antibodies.[11–13] The American Gastroenterological Association [AGA][14] guideline recommends early pharmacological prophylaxis [started within 8 weeks after surgery] over endoscopically guided pharmacological treatment. However, given the costs and potential adverse events associated with pharmacological therapies, the American[14] and European[15] guidelines categorize patients into high and low risk of postoperative recurrence, as determined by a number of clinical risk factors. Nonetheless, other than the absence of anti-TNF treatment after surgery, active smoking is the only clinical feature that has been independently and consistently associated with an increased risk of endoscopic recurrence in prospective studies.[16–19] Studies examining the association between endoscopic recurrence and other clinical characteristics employed for patient risk stratification such as prior intestinal resection, short interval between the time of diagnosis and surgery, young age at disease diagnosis, penetrating disease at index surgery, perianal disease, and extensive small bowel resection have yielded conflicting results.[20–22] Thus, use of such clinical factors to risk-stratify and select patients for early postoperative therapy may be inappropriate. More robust data are required to evaluate the performance of these clinical factors when determining which patients are at high risk of recurrence and thus warrant postoperative prophylactic treatment. Utilizing a large prospectively recruited, multinational and multicentre cohort of Crohn's disease patients undergoing ileocolonic resection with a rigorous and extensive clinical data collection, we aimed to identify independent clinical predictors of endoscopic recurrence at first [early recurrence] and subsequent [late recurrence] colonoscopies.

2. Material and methods

2.1. Patient cohort

This study was conducted within a broader project designed to investigate genetic, dietary, serological, and microbial factors associated with recurrence of inflammation following ileal resection for Crohn's disease by means of an extensive prospective clinical data and biospecimen collection.[23] Adult patients with a diagnosis of Crohn's disease based on standard criteria and undergoing ileocaecal or ileocolonic resection were prospectively identified during the perioperative period across six participating Genetics Research Centers [GRCs] of the NIDDK Inflammatory Bowel Disease Genetics Consortium [IBDGC]. The participant centres comprise Icahn School of Medicine at Mount Sinai, New York; Cedars-Sinai Medical Center, Los Angeles; University of Pittsburgh, Pennsylvania; Johns Hopkins University, Baltimore; Mount Sinai Hospital, Toronto; and University of Montreal, Montreal, along with their affiliated satellite centres. Patients with confirmed Crohn's disease with ileal involvement based on the surgical pathology review were included. Participants were excluded if they underwent ileal resection with ileal–ileal anastomosis leaving an intact ileocaecal valve, a sub-total or near sub-total colonic resection [i.e. beyond ileal-descending anastomosis], resection with temporary or permanent diverting ileostomy or more than two prior surgeries [i.e. a total of three or more surgeries]. The therapeutic approach after surgery, as well as the timing for colonoscopies following resection was determined by the attending gastroenterologist according to standard clinical practice.[14] Patients were mostly identified and recruited in the perioperative period; however, patients could also be enrolled at the first post-surgical endoscopy, as long as that occurred within 18 months after surgery. Only those participants who were amenable to clinical follow-up at the GRC or collaborating site were included. The study received institutional research ethics board approval at each of the participating institutions.

2.2. Clinical data collection and definitions

Demographic, perioperative, and postoperative clinical data were collected at recruitment and follow-up visits by patient interview and chart review using a standardized protocol. Demographic data included age at surgery, gender, ethnicity, and smoking status before surgery [never-smoker, ex-smoker, and current smoker]. Gender and ethnicity were self-reported by study participants. Presurgical clinical data included age at Crohn's disease diagnosis, disease duration between diagnosis and index surgery, prior small bowel resection, disease location and behaviour, and perianal disease. The Montreal Classification[24] for disease location [L1: ileal; L3: ileocolonic] and behaviour [B1: non-stricturing, non-penetrating; B2: structuring; B3: penetrating] were based on the patient's documented medical history [including endoscopy and imaging reports] and surgical findings at index surgery. Crohn's disease medication before surgery [i.e. any time before surgery] including thiopurines, methotrexate, anti-TNF drugs [i.e. infliximab, adalimumab, and certolizumab], vedolizumab, and ustekinumab were recorded. Additionally, the following information at index surgery was collected from the surgical and pathology reports: presence of penetrating complications [i.e. abscess or fistula], length of small bowel resection, presence of gross inflammation at the proximal margin [based on the surgical and pathology macroscopic report], type of anastomosis [end-to-end, side-to-side, or end-to-side], and anastomosis method [hand-sewn or stapled]. Postoperative clinical data including smoking status and medications [antibiotics, corticosteroids, thiopurines, methotrexate, and biologics] were updated and recorded at each follow-up colonoscopy. The Rutgeerts score[7] was evaluated and recorded at each postoperative colonoscopy by the endoscopist performing the procedure. Endoscopic remission was defined as i0 [no lesions-normal] or i1 [≤5 aphthous lesions]; and endoscopic recurrence as i2 [>5 aphthous lesions with normal intervening mucosa or skip areas between larger lesions or lesions confined to the ileocolic anastomosis], i3 [diffuse aphthous ileitis with diffusely inflamed mucosa], or i4 [diffuse inflammation with severe ulceration, nodules, or stricture]. Crohn's disease patients with endoscopic recurrence at first colonoscopy were defined as early recurrence and those with first evidence of endoscopic recurrence [Rutgeerts score ≥i2] at subsequent colonoscopies as late recurrence. Other Rutgeerts score cut-offs were explored to evaluate a more stringent definition of remission [i1–i4 vs i0] and severe recurrence [i3–i4 vs i0–i1]. The modified Rutgeerts score that excludes lesions confined to the ileocolic anastomosis [i2a] from the definition of recurrence [i2b–i4] was also assessed.[25] Colonoscopies without Rutgeerts score reported were excluded. All the study data

were collected and managed using REDCap electronic data capture tools hosted at the University of Chicago.[26,27]

2.3. Statistical analysis

Numerical variables were summarized by mean and standard deviation [SD] or median and interquartile ranges [IQR] according to their distribution. Categorical variables were summarized by frequency and percentage. Unadjusted bivariate comparison between patients without and with endoscopic recurrence was performed by using Student's t-test or Mann–Whitney U test according to the data distribution of numerical variables and by using χ^2 or Fisher's exact tests according to group sizes for categorical variables. Given the expected differences between GRCs in aspects such as patient characteristics and management, multivariable analyses intended to establish the clinical factors independently associated with endoscopic recurrence at first colonoscopy [primary aim] were carried out by fitting a mixed-effects multiple logistic regression model with GRC as a random effect to account for clustered data. The multivariable model a priori included the following fixed-effect variables previously reported in the literature and frequently used for risk stratification[14,15]: age at Crohn's disease diagnosis, disease duration, perianal disease, prior small bowel resection, penetrating complication at index surgery, proximal margin free of gross inflammation, small bowel resection length, smoking status, and anti-TNF use after surgery. The demographic features, gender and ethnicity, recently reported as risk factors of postoperative recurrence[16,28] were also included in the multivariable analysis. As clinical practice variation determined different intervals between surgery and timing of postoperative colonoscopy, this interval was also included as a covariate. Other significant variables at $p < 0.1$ in the univariable analysis were also included in the multivariable model. Odds ratios [ORs] with 95% confidence intervals [CIs] were reported. The lmer4[29] package implemented in R was used for multivariable analyses. Interaction effects of independent variables on endoscopic postoperative recurrence were explored one at a time in the model by including individual interaction terms. Several secondary and subgroup analyses were performed to evaluate the impact on the associations of different definitions of endoscopic recurrence and medical therapy before and after surgery. Univariable and multivariable analyses were separately applied to the first [early recurrence], second, and third or greater colonoscopies [late recurrence]. For second and third or greater colonoscopies, the Rutgeerts score at previous colonoscopy was included as a covariable. Finally, taking advantage of the serial postoperative colonoscopies recorded, we analysed the clinical variables associated with the first occurrence of postoperative endoscopic recurrence and time-to-event [recurrence] using a mixed-effects Cox proportional regression model with GRC as the clustering variable. Two-sided p-values of <0.05 were considered significant. All data were prepared and analysed with R software v4.1.1 [https://www.R-project.org/].

3. Results

3.1. Cohort description

In total, 553 Crohn's disease patients were screened for participation in the study between May 2011 and May 2021. A flow chart presenting the number of included and excluded patients and postoperative colonoscopies is shown in Supplementary Figure S1. A total of 674 colonoscopies from 365 Crohn's disease patients were included in the analyses. Overall, the median age at surgery was 32 years [IQR 25–43], 189 [51.8%] were male, 328 [89.9%] were White, and only 35 [9.6%] patients were active smokers before surgery. Ninety-eight [26.8%] had prior ileocolic resection. Simultaneous with the index ileocaecal or ileocolic resection, only 23 [6.3%] patients had a more proximal small bowel resection, 11 [3.0%] underwent segmental large bowel resection, and ten [2.7%] had a stricturoplasty. Other demographic, presurgical, and surgical clinical characteristics are shown in Table 1. All analysed patients had at least one postoperative colonoscopy, 208 had two postoperative colonoscopies, and 101 had three or more postoperative colonoscopies. The median interval between surgery and first, second, and third or greater colonoscopies was 7 [IQR 5–9], 21 [17–28], and 42 [31–60] months, respectively. The postoperative characteristics of the cohort are shown in Table 2. Overall, after surgery only 30 [8.2%] patients were active smokers and 133 [36.4%] were treated with anti-TNF agents. Among patients on postoperative anti-TNF therapy, 109 [81.9%] had already used an anti-TNF agent before surgery. Forty-three out of 133 [32.3%] patients on anti-TNF therapy received combination therapy with an immunomodulator [i.e. thiopurine or methotrexate]. Only 25 [6.8%] and six [1.6%] patients were treated with thiopurine or methotrexate monotherapy, respectively. Thirty-nine [10.7%] and 28 [7.7%] patients used ustekinumab and vedolizumab after surgery, respectively. In total, 133 [36.4%] patients received neither biological nor immunomodulator therapy after surgery.

3.2. Clinical predictors of endoscopic recurrence at first postoperative colonoscopy

We first undertook an analysis of clinical factors associated with early endoscopic recurrence at first postoperative colonoscopy [Figure 1]. No endoscopic recurrence was found in 256 [70.1%] patients (i0 = 189 [51.8%], i1 = 67 [18.4%]), while endoscopic recurrence was found in 109 [29.9%] patients (i2 = 67 [18.4%], i3 = 32 [8.8%], and i4 = 10 [2.7%]). The crude bivariate analysis [Tables 1 and 2] identified that male gender was associated with an increased risk of endoscopic recurrence, while proximal margin free of gross inflammation and postoperative prophylaxis with thiopurines and anti-TNF were associated with a reduced risk of endoscopic recurrence. However, there was no association between prophylactic thiopurine use and endoscopic recurrence [$p = 0.6$] when only monotherapy with this medication was analysed; therefore, thiopurine use after surgery was not included in the model. Only two additional variables had a p-value <0.1 in the crude bivariate analysis [smoking after surgery and postoperative prophylaxis with ustekinumab]. These variables along with the remaining a priori defined variables were included in the multivariable analysis. The results of the multivariable analysis with all the variables included in the model are given in Table 3. Using a mixed-effects logistic regression model with GRC as a random effect variable, male gender [OR = 1.95, 95% CI 1.12–3.40], non-White ethnicity [OR = 2.48, 95% CI 1.09–5.63], smoking after surgery [OR = 2.78, 95% CI 1.16–6.67], and a longer interval between surgery and endoscopy [OR = 1.09, 95% CI 1.002 -1.18] were independently associated with a higher risk of recurrence, while anti-TNF use after surgery [OR = 0.28, 95% CI 0.14–0.55] was independently associated with a decreased risk of recurrence. The

Table 1. Demographics, and presurgical and surgical clinical characteristics of the cohort. Univariable analysis according to recurrence status at first colonoscopy.

	Total [*n* = 365]	Rutgeerts i0–i1 [*n* = 256]	Rutgeerts ≥i2 [*n* = 109]	*p*-value
Median age at surgery, years [IQR]	32.0 [25–43]	32.0 [25–41]	32.0 [24–47]	0.452
Gender				**0.021**
Female	176 [48.2]	134 [52.3]	42 [38.5]	
Male	189 [51.8]	122 [47.7]	67 [61.5]	
Country				0.162
USA	216 [59.2]	158 [61.7]	58 [53.2]	
Canada	149 [40.8]	98 [38.3]	51 [46.8]	
Ethnicity				0.191
Non-White	37 [10.1]	22 [8.6]	15 [13.8]	
White	327 [89.9]	234 [91.4]	94 [86.2]	
Jewish	93 [25.5]	64 [25.0]	29 [26.6]	0.859
Unknown	4 [1.1]	3 [1.2]	1 [0.9]	
Hispanic	13 [3.6]	12 [4.7]	1 [0.9]	0.147
Unknown	3 [0.8]	1 [0.4]	2 [1.8]	
Smoking pre-surgery				0.185
Never smoker	272 [74.5]	198 [77.3]	74 [67.9]	
Ex-smoker	54 [14.8]	35 [13.7]	19 [17.4]	
Current smoker	35 [9.6]	21 [8.2]	14 [12.8]	
Unknown	4 [1.1]	2 [0.8]	2 [1.8]	
Median age at diagnosis, years	21.0 [16–28]	21 [17–27]	21.0 [15–30]	0.918
Median disease duration, years	9.0 [3–16]	8.0 [3–15]	9.0 [3–19]	0.323
Disease location of Montreal classification				0.113
L1 [isolated ileal]	146 [40.0]	110 [43.0]	36 [33.0]	
L3 [ileocolonic]	212 [58.1]	142 [55.5]	70 [64.2]	
Unknown	7 [1.9]	4 [1.6]	3 [2.8]	
Disease behaviour of Montreal classification				0.775
B1 [non-stricturing, non-penetrating]	6 [1.6]	5 [2.0]	1 [0.9]	
B2 [stricturing]	161 [44.1]	111 [43.4]	50 [45.9]	
B3 [penetrating]	198 [54.2]	140 [54.7]	58 [53.2]	
Perianal disease	82 [22.5]	58 [22.7]	24 [22.0]	0.998
Unknown	7 [1.9]	5 [2.0]	2 [1.8]	
Prior small bowel resection	98 [26.8]	62 [24.2]	36 [33.0]	0.108
Surgical findings in terminal ileum				0.588
Only stricturing	171 [46.8]	117 [45.7]	54 [49.5]	
Only penetrating	88 [24.1]	64 [25.0]	24 [22.0]	
Stricturing-penetrating	66 [18.1]	49 [19.1]	17 [15.6]	
Non-stricturing/non-penetrating	38 [10.4]	24 [9.4]	14 [12.8]	
Unknown	2 [0.5]	2 [0.8]	0	
Anastomosis type				0.158
Side-to-side	239 [65.5]	160 [62.5]	79 [72.5]	
End-to-end	76 [20.8]	57 [22.3]	19 [17.4]	
End-to-side	23 [6.3]	19 [7.4]	4 [3.7]	
Unknown	27 [7.4]	20 [7.8]	7 [6.4]	
Anastomosis method				0.313
Stapled	300 [82.2]	206 [80.5]	94 [86.2]	
Hand-sewn	59 [16.2]	45 [17.6]	14 [12.8]	
Unknown	6 [1.6]	5 [2.0]	1 [0.9]	
Median small bowel resection length, cm	23.0 [15–32]	22.7 [15–32]	24.2 [15–33]	0.748
Proximal margin free of gross inflammation	313 [85.6]	226 [88.3]	87 [79.8]	**0.048**
Unknown	3 [0.8]	2 [0.8]	1 [0.9]	
Previous use of thiopurines	186 [51.0]	133 [52.0]	53 [48.6]	0.733
Unknown	3 [0.8]	1 [0.4]	2 [1.8]	

Table 1. Continued

	Total [*n* = 365]	Rutgeerts i0–i1 [*n* = 256]	Rutgeerts ≥i2 [*n* = 109]	*p*-value
Previous use of methotrexate	67 [18.4]	42 [16.4]	25 [22.9]	0.188
Unknown	4 [1.1]	3 [1.2]	1 [0.9]	
Previous use of anti-TNF	227 [62.2]	164 [64.1]	63 [57.8]	0.320
Unknown	6 [1.6]	4 [1.6]	2 [1.8]	
Prior use of infliximab	146 [40.0]	104 [40.6]	42 [38.5]	0.872
Unknown	10 [2.7]	6 [2.3]	4 [3.7]	
Prior use of adalimumab	140 [38.4]	96 [37.5]	44 [40.2]	0.675
Unknown	6 [1.6]	4 [1.6]	2 [1.8]	
Prior use of certolizumab	16 [4.4]	8 [3.1]	8 [7.3]	0.121
Unknown	10 [2.7]	6 [2.3]	4 [3.7]	
Prior use of vedolizumab	28 [7.7]	16 [6.3]	12 [11.0]	0.173
Unknown	9 [2.5]	6 [2.3]	3 [2.8]	
Prior use of ustekinumab	39 [10.7]	26 [10.2]	13 [11.9]	0.733
Unknown	8 [2.2]	5 [2.0]	3 [2.8]	

TNF, tumour necrosis factor. Continuous variables are summarized as median [IQR] and categorical variables as *n* [%]. *p* values were calculated based on bivariate comparisons using χ^2 or Fisher's exact tests for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables as appropriate. Bold values denote $p < 0.1$.

distribution of variables included in the model according to gender, ethnicity, interval between surgery and first colonoscopy, smoking status, and anti-TNF use after surgery are shown in Supplementary Tables S1–S5. Although there were minor differences in the distribution of some variables when patients were stratified according to the significant predictors, the only interaction identified in the model occurred between smoking status and perianal disease with an increased probability of recurrence for the product of these two variables [OR = 10.48, 95% CI 1.18–92.63]. No other interactions were identified.

3.3. Anti-TNF as a protective factor of endoscopic postoperative recurrence

Given anti-TNF was the only prophylactic medication independently associated with postoperative recurrence at first colonoscopy in our cohort, we explored whether the type of anti-TNF and pattern of use after surgery influenced the association. Our model identified anti-TNF use after surgery as a protective factor when combined therapy [OR 0.33, 95% CI 0.12–0.96] or monotherapy [OR 0.41, 95% CI 0.20-0.82] was used, as well as when only infliximab [OR = 0.13, 95% CI 0.04–0.41] or adalimumab [OR = 0.27, 95% CI 0.11–0.66] users were included. When the analysis was limited to certolizumab users [*n* = 10], there was no association with recurrence [OR = 2.82, 95% CI 0.55–14.52]. We also analysed the association between anti-TNF prophylaxis and postoperative recurrence according to whether patients were exposed to anti-TNF before surgery [Supplementary Table S6]. Among patients with a history of anti-TNF use before surgery [*n* = 227], 109 [48.0%] had anti-TNF therapy after surgery and 63 [27.7%] had recurrence at first endoscopy. In this subgroup, anti-TNF significantly reduced the probability of endoscopic recurrence independent of the other clinical variables [OR = 0.16, 95% CI 0.06–0.39]. This effect remained significant after excluding patients on ustekinumab [*n* = 51] and vedozilumab [*n* = 10] prophylaxis [OR = 0.12, 95% CI 0.04–0.35] and patients on combination therapy [*n* = 37] after surgery [OR = 0.15, 95% CI 0.05–0.47]. Conversely, among patients who were anti-TNF naive prior to index surgery [*n* = 132], only 24 [18.1%] started anti-TNF after surgery and 44 [33.3%] of these had recurrence at first colonoscopy. In this subgroup, anti-TNF prophylaxis was not protective against endoscopic recurrence [OR = 0.63, 95% CI 0.16–2.48].

3.4. Sensitivity and subgroup analyses for endoscopic recurrence at first colonoscopy

Using the modified Rutgeerts score, only 85 [23.3%] patients had endoscopic recurrence [≥i2b] and 280 [76.7%] remained in remission [i0–i2a]. Male gender [OR = 1.93, 95% CI 1.06–3.53], non-White ethnicity [OR = 2.78, 95% CI 1.20–6.44], smoking after surgery [OR = 3.30, 95% CI 1.33–8.17], and anti-TNF use after surgery [OR = 0.24, 95% CI 0.12–0.51] remained independent predictors of endoscopic recurrence using the modified Rutgeerts score. Using a stricter definition of endoscopic remission [Rutgeerts score i1–i4 vs i0], 176 [48.2%] patients had endoscopic recurrence and only male gender [OR = 1.78, 95% CI 1.09–2.90] and anti-TNF use after surgery [OR = 0.36, 95% CI 0.20–0.63] remained associated with endoscopic recurrence. A total of 42 [11.5%] patients developed severe endoscopic recurrence [Rutgeerts i3–i4] at first colonoscopy. None of the previously identified risk factors were associated with severe recurrence. Looking at the 133 patients who were not treated with biological or immunomodulator therapy following surgery, 49 [36.8%] developed recurrence at first colonoscopy. We did not identify predictors of recurrence in this subgroup; however, a similar direction of effect was observed for male gender [OR = 1.99, 95% CI 0.83–4.79], non-White ethnicity [OR 2.75, 95% CI 0.62–12.2], and smoking status [OR = 2.7, 95% CI 0.67–10.9].

Additionally, as time to first colonoscopy following surgery in our cohort was longer than currently recommended for a minority of patients,[14,15] an analysis excluding colonoscopies performed more than 1 year after surgery [*n* = 28] was performed. Multivariable analysis on 337 patients [Rutgeerts score ≥i2 = 94, Rutgeerts score ≥i0–i1 = 243] including the

Table 2. Postsurgical clinical characteristics of the cohort. Univariable analysis according to recurrence status at first colonoscopy.

	Total [*n* = 365]	Rutgeerts i0–i1 [*n* = 256]	Rutgeerts ≥i2 [*n* = 109]	*p*-value
Median interval between surgery and first endoscopy, months	7 [5–9]	7 [5–9]	7.0 [5–10]	0.267
Time to first endoscopy				0.201
Before 6 months	116 [31.8]	85 [33.2]	31 [28.4]	
Between 6 and 12 months	208 [57.0]	147 [57.4]	61 [56.0]	
After 12 months	41 [11.2]	24 [9.4]	17 [15.6]	
Smoker after surgery	30 [8.2]	16 [6.3]	14 [12.8]	**0.058**
Unknown	7 [1.9]	5 [2.0]	2 [1.8]	
Antibiotics after surgery	7 [1.9]	4 [1.6]	3 [2.8]	0.744
Unknown	3 [0.8]	3 [1.2]	0	
Corticosteroid after surgery	20 [5.5]	11 [4.3]	9 [8.3]	0.206
Unknown	4 [1.1]	3 [1.2]	1 [0.9]	
Thiopurines after surgery	53 [14.5]	45 [17.6]	8 [7.0]	**0.016**
Unknown	2 [0.5]	2 [0.8]	0	
Thiopurine monotherapy	25 [6.8]	19 [7.4]	6 [5.5]	0.662
Methotrexate after surgery	25 [6.8]	17 [6.6]	8 [7.3]	1
Unknown	3 [0.8]	3 [1.2]	0	
Methotrexate monotherapy	6 [1.6]	5 [2.0]	1 [0.9]	0.793
Anti-TNF after surgery	133 [36.4]	110 [43.0]	23 [21.1]	**<0.001**
Unknown	9 [2.5]	5 [2.0]	4 [3.7]	
Infliximab	57 [15.6]	50 [19.5]	7 [6.4]	**0.003**
Unknown	9 [2.5]	5 [2.0]	4 [3.7]	
Adalimumab	66 [18.1]	55 [21.5]	11 [10.1]	**0.017**
Unknown	9 [2.5]	5 [2.0]	4 [3.7]	
Certolizumab	10 [2.7]	5 [2.0]	5 [4.6]	0.283
Unknown	8 [2.2]	5 [2.0]	3 [2.8]	
Anti-TNF combo	43 [11.8]	37 [14.5]	6 [5.5]	**0.024**
Anti-TNF monotherapy	90 [24.7]	73 [28.5]	17 [15.6]	**0.012**
Vedolizumab after surgery	14 [3.8]	8 [3.1]	6 [5.5]	0.423
Unknown	8 [2.2]	5 [2.0]	3 [2.8]	
Ustekinumab after surgery	52 [14.2]	31 [12.1]	21 [19.3]	**0.099**
Unknown	9 [2.5]	6 [2.3]	3 [2.6]	

TNF, tumour necrosis factor. Continuous variables are summarized as median [IQR] and categorical variables as *n* [%]. *p* values were calculated based on bivariate comparisons using χ^2 or Fisher's exact tests for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables as appropriate. Bold values denote $p < 0.1$.

same predictors showed that male gender [OR = 2.43, 95% CI 1.32–4.45], non-White ethnicity [OR = 3.09, 95% CI 1.31–7.30], and smoking after surgery [OR = 2.85, 95% CI 1.15–7.05] remained significant risk factors for endoscopic recurrence, while anti-TNF after surgery [OR = 0.26, 95% CI 0.12–0.54] remained a significant protective factor. Finally, given our study spanned a 10-year period with important changes implemented in the clinical practice, particularly the use of biological therapy, we split the cohort into two 5-year periods [2011–2016 and 2017–2021]. As expected, from the first [*n* = 155 patients] to the second period [*n* = 210 patients], there was an increased use of anti-TNF [29.0% to 41.9%], ustekinumab [1.9% to 23.3%], and vedolizumab [2.6% to 4.8%]. However, no changes were observed in endoscopic recurrence rate [30.3% to 29.5%] between these two intervals. The inclusion of the study period variable in the model did not modify the previously mentioned independent predictors.

3.5. Clinical predictors of late endoscopic recurrence

We further explored the clinical factors associated with late endoscopic postoperative recurrence at the second postoperative colonoscopy. Eighty-four out of 208 [40.4%] second colonoscopies showed endoscopic recurrence [Figure 1]. However, 50 out of 84 [59.5%] patients who had endoscopic recurrence at second colonoscopy had already experienced endoscopic recurrence at first endoscopy. Of the 135 patients without recurrence at first colonoscopy who had a second colonoscopy, 34 [25.1%] had endoscopic recurrence at that second colonoscopy. Univariable analysis of factors associated with endoscopic recurrence at second colonoscopy is shown in Supplementary Tables S7 and S8. Including Rutgeerts score at first colonoscopy as a covariable [i1 vs i0], the interval between first and second colonoscopy, and the previously identified risk factors for endoscopic recurrence, only Rutgeerts score i1 at first colonoscopy [OR = 4.43, CI

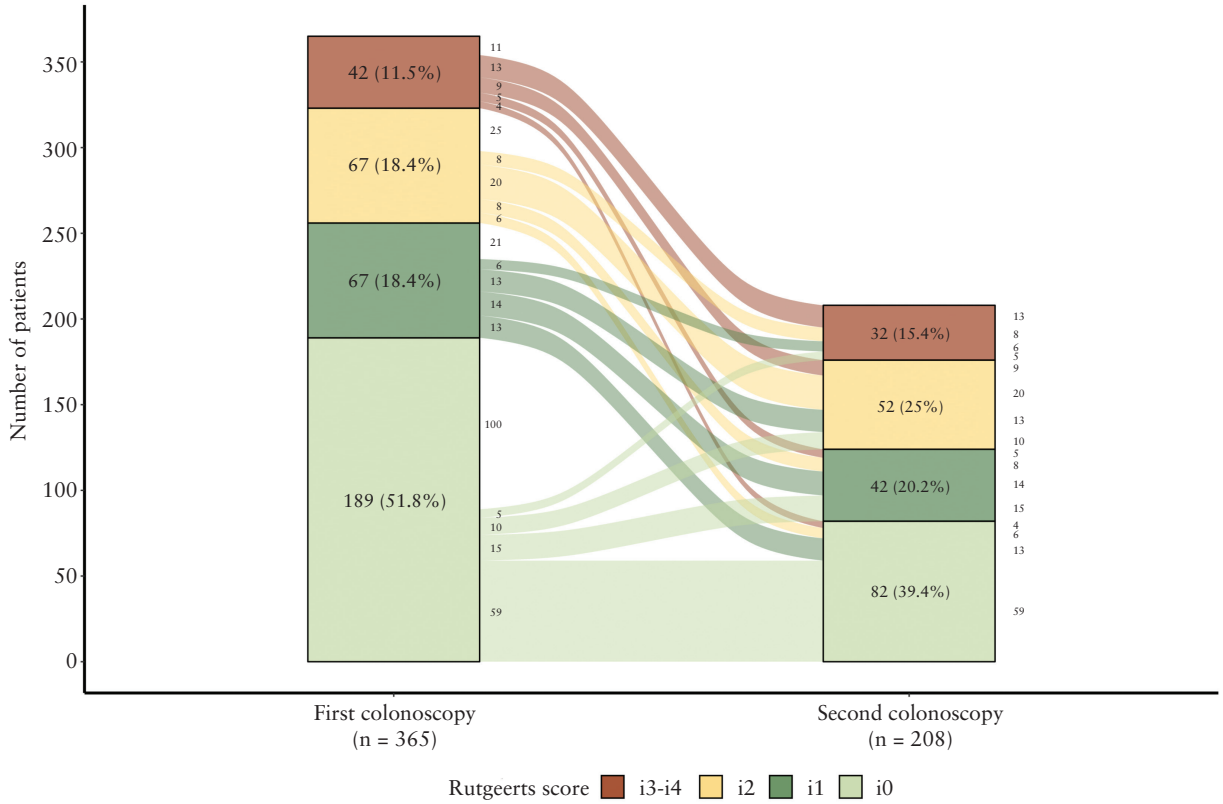

Figure 1. Alluvial bar plot depicting the changes in Rutgeerts score between the first and second colonoscopy. Numbers outside the bars show the number of patients moving [flow line] to the second endoscopy categories. Patients without flow are those without second colonoscopy. Rutgeerts scores i3 and i4 were merged to facilitate visualization.

Table 3. Multivariable analysis of clinical variables associated with endoscopic recurrence at first endoscopy including recruiting centre as random effect.

	Odds ratio	95% CI	*p*-value
Male [vs female]	**1.95**	**1.12–3.40**	**0.019**
Non-White [vs White]	**2.48**	**1.09–5.63**	**0.030**
Age at diagnosis [per year increase]	1.02	0.99–1.04	0.151
Disease duration [per year increase]	0.99	0.96–1.02	0.697
Perianal disease	0.91	0.48–1.72	0.762
Penetrating complication	0.57	0.32–1.02	0.058
Prior small bowel resection	1.13	0.59–2.17	0.703
Proximal margin free of gross inflammation	0.63	0.31–1.28	0.200
Small bowel resection length [per cm increase]	1.00	0.99–1.02	0.646
Interval between surgery and colonoscopy [per month increase]	**1.09**	**1.002–1.18**	**0.045**
Smoking after surgery	**2.78**	**1.16–6.67**	**0.022**
Anti-TNF after surgery	**0.28**	**0.14–0.55**	**<0.001**
Ustekinumab after surgery	1.32	0.59–2.97	0.496

CI, confidence interval; TNF, tumour necrosis factor. Bold values denote statistical significance at the $p < 0.05$ level.

95% 1.73–11.35] and non-White ethnicity [OR = 5.18, CI 95% 1.10–24.50] were associated with a higher risk of recurrence at second colonoscopy [Supplementary Table S9]. Only 39 patients who had a third or greater colonoscopy had not experienced previous recurrence at first and second colonoscopy, with 14 [35.8%] having endoscopic recurrence at third or subsequent colonoscopy, thus preventing a reliable analysis of independent risk factors at this timepoint. Only the univariable analysis is shown in Supplementary Tables S7 and S8.

3.6. Clinical factors associated with a first episode of endoscopic recurrence

Taking advantage of the varied time interval between surgery and postoperative colonoscopies and the multiple follow-up colonoscopies for numerous patients, we analysed

the time-to-first endoscopic recurrence [Rutgeerts ≥i2] using survival analysis. Within a median follow-up of 11 months [range 3–101], 150 out of 365 [41.1%] patients experienced endoscopic recurrence. Given a small proportion of patients [*n* = 12, 3.3%] had follow-up longer than 48 months [Supplementary Figure S2], the survival analysis was performed between 0 and 48 months after surgery. This analysis included 353 participants, of whom 145 [41.1%] experienced recurrence. Multivariable Cox regression analysis [Table 4] confirmed that male gender (adjusted hazard ratio [aHR] = 1.28, 95% CI 1.06–1.55), non-White ethnicity [aHR = 1.92, 95% CI 1.43–2.58], and smoking after surgery [aHR = 1.85; 95% CI 1.39–2.46] were independent risk factors for endoscopic recurrence. Anti-TNF use after surgery was again independently associated with a reduced risk of endoscopic recurrence [aHR = 0.37, 95% CI 0.19–0.74]. Additionally, our time-to-event multivariable analysis showed that proximal margin free of gross inflammation [aHR = 0.54, 95% CI 0.31–0.92] was a predictor of lower risk of endoscopic recurrence. Repeating this time-to-event analysis among patients without medical prophylactic therapy after surgery [*n* = 138] with 70 [50.7%] experiencing recurrence, non-White ethnicity [aHR = 2.05, 95% CI 1.22–3.43] and smoking after surgery [aHR = 2.04, 95% CI 1.45–2.88] were significantly associated with recurrence, while male gender preserved the same direction of effect [aHR = 1.07, 95% CI 0.85–1.35]. In this subgroup, proximal margin free of gross inflammation [aHR = 0.38; 95% CI 0.29–0.50] was also associated with a lower risk of endoscopic recurrence.

3.7. Endoscopic recurrence according to cumulative clinical risk factors and previously proposed risk stratification strategies

Previous studies have shown an increased rate of endoscopic recurrence at first postoperative colonoscopy according to the number of risk factors.[16] Likewise, we found that an increased number of the identified risk factors including male gender, non-White ethnicity, and smoking after surgery was accompanied by a higher rate of recurrence at first colonoscopy even after adjusting for other confounders [one risk factor: OR = 2.26, 95% CI 1.23–4.15; two risk factors: OR = 4.88, 95% CI 1.93–12.3; compared to no risk factors]. The percentage of recurrence according to number of risk factors is shown in Figure 2. To analyse the impact of smoking on this model and risk profile, we repeated the previous analysis removing the small proportions of smokers (*n* = 35 [9.6%]). The cumulative effect of male gender and non-White ethnicity remained significant [one risk factor: OR = 2.20, 95% CI 1.17–4.16; two risk factors: OR = 6.31, 95% CI 1.98–20.1; compared to no risk factors]. The percentage of colonoscopies demonstrating disease recurrence according to number of risk factors considering only gender and ethnicity is shown in Supplementary Figure S3. We then explored the performance of the risk categories proposed by the Technical Review panel of the AGA guidelines[14] in our cohort. According to this proposal, lower risk patients are those older than 50 years, non-smokers, first surgery for a short segment of fibrostenotic disease [<20 cm], and disease duration >10 years, and higher risk patients are those younger than 30 years, smokers, and two or more prior surgeries for penetrating disease with or without perianal disease. Only three patients in our cohort fell into the lower risk category and none into the higher risk category based on these criteria. Given only 43 patients were older than 50 years in our cohort and the proportion of smokers was small, we analysed the risk categories removing this criterium and analysing only non-smokers. Based on this categorization, 12 patients fell into the lower risk category [i.e. first surgery for a short segment of fibrostenotic disease and disease duration >10 years] and 15 in the higher risk category [i.e. younger than 30 years and prior surgery for penetrating disease]. This categorization did not predict endoscopic recurrence [lower risk: OR 1.65, 95% CI 0.41–6.73; higher risk: OR 0.82, 95% CI 0.18–3.79, compared to patients who do not meet lower and higher risk criteria]. The percentage of colonoscopies demonstrating disease recurrence according to these risk categories is shown in Supplementary Figure S4. We finally tested whether the additive effect of the AGA-proposed risk factors would result in a higher risk of endoscopic recurrence, but a consistent cumulative effect was not seen [one risk factor: OR = 0.71, 95% CI 0.35–1.45; two risk factors:

Table 4. Univariable and multivariable Cox regression analysis of clinical variables associated with time to first episode of endoscopic recurrence [Rutgeerts score ≥i2].

	Univariable analysis		Multivariable analysis		
	HR	*p*-value	aHR	95% CI	*p*-value
Male [vs female]	1.36	0.064	**1.28**	**1.06–1.55**	**0.010**
Non-White [vs White]	1.50	0.100	**1.92**	**1.43–2.58**	**<0.001**
Age at diagnosis [per year increase]	1.01	0.200	1.00	0.98–1.02	0.900
Disease duration [per year increase]	1.01	0.200	1.00	0.98–1.03	0.800
Perianal disease	1.08	0.700	0.99	0.70–2.41	0.900
Penetrating complication	0.90	0.600	0.80	0.63–1.01	0.059
Prior small bowel resection	1.11	0.600	0.93	0.50–1.74	0.800
Proximal margin free of gross inflammation	0.55	0.007	**0.54**	**0.31–0.92**	**0.024**
Small bowel resection length [per cm increase]	1.00	0.400	1.00	0.99–1.02	0.500
Smoking after surgery	1.50	0.14	**1.85**	**1.39–2.46**	**< 0.001**
Anti-TNF after surgery	0.45	<0.001	**0.37**	**0.19–0.74**	**0.005**
Ustekinumab after surgery	1.26	0.3	0.99	0.75–1.32	0.900

aHR, adjusted hazard ratio; CI, confidence interval; TNF, tumour necrosis factor. Bold values denote statistical significance at the $p < 0.05$ level.

OR = 1.30, 95% CI 0.68–2.49; three or more risk factors: OR = 4.37, 95% CI 0.85–22.5; compared to no risk factors], especially when only non-smokers were analysed [one risk factor: OR = 0.63, 95% CI 0.29–1.38; two risk factors: OR = 1.36, 95% CI 0.67–2.75; three or more risk factors: OR = 3.10, 95% CI 0.13–76.0; compared to no risk factors]. The percentage of colonoscopies demonstrating disease recurrence according to the number of risk factors proposed by AGA guidelines is shown in Supplementary Figure S5.

4. Discussion

Recurrence of ileal Crohn's disease after a 'curative' resection is common; however, reported rates of early endoscopic recurrence during the first year after resection vary widely between 30% and 90%.[14] This large difference might be related to variations in patient characteristics [e.g. smoking] and rates of use of postoperative prophylactic therapy [e.g. anti-TNF]. Our large multicentre and multinational cohort allowed us to capture a substantial phenotypic heterogeneity and varied clinical practice approaches in postsurgical Crohn's disease patients in a real-world setting. Our overall rate of endoscopic recurrence at first postoperative colonoscopy is among the lowest reported [29.9%]. We observed a slightly higher incidence of endoscopic recurrence in Canadian compared to US centres [34.2% vs 26.9%, $p = 0.16$] despite a significantly smaller proportion of anti-TNF prophylaxis use [22.0% vs 46.3%, $p < 0.001$] and a higher proportion of smokers [10.7% vs 6.5%, $p = 0.23$] after surgery in Canadian compared to US patients. Along with the lack of reduction of endoscopic recurrence over the 10-year period of our study [despite the increasing use of biological therapy], these observations stress the need to improve the risk stratification of Crohn's disease patients following ileocolic resection. To account for these and other confounding factors that could differ between our six participant GRCs, we incorporated GRC site as a random [clustered] effect in a mixed-effects logistic regression model to determine the clinical features independently associated with endoscopic recurrence. On top of this centre-related heterogeneity and multiple others potentially confounding features included in the model, five clinical factors were independently associated with endoscopic recurrence at first postoperative colonoscopy in our cohort: gender, ethnicity, time between surgery and first colonoscopy, smoking, and anti-TNF use after surgery.

Male gender and non-White ethnicity have recently been identified as risk factors for postoperative recurrence.[16,28] Auzolle *et al.* analysed the clinical factors associated with endoscopic recurrence at first colonoscopy in the prospective REMIND cohort and found that male gender was an independent risk factor [OR 2.48, 95% CI 1.40–4.46]. Our analysis confirms this association [OR 1.95, 95% CI 1.12–3.40]. Like the REMIND cohort, there were no differences in smoking status [7.4% vs 9.1%, $p = 0.6$] or anti-TNF use [37.0% vs 35.8%, $p = 0.8$] between males and females in our cohort, and no difference regarding intervals between surgery and first colonoscopy (median 6 months [5–9] vs 7 months [5–9], $p = 0.2$). However, in our cohort, males were younger than females at diagnosis (median 20.0 years [15–28] vs 23.0 years [18–29], $p = 0.005$). Nonetheless, male gender remained as an independent risk factor after adjusting for this and other covariables and no interactions with other clinical factors were identified. Similarly, racial differences in the postoperative course of Crohn's disease patients were recently reported by Anyane-Yeboa *et al.*[28] The majority of our patients [89.9%] were Whites. The non-White population [$n = 37$] consisted of 12 [32.4%] Asians, 11 [29.7%] African Americans, and seven [18.9%] non-White Hispanics, among others. Although we were not able to find differences between these subgroups given the small sample size, the multivariable pooled analysis of non-White vs White patients revealed that the former group had an increased risk [OR = 2.48, 95% CI 1.09–5.63] of endoscopic recurrence at first colonoscopy independent of other clinical characteristics. Like gender, no differences were identified between non-White and White patients in smoking status [8.2% vs 8.4%, $p = 1$], anti-TNF use [36.0% vs 40.5%, $p = 0.8$], and interval between surgery and first colonoscopy (median 7 months [5–9] vs 7 months [5–8], $p = 0.8$), as well as other covariables. Gender- and ethnicity-based differences in Crohn's disease pathogenesis, disease course, and even response to therapy have been increasingly recognized[30,31]; however, it is difficult to ascertain the means by which these

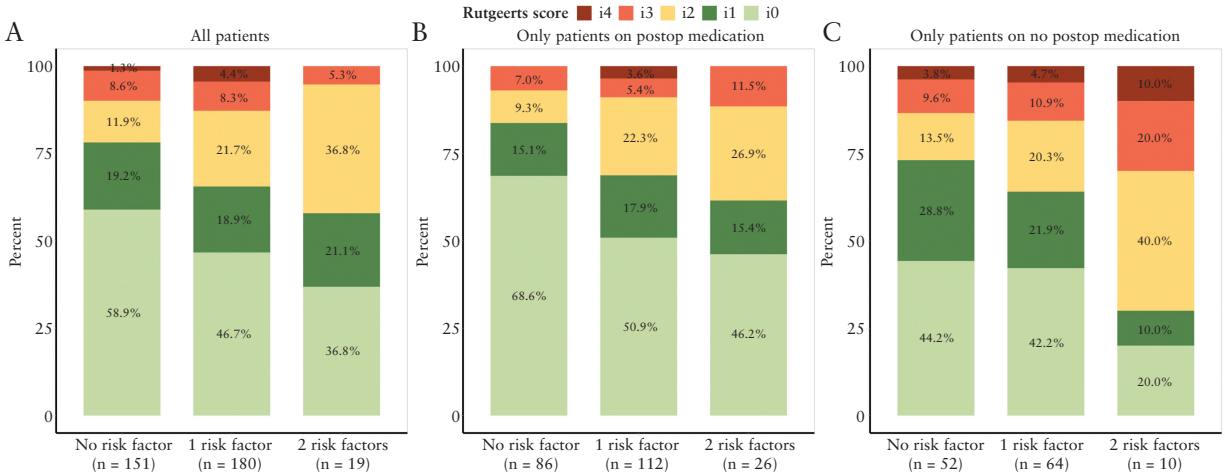

Figure 2. Rutgeerts score at first colonoscopy according to the number of risk factors. Unweighted sum of the following clinical factors: gender [female = 0, male = 1], ethnicity [White = 0, non-White = 1], and smoking after surgery [no = 0, yes = 1]. [A] Including the entire cohort, [B] including only patients on postoperative medication after surgery [i.e. immunomodulators and biologics], and [C] including only patients without postoperative medication.

features affect differences in postoperative endoscopic recurrence rates and whether these may be related to biological [genetic, hormonal, or microbial], environmental [diet] factors or non-biological factors including differential access to health care. Experimental and translational models to test the mechanisms for these observed differences are needed.

We also observed that a longer interval between surgery and first endoscopy is associated with a slightly higher rate of endoscopic recurrence [OR = 1.09, 95% CI 1.002–1.18]. Although the first postoperative colonoscopy was performed later in patients on anti-TNF prophylaxis compared to patients without this treatment (median 6 months [IQR 5–9] vs 7 months [5–10], $p = 0.02$), the effect of interval between surgery and first colonoscopy was independent of anti-TNF treatment and no interaction was observed between these two variables. The higher proportion of patients with Rutgeerts score ≥i2 when first colonoscopy was performed over 12 months after surgery [41.5%] compared to those with colonoscopies performed at 6–12 months [29.3%] emphasizes the importance of timely endoscopic evaluation following surgery in accordance with current guidelines.[14]

The other two independent clinical factors associated with early endoscopic recurrence in our study—smoking and prophylactic anti-TNF therapy after surgery—have been extensively reported in the literature.[16,18,32] Active smoking is the strongest and most consistently associated modifiable clinical risk factor for endoscopic, clinical, and surgical postoperative recurrence.[16,18] In fact, the low proportion of smokers in our study cohort could partially explain why the rate of early endoscopic recurrence is among the lowest [29.9%] reported in prospective studies.[16,33] Prospective multicentre studies undertaken in France[16] [REMIND study] and Italy[33] reported 47.7% and 48.2% of patients with Rutgeerts score ≥i2 at first postoperative endoscopy, respectively. The corresponding proportion of smokers in these studies was 32.0% and 32.4%, compared to <10% of active smokers around surgery in our study. Notably, there were no remarkable differences in anti-TNF postoperative prophylaxis between the REMIND and our cohort [29% vs 36%]. Consequently, smoking cessation counselling should be a priority in Crohn's disease patients. Moreover, smoking after surgery along with male gender and non-White ethnicity showed an additive effect, increasing the proportion of patients with recurrence at first colonoscopy when more than one of these features are present.

Anti-TNF was the only therapy associated with a lower risk of recurrence [OR = 0.28, 95% CI 0.14–0.55] in our cohort, although the frequency of immunomodulator [thiopurines and methotrexate], vedolizumab, and ustekinumab use as monotherapy in our patients was small, thus precluding reliable conclusions regarding the association of these agents with endoscopic recurrence. Compared to infliximab, which has proven efficacy in the prevention of endoscopic recurrence as demonstrated in a randomized, placebo-controlled trial,[12] there are limited data assessing the efficacy of vedolizumab and ustekinumab in the postoperative setting.[34,35] Future large, randomized control trials are necessary to determine their role in preventing postoperative recurrence. The protective effect of anti-TNF in our study was observed for both monotherapy and combination therapy [i.e. with an immunomodulator], as well as for the specific anti-TNF agents, infliximab and adalimumab. The lack of association for certolizumab is probably related to the small number of patients using this medication in our cohort. Strikingly, anti-TNF prophylaxis was a significant protective factor in patients with prior exposure to anti-TNF agents, though this effect was not observed on anti-TNF naïve subjects. This could be related to the fact that only 18% of anti-TNF naïve participants were initiated on anti-TNF postoperatively; therefore, given the small sample size, a beneficial effect of anti-TNF prophylaxis on this group cannot be excluded. Our data suggest that, following surgery, continuing anti-TNF therapy can be clinically appropriate, and that the perceived lack of anti-TNF efficacy before surgery may be explained by already established irreversible bowel damage [stricturing and penetrating complications] that would not respond to medical therapy. This has been recently shown in a retrospective study.[36] Moreover, the significant protective effect of postoperative anti-TNF therapy on anti-TNF experienced patients observed in our study could denote a subgroup of patients with more aggressive disease that may obtain a greater benefit from postoperative prophylaxis compared to biologic-naïve patients.

Our analysis searching for predictors of time-to-first episode of postoperative recurrence [which was not limited to first postoperative colonoscopy] confirmed the association of male gender, non-White ethnicity, and smoking after surgery with a higher risk of recurrence and the protective effect of anti-TNF prophylaxis. Proximal resection margin free of gross inflammation was also significantly associated with a lower risk of recurrence. This finding is in agreement with a recent meta-analysis of histological features predicting postoperative recurrence.[37] Interestingly, our analysis, considering time-to-event which captures all patients experiencing recurrence over the period analysed, revealed that non-White ethnicity and smoking status are associated with higher rates of recurrence, and proximal margin free of gross inflammation is a protective factor for postoperative recurrence among patients without any medical prophylaxis after surgery. This highlights the potential utility of these factors to select patients for immediate postoperative medical prophylaxis.

Multiple other clinical features inconsistently associated with postoperative endoscopic recurrence in the literature and employed for patient stratification such as young age at disease onset, disease duration, perianal disease, penetrating behaviour, prior small bowel resection, and extent of small bowel resection did not influence the probability of endoscopic recurrence in our cohort. Of note, prior small bowel resection and penetrating disease place Crohn's disease patients in a high-risk category suggesting early postoperative therapy according to the American[14] and European[33] guidelines, and have been used for selection of high-risk patients in clinical trials evaluating the efficacy of preventative strategies.[12,17] In particular, penetrating disease behaviour has not been found to be associated with endoscopic recurrence in other large prospective cohorts.[16,38] In fact, a lower risk of endoscopic recurrence has been observed in patients undergoing surgery due to penetrating complications.[38] Interestingly, a similar trend was identified in our cohort [OR = 0.57, 95% CI 0.32–1.02]. Caution should be exercised when using these features to stratify Crohn's disease patients for risk of endoscopic postoperative recurrence. They may reflect preoperative disease severity and/or complicated disease course rather than independent risk factors for recurrence.[14] The lower risk and higher risk categories defined by the AGA[14] did not predict endoscopic recurrence at first colonoscopy in our cohort. Although they developed these two illustrative risk groups with the corresponding

theoretical rates of endoscopic recurrence at 18 months in the absence of any intervention in postsurgical patients with Crohn's disease,[14] our survival analysis that included late endoscopic recurrence and patients off medication after surgery did not reveal associations between the components of this risk stratification algorithm and endoscopic recurrence. Furthermore, adding the proposed clinical risk factors did not clearly increase the risk of recurrence compared to patients with no risk factors.

Notably, our identified risk factors, including anti-TNF prophylaxis, were not able to predict severe endoscopic recurrence [Rutgeerts score i3–i4 vs i0–i2]. This could be related to the small proportion of patients developing early severe inflammatory lesions; nevertheless, determinants of rapid disease progression after surgery need to be further investigated. Clinical variables to stratify patients for early pharmacological prophylaxis should be revised and other predictive biomarkers need to be explored to improve categorization of patients at high risk of postoperative recurrence who need immediate prophylactic therapy.[39]

Unique to this study, we have also prospectively sought out clinical risk factors for endoscopic recurrence at the second colonoscopy in Crohn's disease patients who have no neoterminal ileum lesions [Rutgeerts score i0] or mild disease recurrence [Rutgeerts score i1] at the first colonoscopy. This analysis is relevant given that current guidelines define endoscopic recurrence as Rutgeerts score ≥i2 and recommend starting or optimizing medical treatment in this scenario.[14,15] We have identified that Rutgeerts score i1 at first colonoscopy [OR = 4.43, 95% CI 1.73–11.35] and non-White ethnicity [OR = 5.18, 95% CI 1.10–24.50] are associated with endoscopic recurrence at the second postoperative colonoscopy. These findings should be interpreted carefully due to the wide CI and the lack of central reading that could confound and make the association uncertain. In fact, it has been demonstrated that the interobserver variation of Rutgeerts score is moderate, especially when differentiating <i2 from ≥i2.[40] Given the difference between Rutgeerts score i1 and i2 could lie on only the number of aphthous lesions [fewer or more than 5] in some patients, disease progression [i1 to i2] could be explained by a disagreement in the scoring criteria. However, another study has also suggested that Crohn's disease patients with mild ileal lesions following ileal resection have a higher risk of progression and poorer clinical outcomes compared to those without endoscopic lesions, and consequently they may benefit from prophylactic therapy.[8] Another important limitation of this specific subanalysis is the multiple options of therapy modification/optimization that Crohn's disease patients could have experienced based on the findings at the first colonoscopy. Therefore, we were unable to include this variable in the model considering its complexity and the small sample size for this analysis.

Our study has several strengths including the large sample size and the extensive prospective and standardized clinical data collection that enabled us to correct for multiple confounders. We have included second and third and greater colonoscopies for a subset of patients to assess potential risk factors for recurrence which occurs subsequent to the first postoperative colonoscopy. The inclusion of several centres from two countries with different practice patterns and patient demographics make our results more generalizable. However, it is worth noting that our cohort was recruited in tertiary centres with multidisciplinary teams including colorectal surgeons and gastroenterologists with significant expertise in IBD that could also explain the low rates of endoscopic recurrence observed. A number of specific limitations to our study have already been described in the Discussion but additional limitations are related to the loss to follow-up of participants and missing clinical data which could introduce bias to our observations, especially for low-frequency features such as smoking status or non-White ethnicity. Comparison of baseline clinical features of patients who have no follow-up to those analysed in this study showed a significantly higher proportion of patients with penetrating behaviour in the former group with no differences in other clinical variables [data not shown]. Although we adjusted for disease behaviour, a selection bias with underrepresentation of this phenotype could have occurred in our study. Finally, given our main goal in this study was to establish clinical independent risk factors of endoscopic recurrence, we have included a large number of variables, mostly based on the prior literature and clinical guideline recommendations.[14,15,20–22] We analysed 13 potential predictors on 109 events of the smallest outcome category [endoscopic recurrence]—this was close to the common rule of thumb [one predictive variable for every ten events].[41] Furthermore, a study has criticized this rule as too conservative.[42] Our results were consistent when weakest predictors were removed [data not shown].

In conclusion, using a large multicentre and multinational cohort of Crohn's disease patients undergoing ileocolic resection and extensive prospective clinical data collection, we have identified independent risk factors for postoperative disease recurrence. Male gender and non-White ethnicity, as well as modifiable risk factors such as time between surgery and first endoscopy, smoking, and lack of anti-TNF prophylaxis after surgery were significantly associated with an increased probability of endoscopic recurrence. Other commonly used clinical features such as penetrating disease behaviour were not associated with endoscopic recurrence after accounting for other covariables. Our study emphasizes the need to revise current international guidelines so that patients at highest risk of postoperative disease recurrence can be appropriately identified and treated with the aim of improving clinical outcomes.

Conference Presentation

Preliminary data from this study were presented at Digestive Disease Week, San Diego, 2022.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary Data

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

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