Clinical and Genetic Factors Impact Time to Surgical Recurrence After Ileocolectomy for Crohn's Disease

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Objective: The aim of this study was to evaluate factors associated with time to surgical recurrence after Crohn's ileocolectomy.

Summary Background Data: The most common surgery performed for Crohn's disease is ileocolectomy. Identifying patients at high risk for surgical recurrence may assist with medical and surgical decision-making.

Methods: Data were obtained from 409 patients with Crohn's disease (CD) who had undergone ≥1 ileocolectomies at Penn State Hershey Medical Center. Six single-nucleotide polymorphisms (SNPs) associated with CD were evaluated in these patients: rs2076756, rs2066844, and rs2066845 in *NOD2*, rs4958847 and rs13361189 in *IRGM*, and rs2241880 in *ATG16L1*. Genotype and clinical factors were analyzed to determine associations with time to recurrent ileocolectomy. A subgroup analysis was performed on 241 patients naïve to biologics before initial ileocolectomy to assess the effect of biologic therapy on time to recurrent surgery.

Results: There were 286 patients who underwent a single ileocolectomy, whereas 123 required multiple ileocolectomies. Ileocolonic involvement [hazard ratio (HR) 1.90, 95% confidence interval (CI) 1.21–3.00, $P = 0.006$] and rs2066844 in *NOD2* (HR 1.8, 95% CI 1.17–2.77, $P = 0.007$) were associated with decreased time to surgical recurrence by multivariate analysis. In patients naïve to preoperative biologics, the initiation of postoperative biologics was associated with a 40% decreased incidence of surgical recurrence (HR 0.60, CI 0.39–0.93, $P = 0.02$) over time.

Conclusions: Ileocolonic distribution of disease and the rs2066844 SNP in *NOD2* are associated with shorter time to recurrent ileocolectomy. The initiation of postoperative biologics in naïve patients was associated with a reduced incidence of recurrence over time.

Keywords: Crohn's disease, ileocolectomy, TNF-α antagonists

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Crohn's disease (CD) is an inflammatory disease of the gastrointestinal tract which is most commonly seen in Western countries. The prevalence of CD in North America is as high as 249 per 100,000, and the median age of onset is 30 years.[1] Although the disease can involve any part of the gastrointestinal tract, it most commonly affects the terminal ileum, which is involved in over half of all patients.[2] Despite recent advances in medical therapy, surgery is often required both for medically refractory CD and for complications of the disease, with 50% of patients requiring resection of diseased bowel within 10 years of disease diagnosis.[3] Surgery is not curative however, and 40% to 50% of patients will have recurrence of clinical symptoms within 10 years of initial resection.[3]

The majority of studies evaluating Crohn's recurrence after ileocolectomy have focused on endoscopic or symptomatic clinical recurrence. These studies have identified risk factors affecting earlier recurrence including Montreal disease behavior, early age of onset, and smoking. Interventions such as smoking cessation or addition of immunomodulatory medications have been proposed to decrease or delay recurrence.[4] Most recently, the use of biologic medications such as tumor necrosis factor (TNF)-α antagonists have also been recommended as postoperative management of high-risk patients.[5] Previous studies assessing biologic use are typically associated with shorter follow-up time and therefore are less likely to evaluate surgical recurrence, or the need for recurrent ileocolectomy.

In addition to clinical risk factors, there has been an increase in the investigation of genetic factors that may be associated with disease behavior. There have been several large genome-wide association studies that identified single-nucleotide polymorphisms (SNPs) associated with CD. There are now approximately 150 CD-associated SNPs that suggest multiple pathophysiologic mechanisms that predispose the individual to the development or recurrence of CD.[6] It has been suggested that these SNPs could be used as markers to predict disease severity or related outcomes such as clinical or surgical recurrence.

No long-term study has evaluated both genetic and clinical factors in concert in an attempt to identify a severe phenotype of Crohn's patients that would warrant more aggressive therapy. Therefore, this study evaluated both clinical and selected genetic SNPs to determine which may be associated with time to surgical recurrence after ileocolectomy for CD. As biologic therapy would be most appropriately administered to this higher-risk phenotype, we also assessed the efficacy of biologic therapy in prolonging the surgical interval between sequential ileocolectomies. We hypothesized that both clinical and genetic risk factors are associated with surgical recurrence after ileocolectomy.

METHODS

Patient Cohort

A retrospective review was performed on patients who had been prospectively recruited into the Institutional Review Board (IRB)-approved Colorectal Disease Biobank at the Pennsylvania State University College of Medicine in Hershey, Pennsylvania. All patients were recruited during the 20-year period between July 1998 and July 2018. Review was limited to patients with a diagnosis of CD who had undergone at least 1 ileocolectomy. Patients were excluded if diagnosed with any gastrointestinal cancer or if they underwent total proctocolectomy or total abdominal colectomy for CD. A total of 409 recruited patients with CD requiring ileocolectomy were identified. Ileocolectomy was defined as resection involving a contiguous region of small bowel and colon. This could include the ileocecal valve (initial ileocolectomy) or include the previous ileocolic anastomosis (recurrent ileocolectomy).

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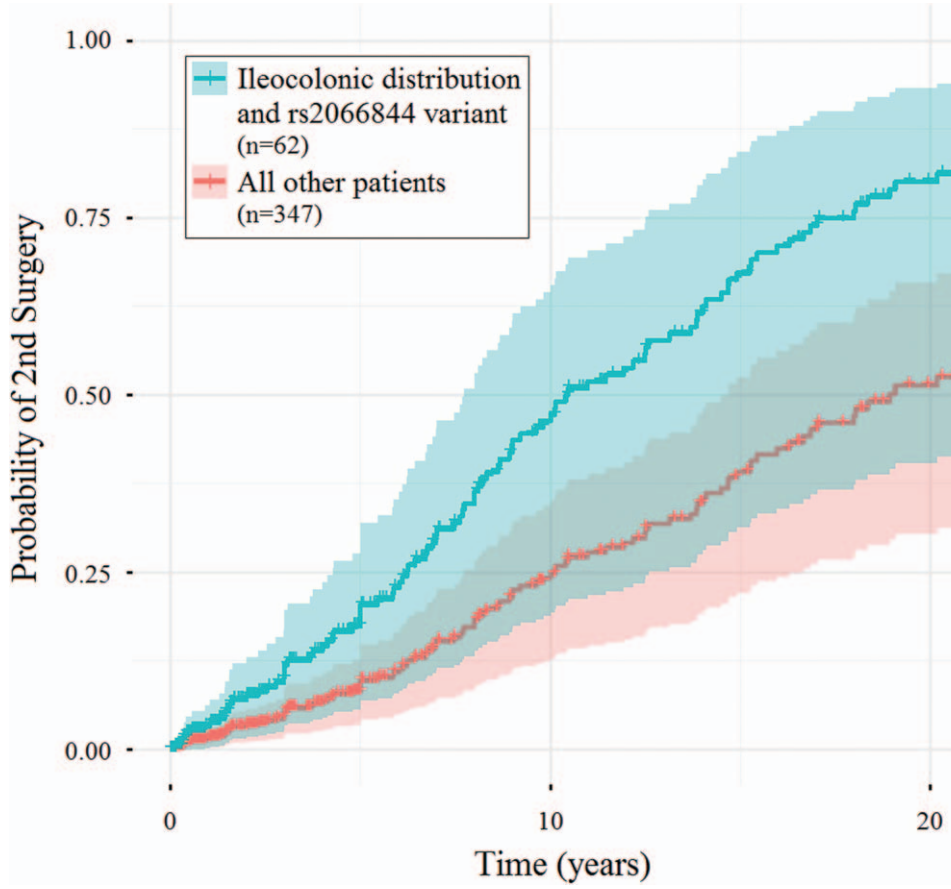

FIGURE 1. Results of the Cox proportional hazards model for time to recurrent ileocolectomy. The survival curves compare the patients with ileocolonic distribution and an rs2066844 variant to all other patients assuming the following fixed values for the covariates: nonsmoking male aged 17 and 40 with penetrating disease, no perianal involvement, and no family history.

Clinical characteristics gathered from the identified patients included sex, race, family history, smoking history, and age at inflammatory bowel disease diagnosis. Montreal classification[7] was used to categorize patients by age of diagnosis (<17 years, 17–40 years, or >40 years), distribution of disease (ileal or ileocolonic), and disease behavior (inflammatory, stricturing, or perforating). Surgical characteristics included number of ileocolectomies, date of each ileocolectomy, and length of bowel resected. Comorbidities gathered were placed in the following categories: psychiatric, cardiac, respiratory, renal, endocrine, and anemia. Medications were documented and included anti-TNF-α agents (infliximab, adalimumab, certolizumab), other biologics (vedolizumab, ustekinumab), immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and 5-aminosalicylic acid derivatives. Finally, the most recent clinic appointment was reviewed to calculate follow-up time from date of diagnosis and date of ileocolectomy.

DNA Samples and Genotyping

All patients included in this study donated whole blood samples using standard ethylenediaminetetraacetic acid collection tubes to be stored in our Colorectal Disease Biobank. DNA was extracted from peripheral blood mononuclear cells using the NucleoSpin Blood L kit (Macherey-Nagel, Bethlehem, PA). DNA concentrations were measured using a NanoDrop 2000 spectrophotometer (Thermo Scientific, Waltham, MA), and working stocks were prepared in 10 mmol/L Tris-HCL. We evaluated 6 SNPs within 3 genes for this study. These were rs2066844, rs2066845, and rs2076756 in NOD2, rs4958847 and rs13361189 in *IRGM*, and rs2241880 in *ATG16L1*. These SNPs were chosen because of their identification in previous short-term studies suggesting an association with increased risk for surgical recurrence.[8–10]

Samples were genotyped using a customized DNA microarray developed by Illumina (Illumina, San Diego, CA) or by TaqMan assay. Our laboratory has previously performed genotyping using the custom microarray run on Illumina's BeadXpress Reader in the Penn State College of Medicine Genome Sciences Facility.[8] For patient samples that had not been previously genotyped by the custom microarray (96/409) a TaqMan assay was used. TaqMan Genotyping Master Mix (Thermo Scientific, Waltham, MA) was combined with Predesigned TaqMan SNP Genotyping Assays (C_11717468_20 for rs2066844, C_11717466_20 for rs2066845, C_15863571_20 for rs2076756, C_1398968_10 for rs4958847, C_31986315_10 for rs13361189, and C_9095577_20 for rs2241880), 10 ng of DNA, and water. Polymerase chain reaction was performed using the ABI QuantStudio12KFlex. Any patient with at least 1 variant allele at a particular SNP was considered to be a variant for that SNP.

Statistical Methods

The statistical analysis was conducted using R (www.r-project.org) and R Markdown (www.rmarkdown.rstudio.com). Univariate analyses were performed using Fisher exact test for categorical variables and Student *t* test to compare means. To account for potential differences in follow-up time, and for multiple variables, time to recurrent ileocolectomy was modeled with a Cox proportional hazards model evaluating both the Crohn's-associated clinical and genetic variables gathered as listed above. The genetic variables

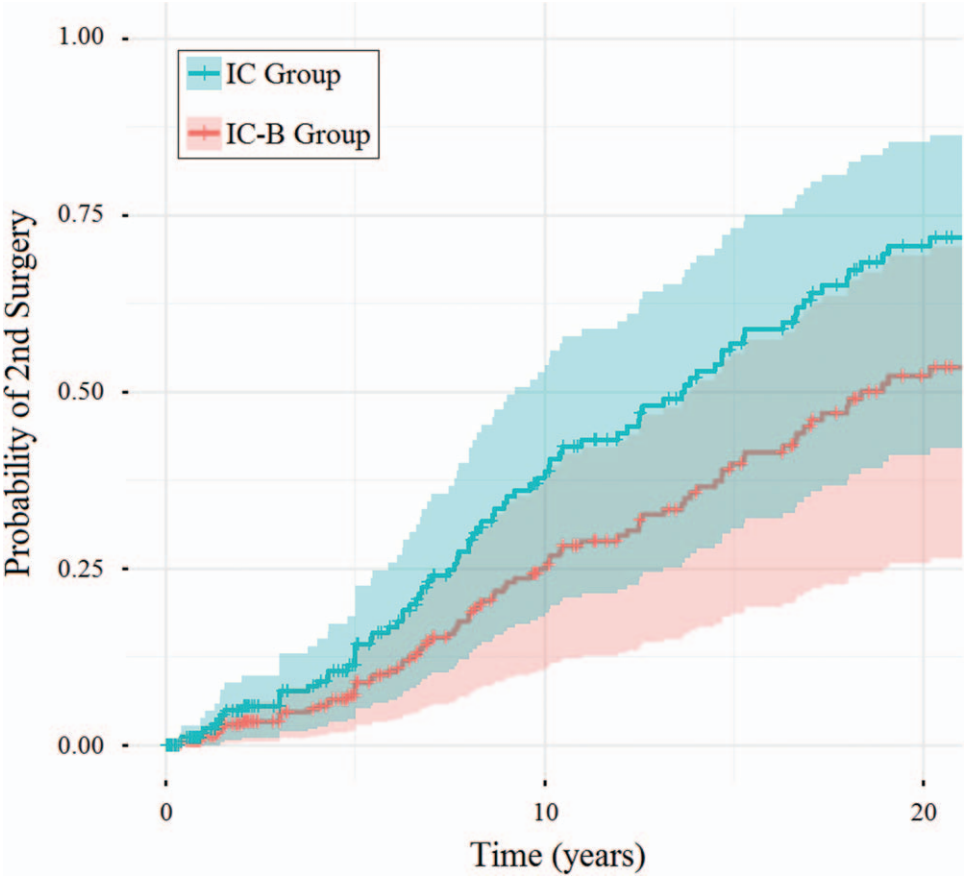

FIGURE 2. Results of the Cox proportional hazards model for time to recurrent ileocolectomy. The survival curves compare the biologic-naïve patients taking postoperative biologics to those not taking postoperative biologics assuming the following fixed values for the covariates: nonsmoking male aged 17 and 40 with penetrating disease, no perianal involvement, and no family history.

(SNPs) in the Cox model were analyzed following an additive genetic association model. Patients naïve to biologics before initial ileocolectomy (n = 241) were identified. From this group, 106 patients who received postoperative biologics were compared to 135 who did not. Another multivariate Cox proportional hazards model with covariate adjustment analyzed the effect of biologics on time to recurrent ileocolecomy in patients receiving or not receiving postoperative biologic therapy. Results of the Cox models are displayed in Figures 1 and 2 using the ggsurvplot function in the R package survminer.[11]

RESULTS

Ileocolonic Distribution and rs2066844 are Associated With a Shortened Time to Surgical Recurrence

Of all 409 patients who underwent ileocolectomy, the mean age of diagnosis was 25.8 and the mean time from diagnosis to initial surgery was 7.1 years. The mean follow-up time was 9.2 years after initial ileocolectomy. The overall characteristics of all 409 patients are included in Table 1. Of the 409 patients, 286 (70%) underwent a single ileocolectomy, whereas 123 (30%) underwent multiple ileocolectomies. The average number of ileocolectomies per patient was 1.4 (range 1–5). In the 123 patients with multiple ileocolectomies, recurrent surgery was performed for obstruction from stricture in 84 patients (68%), fistula in 19 patients (15%), symptoms refractory to maximal medical management in 11 patients (9%), and perforation and/or abscess in 9 patients (7%). A comparison of patients with a single ileocolectomy and patients with multiple ileocolectomies is shown in Table 2. There were significantly more current or ex-smokers ($P < 0.001$), more use of other biologics ($P = 0.02$), and more ileocolonic distribution of disease ($P = 0.008$) in the multiple ileocolectomy group.

Multivariate analysis showed that ileocolonic distribution of disease [hazad ratio (HR) 1.90, confidence interval (CI) 1.21–3.00, $P = 0.006$) and the presence of rs2066844 in *NOD2* (HR 1.80, CI 1.17–2.77, $P = 0.007$) were significantly associated with risk of earlier recurrent ileocolectomy (Table 3). There was no significant association between time to recurrent ileocolectomy and smoking status at initial surgery. When comparing the patients with both ileocolonic distribution and rs2066844 ($n = 62$) to all other patients ($n = 347$), the first group had a nearly 2-fold higher probability of recurrence over time (48% vs 25% at 10 years, Fig. 1).

Postoperative Biologics in Naïve Patients Increase Time to Surgical Recurrence

To evaluate the effect of postoperative use of biologics, a cohort of 241 patients was identified that were naïve to biologic medications at the time of their initial ileocolectomy. These patients were further separated into those receiving postoperative biologics (IC-B) group (n = 106), and those that did not receive biologics after ileocolectomy (IC) (n = 135). All 106 patients in the biologic group were initially placed on anti-TNF-α medications (infliximab and/or adalimumab). Nineteen patients in the IC-B group (18%) were subsequently switched to other biologics such as vedolizumab or ustekinumab. A comparison of the 2 groups showed 34 patients

TABLE 1. Characteristics of all 409 Patients Included in Study

Characteristic	*n* (%)
Clinical characteristics	
Sex	
Male	185 (45%)
Female	224 (55%)
Age of diagnosis	
Mean ± standard error	25.8 +/− 0.6
Median (IQR)	23.6 (18–31.7)
Family history of IBD	
Yes	155 (38%)
No	253 (62%)
Smoking at initial surgery	
Current	69 (17%)
Ex-smoker	127 (31%)
Never smoked	213 (52%)
Medications	
Anti-TNFs	288 (70%)
Other biologics	82 (20%)
Immunomodulators	198 (48%)
5-ASA	257 (63%)
Montreal criteria	
Age of diagnosis	
A1: <17	85 (21%)
A2: 17–40	281 (69%)
A3: >40	43 (10%)
Location	
L1: ileal	132 (32%)
L3: ileocolonic	277 (68%)
Behaviour	
B1: inflammatory	24 (6%)
B2: structuring	144 (35%)
B3: penetrating	241 (59%)
Perianal involvement	
Yes	130 (32%)
No	279 (68%)
Comorbidities	
Psychiatric	115 (28%)
Cardiac	100 (242%)
Respiratory	74 (18%)
Renal	60 (15%)
Endocrine (diabetes, thyroid)	32 (8%)
Anemia	158 (39%)

5-ASA, aminosalicylic acid; IBD, inflammatory bowel disease; IQR, interquartile range. Medications refer to therapy at any point during the patient's disease.

TABLE 2. Comparison of Patients With Single Ileocolectomy Versus Multiple Ileocolectomies

	Single ileocolectomy (n = 286)	Multiple ileocolectomies (n = 123)	*P*
Sex			0.39
Male	125 (44%)	60 (49%)	
Female	161 (56%)	63 (51%)	
Family history of IBD			0.44
Yes	112 (39%)	43 (35%)	
No	174 (61%)	80 (65%)	
Smoking at initial surgery			<0.001*
Current	43 (15%)	26 (21%)	
Ex-smoker	73 (26%)	54 (44%)	
Never smoked	170 (59%)	43 (35%)	
Medications			
Anti-TNFs	203 (71%)	85 (69%)	0.72
Other biologics	48 (17%)	34 (28%)	0.02*
Immunomodulators	131 (46%)	67 (54%)	0.13
5-ASA	182 (64%)	75 (61%)	0.66
Age at diagnosis			0.77
A1: <17	60 (21%)	25 (20%)	
A2: 17–40	194 (68%)	87 (71%)	
A3: >40	32 (11%)	11 (9%)	
Location			0.008*
L1: ileal	104 (36%)	28 (23%)	
L3: ileocolonic	182 (64%)	95 (77%)	
Behavior			0.098
B1: inflammatory	21 (7%)	3 (2%)	
B2: stricturing	95 (33%)	49 (40%)	
B3: penetrating	170 (60%)	71 (58%)	
Perianal involvement			0.082
Yes	83 (29%)	47 (38%)	
No	203 (71%)	76 (62%)	
Initial resection length, cm			0.98
Mean ± standard error	30.9 +/− 1.0	30.8 +/− 2.3	
ATG16L1			0.52
rs2241880	177 (62%)	72 (59%)	
IRGM			
rs4958847	70 (24%)	22 (18%)	0.14
rs13361189	73 (26%)	25 (20%)	0.26
NOD2			
rs2066844	64 (22%)	26 (21%)	0.78
rs2066845	25 (9%)	6 (5%)	0.18
rs2076756	178 (62%)	75 (61%)	0.81

5-ASA, aminosalicylic acid.
*Represents significant *P* value ($P < 0.05$).

(32.1%) in the IC-B group required recurrent surgery after a median follow-up time of 9.8 years, whereas 65 (48.1%) in the IC group required surgery after median follow-up of 10.8 years ($P = 0.017$). There were no significant differences in sex, family history, smoking status, age, disease distribution, disease behavior, or follow-up time (Table 4). Multivariate analysis showed that postoperative biologic administration was statistically significantly associated with increased time to recurrence (HR 0.60, CI 0.39–0.93, $P = 0.02$, Table 5). When the probability of second surgery over time in both IC-B and IC group was plotted on a time to event curve, the IC-B group had a lower probability of second surgery over time (Fig. 2).

DISCUSSION

Owing to the wide spectrum of disease severity in CD, there would be great benefit in identifying specific factors that could predict the future course of disease in each individual patient. Although many patients require resection, it is difficult to determine which will have symptomatic disease recurrence, and more specifically, which will require recurrent surgery. Several studies have attempted to identify clinical and/or genetic factors associated with recurrence, but most have not focused on surgical recurrence, had short follow-up time, or had a relatively small patient sample.[12–15] Our present study included 409 patients and had a mean follow-up time of 9.2 years after initial ileocolectomy, making it the largest and longest study on surgical CD recurrence after ileocolectomy to date in the literature. When controlling for differences in follow-up time between individual patients, we have identified both ileocolonic distribution of disease and the rs2066844 SNP in the *NOD2* gene as risk factors for decreased time to recurrent ileocolectomy. We have also confirmed that postoperative biologic use delays the need for recurrent ileocolectomy in biologically naïve patients.

Evaluation of all 409 patients showed that ileocolonic distribution (as opposed to ileal distribution alone) was the only clinical factor associated with shorter time to surgical recurrence. According to the Montreal classification and previous Vienna classification, ileal distribution is involvement of the terminal ileum with or without cecal involvement, whereas ileocolonic involves both terminal ileum

TABLE 3. Factors Associated With Time to Recurrent Ileocolectomy

	HR	95% CI	P
Biologic use	0.78	0.53–1.16	0.22
Male	1.26	0.87–1.82	0.23
Family history	0.72	0.49–1.07	0.11
Smoking at initial surgery	1.12	0.69–1.80	0.65
Montreal age at diagnosis			
A1: <17	Ref	—	—
A2: 17–40	0.92	0.58–1.46	0.72
A3: >40	1.26	0.58–2.73	0.56
Montreal location			
L1: ileal	Ref.	—	—
L3: ileocolonic	1.90	1.21–3.00	0.006*
Montreal behavior			
B1: inflammatory	Ref.	—	—
B2: stricturing	2.88	0.87–9.46	0.08
B3: Penetrating		0.72–7.77	0.16
Perianal disease	1.36	0.92–2.00	0.12
ATG16L1			
0.92	0.92	0.69–1.22	0.56
IRGM			
rs4958847	0.88	0.48–1.61	0.68
rs13361189	1.36	0.77–2.42	0.29
NOD2			
rs2066844	1.80	1.17–2.77	0.007*
rs2066845	0.52	0.22–1.22	0.14
rs2076756	0.73	0.53–1.01	0.06

*Represents significant *P* value ($P < 0.05$)

and any location between the ascending colon and the rectum.[7,16] In our patients, ileocolonic distribution was more common than ileal, which is similar to the overall CD population.[17] Ileocolonic distribution has previously been shown to be associated with a higher risk of surgical resection[18] and a higher risk of clinical recurrence.[12] However, neither of these studies followed patients after initial surgery to identify their possible effect on surgical recurrence.

TABLE 4. Comparison of IC-B Group to IC Group

	IC-B Group (n = 106)	IC Group (n = 135)	P
Median years follow-up	9.8	10.8	0.48
Sex			0.09
Male	56 (53%)	56 (41%)	
Female	50 (47%)	79 (59%)	
Family history of IBD			0.19
Yes	45 (42%)	45 (33%)	
No	61 (58%)	90 (67%)	
Smoking at initial surgery			1
Yes	57 (54%)	72 (53%)	
No	49 (46%)	63 (47%)	
Surgical recurrence	34 (32%)	65 (48%)	0.017*
Post-op immunomodulator use			0.06
Yes	50 (47%)	47 (35%)	
No	56 (53%)	88 (65%)	
Montreal age at diagnosis			0.10
A1: <17	26 (24%)	22 (16%)	
A2: 17–40	74 (70%)	97 (72%)	
A3: >40	6 (6%)	16 (12%)	
Montreal location			0.41
L1: ileal	36 (34%)	38 (28%)	
L3: ileocolonic	70 (66%)	97 (72%)	
Montreal behavior			0.37
B1: inflammatory	8 (8%)	8 (6%)	
B2: stricturing	31 (29%)	51 (38%)	
B3: penetrating	67 (63%)	76 (56%)	

*Represents significant *P* value ($P < 0.05$).

TABLE 5. Factors Associated With Recurrence in Patients Naïve to Biologics at Initial Ileocolectomy

	HR	95% CI	P
Postoperative biologics	0.60	0.39–0.93	0.02*
Male	1.10	0.44–1.65	0.66
Family history	0.68	0.44–1.07	0.09
Smoking at initial surgery	1.08	0.70–1.67	0.73
Montreal age at diagnosis			
A1: <17	Ref.	—	—
A2: 17–40	0.83	0.50–1.40	0.50
A3: >40	0.96	0.39–2.37	0.93
Montreal location			
L1: ileal	Ref.	—	—
L3: ileocolonic	1.59	0.98–2.58	0.06
Montreal behavior			
B1: inflammatory	Ref.	—	—
B2: stricturing	2.27	0.69–7.42	0.18
B3: penetrating	1.75	0.53–5.73	0.36
Perianal disease	1.28	0.83–1.97	0.26

*Represents significant *P* value ($P < 0.05$).

There have only been a few studies attempting to associate genetics with CD recurrence. A study in 2004 of 180 patients with CD found that *NOD2* mutations (including rs2066844) were associated with more frequent recurrent ileocolectomy, although follow-up times after initial ileocolectomy were not reported.[13] The association between *NOD2* variants and surgical recurrence has been proposed to be related to an increase in stricturing disease, the most common indication for ileocolectomy.[10] There are several studies that have examined the association between *NOD2* mutations and more aggressive phenotypes of CD. A recently proposed surgical risk stratification model identifies the rs2066844 SNP in *NOD2* as one of several factors associated with the need for surgery in stricturing CD.[19] A meta-analysis of 49 studies found any NOD2 mutation was associated with a 58% increased risk of any surgery and 8% increased risk of complicated CD.[20] Association of other genes with Crohn's severity is less clear. One of our own previous studies in a smaller group of 66 patients found an association between the *IRGM* SNP rs4958847 and more frequent surgery in CD.[8] However, this was not confirmed in this present larger study, discounting the role of *IRGM* variants in surgical recurrence in ileocolonic disease. The cause of this difference is unclear, but may relate to the use of biologics, which was not evaluated in the earlier study, with shorter follow-up and a smaller study group. Prospective studies evaluating SNP associations with surgical recurrence would be most compelling, but would require several years of follow-up. The present relatively large study further reinforces these previous reports that suggest allele variants in *NOD2* appear to identify patients with a more aggressive clinical course in general and the need for surgical intervention more specifically.

Although our initial analysis did not show an association between overall anti-TNF-α use and surgical recurrence, we performed further analysis on the 241 patients who had not received biologics before initial ileocolectomy to determine whether there was an effect on surgical recurrence in biologically naove patients. Both the American College of Gastroenterology and European Crohn's and Colitis Organization recommend starting anti-TNF-α medications after surgery to prevent recurrence in high-risk patients (defined by young age, ileal/ileocolonic involvement, and/or penetrating/stenosing disease).[5,21] These recommendations are based on limited evidence from few prospective studies, most of which had small

sample sizes. The largest study evaluated 297 patients randomized to infliximab or placebo.[22] That study showed decreased endoscopic recurrence in the infliximab group at 76 weeks after initial ileocolectomy, but there was no difference in clinical recurrence, and surgical recurrence was not assessed.[22] The largest study to date evaluating the effect of postoperative biologics on surgical recurrence was a relatively small sex and age-matched retrospective study comparing 50 patients on infliximab postoperatively to 50 patients on placebo. In that study, surgical recurrence was a remarkably high 68% in the control group versus only 6% patients in the treated group.[23] The study had a very limited median follow-up period of 51 months in the control group and 36 months in the treatment group, and was done in an Asian population. The pathophysiology of CD in this racial demographic may be unique as evidenced by the relative absence of *NOD2* mutations. Although our subgroup analysis was also retrospective, it was in predominantly whites and had a median followup time of nearly 10 years. Our finding of nearly a 50% decrease over controls in surgical recurrence (32% vs 48%) in anti-TNF-treated patients by 10 years adds evidence for the use of biologic medications after ileocolectomy in high-risk patients.

There were some limitations to this study. Its retrospective nature allowed for possible preselection bias in the timing of surgery. However, the genetic status of the patients was unknown at the time of surgery, and therefore did not suffer from this limitation. Not all ileocolectomies were performed at our institution, so clinical and endoscopic correlates were not available for all surgeries, and therefore could not be included. Additionally, as the use of antibiotics and corticosteroids is variable, the effect of these medications on surgical recurrence could not be assessed. Finally, although this study is the longest and largest study on surgical recurrence to date, it is still too small to evaluate subgroup populations and determine the effect of biologics in variants at each genotype. Larger, broader based prospective studies could aid in these specific evaluations.

In conclusion, our evaluation of 409 patients with CD who had undergone ileocolectomy found that ileocolonic disease distribution and the SNP rs2066844 in the *NOD2* gene were associated with decreased time to surgical recurrence (HR 0.60, CI 0.39–0.93, $P = 0.02$). In patients who were naïve to biologic medications before initial ileocolectomy, postoperative biologics were associated with a statistically significant extended time to surgical recurrence. This study suggests assessing *NOD2* status may assist in surgical and medical decision-making by identifying patients at high risk for surgical recurrence after ileocolectomy.

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