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What are the predictors for recurrence of Crohn's disease after surgery?

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Abstract

Surgical resection is an unavoidable part of the current treatment options for Crohn's disease (CD), and more than half of patients develop recurrence. The aim of this study was to investigate the predictors for recurrence in the long-term follow-up of CD patients after surgery.

Medical records of consecutive CD patients who were operated on between January 2003 and January 2015 were retrospectively analyzed. Data including demographic and clinical characteristics of the patients were recorded. Recurrence was evaluated based on the Crohn's Disease Activity Index or endoscopic findings.

The majority of 112 patients were males (n = 64, 57.1%), and 61 (54.4%) of them were active smokers. The median follow-up was 113 (range: 61–197) months. Disease recurrence occurred in 16 (14.3%) patients at a median of 13.5 months. The endoscopic recurrence rate was 8% (n = 9) at 1 year, 12.5% (n = 14) at 5 years, and 13.4% (n = 15) at 10 years. One (0.9%) patient underwent colonoscopic balloon dilatation at 1 year, and 7 (6.3%) patients needed re-resection at a median of 36 months. The age of the patient at the time of diagnosis ($P = .033$), penetrating disease behavior ($P = .011$), intra-abdominal abscess ($P = 0.040$) and, concomitant fistula and intra-abdominal abscess ($P = .017$) were associated with disease recurrence.

Our study results suggest that the patients' age at the time of diagnosis, penetrating disease, intra-abdominal abscess, and concomitant fistula and abscess are the risk factors for CD recurrence after surgery.

Abbreviations: ACG = American College of Gastroenterologists, CD = Crohn's disease, CDAI = Crohn's Disease Activity Index, ECCO = European Crohn's and Colitis Organization, POR = postoperative recurrence, SD = standard deviation, TNF = tumor necrosis factor.

Keywords: Crohn's disease, recurrence, surgery

1. Introduction

Crohn's disease (CD) is a chronic inflammatory disease that can involve any part of the gastrointestinal system. The nature of the disease course is unpredictable and, despite advanced medical therapeutic options, its recurrence still remains high. Although medical treatment is the first-line choice of treatment and surgery is reserved for complications, both, indeed, are palliative modalities. The main goal of treatment is to resolve symptoms. Recently, in the early settings of disease course, timely surgery has been adopted as a promising treatment option. Unfortunately, up to 90% of CD patients require at least 1 surgical intervention during the course of the disease.[1] Postoperative recurrence (POR) of CD is not uncommon. More than 80% of patients develop and suffer from disease recurrence, and nearly half of them require further interventions. The high rates of disease recurrence and complications necessitate close follow-up and a mandatory multidisciplinary approach.

As our understanding of the underlying mechanisms of CD has improved, novel drugs have yielded promising results in clinical trials. Novel biological agents may offer treatment options even in patients refractory to antitumor necrosis factor-alpha (anti-TNF-α).[2] In addition, recently approved monoclonal antibodies such as natalizumab,[3] vedolizumab,[4] and ustekinumab[5] show promise in the treatment of refractory CD. To avoid long-term bowel damage and disability, a treat-to-target strategy has been also advocated in recent years. The basic principle of this strategy is to adjust treatment based on the regular evaluation of disease activity.[6] Despite an increasing number of treatment options and treatment paradigms, POR is still a major problem in patients with CD.

Identification of possible risk factors associated with POR of CD is valuable to select high-risk patients for recurrence and to

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tailor the most optimal medical treatment after the initial surgery. Although several factors have been described related to disease recurrence to date, the results vary across the studies and communities in which the study was conducted.[7–12] In the present study, we aimed to investigate the possible predictors for recurrence in the long-term follow-up of CD patients after surgery.

2. Materials and methods

2.1. Study design and study population

This single-center, retrospective study was conducted at Istanbul University, Department of General Surgery between January 2003 and January 2015. Medical records of consecutive CD patients who underwent surgery were retrospectively reviewed. Of these patients, only who were followed in our gastroenterology and/or general surgery outpatient clinics were included in the study. The study flow chart is shown in Figure 1. Data including demographic data, smoking status, disease behavior and location, extraluminal disease status, medications used, biological agent usage, corticosteroid usage and duration, immunosuppressive medication type and duration, prior surgery, type of surgery selected, type of anastomosis, stoma creation, and recurrence were retrieved from the patient charts. Written informed consent was obtained from each patient. The study protocol was approved by the İstanbul University Ethics Committee with decision number 04/2021. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Surgical decision

The decision to pursue surgery was made based on the multidisciplinary team consisting of the general surgery, gastroenterology, and radiology departments on a weekly basis. All surgeries were performed by a single colorectal surgical team. The patients included had an intestinal resection and/or a stricturoplasty. The anastomosis was created with a stapler or handsewn, according to the surgeon's preference.

2.3. Medication use

Preoperative medical treatment was defined as the steroid use, until the day of surgery; azathioprine, 6-mercaptopurine, or methotrexate within 4 weeks of surgery; and anti-TNF-α treatment within 8 weeks of surgery.

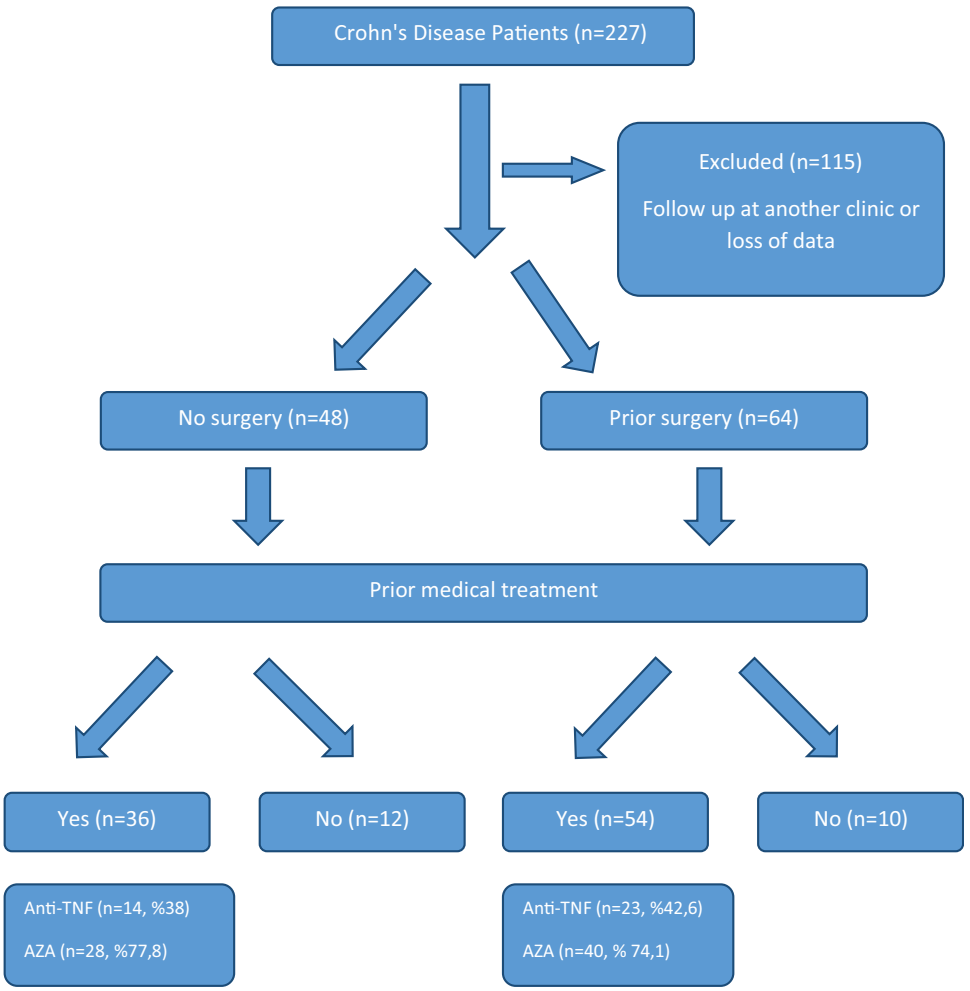

Figure 1. Study flow chart.

2.4. Follow-up

All patients were followed at the general surgery and gastroenterology outpatient clinics at 1 and 6 months following surgery. A control colonoscopy was performed in the first postoperative year unless required earlier.

2.5. Assessment of potential variables

Several variables were evaluated as potential risk factors for POR. The patient-related risk factors included sex, age (≥40 vs < 40 years), age at the time of operation (A1: ≤16, A2: 17–40, and A3 > 40 years), smoking habit, serum hemoglobin, and albumin level. The disease location (ileal [L1], colonic [L2], ileocolonic [L3], isolated upper disease [L4]), disease behavior (non-penetrating/non-stricturing [B1], stricturing [B2], penetrating [B3]), presence of perianal disease, disease duration, age at the time of disease onset, extraluminal disease, intraperitoneal abscess, fistula other than a perianal disease, coexisting fistula and abscess, and percutaneous drainage of the abscess were the disease-related risk factors. The medical treatment-related risk factors included the use of medical treatment before surgery, medical treatment duration, steroid use, biological agent use, multiple drug use, need for replacement in medical treatment before surgery, use of total parenteral nutrition before surgery, and preoperative antibiotic use. The operative risk factors were defined as the surgical approach (laparoscopic vs open), surgery type (elective vs emergent), stoma formation, presence and type of anastomosis (handsewn vs stapled).

2.6. Disease recurrence

Recurrence was defined as symptomatic CD requiring further medical or surgical intervention and/or the appearance of objective signs of active disease in a colonoscopy or colonoscopic biopsy. Clinical recurrence was defined using the Crohn's Disease Activity Index (CDAI) and was evaluated at each visit starting from the sixth month after surgery. It consists of 8 items including the number of liquid stools, the extent of abdominal pain, general well-being, the occurrence of extraintestinal symptoms, need for anti-diarrheal drugs, and presence of abdominal masses, hematocrit, and body weight. A CDAI score of > 150 indicates disease recurrence.[13] Endoscopic recurrence refers to visible inflammation and/or ulceration observed during a planned or indicated postoperative colonoscopy according to the Rutgeerts score.[8] Surgical recurrence was defined as the need for a repeated surgical intervention.

2.7. Statistical analysis

Using a Microsoft Excel database (Microsoft Corp, Redmond, WA), the data were imported, and statistical analysis was performed using the SPSS for Windows version 22.0 software (IBM Corp, Armonk, NY). Descriptive data were expressed in mean ± standard deviation, median (min-max), or number and frequency, where applicable. Categorical variables were analyzed using the χ^2 or Fisher exact test. Univariate regression analysis was performed to identify risk factors of disease recurrence and the significant variables were included in the multivariate regression analysis. A P value of < .05 was considered statistically significant.

3. Results

Of a total of 112 patients, 64 (57.1%) were males, and 61 (54.4%) were smokers. The mean age at the time of surgery was 38 ± 12.3 (range: 19–80) years and the mean age at the time of diagnosis was 30.8 ± 11.4 (range: 7–63) years. Ileocolonic disease (n = 85, 75.9%) was the most common localization. Fifty-one (45.5%) patients had a penetrating disease, while a stricturing disease was observed in 44 (39.3%) patients. Demographic and clinical characteristics of the patients and recurrence-associated factors are shown in Table 1.

Of the patients, 90 (80.4%) were receiving medical treatment for a mean of 65.5 ± 56.4 (range: 12–324) months, and 79 (70.5%) were using more than 1 medication before surgery (Table 2). Nearly 90% of patients underwent elective surgery, while open surgery (n = 93, 83%) and ileocolonic resection were the most frequent types of surgery (Table 3). Fourteen patients (n = 14, 12.5%) needed an emergency surgery. Laparoscopy was performed in 19 (17%) patients with a 15.8% (n = 3) conversion rate to open surgery. A stapled anastomosis (n = 74, 66.1%) was more common than a handsewn technique (n = 11, 12.9%), and 27 (24.1%) patients had no anastomosis.

All patients with endoscopic recurrence had clinical recurrence. Endoscopic recurrence occurred in 16 (14.3%) patients, and the mean time to recurrence was 40.8 ± 13.5 (range: 8–240) months. The endoscopic recurrence rate was 8% (n = 9) at 1 year, 12.5% (n = 14) at 5 years, 13.4% (n = 15) at 10 years, 14.3% (n = 16) at 17 years. The surgical recurrence rate was 1.8% (n = 2) at 1 year, 5.4% (n = 6) at 10 years, and 7.1% (n = 8) at 17 years.

Colonoscopic balloon dilatation was performed in 1 patient (0.9%) in the first postoperative year. Eight (7.1%) patients needed reresection at a median of 36 (range: 12–240) months. The remaining 7 (6.3%) patients were followed with only medical treatment. The patients who experienced recurrence had a longer disease duration (P = .322) and a longer length of medical treatment (P = .491), although these findings did not reach statistical significance. Sex (P = .242), medical treatment prior to surgery (P = .145), steroid use (P = .681), biological agent use (P = .453), multiple drug use (P = .310), hemoglobin level (P = .453), albumin level (P = .466), age at the time of diagnosis (≤16, 17–40, and > 40 years; P = .098), and smoking habit (P = .699) were similar in patients with and without recurrence, indicating no statistically significant difference. Analysis of the type of medication used also revealed no statistically significant effect on disease recurrence; however, preoperative thiopurine use was found to decrease POR, although not statistically significant (P = .069) (Table 4).

Independent risk factors associated with surgical recurrence were analyzed. Univariate analysis revealed the age at diagnosis (P = .033), penetrating disease behavior (P = .011), intra-abdominal abscess (P = .040), and concomitant fistula and intra-abdominal abscess (P = .017) were associated with recurrence. However, multivariate analysis revealed no independent risk factor associated with surgical recurrence (Table 5).

4. Discussion

The incidence and prevalence of CD have been increasing worldwide every year, and most patients require ≥1 surgical intervention during the disease course. Recurrence after surgery is a characteristic of CD. The rate of postoperative surgical recurrence has been reported to be 32% at 5 years and 44% at 10 years, whereas the endoscopic recurrence rate is even higher, up to 90%, at 12 months, particularly if left untreated with postoperative medication alone.[14] Several risk factors associated with recurrence have been investigated so far; however, the

Table 1

Demographic and clinical characteristics of the patients and recurrence-associated factors.

Variable	Total		Recurrence		Remission		*P*	OR
	n	%	n	%	n	%		
Sex							.242	1.879
Female	48	42.9	9	18.8	39	81.2		
Male	64	57.1	7	10.9	57	89.1		
Age, y							.477	0.664
A1 (≤16)	–	–	–	–	–	–		
A2 (17–40)	68	60.7	11	16.2	57	83.8		
A3 (>40)	44	39.3	5	11.4	39	88.6		
Mean age, y	38 ± 12. 3 (19–80)		37.4 ± 8.6		38.9 ± 12.7		.648	
Age at diagnosis, years							.098	
A1 (≤16)	7	6.3	1	14.3	6	85.7		
A2 (17–40)	83	74.1	15	18.1	68	81.9		
A3 (>40)	22	19.6	0	0	22	100		
Age at diagnosis							.033	0.822
≤40	90	80.4	16	17.8	74	82.2		
>40	22	19.6	0	0	22	100		
Mean age at diagnosis, y	30.8 ± 11.4 (7–63)		28.3 ± 5.6		31.3 ± 12		.328	
Disease location							.316	
L1 (ileal)	10	8.9	3	30	7	70		
L2 (colonic)	8	7.2	1	12.5	7	87.5		
L3 (ileocolonic)	85	75.9	12	14.1	73	85.9		
L4 (isolated upper disease)	9	8	0	0	9	100		
Disease location							.184	0.379
L1 (ileal)	10	9.7	3	30	7	70		
L2 (colonic) +L3 (ileocolonic)	93	90.3	13	14	80	86		
Disease behavior							.012	
B1 (nonpenetrating/nonstricturing)	17	15.2	3	17.6	14	82.4		
B2 (stricturing)	44	39.3	1	2.3	43	97.7		
B3 (penetrating)	51	45.5	12	23.5	39	76.5		
Disease behavior							.011	4.385
B1 + B2	61	54.5	4	6.6	57	93.4		
B3 (penetrating)	51	45.5	12	2.5	39	76.5		
Perianal disease							.933	1.050
Yes	34	30.4	5	14.7	29	85.3		
No	78	69.6	11	14.1	67	85.9		
Smoking							.699	0.811
Current smoker	61	54.5	8	13.1	53	86.9		
Nonsmoker or ex-smoker	48	42.8	8	16.7	40	83.3		
No data	3	2.7						
Disease duration, mo	95.9 ± 64.7 (6–324)		110.6 ± 63 (24–228)		93.4 ± 64.1 (6–324)		.322	
Medical treatment duration before surgery, mo	65.5 ± 56.4 (12–324)		75.1 ± 51.5 (12–324)		63.8 ± 57.4 (12–240)		.491	
Anti-TNF medication use, mo (37 patients)	6.7 ± 5. 9 (6–30)		11.5 ± 12.5		6.1 ± 4.6		.084	
Steroid use, months (42 patients, 6 with no data)	11.9 ± 19.5 (6–108)		23.3 ± 37.5		9.3 ± 11.8		.046	
Prior medical treatment							.145	4.200
Yes	90	80.419.6	15	16.7	75	83.3		
No	22		1	4.5	21	95.5		
Change in medical treatment							.802	1.158
Yes	68	60.7	11	16.2	57	83.8		
No	35	31.2	5	14.3	30	85.7		
No data	9	8.1						
Use of multiple drugs							.310	1.970
Yes	79	70.5	13	16.5	66	83.5		
No	33	29.5	3	9.1	30	90.9		
Steroid use							.681	1.250
Yes	48	42.8	8	16.7	40	83.3		
No	58	51.8	8	13.8	50	86.2		
No data	6	5.4						
Anti-TNF medication use							.453	0.628
Yes	37	33	4	10.8	33	89.2		
No	68	60.7	11	16.2	57	83,8		
No data	7	6.25						
Prior abdominal surgery							.533	0.714

(*continued*)

Table 1

(continued).

Variable	Total		Recurrence		Remission		*P*	OR
	n	%	n	%	n	%		
Yes	64	57.1	8	12.5	56	87.5		
No	48	42.9	8	16.7	40	83.3		
Extra-luminal involvement							.923	0.935
Yes	22	19.6	3	13.6	19	86.4		
No	90	80.4	13	14.4	77	85.6		
Intra-abdominal abscess							.040	3.039
Yes	44	39.3	10	22.7	34	77.3		
No	68	60.7	6	8.8	62	91.2		
Fistula							.183	2.050
Yes	46	41.1	9	19.6	37	80.4		
No	66	58.9	7	10.6	59	89.4		
Intra-abdominal abscess and fistula							.017	3.571
Yes	29	25.9	8	27.6	21	72.4		
No	83	74.1	8	9.6	75	90.4		
Percutaneous drainage							.202	1.630
Yes	23	52.3	7	30.4	16	69.6		
No	21	47.7	3	10.1	18	89.9		
Preoperative antibiotics							.533	1.526
Yes	84	75	13	15.5	71	84. 5		
No	28	25	3	10.7	25	89.3		
Surgical approach							.607	0.664
Laparoscopic	19	17	2	10.5	17	89.5		
Open	93	83	14	15.1	79	84.9		
Surgery type							1.000	1.000
Emergent	14	12.5	2	14.3	12	85.7		
Elective	98	87.5	14	14.3	84	85.7		
Anastomosis							.471	0.654
Yes	85	75.9	11	12.9	74	87.1		
No	27	24.1	5	18.5	22	81.5		
Anastomosis type							.683	1.563
Handsewn	11	12.9	1	9.1	10	90.9		
Stapled	74	87.1	10	13.5	64	86.5		
Anastomosis structure							.382	
End-to-end	2	2.4	1	50	1	50		
End-to-side	2	2.4	0	0	2	100		
End-to-end functional	81	95.2	10	12.3	71	87.7		
Stoma formation							.145	0.238
Yes	22	19.6	1	4.5	21	95.5		
No	90	80.4	15	16.7	75	83.3		
Complication							.241	0.406
Yes	27	24.1	2	7.4	25	92.683.5		
No	85	75.9	14	16.5	71			

Data are given in mean ± standard deviation (SD) or number and frequency, unless otherwise stated.
OR = odds ratio, TNF = tumor necrosis factor.

Table 2

Medical treatment.

	Before surgery		After surgery	
	n	%	n	%
5-aminosalicylic acid	82	73.2	47	42
Thiopurine	68	60.7	66	58.9
Steroid	52	46.4	6	5.4
Anti-TNF medication	37	33	24	23.5
Infliximab	35	31.3	15	13.4
Adalimumab	6	5.4	9	8.1
Tacrolimus	1	0.9	–	
No treatment	22	19.6	21	18.8

Data are given in mean ± standard deviation (SD), unless otherwise stated.
TNF = tumor necrosis factor.

statistical relevance of these factors differs across the studies and communities.[15,16] The present study is a report of clinical characteristics and risk factors for recurrence of surgical intervention among CD patients in a single institution over a 17-year follow-up. The results of the univariate analysis showed that the age younger than 40 years at the time of diagnosis, having penetrating disease, presence of an intra-abdominal abscess, and presence of concomitant intra-abdominal abscesses and fistulas were significantly associated with recurrence. However, no significant risk factor of disease recurrence after surgery was found in the multivariate analysis, probably due to the fact that the data of the patients followed in our clinic only were included, the study had relatively a long follow-up period, and there were changes in the treatment of CD during the study period. In addition, the inability to identify the possible risk factors can be

Table 3

Surgical procedures.

Surgical procedure	n	%
IC	95	84.8
Colon resection (right-left hemicolectomy/anterior or segmental resection/total-subtotal colectomy)	7	6.3
Perineal abscess drainage	5	4.5
Jejunal resection	3	0.9
IC + jejunal resection	1	0.9
Colon + jejunal resection	1	0.9
Proctectomy	1	0.9
Stricturoplasty	6	5.4
Stoma creation	22	19.6
Total patients	112	

Data are given in number and frequency, unless otherwise stated.
IC = ileocolonic resection.

attributed to the fact that the majority of the patients in this study had different levels of clinical severity at the time of admission and remained unresponsive and/or refractory to previous treatments.

On the other hand, surgery is not curative for CD and is inevitable for most CD patients.[6] The management of surgical recurrence is challenging,[17] due to the high rate of necessary re-resections.[18] Colonoscopy control data have revealed that the POR site is almost always proximal to the anastomosis, which is defined as an endoscopic recurrence, and the timing is usually within the first year of surgery.[19] Clinical symptoms usually develop after luminal disease progression, which occurs at a later stage. In other words, disease recurrence manifests itself as endoscopic recurrence initially, followed by symptomatic recurrence with clinical signs. A planned postoperative colonoscopy is recommended for disease control. Up to 30% of symptomatic recurrent patients need a surgical intervention within the first 5 years.[1,20] In our study, the endoscopic recurrence rate was 8% at 1 year and 12.5% at 5 years. The cumulative endoscopic recurrence rate was 14.3% at 17 years. The surgical recurrence rate was 1.8% at 1 year, 5.4% at 10 years, and 7.1% at 17 years. In our study, the patients had significantly lower rates of surgical recurrence, compared with the literature.[1,20]

Risk factors can be further divided into subgroups, such as factors related to the patient, disease, surgery type, and postoperative medical treatment. Factors related to the patient include age, sex, and smoking habit. There are conflicting data in the literature data regarding the correlation between disease recurrence and age. Some authors have reported that there is a higher recurrence rate with the early-age onset of the disease,[21–23] while the others have not.[24,25] Similarly, sex has been reported as a significant factor for the rate of recurrence in both men[26] and women,[27] and yet in many other studies, no sex predominance has been shown.[15,24] In the present study, the recurrence rate was similar in male and female patients ($P = .242$), and was not associated with the age of the patient, while it was associated with age at the time of disease onset ($P = .033$). Smoking is also common among CD patients and it is a well-established risk factor for disease recurrence.[10,11,16,21,28] Smoking not only increases the recurrence rate of the CD but also aggravates the disease course, causing frequent relapses and extraintestinal manifestations.[29] Cottone et al [30] defined smoking as a risk factor for any type of recurrence. Additionally, patients smoking more than 10 cigarettes per day had a greater risk for both disease recurrence and surgical recurrence.[31] However, recent studies are unable to find a significant correlation between smoking and disease recurrence.[32,33] The rate of smoking in our study was high since the patients who smoked even one cigarette a day were considered smokers, and the recurrence rate was similar between the patients with recurrence and remission (13.1% vs 16.7%, respectively; $P = .699$). The rate of tobacco use may be a determinant for the absolute effect of smoking on disease recurrence.

Several disease classifications for CD, including the Vienna, Montreal, and Paris classifications, have been proposed to fulfill the unmet need for predicting the disease course based on disease

Table 4

Effects of drugs on recurrence.

	Before surgery				After surgery			
Drug	**n**	**%**	**OR**	***P***	**n**	**%**	**OR**	***P***
5-aminosalicylic acid								
Yes	10	12.2	0.556	.296	6	12.8	0.805	.696
No	6	20			10	15.4		
Thiopurine								
Yes	13	19.1	3.230	.069	11	16.7	1.640	.388
No	3	6.8			5	10.9		
Steroid								
Yes	8	16.7	1.250	.681	1	16.7	1.213	.864
No	8	13.8			15	14.2		
Anti-TNF*								
Yes	4	10.8	0.628	.453	6	25	2.556	.103
No	11	16.2			9	11.5		
Medical treatment								
Yes	15	16.7	0.145	4.200	14	15.4	0.579	.489
No	1	4.5			2	9.5		
Medical treatment change								
Yes	11	68.7	1.158	.802	9	69.2	2.093	.241
No	5	31.3			4	30.8		

OR = odds ratio, TNF = tumor necrosis factor.
* Missing data on anti-TNF use in one patient with disease recurrence. Data are given in mean ± standard deviation (SD), unless otherwise stated.

Table 5

Correlation analysis results.

	Univariate			Multivariate		
Variable	***P***	**OR**	**LR**	**HR**	**%95 CI**	***P***
Age at diagnosis ≤ 40 vs > 40 y	.033	0.822	7.625	2.891	0.000–34.929	.998
Disease behavior B1 + B2 vs B3	.011	4.385	6.687	0.297	0.068–1.309	.109
Intra-abdominal abscess existence	.040	3.039	4.114	1.656	0.202–13.552	.638
Intra-abdominal abscess and fistula	.017	3.571	5.071	0.619	0.100–3.818	.605

CI = confidence interval, HR = hazard ratio, LR = likelihood ratio, OR = odds ratio.

behavior, location, and age at the time of diagnosis. In all of the classification systems, the fistulizing disease has been scored with the highest rate of disease recurrence. The occurrence of postoperative complications has been reported at a greater rate among patients with fistulizing disease.[15,24] The perforating disease is associated with a shorter disease recurrence time compared with the non-perforating disease.[15,24] However, Yamamoto et al [34] reported a similar POR rate in perforating and non-perforating diseases. In our study, the POR rate was significantly higher in patients with penetrating disease behavior. In total, our study group had a low POR rate, which can be explained by the low rate of fistulizing disease.

There are also conflicting results in the literature regarding a higher rate of POR based on the primary disease location. Louis et al [23] reported an increased POR rate among patients with the primary ileal disease. In contrast, patients with a primary colonic localization had a higher redo surgery rate in a study by Chardavoyne et al.[35] Longer disease duration was also associated with a higher POR rate.[15,36] Conversely, the American College of Gastroenterologists considers a shorter disease course a potential risk factor for disease recurrence.[37] The POR rate in our study was higher among the patients with the ileal disease compared with those with colonic involvement, although the difference was not statistically significant. The presence of perianal disease was similar in both groups. We found that patients diagnosed before aged < 40 years with early onset of the disease had a significantly higher rate of POR (17.8% vs 0%, respectively; $P = .033$), which is consistent with the European Crohn's and Colitis Organization (ECCO) guidelines.[38] An intraperitoneal abscess indicates perforating disease and should be accepted as a risk factor for disease recurrence.[39] Percutaneous drainage of an intra-abdominal abscess seems to be a reasonable option with a shorter hospital stay and a lower rate of complications and need for the creation of an ostomy, despite contradictory data in the literature.[40] In a meta-analysis, percutaneous drainage increased the increased likelihood of abscess recurrence, compared with surgery, as the initial treatment.[40] The authors reported a similar length of hospital stay, complication rate, and ostomy requirement between the patients undergoing percutaneous drainage and surgery. In our study, the presence of an intra-abdominal abscess, as well as a concomitant abscess and a fistula before surgery, were found to be significantly correlated with the disease recurrence. This finding also supports the ECCO recommendation that the perforating disease phenotype is accepted as a risk factor for disease recurrence.

Medical treatment for CD patients must be individualized according to response, remission, tolerance, and side effects. In our study, most of the patients used thiopurine, 5-aminosalicylic acid, and/or a corticosteroid before surgery. Although not statistically significant, most of the patients with recurrence were receiving medical treatment, changed medical treatment, or were using multiple drugs before surgery. The rate of steroid use was higher among patients with POR. Both steroids and anti-TNF drugs were used for a longer duration before surgery among patients with recurrence, which can be interpreted as the exhaustion of all medical choices. In this study, the treatment duration was 17 months longer in patients with recurrence, compared with patients with remission. Many randomized-controlled trials compared the postoperative treatment data to prevent endoscopic recurrence of postoperative CD, and the results varied depending on the study criteria, such as medications. In a meta-analysis, sulfasalazine was reported to provide a modest benefit in the prevention of POR. Mesalamine is recommended in the prevention of POR for immunosuppressive patients with modest benefit.[37,41,42] However, patients without risk factors and prophylactic mesalamine use were found to be candidates for relapse.[38] Imidazole antibiotics were shown to have beneficial effects in terms of POR, compared with placebo, although this effect was lost with the discontinuation of the drug and most patients remained intolerant.[38,43] Thiopurines are often recommended in disease prophylaxis treatment after surgical resection, particularly for patients with ≥ 1 risk factor.[37,38] The results of a meta-analysis of the effectiveness of thiopurine drugs in the prevention of POR yielded a significant reduction in the recurrence rate, compared with both a placebo and mesalamine.[44,45] In randomized-controlled trials and a meta-analysis, anti-tumor necrosis factor therapy has been reported as the most effective treatment option to reduce the POR rate.[46–48] Combination therapies are recommended with a high response rate.[49,50] Careful risk stratification should be performed to identify those patients at a greater risk for POR and administer the appropriate treatment.

In the present study, surgery type, surgical approach, and anastomosis-related conditions (existence, type, structure) did not affect the rate of disease recurrence. A laparoscopic approach was reported to be safe and effective, even in complex cases.[51] The anastomotic technique and structure are important, and a sufficiently wide anastomosis is necessary.[52–54] A stapled, end-to-end functional anastomosis was found to lead to fewer leaks than a handsewn anastomosis.[55] The absence of granuloma in a specimen and disease-free margins were associated with a low recurrence rate, while the opposite proposal was demonstrated. Fazio et al [56] demonstrated that CD recurrence was not affected by microscopically and macroscopically involved margins. The current common recommendation is to avoid resection with extensive disease-free margins.

Nonetheless, this study has some limitations due to its retrospective nature and heterogeneous patient group, which is the natural character of the CD clinic. The long follow-up period

also bears the limitation of dynamic changes in the disease treatment during all these years. Emerging new drugs in the treatment cascade of the disease changed the treatment approach or previously surgery was the last resort for CD patients in the former decade, whereas surgery is, currently, handled as a part of initial treatment in selected eligible patients. Although the present study is a single-center study, it consists of a patient group receiving a standard treatment approach conducted by a single surgical and gastroenterology team in the long-term, which is one of the strengths of the study. Some bias may be present since the study site is a surgical referral center and mostly admits complicated cases or patients with little remedy. A large number of patients were inaccessible for long-term follow-up, which reduced the number of patients included. Indeed, we had the initial surgical data, while some patients attended their follow-up at external clinics. Lower recurrence rates, long-term follow-up, and the fact that treatment was administered by a single multidisciplinary team are the main strengths of the present study.

5. Conclusions

In conclusion, our study suggests that there are several risk factors for disease recurrence after surgery for CD including age at the time of diagnosis, penetrating disease, intra-abdominal abscess, and concomitant abscesses and fistulas. In addition, corticosteroid treatment, any medical treatment before the initial surgery, prolonged medical treatment before surgery, and multidrug treatment do not seem to be risk factors for disease recurrence, *per se*. However, further large-scale, prospective studies are needed to draw firm conclusions on this subject.

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