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**LONG-TERM OUTCOMES AND PREDICTORS OF DISABLING DISEASE IN A
POPULATION-BASED COHORT OF PATIENTS WITH INCIDENT CROHN'S DISEASE
DIAGNOSED BETWEEN 1994 AND 1997**

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Conflicts of Interest

Guillaume BOUGUEN received lecture fees from Abbvie, Ferring, MSD, Takeda and Pfizer and consultant fees from Takeda, Janssen. Laurent SIPROUDHIS received lecture fees from Abbvie, Amgen, Ferring, Janssen, MSD, Takeda and consultant fees from Takeda. Charlène BROCHARD received lecture fees from IPSEN. The other authors declare no conflict of interest

Authors' contributions: conception and design of the study: GB, MLB, JFB, IT; acquisition of data: MLB, AG, GB, MP; analysis and interpretation of data MLB, GB, EB, SH, JFV, JFB,

AD; drafting the article: MLB, GB; and revising the article critically for important intellectual content: all authors. The manuscript was approved by all authors.

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Highlights

- Population-based studies based on individual data remains a key report to capture the overall Crohn's disease course
- The identification of early predictor of poor CD disease outcomes remains needed to avoid delayed introduction of effective treatments
- A majority of patients developed a Crohn's disease complication
- Perianal disease including non-fistulizing lesions are the main predictor of disabling disease

ABSTRACT (250 words)

Background The identification of early prognostic factors during Crohn's disease (CD) remains needed for physician decision-making to minimize structural bowel damage, which this study aimed to assess in a population-based setting.

Methods

All incident cases of CD were prospectively registered from 1994 to 1997 in Brittany, a limited area of France. All charts of patients were reviewed from the diagnosis to the last clinic visit in 2015. Disabling CD course was defined according to the Saint-Antoine criteria.

Results

Among the 331 incident cases of CD, 272 (82%) were followed-up for a median time of 12.8 years. The cumulative probability of developing stricturing or fistulizing CD was 66% at 15 years, and 107 (39%) patients underwent surgery. The cumulative probabilities of immunosuppressant and TNF antagonist use at 15 years were 37% and 22%, respectively. The cumulative risks for disabling disease and bowel damage were 74% and 71% at 15 years, respectively. Systemic symptoms and perianal lesions at diagnosis were independently associated with a disabling disease course. Perianal disease and short disease extension were associated with the onset of bowel damage. Deep ulcers was not predictive of any outcome.

Conclusions

A disabling disease course and bowel damage occurred early in the course of CD, which suggests the need for early diagnosis and early treatment, particularly for patients with systematic symptoms and perianal disease.

Keywords: Crohn's disease, population-based, outcomes

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease that leads to a sequence of flares and remissions of varying durations¹. This unremitting inflammatory process results in progressive and irreversible segmental damage of the gastrointestinal tract. Based on several studies, 70-80% of patients with CD require intestinal surgery at 20 years²⁻⁴. The disabling course of the disease is also outlined by other dreaded outcomes, such as the need for hospitalization and the onset of behavioural complications, such as strictures and fistulas, that ultimately impact the quality of life of CD patients⁵. However, most studies assessing the course of the disease in the long term are old, before the era of biologics, or are based on a select cohort of patients, which may overestimate the risk of disabling disease.

During recent decades, significant therapeutic advances have changed the way to treat CD. Early introduction of combined immunosuppression was shown to be the most effective treatment to reach the target of mucosal healing that was associated with improved outcomes⁵⁻¹⁰. Thus, the traditional management of CD, with stepwise therapeutic intensification, switched progressively to the early initiation of highly effective therapy to adequately control digestive inflammation and subsequent complications¹¹.

However, several pitfalls preclude the systematic use of a top-down approach for CD patients. CD is a heterogenic condition with a highly variable prognosis, and up to half of patients may have a benign disease course³. No valid prediction rules have been assessed, and most known predictors are derived from biased referent cohorts or selected study populations^{11, 12}. In addition, the use of immunosuppressive treatments increases the risk of (severe) treatment-related complications, such as infection and cancer, that preclude such a strategy for all patients with the inherent risk of overtreating some of them^{13, 14}.

Having a description of CD outcomes and identifying early prognostic factors that predict a severe course appear crucial for physician decision-making to minimize structural bowel damage, complications of disease and side effects related to treatment.

Only population-based studies are able to assess these questions given the selection bias of referral centre studies. The aim of this study was, consequently, to describe the long-term outcomes of CD based on a population-based cohort and to determine risk factors for a disabling course as well as for the onset of bowel damage.

METHODS

THE ABERMAD REGISTRY

The ABERMAD Registry included prospectively all incident CD cases between 1994 and 1997 in a large area of western France (called Brittany), with almost 2 870 000 inhabitants, representing 4.8% of the entire French population. Brittany is divided into four departments: Côtes d'Armor, Finistère, Morbihan and Ille et Vilaine.

The ABERMAD cohort was built according to the EPIMAD registry's methodology and is described elsewhere¹⁵. Briefly, the private and public gastroenterologists (n=139) (adult and paediatric) of Brittany prospectively referred all patients consulting for the first time in 1994-1997 with clinical symptoms compatible with inflammatory bowel disease. Only patients who were residents in the defined study area at the time of diagnosis were included. An interviewer practitioner completed a standard questionnaire for each patient in the gastroenterologist's consulting room.

The main collected data were age, sex, and time between the onset of symptoms and diagnosis as well as clinical, endoscopic, radiological and histological findings at the time of the declaration of the case by the gastroenterologist. Endoscopic and radiological findings were prospectively collected at diagnosis. Data from colonoscopy, upper gastrointestinal endoscopy, small bowel transit and barium enema were gathered prospectively at diagnosis. Regarding the endoscopic procedure, aphthous, superficial and deep ulcers as well as stenosis and fistula were reported on each segment and were defined according to the CDEIS definition¹⁶ for each of the following intestinal segments: rectum, sigmoid and left colon, transverse and right colon, caecum and ileum. Disease extent was defined as follows: bifocal involvement or small bowel involvement more or less than 15 cm or colonic involvement more or less than 15 cm. CT scans and MRI scans were not usually used between 1994 and 1997, and mural and extramural complications were assessed by small bowel transit and barium enema.

A panel of four expert gastroenterologists reviewed each case independently. They assigned a diagnosis of definite, probable or possible Crohn's disease, ulcerative colitis, unclassifiable chronic colitis or acute colitis according to the validated Lennard-Jones criteria.

STUDY POPULATION

For the present study, 370 patients originally included with definite or probable diagnosis of CD were reviewed. All patients with at least one clinic after the inclusion were included for the assessment of longterm outcomes. During the follow-up, the diagnosis was changed to ulcerative colitis for 8 patients, and 31 patients did not have IBD (supplementary Figure 1). A total of 59 patients (15.9%) were lost to follow-up, and 272 patients constituted the study

population. The baseline characteristics of these 59 patients were broadly similar to those who were followed up (supplementary Table 1).

All charts of patients were reviewed retrospectively from the diagnosis to 2015 to assess the long-term outcomes of the cohort. An interviewer went to the gastroenterologist's consulting room and collected data through the medical records from the date of CD diagnosis until the last follow-up or the date of the last medical record.

DATA COLLECTION

The following data were collected: a family history of inflammatory bowel disease (IBD), extraintestinal manifestations, smoking habit, the date of death, and cancer. Extraintestinal manifestation was defined by the occurrence of reactive (such as peripheral arthritis, erythema nodosum ...) or non-reactive (spondylarthritis, primary sclerosing cholangitis...) manifestation known to be associated with IBD. Associated autoimmune diseases were also defined as EIM. CD location and disease behaviour were based on the Montreal classification¹⁷. Major abdominal surgery was defined by bowel resection related to CD. Perianal disease was recorded according to the Hughes classification. All anal surgeries were recorded separately. All treatments during the study period were retrieved, including 5-aminosalicylates (5-ASA), corticosteroids (oral and topical steroids), purines (azathioprine, 6-mercaptopurine), methotrexate (MTX), and anti-TNF therapies (infliximab [IFX] and adalimumab [ADA]). All hospitalizations related to CD were retrieved from the follow-up. The study was approved by the ethics committee (n° 13.64).

OUTCOME MEASURES AND DEFINITIONS

No consensus exists on the definition of disabling CD, and two outcomes were independently assessed. The first one was derived from the Saint-Antoine cohort study, with a definition of disabling disease as follows¹²: two or more courses of steroids or steroid dependency or resistance as defined by the physician and/or hospitalization for ongoing active disease or complications of CD and/or the need for immunosuppressant (IS) drugs (purine/methotrexate) or anti-TNF therapy and/or surgery (bowel or anal related to CD). The second is the onset of bowel damage defined by the items that weight the Leman score: surgery and/or complicating behaviour (fistulizing or stricturing disease) and/or fistulizing or stricturing anoperineal involvement. Both non-fistulizing and fistulizing perianal CD was considered an explanatory variable for disabling CD, but only perianal ulceration was taken into account for bowel damage to avoid confusion between the explanatory and explained variables for bowel damage.

STATISTICAL ANALYSIS

A descriptive analysis of the population study was conducted, specifying the baseline demographic, clinical, and endoscopic characteristics; the disease's clinical evolution; complications; and the treatments implemented. The quantitative data are expressed as the means (+/- the standard deviations), and the qualitative data are expressed as numbers and percentages. Kaplan-Meier survival curves were plotted for variables with censored data.

Factors potentially associated with these outcomes were tested in univariate analysis using the log rank test: age at diagnosis (Montreal classification), sex, family history of IBD, gastroenterologist practice, time from first symptoms to diagnosis, digestive symptoms, systemic symptoms (defined by fever and/or weight loss and/or growth deficiency), extraintestinal manifestations, anal fistula, upper gastrointestinal lesions (Montreal classification L4), extensive lesion defined by two or more locations of the disease, epithelioid granuloma and deep ulcers.

Additionally, variables that had a univariate p-value <0.15 were included in a multivariate Cox proportional hazard model. Only variables that had a p-value <0.05 in multivariate analysis were retained in the final model. The results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs).

The proportional hazards assumption was checked for each factor, and the interaction between time and individual covariates was introduced in the model if required. Interactions were tested between all significant factors in the Cox model.

Statistical significance was defined as $p < 0.05$. All analyses were performed using the statistical software programme SAS 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS

The main clinical characteristics at diagnosis of the 272 patients who constituted the cohort are depicted in Table 1. The mean time from symptom onset to diagnosis was 8.3 months (+/-13.9, range 0-120), with a mean age at diagnosis of 35 years (+/- 19.35, range 4.8-87). Systemic symptoms (fever, weight loss or growth deficiency) were present in 153 patients (61.2%) at diagnosis, and digestive symptoms (abdominal pain or liquid stools) were present in 254 patients (93.7%). Extraintestinal manifestations were present in 35 patients (14.1%). A total of 67 (24.6%) patients ultimately developed one or more EIM, including notably 37 (13%) rheumatologic manifestations, 20 (7.3%) skin manifestations and 10 (3.7%) ocular manifestations.

A complete colonoscopy at diagnosis was performed in 249 patients (91.5%) with ileum intubation in 197 (72%) patients, and upper gastrointestinal endoscopy was performed in 137 patients (50.6%). Data from small bowel transit and barium enema were presented in 110 and 241 patients (40.4% and 89.3%), respectively. Deep ulcers were observed in at least one segment of the digestive tract for 138 (50.7%) patients and in at least 2 segments for 86 (31.6%) patients (supplementary Table 2). Colonic involvement above 15 cm was found in 203 patients (75.5%), and more than 15 cm of the small bowel was involved in 117 patients (59.9%). Finally, pathology showed granuloma in 108 patients (42.9%) and other histological features of CD in 140 patients (54.5%).

DISEASE OUTCOMES

Treatments

After a mean follow-up of 12.8 years (+/- 6.2), 5-ASA treatments were given at least one time in 246 patients (91.1%) and steroids in 179 patients (65.8%). The cumulative probabilities of being treated with corticosteroids were 43% (37%-49%) at 1 year, 55% (49%-55%) at 5 years, 64% (58%-70%) at 10 years, and 71% (77%-64%) at 15 years (supplementary Figure 2).

Thiopurines and methotrexate were used in 102 (37.5%) and 13 (4.8%) patients, respectively. The cumulative probabilities of being treated with thiopurines were 6% (4%-10%) at 1 year, 21% (16%-26%) at 5 years, 34% (28%-41%) at 10 years, and 43% (36%-50%) at 15 years (supplementary Figure 2).

A total of 60 patients (22.1%) were treated with a TNF antagonist (17.7% with infliximab and 8.5% with adalimumab). The pooled cumulative probability of being treated with anti-TNF treatments (infliximab and/or adalimumab) was 2% (1%-4%) at 5 years, 13% (9-19%) at 10

years, and 25% (19%-32%) at 15 years (supplementary Figure 2). No patient was treated with vedolizumab during the follow-up

Crohn's disease behaviour

At the last follow-up, 113 patients (41.5%) had non-stricturing, non-fistulizing behaviour. The cumulative probabilities of developing stricturing disease were 46.7% at 1 year (40.9%-52.7%), 52.4% at 5 years (46.2%-58.6%), 54.9% at 10 years (48.5%-61.2%) and 56.3% at 15 years (49.8%-62.6%). The cumulative probabilities of developing penetrating disease were 18.6% at 1 year (14.6%-23.4%), 22.4% at 5 years (17.7%-28.1%), 24.4% at 10 years (19.1%-30.5%) and 25.5% at 15 years (20.1%-31.9%). Finally, the pooled cumulative risks for stricturing and/or penetrating disease were 54.3% at 1 year (48.6%-59.7%), 61.1% at 5 years (55.1%-66.8%), 64.1% at 10 years (57.9%-69.8%) and 65.9% at 15 years (59.6%-71.6%) (Figure 1).

Hospitalizations and surgeries

A total of 125 patients (46%) required at least one medical hospitalization related to CD, and 69 patients (25%) required two hospitalizations. The mean duration of hospitalization per patient during the follow-up was 18 days (+/- 19, range 1-123). Most hospitalizations were related to disease flare (81% of all hospitalizations). The cumulative probabilities of being hospitalized were 34% (28%-40%) at 5 years, 42% (36%-48%) at 10 years and 48% (42%-55%) at 15 years.

A total of 107 patients (39%) underwent at least one major abdominal surgery related to CD, 69 patients (25.4%) underwent two surgeries, and 40 patients (14.7%) underwent three surgeries. The cumulative probabilities of surgery occurrence were 14% at 1 year (10%-19%), 29% at 5 years (24%-35%), 36% at 10 years (30%-42%) and 45% at 15 years (38%-52%) (Figure 2).

Cancer

During the follow-up, 19 patients (6.99%) experienced cancer or lymphoma. Of them, 4 patients (1.5%) developed colorectal or small intestine cancer. Other cancer included melanoma skin cancer (n= 2), non-melanoma skin cancer (n= 1), breast cancer (n= 1), lung cancer (n= 1), thyroid cancer (n= 1), ORL cancer (n= 1) and lymphoma (n= 4). Screening colonoscopy was performed in 7 patients (26%) with colonic involvement above 50%.

Disabling disease

The cumulative probabilities of having disabling disease course, as defined in the Methods section were 35% (29%-41%) at 1 year, 57% (50%-63%) at 5 years, 67% (61%-73%) at 10 years and 74% (68%-79%) at 15 years (Figure 3). Factors associated with having a disabling outcome are presented in Table 3. By multivariate analysis, only 2 factors were independently associated with a disabling disease course: systemic symptoms at diagnosis (HR: 1.65 [1.13-2.41], $p=0.01$) and perianal disease (HR: 3.92 [1.79-8.60], $p= 0.0012$) (Table 2 and Figure 3).

Occurrence of bowel damage

Bowel damage, including bowel surgery and/or complicating behaviour (fistulizing or stricturing disease) and/or fistulizing or stricturing anoperineal involvement, occurred in 187 (68.7%) patients. The cumulative probabilities of bowel damage were 61.0% (55.4-66.3), 66.8% (60.9-72.1), 69.2% (63.3-74.6) and 70.7% (64.7-75.9) at 1 year, 5 years, 10 years and 15 years, respectively. By multivariate analysis, the L3 phenotype, systemic symptoms at diagnosis and non-fistulizing perianal disease at diagnosis were independently associated with the occurrence of bowel damage. Conversely, an extended disease at diagnosis (at least two intestinal segments involved) was associated with a decreased risk of bowel damage (Table 2 and Figure 4).

DISCUSSION

The present population-based study reports CD outcomes in the long term with a mean 13-year follow-up. At the last follow-up, only 113 patients (41.5%) had non-stricturing, non-fistulizing behaviour. Of note, a high rate of complicating behaviour was observed at the time of CD diagnosis, in line with population-based studies set up within the same historical period of time^{18, 19}. This high rate of complicated Crohn's may be related to the absence of a widespread use of accurate diagnostic tools during the nineties that led to a delay diagnostic of 8.3 months. A delayed diagnosis of CD precludes early prescription of effective treatment and increases the risk of a diagnosis at the time of a CD complication^{20,21}. Following the diagnosis, the approximately 10% rate of change per 5 years from inflammatory behaviour (B1) to either stricturing (B2) or penetrating (B3) remained stable over 15 years. This is broadly comparable to other studies or even lower than that observed in some recent cohorts, such as a Hungarian cohort, with a behaviour change at 5 years decreasing from 35.5% for the 1977-1988 cohort to 15.2% for the 1999-2008 cohort^{19, 22, 23}.

This low behaviour change may be related to a high rate of complicating behaviour at diagnosis and different medical treatment strategies. However, this study was not able to assess the impact of the use of immunosuppressants or anti-TNF treatment on the disease course. Only one-fifth of the patients were treated during the first year with an immunosuppressant, with an increasing use over time following Crohn's disease complications rather than to prevent CD complicating behaviour. Similarly, anti-TNF treatments were approved at the end of the 1990s, which explains their infrequent use during the first five years of follow-up in the present study. The use of anti-TNF treatment progressively increased following drug approval but remained overall low since only 22.1% of the population received this treatment. Similar trends of anti-TNF use were observed in the Copenhagen cohort for 23.5% of CD patients, which is slightly lower than that observed in this French population^{4,14}. Regarding other treatments, the use of systemic steroids remains high, prescribed for 65.8% of patients with a cumulative probability of use of 43% at 1 year and 55% at 5 years, underlining a large use for nearly one of two patients for the first flare, as reported in another population-based cohort²⁴. Surprisingly, the 5-ASAs remained the most prescribed treatment in this CD cohort, probably due to their tolerance and cost while there are no more recommended²⁵.

Despite a significant decrease from the 1930s up to the 1990s, the requirement for surgery remains high in the biologic era, and up to one-third of patients with CD require major abdominal surgery at 5 years without a drastically decreasing trend in the era of biologics.²⁶ The current study observed a similar feature of the need for surgery, with a cumulative risk estimated at 29% at 5 years and up to 45% at 15 years. Of note, 69 of the 107 operated patients

(64.5%) required a second surgery. The LIR!C trial that compared ileocaecal resection to anti-TNF treatment suggested similar outcomes at one year regarding quality of life.²⁷ Long-term surgical outcomes following the first surgery may question about surgery as a first treatment option for non-complicated Crohn's disease.

A main objective of this study was to look for factors associated with a disabling CD course in a population-based cohort. The definition of a disabling CD outcome remains debated. The first one was derived from the Saint-Antoine cohort study¹². With these criteria, Beaugerie and colleagues reported an 85.2% rate of patients with a disabling disease course at 5 years, which is much higher than that observed in the current study for 35% and 57% of patients at 5 and 15 years after diagnosis, respectively¹². This difference is probably related to the study cohort, which was from a referral centre with more severe patients for the Saint-Antoine cohort and, here, from a population-based cohort better reflecting the real-world for CD prevalence. Contrary to the first study, steroids at CD diagnosis were not assessed because of a part of the definition of disabling CD. There was a trend for the age at CD diagnosis since older patients were found to be associated with a disabling course by univariate analysis but not by multivariate analysis. Interestingly, systemic symptoms at diagnosis, often observed for severe relapse of Crohn's disease, were associated with a disabling course that was previously reported in another referral centre study²⁸. This factor was associated with both disabling disease and bowel damage outcomes and may be considered as a criteria of choice when thinking for early introduction of disease modifying drug. Perianal disease (ulceration and/or fistula and/or stricture) was confirmed to be the main driver of a disabling disease, increasing this outcome by 4.4-fold.

The concept of bowel damage was also assessed in this population-based study since hospitalization and the need for immunosuppressants may not actually represent a disabling course²⁹. The Lemann score could not be properly assessed due to the lack of MRI data related to the study design, but the items that weighted this score were taken into account. Perianal disease was also associated with the occurrence of bowel damage. Interestingly, only baseline non-fistulizing, non-stricturing perianal disease was considered for statistical analysis. This means that not only perianal fistula but perianal fissure and ulcers should be taken into account for physician decision-making. Of note, the presence of deep ulcers was not associated with a disabling disease course or bowel damage, contrary to the findings of a previous retrospective study³⁰. Of note, the presence of deep ulcers was not associated with a disabling disease course or bowel damage, contrary to the findings of a previous retrospective study³⁰, but in line with a recent prospective study on 112 patients by Jauregui-Amezaga and colleagues on severe

endoscopic lesion.³¹ However, a thorough full analysis by each intestinal segments was not performed in the current study.

Although this cohort was prospectively built on a population-based study, there are some other limitations in this study. Data collected for long-term outcomes were retrieved from the charts of patients and were thus dependent on the availability and accuracy of medical records after 15 years. Some data, such as tobacco use or a family history of IBD, were not deeply assessed due to the various notifications in the charts of patients. Some patients moved out of the study area, and some gastroenterologists had retired and did not keep or transmit patient files. Despite these pitfalls, only 15.9% of patients were lost to follow-up of the 370 patients at the inception of the cohort, and no difference in baseline characteristics was observed between patients with and those without follow-up.

To conclude, a majority of CD patients develop complications. Perianal lesions, including non-fistulizing perianal disease, remain the main factor associated with disabling outcomes. ~~The high rate of disabling outcomes may underline the need to treat CD patients with effective treatment regardless of the disease characteristics at diagnosis, including endoscopic lesions.~~

Conflicts of Interest:

ALM, AD, LBH, KC, CB, and CB received lecture fees from IPSEN. **CR, BB, and LS** received lecture fees from Abbvie, Amgen, Ferring, Janssen, MSD, and Takeda and consultant fees from Takeda. **GB** received lecture fees from Abbvie, Ferring, MSD, Takeda and Pfizer and consultant fees from Takeda, Janssen, Mylan, and Abbvie. **VB** and **AN** declared no conflict of interest.

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Figures and Tables legends:

Table 1: Demographic and clinical characteristics at diagnosis

Table 2: Baseline characteristics associated with a disabling disease course and the onset of bowel damage by uni- and multivariate analysis

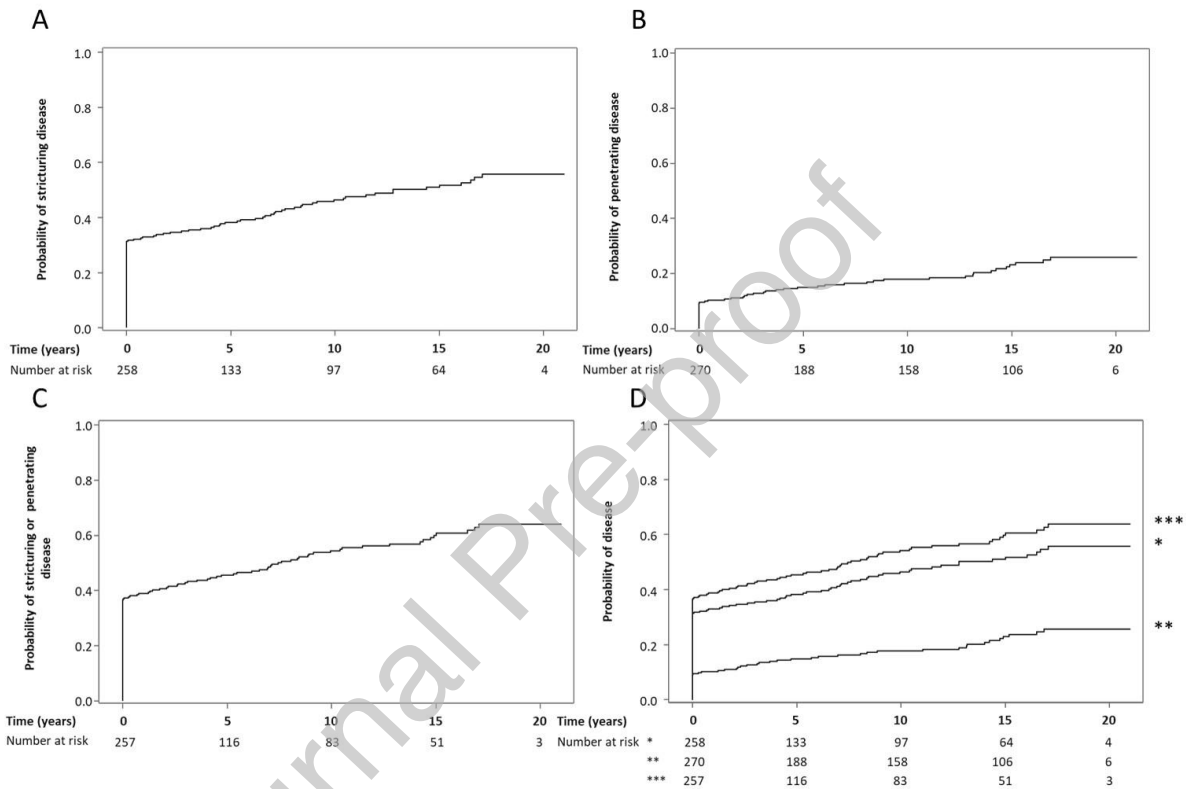


Fig. 1

Figure 1: Cumulative risk of strictureing disease (A), penetrating disease (B), or both (C and D ;

*:strictureing disease, **:penetrating disease, ***: both)

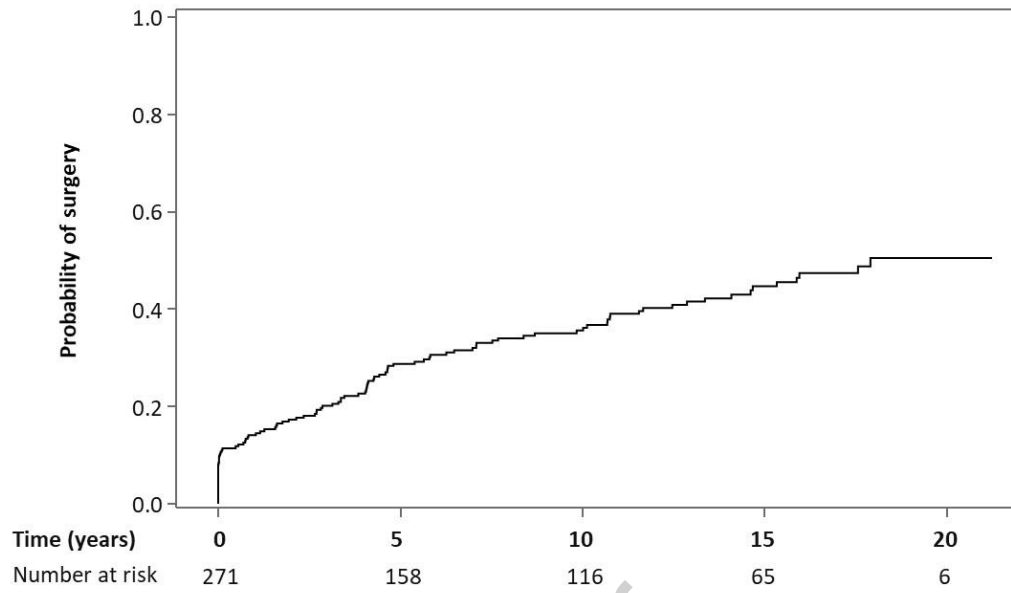


Fig. 2

Figure 2: Cumulative probabilities of being surgery-free

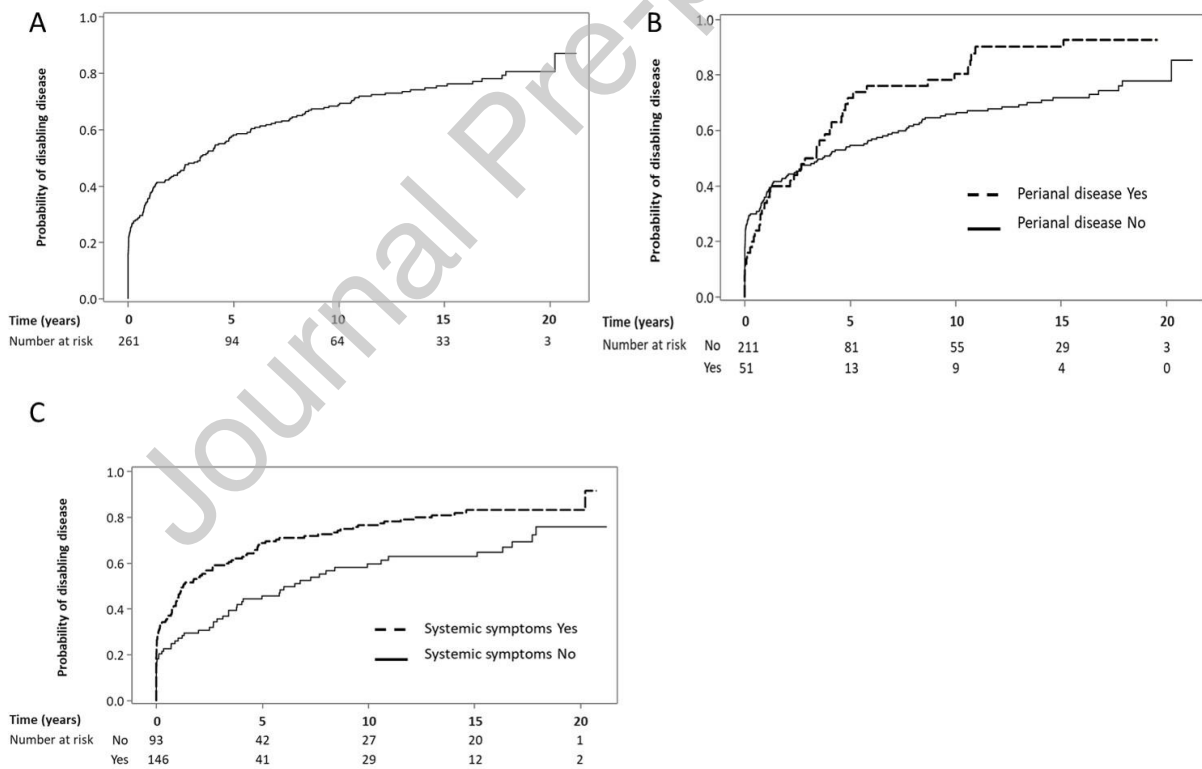


Fig. 3

Figure 3: Cumulative risk of disabling disease (A) and factors associated with the onset of disabling disease: perianal disease (B) and systemic symptoms (C)

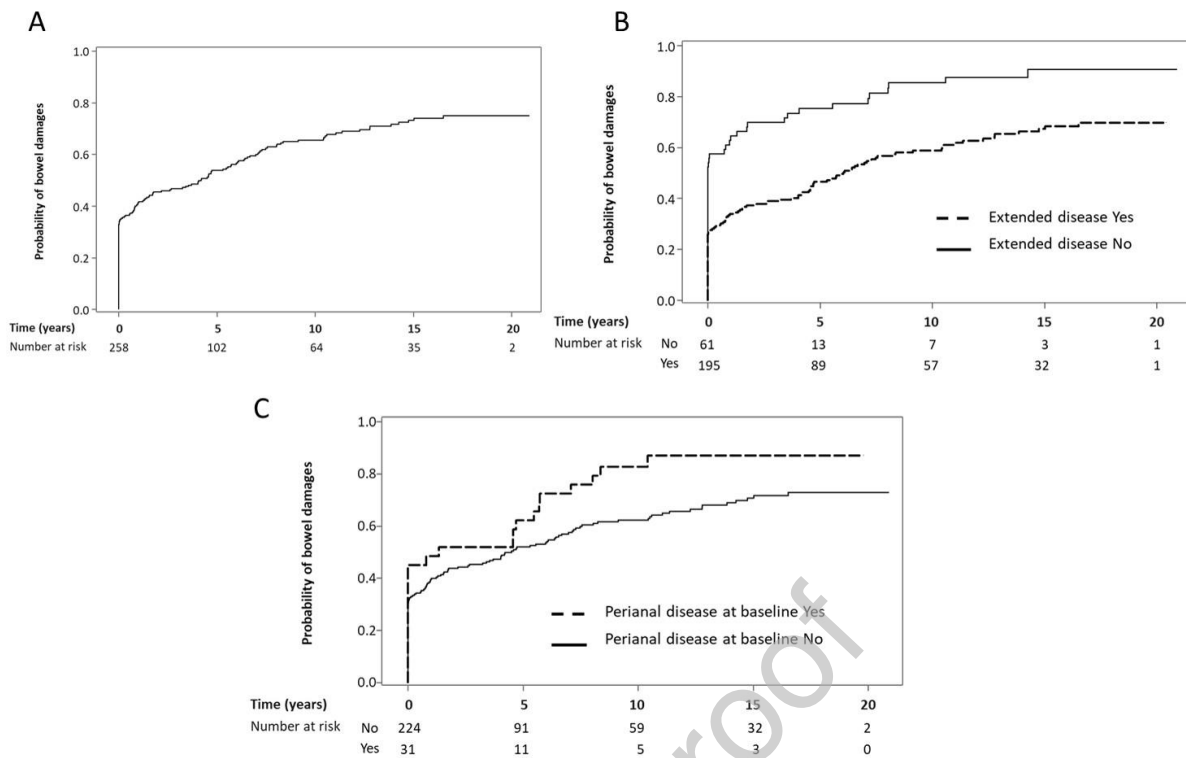


Fig. 4

Figure 4: Cumulative risk of bowel damage and factors associated with the onset of bowel damage (A): extended disease (B) and anal ulceration (C)

Supplementary materials

Supplementary Table 1: Comparison of baseline characteristics of Crohn's disease patients according to the presence or absence of a follow-up

Supplementary Table 1: Endoscopic lesions at diagnosis in 249 (91.5%) complete colonoscopies

Supplementary Figure 1: Flowchart of the study

Supplementary Figure 2: Cumulative risks of receiving steroids (A), purines (B), and anti-TNF (C)

Table 1: Demographic and clinical characteristics at diagnosis

Item	n (%) or mean (+/-SD)
<i>Demographic features</i>	
Workplace	
Referral centres	35 (12.9)
Regional hospitals	62 (22.8)
Private practice	175 (64.3)
Male	126 (46.3)
Age (Montreal classification)	
A1 - <17	36 (13.2)
A2 - 17-40	154 (56.6)
A3 - >40	82 (30.2)
Family history of inflammatory bowel disease	21 (11.3)
<i>Clinical features</i>	
Time from the onset of symptoms to diagnosis >9 months	68 (25.0)
Diarrhoea – n (%)	177 (65.1)
Rectal bleeding – n (%)	72 (26.9)
Abdominal pain – n (%)	221 (82.2)
Fever – n (%)	72 (28.7)
Weight loss – n (%)	122 (50.6)
Systemic symptoms at diagnosis – n (%)	153 (61.2)
Extraintestinal manifestations – n (%)	35 (14.1)
<i>Disease phenotype</i>	
Disease location (Montreal classification)	
L1 – ileal disease	41 (15.2)
L2 – colonic disease	98 (36.3)
L3 – ileocolonic disease	131 (48.5)
L4 – upper gastrointestinal disease	61 (22.4)
Extension of the lesion	
> 15 cm in the small intestine	117 (59.1)
> 15 cm in the colon	168 (65.9)
Extended disease*	203 (75.5)
Disease behaviour (Montreal classification)	
B1 – non-fistulizing, non-stricturing disease	178 (65.4)
B2 – structuring disease	69 (25.4)
B3 – penetrating disease	25 (9.1)
Perianal disease– n (%)	51 (18.7)
Surgery at diagnosis	20 (7.3)
Epithelioid granuloma	108 (42.9)

Table 2 Baseline characteristics associated with a disabling disease course and the onset of bowel damage by uni- and multivariate analysis

Baseline factor	Risk factor for disabling disease				Risk factor for bowel damage			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)
Physician workplace	0.02	0.70 (0.52-0.93)	0.19		0.81	1.03 (0.75-1.41)	-	
Male	0.57	0.92 (0.69-1.23)	-		0.59	0.92 (0.68-1.24)	-	
Age (years) at diagnosis	0.015		0.29		0.17		-	
A1 <17		1.93 (1.21-3.08)				0.99 (0.60-1.65)		
A2 17-40		1.5 (1.05-2.14)				1.34 (0.94-1.92)		
A3 >40		ref				ref		
<i>Clinical features at diagnosis</i>								
Time from the onset of symptoms to diagnosis >9 months	0.02	1.45 (1.06-2)	0.11		0.13	1.288 (0.92-1.79)	0.28	
Digestive symptoms	0.38	1.30 (0.72-2.33)	-		0.40	1.27 (0.68-2.14)	-	
General symptom (fever, weight loss, growth deficiency)	0.002	1.64 (1.19-2.26)	0.01	1.65 (1.13-2.41)	0.05	1.378 (0.99-1.91)	0.018**	2.86 (1.20-6.83)
Extraintestinal manifestations	0.12	1.40 (0.92-2.12)	0.91		0.66	1.10 (0.68-1.69)	-	
<i>Disease phenotype</i>								
Disease location	0.34		-		0.0001		0.029	
L1		1.4 (0.9-2.09)				2.62 (1.71-4.03)		1.57 (0.81-3.04)
L2		ref				ref		ref
L3		1.19 (0.86-1.64)				1.19 (0.84-1.67)		1.67 (1.09-2.57)
L4	0.27	1.21 (0.86-1.69)	-		0.73	0.94 (0.67-1.35)	-	
Extension of the lesion								
>15 cm bowel involvement	0.87	0.96 (0.57-1.60)	-		0.12	1.46 (0.89-2.39)	0.43	
Absence of extended disease	0.77	0.95 (0.68-1.33)	-		0.0001	1.99 (1.43-2.77)	0.026	2.15 (1.1-4.23)
Perianal disease – n (%)	0.07	1.38 (0.98-1.93)	0.0007*	3.92 (1.79-8.60)				
Non-fistulizing perianal disease					0.071	1.47 (0.97-2.23)	0.041	1.59 (1.02-2.47)
Epithelioid granuloma	0.10	1.29 (0.95-1.75)	0.90		0.36	0.86 (0.63-1.18)	-	
Deep ulcers at colonoscopy	0.11	1.31 (0.94-1.82)	0.60		0.95	1.020.64-1.70)	-	

*the risk is significant after 36 months

**the risk is significant after 60 months