Clinics in Surgery

Research Article
Published: 28 Oct, 2022

Deep Endoscopic Ulcerations are not Associated with the Need for Surgery or Complicated Behavior: A Population-Based Study

*Brunet T[1], Siproudhis L[1], Brochard C[1], Rabilloud ML[2], Bajeux E[3], Pagenault M[1] and Bouguen G[1]**

[1]CHU Pontchaillou, Service des Maladies de l'Appareil Digestif, France

[2]Centre Hospitalier Bretagne Atlantique, France

[3]CHU Pontchaillou, Service de Santé Publique, France

Abstract

Background: Severe Endoscopic Lesions (SEL) during Crohn's Disease (CD) are usually thought to increase disease complications and the need for surgery but based on a low level of evidence. Aims were to assess disease outcomes of patients with SEL at CD diagnosis on a population-based cohort.

Methods: All incident CD cases were prospectively registered from 1994 to 1997 in a limited area of France and charts were reviewed until the last known clinics. SEL was defined by a deep ulceration on at least one intestinal segment. Survival analysis was performed to assess disease outcomes according to SEL at diagnosis on the whole population and restricted to patients with uncomplicated behavior at diagnostic.

Results: Among the 272 followed-up patients, 257 (94%) patients were included (exclusion of 15 (6%) patients without colonoscopy at diagnostic). SEL were present at initial colonoscopy for 59 (23%) patients on at least one segment and on two segments for 27 (10%). There was no association between the presence of SEL and the need for surgery (log rank =0.49), the onset of complicated behavior (log rank =0.81) nor hospitalization (log rank =0.95). Looking at the 164 of the 257 (64%) with a complete colonoscopy and a noncomplicated behavior at diagnostic, no association between SEL and each outcome were observed although patients with SEL were more likely treated with immunosuppressant (log rank =0.0028).

Conclusion: On a population-based cohort, SEL at diagnosis was not associated with an increased risk of surgery nor Crohn's disease complications despite for an increased use of IS.

Keywords: Crohn's disease; Population based; Deep ulceration

OPEN ACCESS

Correspondence:
Guillaume Bouguen, CHU Pontchaillou, Service des Maladies de l'Appareil Digestif, 2 rue Henri le Guillou, 35033 Rennes cedex, France, Tel: (0033)-2-99-28-43-17; Fax: (0033)-2-99-28-41-89;
E-mail: guillaume.bouguen@chu-rennes.fr

Received Date: *21 Sep 2022*
Accepted Date: *20 Oct 2022*
Published Date: *28 Oct 2022*

Citation:
Brunet T, Siproudhis L, Brochard C, Rabilloud ML, Bajeux E, Pagenault M, et al. Deep Endoscopic Ulcerations are not Associated with the Need for Surgery or Complicated Behavior: A Population-Based Study. Clin Surg. 2022; 7: 3582.

Copyright *© 2022 Bouguen G. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

Introduction

Crohn's Disease (CD) is a chronic inflammatory bowel disease that leads to a sequence of flares and remissions of varying durations [1,2]. The unremitting inflammatory process results in a disabling course with bowel complications such as strictures and fistulas [3,4]. These complicated behaviors are not uncommon and still lead to the need for surgery for 50% of patients with CD [3-7]. Patients' quality of life is further altered by the need for hospitalization, the disabling symptoms and the subsequent psychological and nutritional difficulties. The advent of biologics to treat CD patients largely improved their outcomes but early screening of patients at risk, candidates for biologics remains subjective and far away from a personalized approach. The traditional management of CD progressively moved to a treat-to-target strategy with the aim of disease extinction marked by mucosal healing [8-10]. This concept implies the need to early treat selected patients at high risk of disabling outcome with effective treatment [11]. Several studies proposed over the last decades clinical features associated with poor prognosis of CD such as disease location, behavior or biological markers [12-15]. Unfortunately, no accessible prediction rule of disease outcomes is validated for the standard of care. Some studies proposed endoscopic assessment by colonoscopy at diagnosis to predict long term outcome of CD. The landmark French cohort found an association between endoscopic disease severity and surgery: A 5 to 6 fold increased risk of colectomy was observed in cases of Severe Endoscopic Lesion (SEL) [16,17]. The study was retrospective and concerned late CD patients with a three years median follow-up. In addition to the small sample size of the

study (N=102), patients were selected from a tertiary center with more complicated and refractory CD; 59 (58%) patients were already exposed to immunosuppressants during the study. The only other study on this subject has not confirmed this consensual admitted risk factor [18]. The aim of this study was to assess disease outcomes of patients with SEL at CD diagnosis on a population-based cohort.

Material and Methods

ABERMAD registry

The ABERMAD Registry included all incident CD from 1994 to 1997 in a population of 3.3 million inhabitants of Brittany (West of France) which represented 4.6% of the French population. The cohort was built according to EPIMAD registry's methodology described elsewhere [19]. In brief, private and public gastroenterologists (N=139) 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 fulfilled at the gastroenterologist's consulting room a standard questionnaire for each patient. 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 [20].

Colonoscopy

Endoscopic lesions at diagnosis were prospectively recorded. Endoscopic features included unspecific lesion, aphthoid, superficial and deep ulceration as well as stenosis or fistula and were recorded according to the items of the CDEIS [21] for each segment, if available: Left colon, right colon, caecum and ileum. SEL were defined by a deep ulceration on at least one intestinal segment.

Study population

Our study included all incident cases of definite or probable CD of the ABERMAD registry with a colonoscopy at diagnosis. A subgroup analysis was performed to avoid baseline confounding events linked to outcome measure: Patients with a complete colonoscopy (to the caecum) and without stricturing or fistulizing disease at diagnosis or surgery within the first month constituted this subgroup.

Data collection

An interviewer went to the gastroenterologist's consulting room and collected data through the medical records from date of CD diagnosis until last follow-up or date of last medical record. The following data were collected prospectively: Sex, age, family history of Inflammatory Bowel Disease (IBD), extra-intestinal symptoms, time between onset of symptoms and diagnosis, fever, clinical abdominal mass, weight-loss, smoking-habits, hospitalization, department of residence and of diagnosis, presence of granuloma on histology specimens. CD localization and behavior were based on the Montreal classification [3]. All treatments during the study period were retrieved including 5-aminosalicylates, corticosteroids (oral and topical steroids), Immunosuppressant (IS) therapies regrouping: Thiopurines (azathioprine, 6-mercaptopurine), methotrexate, and anti-TNF therapies (infliximab and adalimumab). All hospitalizations related to CD were retrieved from the follow-up. The mean follow-up was 12.8 years (± 6.2). The disease outcomes were: (i) a complicated behavior defined by the onset of a stricturing or fistulizing disease or Perineal Crohn's Disease (PCD). These items were chosen as items of the Leman score defining bowel damage [13]. PCD included rectal stricture and anoperineal fistula but not anal ulcerations; (ii) the need for surgery; (iii) the need for hospitalization related to disease flare and (iv) immunosuppressant initiation.

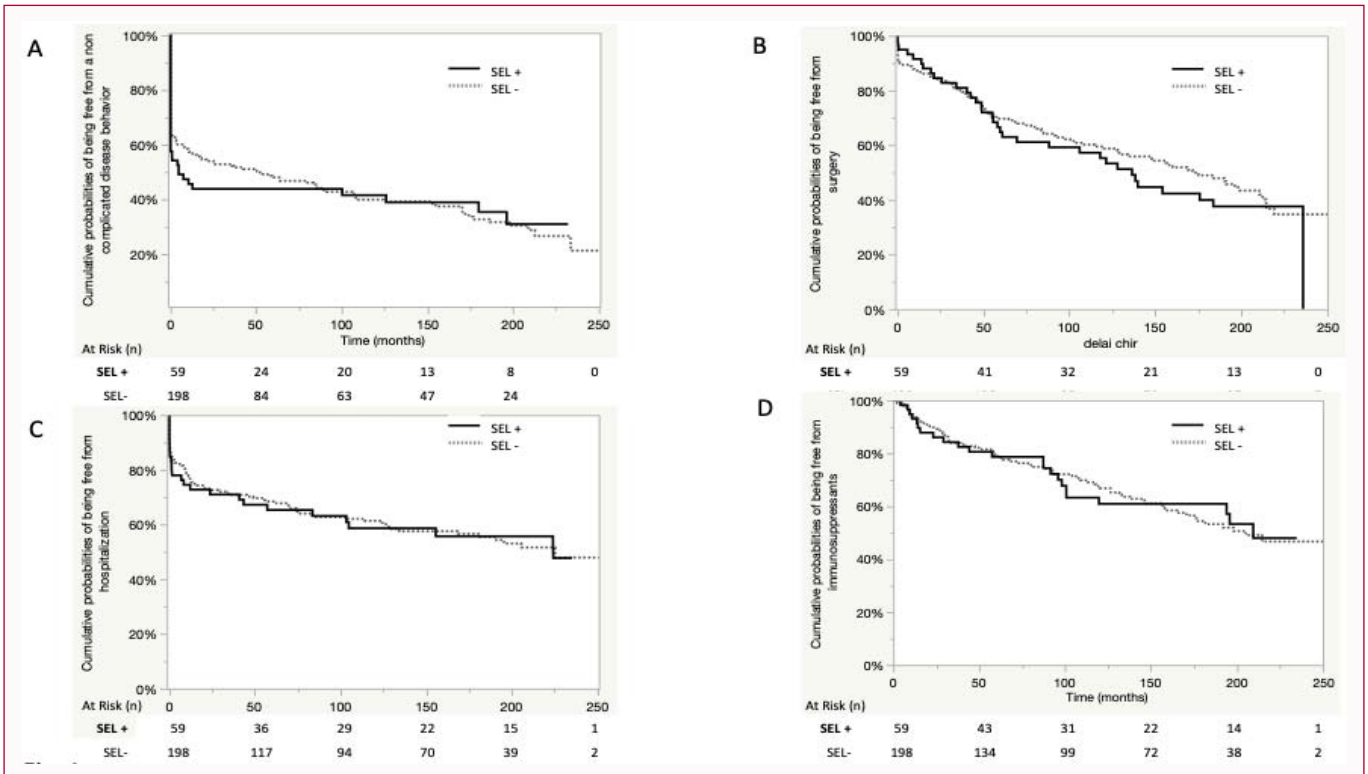

Figure 1: Kaplan-Meier curve of survival free from complicated behavior (1A), surgery (1B), hospitalization (1C) and the use of immunosuppressant (1D) according to the presence (SEL+) or absence (SEL-) of severe endoscopic lesions.

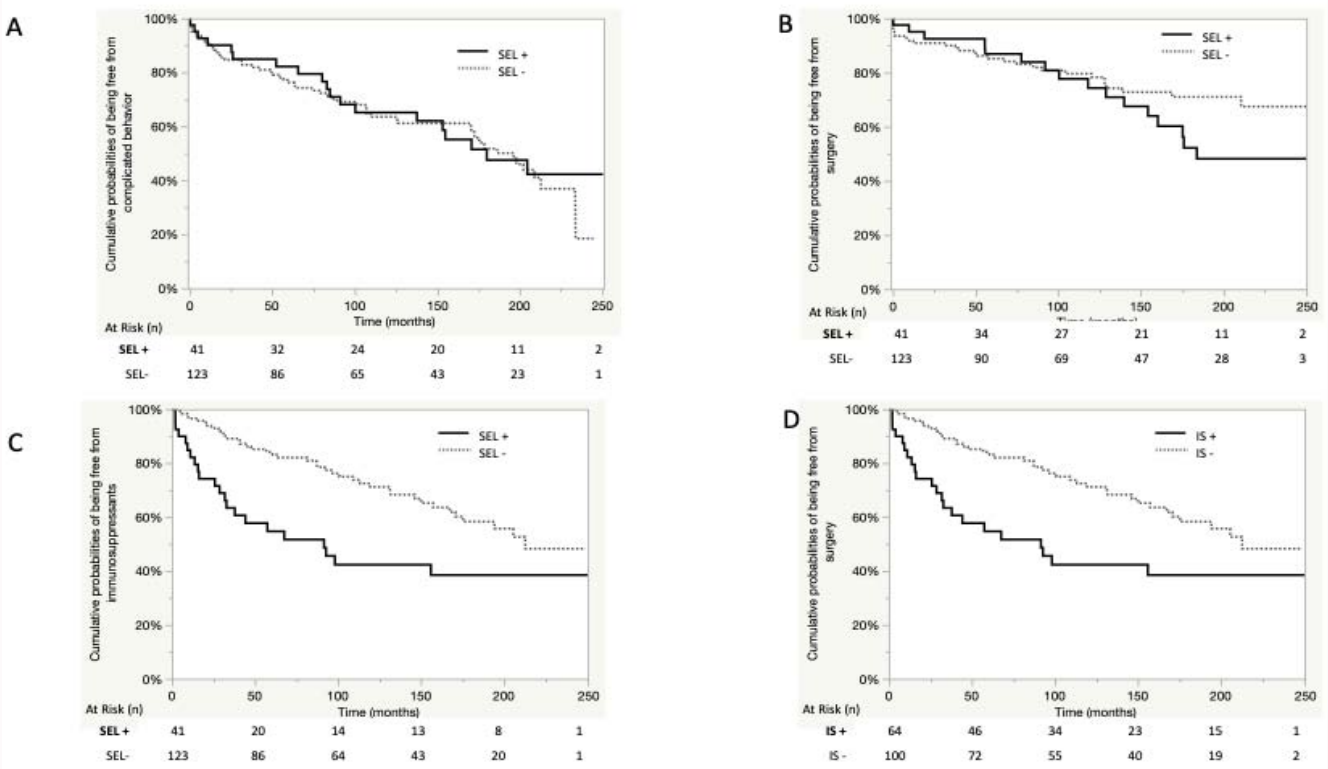

Figure 2: Kaplan-Meier curve within the subgroup of non-complicated Crohn's disease at diagnostic according to the presence of Severe Endoscopic Lesions (SEL+) or absence (SEL-) at diagnosis for the onset of complicated behavior (2A), for the need for surgery (2B), for the need for hospitalization (2C) and the need for surgery according to the use of immunosuppressant (2D).

Statistical analysis

The quantitative data are expressed as means (± standard deviation) and the qualitative data as numbers and percentages. For group comparisons, univariate analysis was performed using the Wilcoxon test for quantitative variables, and a chi-square test (or Fischer test) as appropriate for qualitative variables. Kaplan-Meier survival curves were plotted for variables with censored data. Variables were censored according to each outcome or last known follow-up. A Cox proportional hazards regression model adjusted for baseline difference between groups was performed for group comparison of each disease outcome. The results were shown as Hazard Ratios (HRs) with 95% confidence intervals. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using JMP® Pro 13.2.0 software.

Results

Baseline characteristics

Between 1994 and 1997, 272 followed-up patients with definite or probable CD were included in the ABERMAD cohort. The rate of lost to follow-up of the cohort was 16%. A total of 15 (6%) patients were excluded because they did not undergo a colonoscopy. The study population included 257 patients (Figure 3). There were 136 females (53%) and the mean age was 28 (± 19 years) years old at diagnosis. The mean time from onset of symptoms to diagnosis was 3 months (± 11.9 months). A total of 38 patients (15%) needed hospitalization at diagnosis. PCD was found in 46 (18%) cases upon diagnosis. Baseline characteristics according to the presence or absence of SEL are depicted in Table 1. Patients with SEL did not present a different phenotype. Table 2 summarizes data recorded from the 257 colonoscopies at diagnosis. Deep ulcers were present at initial colonoscopy for 59 (23%) patients on at least one intestinal segment, on two segments for 27 (13%). Among the 257 patients, 164 had a non stricturing, non-fistulizing disease, a complete colonoscopy and no surgery within the first month of diagnosis (Figure 3). Deep ulcers were present at initial colonoscopy for 41 (25%) patients on at least one intestinal segment, on two segments for 21 (13%). The SEL were strictly ileal in 17 (10%) cases, strictly colic in 70 (43%) and ileocolic in 77 (47%) patients. Baseline characteristics are also depicted in Table 1, patients with SEL were more likely hospitalized at diagnosis (p=0.027) with weight loss (p=0.048).

Therapeutic use

The use of corticosteroid during the first month after diagnosis was reported in 79 (30%) cases, significantly higher in the SEL+ group (p=0.02). During the follow-up, a total of 105 patients (41%) were treated with either thiopurines, methotrexate or an anti-Tumor Necrosis Factor (TNF) agent (or two of these IS) as follows: 99 with thiopurines or methotrexate and 57 with an anti-TNF therapy. Purin analogs were used in all cases among which 10 were also knew treatment with methotrexate. Infliximab was the most frequent anti-TNF therapy, used in 45 cases. The mean period between diagnosis and Thiopurin initiation was 5.8 (± 4.9) years and 11.2 (± 4.5) years for anti-TNF initiation. Among these patients, 39 out of 96 patients (40%) received an IS or an anti-TNF before a first surgery or the onset of a complicated behavior.

Disease outcomes

(i) After a mean follow-up of 12.3 years, 163 (63%) patients experienced a complicated behavior with either a luminal stritcturing

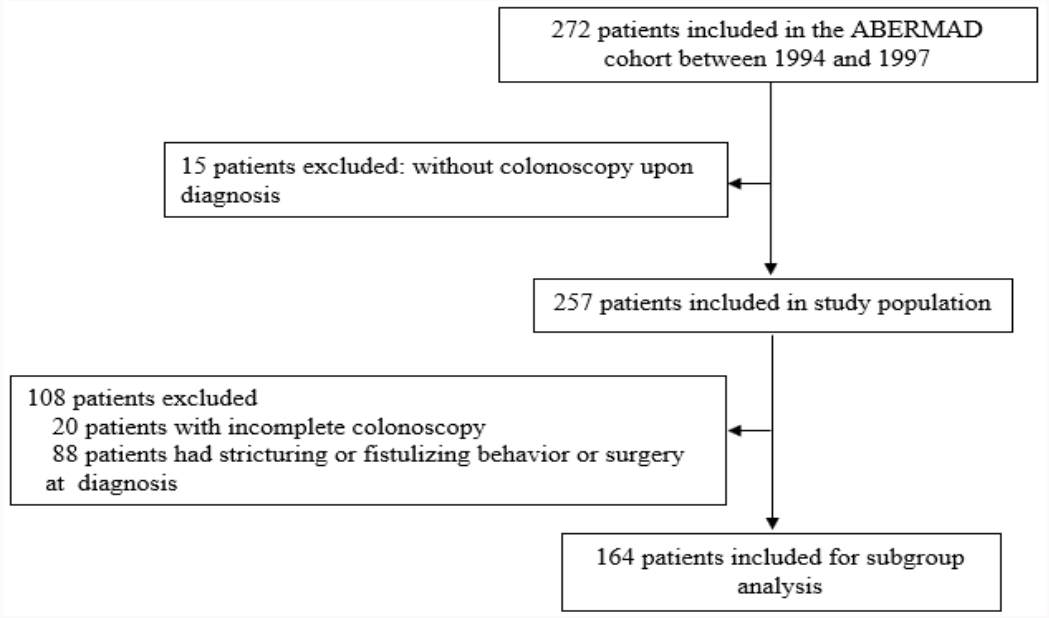

Figure 3: Flow chart of subgroup analysis of patients without complicated disease at the entry in the ABERMAD cohort.

or fistulizing disease or PCD. The cumulative probabilities of developing a complicated behavior as defined were 59%, 63% and 66% at 5, 10 and 15 years respectively. There was no association between SEL and the development of fistula, stricture or PCD (log-rang =0.81 – HR=1.03 IC95[0.7-1.3]) (Figure 1A).

(ii) A total of 130 (51%) underwent an abdominal surgery during the follow-up. The cumulative probabilities of the need for surgery were 36%, 45% and 51% at 5, 10 and 15 years respectively. There was no association between SEL and the need for surgery during follow-up (p=0.49 - HR=1.1 IC95[0.7-1.7]) (Figure 1B).

(iii) The cumulative probabilities of hospitalization for disease flare were 36%, 40% and 43% at 5, 10 and 15 years respectively. No association between SEL and hospitalization during the follow-up was observed (p=0.95 - HR=1.01 IC95[0.6-1.6]) (Figure 1C).

(iv) The cumulative probabilities of IS initiation were 20%, 34% and 45% at 5, 10 and 15 years respectively. No association between SEL and IS use during the follow-up was observed (p=0.98 - HR=0.99 IC95[0.62-1.59]) (Figure 1D).

Subgroup analysis on patients with non-complicated CD at diagnostic

The cumulative probabilities of developing a complicated behavior as defined were 27%, 40% and 49% at 5, 10 and 15 years respectively. There was no association between SEL and the development of luminal fistula, stricture or PCD (p=0.72) after adjustment on significant differences found on baseline characteristics (hospitalization and weight loss). The cumulative probabilities of the need for surgery were 18%, 26% and 31% at 5, 10 and 15 years respectively. There was no association between SEL and the need for surgery during follow-up (p=0.39) after adjustment on significant differences found on baseline characteristics (hospitalization and weight loss). The cumulative probabilities of hospitalization for disease flare were 27%, 35% and 39% at 5, 10 and 15 years respectively. After adjustment on baseline differences (hospitalization and weight loss), no association between SEL and hospitalization during the follow-up was observed (p=0.79). Patients with SEL were more likely treated with an IS (p=0.026) after adjustment on significant differences at baseline (Figure 2). The cumulative probabilities of IS initiation were 22%, 36% and 46% at 5, 10 and 15 years respectively. To assess whether the use of IS may decrease disabling outcomes in this subgroup of patients presenting SEL with a non-complicated CD at diagnosis, further analysis was performed. The use of IS was associated with an increased risk of surgery (p=0.0004) or complicated behavior such as fistula, stricture or PCD during follow-up (p<0.001). The association remained when the analysis was restricted to the use of immunosuppressant before the outcome measure.

Discussion

From this well-defined population-based study, SEL at diagnosis was not associated with an increase of CD complications. Despite a potentially more severe clinical presentation, no association on the long-term was found between SEL and the need for surgery, the onset of luminal stricturing or fistulizing disease nor PCD, hospitalization and IS use. The increase use of IS in uncomplicated CD patients at diagnosis with SEL may not prevent these dreaded outcomes. The prospective population-based cohort on a well-defined geographical area is one of the strengths of this study. This is the first study to address this question of SEL in a non-selected population. This is underlined by the proportion of patients with SEL at baseline: 59 (23%) patients presenting with SEL as compared to the study of Allez et al. or of Jauregui-Amezaga et al. from referral centers with 52% and 46% rates of patients showing SEL, respectively [16,18]. Rates of surgical resections were consistent with previous data from Allez et al. showing a 42% cumulative probability of surgery at 8 years. A high rate of penetrating or fistulizing complications was noted at diagnosis but was similar to population-based studies of the same period of time [22,23]. CD complications were slightly higher in our study probably given the analysis of anoperineal complications that may have overestimated the results. Several limitations have to be noted. The cohort was set up during the nineties and only the CDEIS was used and validated as an endoscopic scoring system

Table 1: Baseline characteristics at diagnosis.

	Overall Population (n=257)			Non-complicated CD at diagnosis (n=164)		
	SEL + n=59	SEL – n=198	p	SEL + n=41	SEL – n=123	p
Demographic features						
Male	27 (45)	94 (47)	0.81	16 (39)	58 (47)	0.36
Age - Montreal Classification			0.68			0.48
A1 - <17 – no. (%)	6 (10)	28 (14)		6 (15)	17 (14)	
A2 - 17-40 – no. (%)	37 (62)	114 (57)		26 (63)	67 (54)	
A3 - >40 – no. (%)	16 (27)	56 (28)		9 (22)	39 (32)	
Smoking status			0.24			0.065
Active upon diagnosis – no. (%)	10 (16)	36 (18)		10 (24)	20 (16)	
History of smoking – no. (%)	10 (16)	23 (11)		10 (24)	10 (8)	
Hospitalization at diagnosis – no. (%)	9 (15)	29 (14)	0.91	9 (22)	11 (9)	0.027
Family history of IBD – no. (%)	4 (10)	17 (12)	0.71	2 (5)	11 (9)	0.36
Initial medical referral			0.98			0.42
University Hospital – no. (%)	7 (11)	25 (12)		7 (17)	16 (13)	
Regional hospital – no. (%)	13 (22)	44 (22)		11 (27)	24 (19)	
Private practice – no. (%)	39 (66)	129 (65)		23 (56)	83 (67)	
Clinical features						
Symptoms – no. (%)						
Symptoms duration before diagnosis (months) – mean (SD)	8 (12)	7.6 (11)	0.84			
Systemic Symptoms – no. (%)	8 (13)	25 (12)	0.79	7 (17)	15 (12)	0.62
Fever – no. (%)	14 (35)	50 (27)	0.26	14 (34)	28 (23)	0.25
Abdominal mass – no. (%)	1 (2)	10 (5)	0.28	1 (2)	5 (4)	0.61
Weight loss – no. (%)	26 (48)	92 (53)	0.51	23 (56)	49 (40)	0.048
Disease characteristics						
Disease Location - Montreal Classification			0.39			0.78
L1 – ileal – no. (%)	5 (8)	30 (15)		3 (7)	13 (10)	
L2 – colonic – no. (%)	24 (41)	70 (36)		19 (46)	51 (41)	
L3 – ileocolonic – no. (%)	30 (51)	96 (49)		19 (49)	58 (47)	
L4 – upper gastrointestinal – no. (%)	11 (27)	45 (22)	0.51	11 (27)	22 (18)	
Disease Behavior - Montreal Classification			0.72			
B1	37 (62)	132 (66)				
B2	2 (4)	9 (4)				
B3	20 (34)	57 (28)				
Granuloma upon histological analysis – no. (%)	24 (43)	77 (40)	0.73	18 (44)	47 (38)	0.54
Corticosteroid use first month – no. (%)	20 (34)	59 (29)	0.55	19 (46)	33 (27)	0.02

Table 2: Endoscopic description at diagnosis.

N (%)	Rectum (n=257)	Sigmoid and left colon (n=257)	Transverse and right colon (n=246)	Caecum (n=237)	Ileum (n=193)
Aphtoid ulceration	50 (19.4)	67 (26.0)	68 (27.6)	63 (26.6)	51 (26.4)
Superficial ulceration	48 (18.6)	74 (28.8)	56 (22.7)	56 (23.6)	51 (26.4)
Deep ulceration	12 (4.7)	28 (10.9)	27 (11.0)	17 (7.2)	22 (11.4)

[21]. While the CDEIS was not calculated at baseline, each item of the score was prospectively recorded by the gastroenterologist at referral. A limited but known interobserver subjectivity regarding endoscopic evaluation exists leading actual trials to systematically perform a central reading of endoscopic procedure that was not done here with a potential misclassification of endoscopic lesion [24,25]. Deep ulcerations are usually thought to reflect the dreaded nature of transmural inflammation in CD leading potentially to complicated behavior and ultimately surgery. Strong data now shows that early deep remission is linked to a decrease in long-term disease progression [26-28]. Although mucosal healing is linked to better prognosis, data concerning the prognostic value of SEL remains contradictory. First

Table 3: Disease outcomes according to endoscopic lesion at diagnosis (HR (IC 95%), p-value).

		Surgery	Complicated behavior	Hospitalization	IS use
Overall Population N=257	Deep ulcer on at least 1 segment	1.14, (0.77-1.69), 0.50	1.05 (0.63-1.74), 0.84	1.01 (0.64-1.58), 0.95	0.99 (0.62 -1.59), 0.98
	Deep ulcer on at least 2 segment	1.02, (0.59-1.76), 0.93	1.05 (0.63-1.74), 0.84	0.87 (0.45-1.69), 0.70	1.05 (0.57- 1.93), 0.87
Non complicated CD at diagnostic N=164	Deep ulcer on at least 1 segment	1.34 (0.68-2.61), 0.38	0.90 (0.52 -1.55), 0.71	1.08 (0.61-1.91), 0.78	1.91 (1.08 -3.38), 0.02
	Deep ulcer on at least 2 segment	1.37, (0.61-3.09), 0.44	0.81 (0.40 -1.62), 0.56	1.01 (0.48-2.10), 0.97	2.21 (1.14-4.31), 0.01

data published in 1992 by Landi et al. showed no prognostic value of endoscopic extent or severity on clinical outcomes following a course of steroids [29]. Conversely, Saint Louis' retrospective study found deep ulcerations to be associated with complicated behaviors or colectomy [16,17]. A more recent prospective study by Jauregui-Amezaga et al. did not observe any predictive value of SEL on 112 patients with CD [18]. The recent post-hoc analysis of the TAILORIX randomized controlled trial confirmed that endoscopic severity at baseline for CD does not modify the rates or delay of mucosal healing [30]. A subgroup analysis was performed given the large number of patients presenting a stricturing or fistulizing disease or the need for surgery at diagnosis. This aimed to limit bias related to baseline confounder with outcome measures such as the increase risk of surgery or complicated behavior. The aim was also to help physician's decision-making faced with non-complicated CD patients. In this sub-group, patients with SEL had a more severe clinical presentation. These clinical features might explain the increased use of IS. One may argue that such therapeutic incrementation may decrease the need for surgery but IS intake was controversially associated with an increase rate of surgery. At the time of inclusion, thiopurines and methotrexate were the only immunosuppressant used. Anti-TNF treatments were later approved and started after a long disease duration and often in operated patients making it difficult to assess whether biologics are disease modifying agents. From a therapeutic point of view, the present population is comparable to the one from the Allez study which was not treated with anti-TNF agents but 58% were exposed to thiopurines and methotrexate whereas 70% of the patients included in the more recent Jauregui-Amezaga's study received anti-TNF. This important factor may explain discrepancies between results. However, the TAILORIX post-hoc analysis confirmed that endoscopic severity does not influence disease outcomes even with biologics [30].

In conclusion, SEL at diagnosis does not alone predict Crohn's disease outcomes. On the other hand, the presence of SEL for non-complicated CD may have led to more IS initiation even before the occurrence of a complication. Patients requiring such incrementation seemed to show a more severe disease course at the time of occasional IS use.

References

1. Peyrin-Biroulet L, Loftus EV, Colombel J-F. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol. 2010;105:289-97.
2. Cosnes J, Gower-Rousseau C, Seksik P. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140:1785-94.
3. Silverberg MS, Satsangi J, Ahmad T. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19:5A-36A.
4. Louis E, Collard A, Oger AF. Behavior of Crohn's disease according to the Vienna classification: Changing pattern over the course of the disease. Gut. 2001;49:777-82.
5. Sands BE, Arsenault JE, Rosen MJ. Risk of early surgery for Crohn's disease: Implications for early treatment strategies. Am J Gastroenterol. 2003;98:2712-8.
6. Thia KT, Sandborn WJ, Harmsen. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. Gastroenterology. 2010;139:1147-55.
7. Solberg IC, Vatn MH, Høie O. Clinical course in Crohn's disease: Results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol. 2007;5:1430-8.
8. Shah SC, Colombel J-F, Sands BE. Systematic review with meta-analysis: Mucosal healing is associated with improved long-term outcomes in Crohn's disease. Aliment Pharmacol Ther. 2016;43:317-33.
9. Peyrin-Biroulet L, Sandborn W, Sands BE. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110:1324-38.
10. Bouguen G, Levesque BG, Feagan BG. Treat to target: A proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol. 2015;13:1042-1050.e2.
11. Khanna R, Bressler B, Levesque BG. Early combined immunosuppression for the management of Crohn's disease (REACT): A cluster randomised controlled trial. Lancet. 2015;386:1825-34.
12. Beaugerie L, Seksik P, Nion-Larmurier I. Predictors of Crohn's disease. Gastroenterology. 2006;130:650-6.
13. Pariente B, Cosnes J, Danese S. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis. 2011;17:1415-22.
14. Ryan JD, Silverberg MS, Xu W. Predicting complicated Crohn's disease and surgery: Phenotypes, genetics, serology and psychological characteristics of a population-based cohort. Aliment Pharmacol Ther. 2013;38:274-83.
15. Siegel CA, Horton H, Siegel LS. A validated web-based tool to display individualised Crohn's disease predicted outcomes based on clinical, serologic and genetic variables. Aliment Pharmacol Ther. 2016;43:262-71.
16. Allez M, Lemann M, Bonnet J. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol. 2002;97:947-53.
17. Allez M, Lémann M. Role of endoscopy in predicting the disease course in inflammatory bowel disease. World J Gastroenterol. 2010;16:2626-32.
18. Jauregui-Amezaga A, Rimola J, Ordás I. Value of endoscopy and MRI for predicting intestinal surgery in patients with Crohn's disease in the era of biologics. Gut. 2015;64:1397-402.
19. Gower-Rousseau C, Salomez JL, Dupas JL. Incidence of inflammatory bowel disease in northern France (1988-1990). Gut. 1994;35:1433-8.
20. Lennard-Jones JE, Shivananda S. Clinical uniformity of inflammatory bowel disease a presentation and during the first year of disease in the north and south of Europe. EC-IBD Study Group. Eur J Gastroenterol Hepatol. 1997;9:353-9.
21. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: A prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989;30:983-9.

22. Lakatos PL, Golovics PA, David G. Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from Western Hungary between 1977-2009. Am J Gastroenterol. 2012;107:579-88.

23. Fumery M, Pariente B, Sarter H. Long-term outcome of pediatric-onset Crohn's disease: A population-based cohort study. Dig Liver Dis. 2019;51:496-502.

24. Reproducibility of colonoscopic findings in Crohn's disease: A prospective multicenter study of interobserver variation. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Dig Dis Sci. 1987;32:1370-9.

25. Panés J, Feagan BG, Hussain F. Central endoscopy reading in inflammatory bowel diseases. J Crohns Colitis. 2016;10:S542-547.

26. Baert F, Moortgat L, Van Assche G. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;138:463-8;quiz e10-11.

27. Narula N, Wong ECL, Aruljothy A. Ileal and rectal ulcer size affects the ability to achieve endoscopic remission: A Post hoc analysis of the SONIC trial. Am J Gastroenterol. 2020;115:1236-45.

28. Ungaro RC, Yzet C, Bossuyt P. Deep remission at 1 year prevents progression of early Crohn's disease. Gastroenterology. 2020;159:139-47.

29. Landi B, Anh TN, Cortot A. Endoscopic monitoring of Crohn's disease treatment: A prospective, randomized clinical trial. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gastroenterology. 1992;102:1647-53.

30. Rivière P, D'Haens G, Peyrin-Biroulet L. Location but not severity of endoscopic lesions influences endoscopic remission rates in Crohn's Disease: A post hoc analysis of TAILORIX. Am J Gastroenterol. 2021;116:134-41.