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Penetrating or Stricturing Diseases are the Major Determinants of Time to First and Repeat Resection Surgery in Crohn's Disease

Valerie Pittet[a] Gerhard Rogler[d] Pierre Michetti[c, b] Nicolas Fournier[a] John-Paul Vader[a] Alain Schoepfer[b] Christian Mottet[a, b, e] Bernard Burnand[a] Florian Froehlich[b, f] for the Swiss Inflammatory Bowel Disease Cohort Study Group (see Appendix)

[a]Healthcare Evaluation Unit, Institute of Social and Preventive Medicine (IUMSP), [b]Department of Gastroenterology and Hepatology, Lausanne University Hospital, and [c]Crohn and Colitis Center, Clinique La Source-Beaulieu, Lausanne, [d]Division of Gastroenterology and Hepatology, University Hospital Zurich, [e]Service of Gastroenterology, Hôpital Neuchâtelois, Neuchâtel, and [f]Division of Gastroenterology and Hepatology, University Hospital Basel, Basel, Switzerland

Key Words
Crohn's disease · Epidemiology · Surgery for IBD

Abstract
Background: About 80% of patients with Crohn's disease (CD) require bowel resection and up to 65% will undergo a second resection within 10 years. This study reports clinical risk factors for resection surgery (RS) and repeat RS. ***Methods:*** Retrospective cohort study, using data from patients included in the Swiss Inflammatory Bowel Disease Cohort. Cox regression analyses were performed to estimate rates of initial and repeated RS. ***Results:*** Out of 1,138 CD cohort patients, 417 (36.6%) had already undergone RS at the time of inclusion. Kaplan-Meier curves showed that the probability of being free of RS was 65% after 10 years, 42% after 20 years, and 23% after 40 years. Perianal involvement (PA) did not modify this probability to a significant extent. The main adjusted risk factors for RS were smoking at diagnosis (hazard ratio (HR) = 1.33; p = 0.006), stricturing with vs. without PA (HR = 4.91 vs. 4.11; p < 0.001) or penetrating disease with vs. without PA (HR = 3.53 vs. 4.58; p < 0.001). The risk factor for repeat RS was penetrating disease with vs. without PA (HR = 3.17 vs. 2.24; p < 0.05). ***Conclusion:*** The risk of RS was confirmed to be very high for CD in our cohort. Smoking status at diagnosis, but mostly penetrating and stricturing diseases increase the risk of RS.

Introduction

About 80% of Crohn's disease (CD) patients undergo resection surgery (RS) during the lifetime course of their disease [1–4]. Of those undergoing surgery, repeat RS is needed in 11–32% of cases after 5 years and 20–44% after 10 years [5–7], depending on the anatomic site involved. Those with ileal or ileocolonic involvement require surgery more frequently. Structural bowel damage occurs progressively in CD patients over time [8]. Later complications, including bowel obstruction, intra-abdominal abscesses or fistulas, need to be treated surgically [9, 10].

Prevention of disease progression and postoperative recurrence are thus particularly important in CD manage-

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Valérie Pittet, PhD
Healthcare Evaluation Unit
Institute of Social and Preventive Medicine (IUMSP), Biopôle 2
Route de la Corniche 10, CH–1010 Lausanne (Switzerland)
E-Mail Valerie.Pittet@chuv.ch

ment and this includes recognition of risk factors and aggressive therapy. Clinical risk factors for the first major resection have not wholly been identified or understood; those currently known are active smoking status, perforating disease phenotype and ileal involvement [11–14]. Moreover, there is no consensus concerning medical treatments and strategies that may modify disease progression or contribute to increasing the time to first surgery. Aminosalicylates, immunomodulators or biological therapies have shown small, uncertain or inconsistent degrees of benefit [6, 14–16].

The Swiss Inflammatory Bowel Disease Cohort (SIBDC), one of the largest national cohorts in Europe, contains demographic, clinical and treatment data on prevalent and incident cases of CD patients in Switzerland. The aim of the study is to describe which CD patients undergo RS and to assess factors associated with time to the first episode and to subsequent episodes of intestinal RS.

Materials and Methods

Study Design and Population

A full description of the cohort profile has been published previously [17], key elements are presented below. This is a retrospective cohort study on patients included in the SIBDC, a national prospective clinical cohort that began in 2006. SIBDC has four main study goals, namely to study (1) the genetic, biological and environmental risk factors associated with the course of the disease, (2) the associations with and influences of psychosocial factors on the recurrence of clinical symptoms, (3) the appropriateness of therapy, and (4) the assessment of medical and hospital resource consumption by inflammatory bowel disease (IBD) patients. Patients were recruited through their gastroenterologist in private practices, regional hospitals and tertiary centers. Inclusion criteria were a diagnosis of CD established at least 4 months before inclusion and confirmed by radiological, endoscopic or surgical assessment, or after at least one recurrence of the disease. CD case ascertainment was made based on the Lennard-Jones criteria [18]. Patients were excluded if they suffered from another form of colitis, were not regularly followed up for CD, had no permanent residency in Switzerland or if they refused to sign the informed consent form. The study population consists of adult patients (>16 years old) included in the cohort from November 2006 to July 2011, with a diagnosis of CD.

Exposure and Outcome Variables

Clinical data were collected during the medical visit at inclusion by means of clinical reporting forms completed by the patient's gastroenterologist or by trained study nurses. Retrospective data since diagnosis were retrieved from patient charts. Data were collected on paper and sent to the cohort data center for data entry, checking and validation. The following information was used as exposure variables: patient demographics (age, gender), clinical status at inclusion (CDAI score, disease location and drug therapies), and past medical history (date of diagnosis, disease location at diagnosis, smoking status at diagnosis, presence of fistulas and/or stenosis, history of RS). The CDAI score was categorized as follows: <150 (remission), 150–300 (mild to low-moderate activity), and >300 (high-moderate to severe activity). Information on smoking status was retrieved from patient self-administrated questionnaires, completed at inclusion and treated as a binary variable. Age at diagnosis, disease location and phenotype were treated as categorical variables, according to the Montreal classification [19]. We described duration of disease in three categories (<5, 5 to <10, and ≥10 years) and analyzed drug exposure according to five main categories, reflecting the step-up approach that is used in Switzerland. Taking into account past and current drug exposure, these were defined as: type 5 (received infliximab, adalimumab or certolizumab), type 4 (received azathioprine, 6-mercaptopurine or methotrexate; never received biologicals), type 3 (received 5-ASA or antibiotics; never received immunomodulators; never received biologicals), type 2 (received steroids; never received 5-ASA or antibiotics; never received immunomodulators; never received biologicals), and type 1 (patient who has never received any drug, 'wait-and-see' approach).

The main outcome variable was having a first episode of RS since the diagnosis was established. The first episode of RS could also be the event that led to establishment of the diagnosis. The secondary outcome was repeat RS, defined as having had two or more resections since diagnosis. Both outcomes were considered as binary variables. For each episode of surgery, type and month/year when performed were noted. Intestinal resection referred to any complete or partial ablation of an intestinal segment. In the case of several resections indicated at different intestinal sites, but at the same month/year, this was considered as the same operation. Indeed, due to the precision of the information collected, it was not possible to assess re-operation if performed within too short a timeframe. We assumed the number of re-operations to be small, thus the rates of repeat surgery not to be affected to a high extent. Surgery for simple fistulas, perianal abscesses (fistulectomy, fistulotomy, abscess drainage, seton, mucosal sliding flaps, fibrin glue instillation), adhesiolysis, appendicectomy and cholecystectomy were not considered in the context of this study.

Statistical Analysis

We described and compared the demographic, clinical and phenotypic characteristics of patients who had undergone RS versus those who had not, and of those who had undergone only one resection versus two or more. We used cross-tabulations, with numbers and percentages, for categorical variables, and χ^2 tests to test the null hypothesis of no association between outcomes and these variables. The mean and standard deviation (SD) of patient age at inclusion in the cohort was calculated and Z tests performed to test the null hypothesis of no difference in drug exposure proportions between patients having had one RS and those having had repeated RS.

Kaplan-Meier curves were used to describe and compare time to first RS and time to repeat RS according to age at diagnosis, disease location at diagnosis, and disease phenotype. Univariate Cox regression analyses were carried out to assess the strength of the association between (1) rates of surgery or (2) rates of repeat surgery and the following independent risk factors: age at diagnosis, gender, duration of disease, smoking status at diagnosis, disease location at diagnosis, and disease phenotype. In our dataset, the starting date of past treatments and detailed chronology of drug treatments were not available for all patients, therefore these parameters could not be included as risk factors in these

Table 1. Demographic and clinical characteristics of CD patients included in the study

	All patients for surgery		All postoperative patients for repeat surgery		
	total	no surgery	1 or more surgeries	only 1 surgery	more than 1 surgery
All patients	1,138	721 (63.4)	417 (36.6)	293 (70.3)	124 (29.7)
Gender					
Female	598 (52.5)	381 (52.8)	217 (52.0)	149 (50.9)	68 (54.8)
Mean (SD) age at inclusion visit	41 (15)	38 (15)	45 (14)	44 (14)	47 (13)
CDAI at inclusion visit					
<150	854 (75.0)	575 (87.7)	279 (79.5)	210 (82.7)	69 (71.1)
150–300	143 (12.6)	77 (11.7)	66 (18.8)	42 (16.5)	24 (24.7)
>300	10 (0.9)	4 (0.6)	6 (1.7)	2 (0.8)	4 (4.1)
Maximum drug exposure since diagnosis					
Type 5	308 (27.1)	201 (27.9)	107 (25.7)	62 (21.2)*	45 (36.3)*
Type 4	623 (54.7)	381 (52.8)	242 (58.0)	179 (61.1)**	63 (50.8)**
Type 3	166 (14.6)	112 (15.5)	54 (13.0)	40 (13.7)	14 (11.3)
Type 2	32 (2.8)	22 (3.1)	10 (2.4)	8 (2.7)	2 (1.6)
Type 1	9 (0.8)	5 (0.7)	4 (1.0)	4 (1.4)	0 (0.0)
Smoking status at inclusion					
No	671 (59.1)	433 (60.2)	238 (57.2)	168 (57.5)	70 (56.5)
Yes	464 (40.9)	286 (39.8)	178 (42.8)	124 (42.5)	54 (43.6)
Age at diagnosis					
≤16 years	123 (10.8)	75 (10.4)	48 (11.5)	25 (8.5)	23 (18.6)
17–40 years	804 (70.7)	498 (69.1)	306 (73.4)	216 (73.7)	90 (72.6)
>40 years	211 (18.5)	148 (20.5)	63 (15.1)	52 (17.8)	11 (8.9)
Duration of disease					
<5 years	431 (37.9)	376 (52.2)	55 (13.2)	54 (18.4)	1 (0.8)
5 to <10 years	214 (18.8)	150 (20.8)	64 (15.3)	54 (18.4)	10 (8.1)
≥10 years	493 (43.3)	195 (27.0)	298 (71.5)	185 (63.1)	113 (91.1)
Smoking status at diagnosis					
No	534 (48.2)	360 (51.5)	174 (42.4)	123 (42.6)	51 (42.2)
Yes	575 (51.8)	339 (48.5)	236 (57.6)	166 (57.4)	70 (57.9)
Disease location at diagnosis					
Terminal ileum	239 (22.9)	155 (23.4)	84 (22.0)	60 (22.1)	24 (21.8)
Colonic	265 (25.4)	200 (30.2)	65 (17.0)	53 (19.5)	12 (10.9)
Ileocolonic	531 (50.9)	302 (45.6)	229 (60.0)	156 (57.4)	73 (66.4)
Upper GI tract only	9 (0.9)	5 (0.8)	4 (1.1)	3 (1.1)	1 (1.0)
Latest disease location					
Terminal ileum	324 (29.2)	183 (26.0)	141 (34.8)	94 (32.9)	47 (39.5)
Colonic	354 (31.9)	261 (37.1)	93 (23.0)	65 (22.7)	28 (23.5)
Ileocolonic	420 (37.9)	256 (36.4)	164 (40.5)	124 (43.4)	40 (33.6)
Upper GI tract only	11 (1.0)	4 (0.6)	7 (1.7)	3 (1.0)	4 (3.4)
Disease phenotype					
Non-stricturing/non-penetrating	522 (45.9)	459 (63.7)	63 (15.1)	53 (18.1)	10 (8.1)
Non-stricturing/non-penetrating with perianal disease	101 (8.9)	80 (11.1)	21 (5.0)	15 (5.1)	6 (4.8)
Stricturing	204 (17.9)	82 (11.4)	122 (29.3)	94 (32.1)	28 (22.6)
Stricturing with perianal disease	70 (6.2)	18 (2.5)	52 (12.5)	33 (11.3)	19 (15.3)
Penetrating	153 (13.4)	50 (6.9)	103 (24.7)	70 (23.9)	33 (26.6)
Penetrating with perianal disease	88 (7.7)	32 (4.4)	56 (13.4)	28 (9.6)	28 (22.6)

Values are numbers and percentages, unless specified otherwise. Z tests to test the null hypothesis of no difference in drug exposure between patients having had 1 RS and those having had >1 RS were made with the following results: * $p < 0.001$, ** $p = 0.05$, otherwise non-significant.

Table 2. Types of surgery according to phenotype for CD patients

Type of surgery	Total n (%)	Non-stricturing/ non-penetrating (B1)	Stricturing (B2)	Penetrating (B3)	Perianal disease[1]
Ileocecal resection	250 (32.3)	48	113	89	76
Ileal resection	145 (18.7)	18	69	58	38
Right colectomy	105 (13.5)	24	35	46	42
Left colectomy	54 (7.0)	14	16	24	24
Sigmoid resection	22 (2.8)	1	3	18	6
Ileostomy	62 (8.0)	11	15	36	31
Colostomy	31 (4.0)	5	2	24	14
Subtotal colectomy	29 (3.7)	8	4	17	10
Total proctocolectomy	13 (1.7)	3	5	5	8
Proctectomy	8 (1.0)	1	1	6	2
Other small bowel resection	35 (4.5)	2	13	20	12
Stricturoplasty	21 (2.7)	1	7	13	9
Total, n (%)	775 (100.0)	136 (17.5)	283 (36.5)	356 (46.0)	272 (35.1)

Values are numbers, unless specified otherwise. [1] Presence of perianal disease in any B1-B3 category.

analyses. Hazard ratio (HR) and 95% confidence intervals (CI) were calculated. Statistical significance was assessed by p value from likelihood ratio testing <0.05. Multivariate Cox regression analyses were then performed to determine the most suitable model for rates of surgery and rates of repeat surgery. Interaction between smoking status at diagnosis and other risk factors was assessed by comparing models with and without interaction terms. The accuracy of models' prediction using Harrell's C concordance coefficient was examined [20]. Analyses were performed using STATA software version 12.1 (StataCorp, College Station, Tex., USA).

Ethical Considerations

The study was approved by the respective ethics committees of the Swiss regions from which patients were recruited. Written informed consent was obtained from each participating patient.

Results

Baseline Description of the Study Population

The total number of adult CD patients included in the study by July 2011 was 1,138; 598 were females (52.6%). Mean (SD) age at inclusion was 41 (15) years. One third (n = 417; 36.6%) had had RS (table 1) and a third of them (n = 124; 29.7%) had undergone repeat RS, i.e. two or more operations. Mean (SD) age at first surgery was 34 (13) years, slightly earlier in females than in males (33 vs. 35; p = 0.045). 60% of patients with ≥10 years of disease duration had RS and 38 of those had undergone repeat surgery. 82% of patients with ileal involvement at diagnosis, mainly ileocolonic, had RS. Most recent disease locations, recorded at the time of inclusion in the cohort, tended to shift towards the terminal ileum among patients having had one or more RS, when compared with location at diagnosis. A large majority of patients who had not undergone resection had non-stricturing/non-penetrating CD. Regarding overall drug exposure of CD patients who underwent RS, we observed that drug exposure that included biologicals (type 5) were more often prescribed to patients who had had two or more resection surgeries (36.3 vs. 21.1%; p < 0.001). The types of surgery performed by disease phenotype of CD patients are shown in table 2. A total of 775 surgical procedures were documented, the majority of them among patients with penetrating or stricturing disease. Resection was performed most often in the presence of ileocecal (32.3%) or ileal disease (18.7%).

Time-to-Event Analyses for First and Repeat RS

65% of patients were free of RS after 10 years, 42% after 20 years, and 23% after 40 years (fig. 1a). Among those who had surgery, almost 15% went on to a have a repeat operation after 5 years (fig. 1b). 29% of patients had repeat surgery after 10 years and 47% remained free of repeat surgery after 20 years.

Rates of RS and Age at Diagnosis

Patients who were diagnosed at age ≥17 had a higher probability of having RS during the first 15 years after diagnosis, but a lower probability after 15 years, compared to those diagnosed before the age of 17 (fig. 2a).

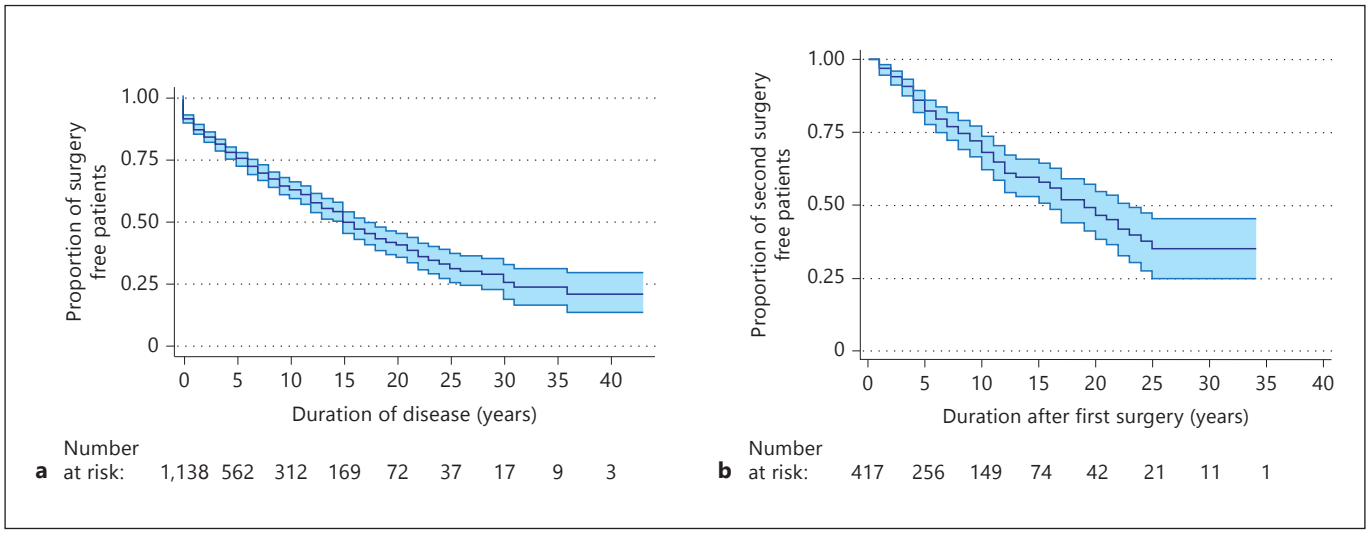

Fig. 1. Kaplan-Meier survival curve for CD patients who had not undergone RS (**a**) or repeat RS (**b**).

The proportion of patients remaining free of RS was 85% after 5 years, respectively 32% after 20 years, if diagnosed at age <17 compared to 75%, respectively 40% if diagnosed after the age of 17. No differences in the likelihood of RS were observed between those who were diagnosed within the range of age 17–40 and after the age of 40. Time to repeat surgery was shorter among patients diagnosed <17 years compared to those diagnosed later (fig. 2b); 50% underwent repeat surgery 12 years after the first resection versus 21 years among those diagnosed aged 17–40 years.

Rates of RS and Disease Location at Diagnosis

The likelihood of RS was higher among groups of patients with a disease located in the terminal ileum at diagnosis, 65% at 20 years versus 48% for isolated colonic disease (fig. 2c). In the first 5 years following a first RS, the probability of being free of repeat surgery was higher for patients with ileal involvement at diagnosis compared to those with isolated colonic disease; this tendency was inverted after 10 years (fig. 2d).

Rates of RS and Disease Phenotype

Either stricturing or penetrating disease greatly increased the probability of requiring RS compared to inflammatory-only disease: 60 vs. 15% at 10 years and 80 vs. 25% at 20 years (fig. 2e). Time to repeat RS for 40% of the patients with penetrating disease was 11 years compared to 16 years for those with stricturing disease and 22 years for those with non-stricturing/non-penetrating disease (fig. 2f).

Risk Factors for RS and Repeat RS

Table 3 presents the results of crude and adjusted HRs for initial RS according to the following independent factors: gender, age at diagnosis, smoking status at diagnosis, disease location at diagnosis, and disease phenotype.

We observed that crude HRs for initial RS among smokers at diagnosis increased by 36% ($p = 0.002$) compared to non-smokers; a colonic-only disease location and having a stricturing or penetrating disease were also identified as crude risk factors for initial RS. After adjustment for all risk factors, smoking at diagnosis remained a risk factor contributing to the most predictable model. Rates of RS were 4–5 times higher for stricturing and penetrating disease ($p < 0.001$). The presence of disease with perianal involvement (PA) did not change the rate of RS to a major extent compared to disease without PA, whatever the phenotype. For non-stricturing/non-penetrating and stricturing disease, the rate of RS further

Fig. 2. a–f Kaplan-Meier survival curve for CD patients who had not undergone RS according to age at diagnosis (**a**), location of disease (**c**), disease phenotype (**e**) or who had not undergone repeat RS according to age at diagnosis (**b**), location of disease (**d**), and disease phenotype (**f**). Location of disease is abbreviated as follows: terminal ileum (L1), colonic (L2), ileocolonic (L3), and upper GI tract only (L4); disease phenotype is abbreviated as follows: non-stricturing/non-penetrating (B1), non-stricturing/non-penetrating with PA (B1p), stricturing (B2), stricturing with PA (B2p), penetrating (B3), and penetrating with PA (B3p).

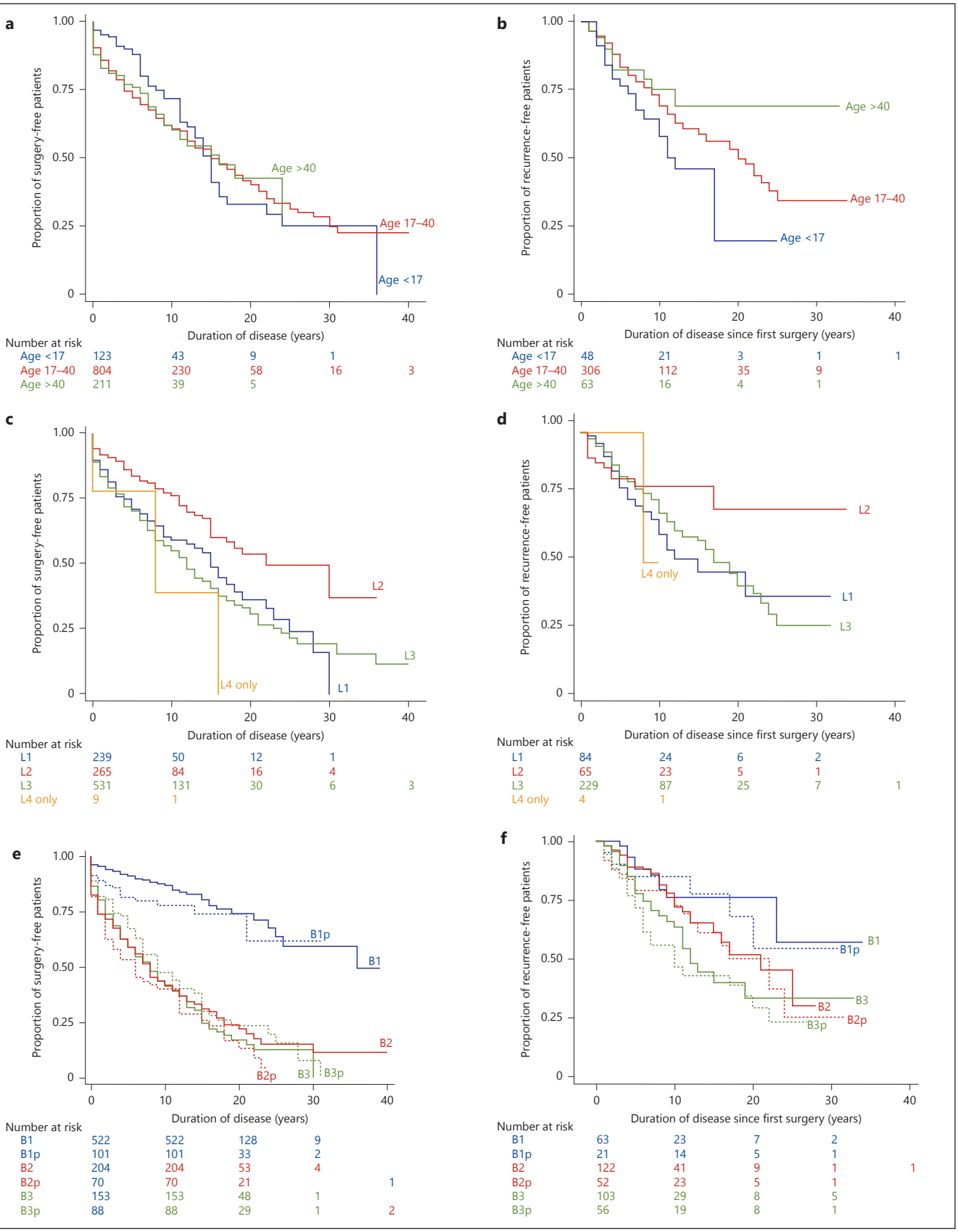

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Table 3. Uni- and multivariate Cox regression showing crude and adjusted HRs and 95% CI for RS

	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Gender				
Male	1.00			
Female	1.01 (0.83–1.23)	0.911		
Age at diagnosis				
A1 (≤16)	1.00			
A2 (17–40)	1.15 (0.85–1.56)	0.374		
A3 (>40)	1.18 (0.81–1–71)	0.398		
Smoking status at diagnosis				
No	1.00		1.00	
Yes	1.36 (1.12–1.66)	0.002	1.33 (1.08–1.64)	0.006
Disease location at diagnosis				
L1 (terminal ileum)	1.00		1.00	
L2 (colonic)	0.56 (0.41–0.78)	<0.001	0.74 (0.53–1.03)	0.075
L3 (ileocolonic)	1.12 (0.87–1.44)	0.358	1.08 (0.84–1.40)	0.550
L4 (upper GI tract only)	1.67 (0.61–4.55)	0.317	2.39 (0.87–6.56)	0.090
Disease phenotype				
B1 (non-stricturing/non-penetrating)	1.00		1.00	
B1p (non-stricturing/non-penetrating with perianal disease)	1.56 (0.95–2.55)	0.080	1.47 (0.87–2.46)	0.148
B2 (stricturing)	4.94 (3.64–6.69)	<0.001	4.11 (2.99–5.66)	<0.001
B2p (stricturing with perianal disease)	6.10 (4.22–8.81)	<0.001	4.91 (3.34–7.22)	<0.001
B3 (penetrating)	5.21 (3.81–7.14)	<0.001	4.58 (3.30–6.34)	<0.001
B3p (penetrating with perianal disease)	4.45 (3.10–6.38)	<0.001	3.53 (2.30–5.22)	<0.001

slightly increased in the presence of PA (HR = 1.47 vs. 1.00 and HR = 4.91 vs. 4.11), but slightly decreased for penetrating disease (HR = 3.53 vs. 4.58). Harrell's C concordance coefficient was 0.54 for the model with smoking status at diagnosis only, 0.57 for location at diagnosis only, and 0.69 for disease phenotype only. The concordance coefficient for the multivariate model was 0.72, showing there was a good relationship between the prognostic score, considering these variables, and survival time. Results of crude and adjusted HRs for repeat RS according to the same potential risk factors are shown in table 4. Phenotype, especially penetrating disease, with or without PA, remained the sole independent risk factor for repeat surgery (HR = 3.17, p = 0.026 vs. 2.24; p = 0.002). Harrell's C concordance coefficient for the predictive model with disease phenotype was 0.61.

Discussion

About one third (36.6%) of SIBDC CD patients had RS since diagnosis; half of which had ≥2 operations. The rate of RS increased from 35% after 10 years since disease diagnosis to 77% after 40 years. Time to repeat RS for patients with penetrating disease was 11 years compared to 16 years for stricturing disease and 22 years for non-stricturing/non-penetrating disease. Independent risk factors for RS were smoking at diagnosis and a stricturing or penetrating disease phenotype. PA did not appear to have any significant influence on rates of first or repeat RS. Ileal disease location at diagnosis was not an independent risk factor for RS after controlling for smoking status at diagnosis and phenotype.

Analyses of data gathered in the SIBDC, one of the largest nationwide IBD cohorts in Europe, led to the confirmation of observations made in previous observational studies in other countries concerning the high risk of undergoing intestinal resection for CD patients during their lifetime disease course. The cumulative risk of surgery after diagnosis has been estimated to be around 80% [10, 12, 13, 21, 22] and the very recent observations from the population-based Olmsted County also confirm surgery rates found after 20 years of disease duration in our study [23]. When comparing the characteristics of the population of postoperative patients, we observed that mean age at first intestinal resection was nearly 10 years higher compared to other cohorts [24], which may indicate either that a significant effort has been made and achieved to delay the

Table 4. Uni- and multivariate Cox regression showing crude and adjusted HRs and 95% CI for repeat surgery

	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Gender				
Male	1.00			
Female	0.97 (0.68–1.39)	0.886		
Age at diagnosis				
A1 (≤16)	1.00			
A2 (17–40)	0.63 (0.40–0.99)	0.047		
A3 (>40)	0.49 (0.24–1.01)	0.054		
Smoking status at diagnosis				
No	1.00			
Yes	0.91 (0.63–1.31)	0.635		
Disease location at diagnosis				
L1 (terminal ileum)	1.00			
L2 (colonic)	0.58 (0.29–1.16)	0.122		
L3 (ileocolonic)	0.86 (0.54–1.36)	0.515		
L4 (upper GI tract only)	1.35 (0.18–10.0)	0.770		
Disease phenotype				
B1 (non-stricturing/non-penetrating)	1.00		1.00	
B1p (non-stricturing/non-penetrating with perianal disease)	1.19 (0.43–3.29)	0.732	1.19 (0.43–3.29)	0.732
B2 (stricturing)	1.56 (0.76–3.21)	0.227	1.56 (0.76–3.21)	0.227
B2p (stricturing with perianal disease)	2.04 (0.95–4.40)	0.068	2.04 (0.95–4.40)	0.068
B3 (penetrating)	2.24 (1.10–4.55)	0.026	2.24 (1.10–4.45)	0.026
B3p (penetrating with perianal disease)	3.17 (1.54–6.55)	0.002	3.17 (1.54–6.55)	0.002

time to first RS, or that the disease remained undetected for a longer period before diagnosis [25], which might be the case for ileal diseases [26]. The proportion of CD smokers at diagnosis was comparable to previous observations [27], and was a determinant for RS, but not for repeated surgery, which confirms results found in some studies [28, 29], but contradicted others [21]. The proportion of patients who still smoked at the time of inclusion was quite similar among those who underwent RS and those free of surgery but decreased as compared to those at diagnosis. We did not collect information on pack-years of smoking and therefore were not able to stratify analyses to see if this observation persisted among low compared to heavy smokers. As we did not collect more precise chronology of smoking status, we were not able to see if smoking continuation after a RS episode had an effect on time to repeated surgery, or if the smoking status effect varied with concomitant drug exposition [30].

In our study, we found that young age at diagnosis was not an independent risk factor for first RS, which was in opposition to studies in which age at diagnosis <40 was shown as being a high predictor for surgery [31]. According to the Kaplan-Meier curves we drew, the effect appeared to differ however according to duration of disease. Our observations may be related to modification in drug treatments over time. Indeed, young diagnosed patients with a short disease duration may have been treated earlier more aggressively than in the past. Therefore, their outcome, in terms of need for RS, may have been delayed compared to patients diagnosed later.

Penetrating disease was found to be a strong risk factor for surgery and for repeat RS, as found in previous studies [14, 21, 31–33] conducted in Europe. PA did not appear, however, to modify rates of RS to a large extent, showing that aggressive disease presentation by itself plays a major role in the need for resective surgery. We observed from Kaplan-Meier curves that having an isolated colonic disease seemed to delay the time to first RS compared to those with an ileal disease involvement; however, we did not find any major effect of disease location distinguishable anymore in the multivariate Cox analysis. Upper gastrointestinal disease was not frequent in our cohort, therefore its influence on first or repeat RS could not been assessed with sufficient precision.

Our study used data from a cohort study, including patients followed up in tertiary centers, but also in regional hospitals and private practices; it may then be considered as a 'snapshot' of CD patients at a national

level. Selection bias may have occurred due to the fact that 60% of the patients were recruited in tertiary centers, thus may have had more severe disease characteristics. Our results show that the proportion of patients with a type 5 (biological) drug exposure history is higher in the group of patients that had repeat surgery. We might assume that biological therapies have been used too late in severely ill patients who could thus not be prevented from repeat surgery. Using biological therapies at an earlier stage would have played a preventive role on surgery, as shown in previous studies [34]; this question will be investigated in a future prospective study. The demographics and patient clinical characteristics were, however, observed to be close to those found in prior European population-based studies, which indicates that our study population is likely closely representative of the general CD population followed up by gastroenterologists. Data were gathered by study nurses or physicians trained in data recording, using dedicated clinical report forms designed specifically for the purpose of the study. This contributed to homogeneous data collection in terms of data types and definitions. Information bias could thus be minimized.

CD patients included in the SIBDC cohort were shown to present a very high risk of RS. Stricturing and penetrating disease patterns as well as smoking at diagnosis increased the risk of surgery, whereas isolated colonic disease and non-stricturing/non-penetrating disease patterns tend to lower this risk.

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Appendix

Members of the SIBDCS Study Group

Peter Bauerfeind, Christoph Beglinger, Stefan Begré, Dominique Belli, José Bengoa, Luc Biedermann, Janek Binek, Jan Borovicka, Christian Braegger, Patrick Bühr, Bernard Burnand, Emanuel Burri, Rafael Camara, Dominique Criblez, Philippe de Saussure, Lukas Degen, Mohamed Ali Delhavi, Joakim Delarive, Christopher Dörig, Gian Dorta, Tobias Ehmann, Ali El Wafa, Christian Felley, Markus Fliegner, Alain Frei, Pascal Frei, Remus Frei, Michael Fried, Michael Friedt, Florian Froehlich, Heiko Frühauf, Raoul Furlano, Suzanne Gallot-Lavallée, Martin Geyer, Marc Girardin, Sébastien Godat, Jean-Jacques Gonvers, Ignaz Good, Oliver Götze, Beat Gysi, Antoine Hadengue, Marcel Halama, Serge Hediger, Pius Heer, Beat Helbling, Mona Hellstern, Peter Hengstler, Denise Herzog, Cyrill Hess, Klaas Heyland, Thomas Hinterleitner, Philippe Hiroz, Claudia Hirschi, Petr Hruz, Patrick Janiak, Christian Jost, Pascal Juillerat, Vera Kessler Brondolo, Christoph Knoblauch, Claudia Krieger, Gerd A. Kullak-Ublick, Markus Landolt, En-Ling Leung-Ki, Philippe Maerten, Michel Maillard, Christine Manser, Michael Manz, Urs Marbet, Igor Marsteller, Rémy Meier, Christa Meyenberger, Pierre Michetti, David Mondada, Darius Moradpour, Patrick Mosler, Christian Mottet, Christoph Müller, Pascal Müller, Beat Müllhaupt, Andreas Nagy, Cristina Nichita, Thierry Nicolet, Hansjürg Nüesch, Andreas Nydegger, Isabelle Pache, Franziska Piccoli, Julia Pilz, Valérie Pittet, Bruno Raffa, Ronald Rentsch, Jean-Pierre Rey, Daniela Rogler, Gerhard Rogler, Markus Sagmeister, Bernhard Sauter, Mikael Sawatzki, Gerold Schacher, Michael Scharl, Nora Schaub, Martin Schellin, Susanne Schibli, Hugo Schlauri, Jean-François Schnegg, Alain Schoepfer, Franck Seibold, Mariam Seirafi, David Semela, Marc Sidler, Johannes Spalinger, Holger Spangenberger, Philippe Stadler, Peter Staub, Michael Steuerwald, Alex Straumann, Michael Sulz, Michela Tempia-Caliera, Joël Thorens, Radu Tutuian, John-Paul Vader, Stephan Vavricka, Dominique Velin, Francesco Viani, Roland Von Känel, Alain Vonlaufen, Dominique Vouillamoz, Gert Wachter, Jürg Wermuth, Paul Wiesel, Samuel Zamora, and Jonas Zeitz.

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