80023_Auto_Edited_check.docx

WORD COUNT	5280	TIME SUBMITTED	21-OCT-2022 09:04PM
		PAPER ID	91813260

Predictors of bowel damage in the long-term progression of Crohn's disease

Fernández-Clotet A *et al*. Bowel damage in Crohn's disease

Abstract

BACKGROUND

Crohn's disease (CD) is a chronic inflammatory bowel disorder that progresses to bowel damage (BD) over time. An image-based index, the Lémann index (LI), has been developed to measure cumulative BD.

AIM

To characterize the long-term progression of BD in CD based on changes in the LI, and to determine risk factors for long-term progression.

METHODS

This was a single-center longitudinal cohort study. Patients who had participated in prospective studies on the accuracy of magnetic resonance imaging using endoscopy as a gold standard and who had a follow-up of at least 5 years were re-evaluated after 5-12 years.

RESULTS

Seventy-two patients were included. LI increased in 38 patients (52.8%), remained unchanged in 9 (12.5%) and decreased in 25 (34.7%). The small bowel score and surgery subscale significantly increased (P = 0.002 and P = 0.001, respectively), whereas the fistulizing subscale significantly decreased (P = 0.001). Baseline parameters associated with BD progression were ileal location (P = 0.026), CD phenotype (stricturing, fistulizing or both with P = 0.007, P = 0.006 and P = 0.035, respectively), disease duration > 10 years (P = 0.019) and baseline LI stricturing score (P = 0.049). No

correlation was observed between BD progression and baseline clinical activity, biological markers or severity endoscopic lesions.

CONCLUSION

BD, as assessed by the LI, progressed in half of the patients with CD over a period of 5-12 years. The main determinants of BD progression are ileal location, stricturing/fistulizing phenotype and disease duration.

Key Words: Crohn's disease; Lémann index; Bowel damage; Inflammatory bowel disease; Magnetic resonance imaging

Fernández-Clotet A, Panés J, Ricart E, Castro-Poceiro J, Masamunt MC, Rodríguez S, Caballol B, Ordás I, Rimola J. Predictors of bowel damage in the long-term progression of Crohn's disease. *World J Clin Cases* 2022; In press

Core Tip: The aim of the study is to characterize the long-term progression of bowel damage (BD) in patients with Crohn's disease (CD) based on changes in the Lémann index (LI). Predictors of BD progression were a baseline stricturing and fistulizing CD phenotype, ileal location, disease duration of more than 10 years and a higher LI stricturing score. Strict monitoring of BD-associated lesions during treatment, especially in those patients with a higher baseline LI score, may help clinicians to improve treatment strategies in order to halt BD progression. Finally, such monitoring should likely be adapted according to the presence of those risk factors identified in the current study.

INTRODUCTION

The notion that Crohn's disease (CD) is a progressive disease is well established. The proportion of patients that require surgery, either due to refractory inflammatory disease or stricturing/fistulizing complications increases over time[1]. Changing this

long-term progressive course is one of the recognized unmet therapeutic needs in patients with CD. In order to develop new therapeutic strategies that are effective in changing the course of the disease, a reliable tool to measure bowel damage (BD) progression is crucial. To that end, the Lémann index (LI) has been developed and validated[2,3]. The LI consists of a scoring system based on a comprehensive assessment of structural BD, which includes the identification of stricturing and penetrating lesions based on cross-sectional imaging and endoscopy, and previous surgery. The LI is a measure of intestinal damage ranging from a minimum value corresponding to absence of damage to a maximum theoretical value corresponding to complete resection of the entire gastrointestinal tract.

The second aspect that is required for efficient design of studies on disease modification is characterization of the kinetics and risk factors for BD progression. Given that the development of the LI is relatively recent, studies determining damage severity have mostly consisted of transversal studies, and the few longitudinal studies evaluating changes in BD measured by the LI involve a relatively short period of observation, whereas damage accumulates over long periods of time.

The objectives of the current study are to characterize the long-term progression of BD in patients with CD based on changes in the LI, to identify which components of the index are the main determinants of progression, and to identify risk factors for long-term progression. To that end, we took advantage of our patient cohorts that had participated in past studies on the accuracy of magnetic resonance imaging (MRI) for characterizing CD inflammatory activity using endoscopy as the gold standard. We invited patients that had undergone these examinations within the past 5 years to 12 years to be reevaluated in the context of the current study.

MATERIALS AND METHODS

Patient population

We performed a longitudinal cohort study in the tertiary referral center Hospital Clinic of Barcelona from April 2018 to December 2019. The study was approved by the local

ethics committee (Reg. HCB/2018/0160) and was conducted according to the European Medicines Agency's good clinical practice guidelines (CMPM/ICH/135/95, July 2002). All patients provided written informed consent before inclusion.

Patients were included if they met the following criteria: ≥ 18 years old, with an established diagnosis of CD according to the European Crohn's and Colitis Organisation guidelines[4], had undergone an MRI or CT scan and an ileocolonoscopy between 2006 and 2013, had a follow-up of at least 5 years and signed a written informed consent to be re-evaluated. Patients with formal contra-indications for a new MRI or colonoscopy were excluded from the study. We used our local database to identify candidates and invited them to participate when they attended the outpatient clinic during the recruitment period.

In those patients who had more than one MRI examination during 2006-2013, the first assessment within this period was considered as the baseline examination.

Data collection

Demographic and clinical characteristics were captured at two time points: Baseline and the second assessment. For baseline, the following variables were recorded: Gender, age at diagnosis, date of CD diagnosis, disease duration at the time of first assessment, CD location and phenotype according to Montreal Classification, current or past history of perianal disease, smoking status, previous intestinal surgeries, previous treatments (exposure to immunosuppressants or biologic therapies), current treatment and C-reactive protein (CRP) level. Clinical disease activity was assessed according to the CD Activity Index (CDAI) and active disease was classified as a CDAI ≥ 150 points. Endoscopic disease activity was recorded using the CD Endoscopic Index of Severity (CDEIS). The cut-offs for remission, mild and severe disease was < 3.5, 3.5-7.0 and > 7.0 points, respectively.

The following clinical variables were recorded at the second assessment: changes in treatment (exposure to immunosuppressants and/or biologic therapy) and surgery

requirements (number, type and indication) during the period between the two assessments.

Cross-sectional imaging acquisition

The MRI examinations were performed using the clinical 1.5 or 3T systems (TrioTim / Aera, Siemens Medical Solutions, Germany). T2 sequences with and without fat saturation in the axial plane, and without fat saturation in the coronal plane were acquired. Next, three-dimensional non-enhanced and contrast-enhanced T1 sequences with fat signal saturation were acquired in the coronal and axial planes. CT examinations were acquired using a multidetector CT scan (Siemens Somaton 64, Germany) with thin (2 mm) axial and coronal plane image reconstructions during the enterographic phase following iodinate contrast injection.

Evaluation of BD using the LI

BD and its progression over time were assessed for each patient using the LI[2]. Imaging examinations (either MRI or CT scan) were performed in all patients at baseline and at the second assessment. Intestinal segments were assessed as normal or abnormal. The length of each abnormal intestinal segment, wall thickness, presence of ulcers, stricturing lesions (including caliber of luminal narrowing, and pre-stenotic diameter) and fistulas or abscesses were collected. Stricturing and penetrating lesions were defined by the imaging results and graded and recorded according to severity on an ordinal scale (from 0: absent to 3: maximum). A documented expert radiologist in gastrointestinal imaging with 15 years of experience in bowel imaging (JR) graded the severity of the lesions according to the LI rules. Imaging procedures were not read by a gastroenterologist since this type of assessment requires expertise in the field and gastroenterologists in Spain are not formally trained in cross-sectional enterographic image interpretation. Additional investigations were recorded based on disease location: physical examination and a pelvic MRI in case of perianal disease, and endoscopic studies in cases of upper gastrointestinal and/or colonic involvement.

At baseline, all of the procedures to calculate the LI were performed within 120 d. For the second assessment, almost all procedures were performed within this period. However, as previously described in other studies using the LI methodology, endoscopies performed less than 1 year prior to the imaging procedures were used in those cases in which it had been performed[5].

The extent of the damage performed in the surgery was documented and graded based on the medical reports. The length of resection was obtained from the pathologist's report.

Radiological, endoscopic and surgical information were generated for each intestinal segment and recorded in the excel file published by the LI development study[2]. The LI was calculated globally (at a patient level), for each organ and for each subscale (stricturing, fistulizing and surgery). BD progression was defined as any increase in the LI between the two evaluations.

Study objectives

The aims of the study were to characterize the long-term (> 5 years) progression of BD in CD based on changes in the LI, to establish which components of the LI are the main determinants of progression, and to identify risk factors for long-term progression.

Statistical analysis

The study aimed to enroll a cohort of approximately 70-80 patients; the sample size was not pre-specified or based on statistical considerations. To analyze factors associated with BD progression, we classified patients according to any increase, or no increase/decrease, of the global LI between the two assessments. Descriptive statistics were used to summarize patient baseline characteristics. Continuous variables are expressed as mean ± SD, while discrete variables are expressed as frequencies and percentages and/or absolute values. For comparisons of continuous variables, the Student's *t*-test was used as appropriate and for comparisons of categorical variables the chi-squared test was applied. Logistic regression modeling was performed to

analyze predictors of BD progression. Covariates tested included gender, age at diagnosis, age at inclusion, disease duration, smoking status, CD location, CD phenotype, and family history of IBD, previous surgery, prior treatment with biological drugs, baseline treatment, baseline CRP, baseline disease activity measured by CDAI, and endoscopic activity measured by CDEIS. Univariate modeling was performed and covariates with a univariate significance of $P \leq 0.10$ were included in the multivariate model. Results were evaluated by means of odds ratios (OR) and their 95% confidence intervals (CI). A receiver operator characteristics curve was used to define the discriminative ability of the logistical model to predict BD progression.

A P value < 0.05 was considered statistically significant. All analyses were performed with the SPSS statistical package V.23.

RESULTS

Patient characteristics

A total of 108 patients were eligible for the study. Twenty patients could not participate because they were lost to follow-up during the previous 12 years. Eighty-eight subjects were invited to participate; 16 declined and 72 accepted and were included in the study (Figure 1). Table 1 summarizes the baseline demographic and clinical characteristics of the patients included in this study.

Evaluation of BD by the LI

Changes in the LI: Calculation of the LI at baseline for each individual was based on cross-sectional enterographies, either MR (n = 71) or CT (n = 1), 67 colonoscopies, 1 upper endoscopy, 3 capsule endoscopy studies and 6 pelvic MRIs (in those patients with active perianal disease). Calculation of the LI at the second assessment for each individual was based on cross-sectional enterographies (68 MRIs and 4 CT scans), 46 colonoscopies, 1 upper endoscopy and 6 pelvic MRIs (in those patients with active perianal disease). One patient developed perianal disease in the interval between the two assessments.

The mean LI at baseline was 5.75 (± 7.54) and ranged from 0 to 58. The second LI assessment was performed between 5 and 12 years after baseline [mean of 8.81 (± 2.17) years]. The mean LI at this point was 7.26 (± 9.04) and ranged from 0 to 52. The mean organ damage evaluations and the mean LI subscales at baseline and follow-up assessments are summarized in Table 2.

Overall, the mean LI change between the baseline and follow-up assessments was an increase of 1.51 (± 6.51) points (P = 0.054). The LI increased in 38 patients (52.8%), remained unchanged in 9 (12.5%) and decreased in 25 (34.7%). BD progression was defined as any progression in the LI between the two evaluations (of note, in all cases the progression was greater than 0.3 points, as previously set as the BD progression cut-off)[6]. The small bowel score was the only organ evaluation that significantly increased (P = 0.002). The fistulizing subscale significantly decreased (P = 0.001), whereas the surgery subscale significantly increased (P = 0.001) between the two assessments.

Surgery between baseline and the final assessments was the main determinant of LI progression. Twenty-four patients (33.3%) required surgery in the period between the two time-point assessments, with a total of 29 surgeries. Indications for surgery included: Stricturing lesions (18 cases), penetrating lesions (6 cases), stricturing and penetrating lesions (1 case), refractoriness to medical treatment (3 cases), and reconstruction of the intestinal tract (colostomy closure with segmental resection of the colon, 1 case). Furthermore, a stricturing baseline LI score was correlated with a future risk of surgery (p=0.002), in contrast to the fistulizing baseline LI score, which was not significantly associated with risk of surgery (P = 0.051).

Factors associated with BD progression over time: The associations between demographic and CD characteristics and BD progression are summarized in Table 3. BD progression was significantly associated with CD phenotype at baseline (P = 0.001), with a progression noted in 71.4% of patients with a penetrating phenotype, in 80.0% of patients with a stricturing phenotype, and in 69.2% of patients with both a stricturing and penetrating phenotype, compared to 23.2% of those patients with an inflammatory

phenotype. Disease duration at baseline was also associated with BD progression (P = 0.001), with 80.0% of patients with a duration of > 10 years showing progression, compared to 38.1% of those with a newly diagnosed disease (< 2 years).

When analyzing which LI components at baseline were associated with BD progression, we observed that patients with BD progression had a significantly higher baseline small bowel LI score (P = 0.040) and a significantly higher baseline stricturing LI score (P = 0.045).

Neither inflammatory markers (CRP) nor clinical or endoscopic severity were associated with LI progression. Although comparisons of endoscopic severity between patients with and without BD progression were of borderline significance, unexpectedly, CDEIS was numerically higher in the groups without CD progression.

Regarding medical therapies used between the two assessments, 67 (93.1%) patients received immunosuppressant therapy (thiopurines or methotrexate) and 63 (87.5%) biological treatment (51 combination therapies). The biological therapy class is detailed in Table 3. Additionally, three patients with refractory disease underwent autologous stem-cell transplantation. The fact that around 90% of patients included in the study were treated during the long follow-up period with biological or immunosuppressive drugs precludes any analysis of the influence of these treatments on damage progression.

Regarding multivariate logistic regression analysis, only ileal location, a CD stricturing or fistulizing phenotype, disease duration of more than 10 years and a baseline LI stricturing score were associated with BD progression (Table 4). The area under the receiver operator characteristics curve (AUC) of the logistic model for predicting BD progression was 0.900 (95% CI 0.824-0.976, P < 0.01) (Figure 2).

DISCUSSION

The results of the current study show that in an unselected population of patients with CD, BD progression occurs in about half of them after a long period of follow-up (5 to 12 years). The main contributors to BD progression, as assessed by the LI, were a

stricturing LI score and surgical components, whereas the fistulizing component significantly decreased during follow-up. Baseline factors that predicted BD progression were a disease duration of more than 10 years, ileal location and the presence of a stricturing or fistulizing phenotype.

Few studies have assessed BD progression over time based on the LI, and the observation period is, in general, limited. In addition, there is the possibility that changes observed in the components of the LI stem from variations in the inflammatory component rather than true BD progression[6,7]. In this regard, some recent studies have evaluated whether the LI is sensitive to changes, but only a few of them have a prospective design[6,7] with a short period of time between evaluations. In fact, in some cases, there is only one morphologic evaluation[5]. In this study, we provide longer-term information on BD progression in patients with CD that may be crucial for selecting of populations at risk of progression in disease modification trials, and to establish the follow-up time required to detect a sufficient number of events.

The mean global LI at baseline and second assessment were 5.75 (± 7.57) and 7.26 (± 9.04) respectively, without significant differences in the LI scores between the two assessment time points in the overall population (P = 0.054). The magnitude of LI increase over time in the current study is lower than other results reported in previous studies based similarly on the LI[8]. This may be, at least in part, due to the retrospective nature of other studies, which can result in the selection of patients who had a complicated disease and were thus subjected to additional MRI studies. Such a design differs from our study in which the assessment of BD progression was based on examinations performed specifically to that end.

Surgery was the major contributor to LI progression, in agreement with prior studies[6], and this would be expected considering the impact that the LI has on intestinal resection. We found that a higher stricturing score at first evaluation predicted LI progression, in most cases due to the need for surgery. Interestingly, the fistulizing score was not associated with LI progression over time as many of these

lesions can heal after medical treatment. Although more data is needed to confirm our observation, a re-evaluation of fistulizing lesions when assessing BD may be required.

Related to CD location, we found that ileal location and a higher stricturing LI score at baseline were related to BD progression. Lunder *et al*. previously reported a high risk of progression in ileocolonic disease vis-à-vis the presence of stricturing lesions[9]. Our group has also reported that severe inflammatory lesions evaluated with MRI were more likely to heal in the colon as compared to the terminal ileum[10]. Additionally, we found that the persistence of the ileal inflammation over time, resulting in fibroblast activation and further development of stricturing lesions, might explain the observed higher LI scores in small bowel locations.

In the current study we did not observe any relationship between the severities of inflammatory lesions as measured by clinical indices, biomarkers (CRP) or endoscopy and future BD progression. Previous studies reported conflicting results; whereas in the work of Lunder et al. the authors reported a positive association between CRP levels and LI score[9], Straksyte *et al*[11] could not confirm such a correlation. A prior retrospective population-based cohort study evaluating 156 patients over a period of 20 years similarly did not find any relationship between severe clinical activity (defined as a Harvey Bradshaw index > 8 points) and the LI[9]. As for the predictive value of inflammatory lesions at endoscopy, the current results are in keeping with a prior observation showing that MRI strictures and fistulas, but not deep ulceration detected at endoscopy, were associated with the future risk of surgery[12].

It has been proposed that components of BD can be reversible with the use of TNF-alfa inhibitors and, therefore, this therapy may prevent BD progression[13]. The study conducted by Fiorino *et al*[6] prospectively evaluated 30 patients with active disease who had begun taking TNF-alfa inhibitors during a median period of 32 mo and found that biological treatment may induce BD regression. Another study conducted by Ribaldone *et al*[14] retrospectively evaluated 91 patients (31 treated with adalimumab and 60 with azathioprine) for 12 mo and found that adalimumab therapy halted BD progression while azathioprine treatment did not. Bodini *et al*[15] retrospectively evaluated 104 CD

patients divided according to the treatment received (biological therapy, azathioprine and mesalazine) for a median time of 29.5 mo and concluded that the LI did not progress in the group receiving biological therapy but increased in the other groups. This suggests that the resolution of inflammation may be associated with halting of BD progression[15]. These three studies had a short follow-up period and focused on the early changes in the LI related to the treatment received. In the current study we did not observe any correlation between biological treatment during follow-up and BD progression or regression. However, it must be noted that 87.5% of the population included in the study were exposed to biologics at some point during follow-up and no firm conclusion can be drawn regarding this finding.

The main strength of our study is the long follow-up time (5-12 years), the longitudinal design, and the prospective design used to assess BD progression. Our design avoided any selection bias with more severely ill populations undergoing repeated evaluations as clinically indicated. In addition, LI was calculated according to the methodology published in the development study and MRIs were evaluated by an experienced radiologist in the field. However, there are certain limitations that must be acknowledged: the size of the cohort is limited and based on a single center cohort, and a majority of patients received biological therapy at some point during follow-up. The latter precludes any study of the association between biologic therapies and BD progression.

CONCLUSION

BD is progressive and accumulative as confirmed with the continued progression of LI over a long period of time in patients with CD. The main indication for surgery was stricturing disease and not presence of ulcers at endoscopy. Predictors of BD progression were a baseline stricturing and fistulizing CD phenotype, ileal location, disease duration of more than 10 years and a higher LI stricturing score. Strict monitoring of BD-associated lesions during treatment, especially in those patients with a higher baseline LI score, may help clinicians to improve treatment strategies in order

to halt BD progression. Finally, such monitoring should likely be adapted according to the presence of those risk factors identified in the current study.

ARTICLE HIGHLIGHTS

Research background

Crohn's disease (CD) progresses to bowel damage (BD) over time. An image-based index, the Lémann index (LI), has been developed and validated to measure cumulative BD. The LI consists of a scoring system based on a comprehensive assessment of structural BD, which includes the identification of stricturing and penetrating lesions based on cross-sectional imaging and endoscopy, and previous surgery.

Research motivation

Risk factors for BD progression are not well identified. Studies that evaluate damage severity have a short period of observation, whereas damage accumulates over long periods of time.

Research objectives

To characterize the long-term progression of BD in patients with CD based on changes in the LI, to identify which components of the index are the main determinants of progression, and to identify risk factors for long-term progression.

Research methods

We performed a longitudinal cohort study in the tertiary referral center Hospital Clinic of Barcelona from April 2018 to December 2019. We took advantage of our patient cohorts that had participated in past studies on the accuracy of magnetic resonance imaging (MRI) for characterizing CD inflammatory activity using endoscopy as the gold standard. We invited patients that had undergone these examinations within the past 5 years to 12 years to be reevaluated in the context of the current study. BD and its

progression over time were assessed for each patient using the LI and calculated at baseline and at the second assessment.

Research results

Seventy-two patients were included. LI increased in 38 patients (52.8%), remained unchanged in 9 (12.5%) and decreased in 25 (34.7%). The small bowel score and surgery subscale significantly increased (P = 0.002 and P = 0.001, respectively), whereas the fistulizing subscale significantly decreased (P = 0.001). Baseline parameters associated with BD progression were ileal location (P = 0.026), CD phenotype (stricturing, fistulizing or both with P = 0.007, P = 0.006, and P = 0.035, respectively), disease duration > 10 years (P = 0.019) and baseline LI stricturing score (P = 0.049).

Research conclusions

BD, as assessed by the LI, progressed in half of the patients with CD over a period of 5-12 years. The main determinants of BD progression are ileal location, stricturing/fistulizing phenotype and disease duration.

Research perspectives

The time point to evaluate BD progression is still not yet established. Some treatment can prevent BD progression but we still not have robust data to confirm these findings.

Figure 1 Flow chart of patients included in the study.

Figure 2 Receiver operator characteristics curve for the prediction of bowel damage progression.

11

Table 1 Baseline demographic and clinical characteristics of patients

Variable	*n* = 72
Female gender, *n* (%)	42 (58.3)
Age at inclusion, mean (SD), yr	34.41 (± 11.1)
Age at diagnosis, *n* (%)	
< 16 yr	8 (11.1)
17-40 yr	57 (79.2)
> 40 yr	7 (9.7)
Disease duration, mean (SD) yr	8.09 (± 7.3)
Disease duration, *n* (%)	
< 2 yr	21 (29.2)
2-10 yr	31 (43.1)
>10 yr	20 (27.8)
Smoking status, *n* (%)	
Never smoker	28 (38.9)
Current smoker	31 (43.1)
Past smoker	13 (18.1)
CD location, *n* (%)	
Terminal Ileum	27 (37.5)
Colon	8 (11.1)
Ileocolic	37 (51.4)
CD upper tract involvement, *n* (%)	6 (8.3)
CD phenotype, *n* (%)	
Inflammatory	30 (41.7)
Stricturing	15 (20.8)
Penetrating	14 (19.4)
Stricturing and penetrating	13 (18.1)
Current or past history of perianal disease, *n* (%)	14 (19.4)
Family history, *n* (%)	5 (6.9)
Previous resective surgery, *n* (%)	
No	51 (70.8)
1 surgery	13 (18.1)

> 1 surgery	8 (11.1)
Biological naïve at baseline, *n* (%)	
Yes	46 (63.9)
No	26 (36.1)
Treatment at baseline, *n* (%)	
None	18 (25.0)
Corticosteroids	4 (5.6)
Immunosuppressants	32 (44.4)
TNF-alfa inhibitors	8 (11.1)
Immunosuppressants plus TNF-alfa inhibitors	10 (13.9)
CRP (mg/L), mean (SD)	2.89 (± 4.2)
CRP, *n* (%)	
Normal (< 1 mg/L)	30 (41.7)
Elevated (≥ 1 mg/L)	42 (58.3)
CDAI, mean (SD)	194.73 (± 95.8)
Clinical activity according to CDAI score, *n* (%)	
Active disease	51 (69.9)
Clinical remission	21 (28.8)
CDEIS, mean (SD)	7.8 (± 6.7)
CDEIS, *n* (%)	
< 3.5	20 (29.9)
3.5-7.0	18 (26.8)
> 7.0	29 (43.3)
NA	5

CD: Crohn's disease; CDAI: Crohn's disease Activity Index.

Table 2 Evaluation of the Lémann index score at baseline, at second assessment and changes over time (mean ± SD)

	LI at baseline	**LI at second assessment**	**Changes in LI**
Global Lémann Index	5.75 ± 7.57	7.26 ± 9.04	1.51 ± 6.51 (*P* = 0.054)
Organ location			
Upper digestive tract	0.03 ± 0.18	0.04 ± 0.35	0.01 ± 0.33 (*P* = 0.721)
Small bowel damage score	1.79 ± 1.62	2.46 ± 2.51	0.67 ± 1.75 **(***P* = 0.002)
Colon/rectum damage score	3.19 ± 3.94	3.39 ± 3.81	0.2 ± 3.38 (*P* = 0.622)
Anus damage score	0.80 ± 4.32	1.38 ± 5.95	0.58 ± 4.28 (*P* = 0.253)
LI subscales			
Stricturing subscale	1.12 ± 1.38	0.88 ± 1.44	-0.24 ± 1.77 (*P* = 0.262)
Fistulizing subscale	1.95 ± 2.39	1.01 ± 1.99	-0.94 ± 2.19 (*P* = 0.001)
Surgery subscale	2.72 ± 6.78	5.32 ± 8.52	2.60 ± 5.82 (*P* = 0.001)

LI: Lémann index.

Table 3 Demographics and Crohn's disease characteristics associated with the Lémann Index progression

	LI progression (*n* = 38)	**No LI progression (*n* = 34)**	***P* value**
Gender, *n* (%)			0.352
Male	18 (60.0)	12 (40.0)	
Female	20 (47.6)	22 (52.4)	
Age at diagnosis, *n* (%)			0.961
< 16 yr	4 (50.0)	4 (50.0)	
17-40 yr	30 (52.6)	27 (47.4)	
> 40 yr	4 (57.1)	3 (42.9)	
Age at baseline, mean (SD)	25.17 (± 10.4)	27.61 (± 10.3)	0.323
CD location at baseline, *n* (%)			0.091
Terminal Ileum	17 (66.6)	9 (33.3)	
Colon	2 (25.0)	6 (75.0)	
Ileocolic	18 (48.7)	19 (51.3)	
CD upper tract involvement, *n* (%)			0.677
Yes	4 (66.7)	2 (33.3)	
No	34 (51.5)	32 (48.5)	
CD phenotype at baseline, *n* (%)			0.001
Inflammatory	7 (23.3)	23 (76.7)	
Stricturing	12 (80.0)	3 (20.0)	
Penetrating	10 (71.4)	4 (28.6)	
Stricturing and penetrating	9 (69.2)	4 (30.8)	
Current or past history of perianal disease at baseline, *n* (%)			0.151

Yes	10 (71.4)	4 (28.6)	
No	28 (48.3)	30 (51.7)	
Disease duration at inclusion, mean (SD)	10.36 (± 8.4)	5.54 (± 4.8)	0.001
Disease duration at inclusion, *n* (%)			0.001
< 2 years	8 (38.1)	13 (61.9)	
2-10 years	14 (45.2)	17 (54.8)	
>10 years	16 (80.0)	4 (20.0)	
Smoking status, *n* (%)			0.342
Never smoker	15 (53.6)	13 (46.4)	
Current smoker	14 (45.2)	17 (54.8)	
Past smoker	9 (69.2)	4 (30.8)	
Family history, *n* (%)			0.541
Yes	2 (40.0)	3 (60.0)	
No	35 (53.0)	31 (47.0)	
Immunosuppressant treatment between intervals, *n* (%)			0.741
Yes	35 (52.2)	32 (47.8)	
No	3 (40.0)	2 (60.0)	
Biological naïve at baseline, *n* (%)			0.143
Yes	21 (45.7)	25 (54.3)	
No	17 (65.4)	9 (34.6)	
Biological treatment between intervals, *n* (%)			0.591
Yes	34 (54.0)	29 (46.0)	
No	4 (44.4)	5 (55.6)	
Biological treatment between intervals, *n* (%)	21 (47.7)	23 (52.3)	0.443
TNF-alfa inhibitors	8 (61.5)	5 (38.5)	

TNF-alfa inhibitors and ustekinumab	2 (66.7)	1 (33.3)	
TNF-alfa inhibitors and vedolizumab	2 (100.0)	0 (0)	
TNF-alfa inhibitors, vedolizumab and ustekinumab	1 (100.0)	0 (0)	
Previous surgery at inclusion, *n* (%)			0.192
Yes	14 (66.7)	7 (33.3)	
No	24 (47.1)	27 (52.9)	
Autologous stem-cell transplantation between intervals, *n* (%)			0.602
Yes	2 (66.7)	1 (33.3)	
No	36 (52.2)	33 (47.8)	
Surgery between intervals, *n* (%)			0.001
Yes	23 (95.8)	1 (4.2)	
No	15 (31.3)	33 (68.8)	
Baseline LI score evaluation, mean (SD)			
Total LI score	5.60 (± 4.40)	5.90 (± 10.10)	0.860
Upper-tract score	0.05 (± 0.30)	0	0.211
Small-bowel score	2.16 (± 1.60)	1.37 (± 1.60)	0.040
Colon/rectum score	2.98 (± 3.00)	3.42 (± 4.80)	0.652
Anus score	0.51 (± 1.90)	1.13 (± 6.00)	0.542
Stricturing score	1.43 (± 1.60)	0.78 (± 1.00)	0.045
Fistulizing score	1.69 (± 2.50)	2.23 (± 2.30)	0.341
Surgical score	2.54 (± 3.40)	2.92 (± 9.30)	0.823
CRP at baseline, mean (SD)	2.93 (± 4.70)	2.84 (± 3.60)	0.921
CRP at baseline, *n* (%)			0.692

Normal (< 1 mg/L)	15 (50.0)	15 (50.0)	
Elevated (≥ 1 mg/L)	23 (54.8)	19 (45.2)	
CDAI, mean (SD)	199.69 (± 94.9)	189.19 (± 97.8)	0.673
Clinical activity at baseline according to CDAI score, *n* (%)			0.610
Active disease	28 (54.9)	23 (45.1)	
Clinical remission	10 (47.6)	11 (52.4)	
CDEIS activity at baseline, mean (SD)	6.2 (5.4)	9.44 (1.3)	0.052
CDEIS activity at baseline, *n* (%)			0.190
< 3.5	12 (60.0)	8 (20.0)	
3.5-7.0	11 (61.1)	7 (38.9)	
> 7.0	11(37.9)	18 (62.1)	

CRP: C-reactive protein; LI: Lémann index; CD: Crohn's disease; CDAI: Crohn's disease Activity Index; CDEIS: Crohn's disease Endoscopic Index of Severity.

Table 4 Multivariate analysis for significant bowel damage progression

Risk factor	OR	95% CI	*P* value
CD location			
Terminal ileum	8.307	1.296-53.251	0.026
Colon	0.580	0.014-24.658	0.776
CD phenotype			
Stricturing	18.447	2.219-153.321	0.007
Fistulizing	17.085	2.217-131.673	0.006
Stricturing and fistulizing	12.296	1.190-127.022	0.035
Disease duration at inclusion			
2-10 years	2.174	0.374-12.652	0.387
> 10 years	15.196	1.557-148.332	0.019
Baseline LI stricturing score	1.929	1.004-3.709	0.049
Baseline LI small bowel score	0.690	0.383-1.243	0.216
CDEIS activity at baseline	0.948	0.837-1.074	0.400

LI: Lémann index; CD: Crohn's disease; CDEIS: Crohn's disease Endoscopic Index of Severity; OR: Odds ratios; 95%CI: 95% confidence intervals.

80023_Auto_Edited_check.docx

ORIGINALITY REPORT

13%
SIMILARITY INDEX

PRIMARY SOURCES

1	Jordi Rimola, Ignacio Alfaro, Agnès Fernández-Clotet, Jesús Castro-Poceiro et al. "Persistent damage on magnetic resonance enterography in patients with Crohn's disease in endoscopic remission", Alimentary Pharmacology & Therapeutics, 2018 Crossref	60 words — 1%
2	Benjamin Pariente, Jean-Yves Mary, Silvio Danese, Yehuda Chowers et al. "Development of the Lémann Index to Assess Digestive Tract Damage in Patients With Crohn's Disease", Gastroenterology, 2015 Crossref	59 words — 1%
3	"UEG Week 2016 Poster Presentations", United European Gastroenterology Journal, 2016 Crossref	52 words — 1%
4	www.revespcardiol.org Internet	48 words — 1%
5	academic.oup.com Internet	39 words — 1%
6	Clémentine Lauriot dit Prevost, Mustapha Azahaf, Maria Nachury, Julien Branche et al. "Bowel damage and disability in Crohn's disease: a prospective study in a tertiary referral centre of the Lémann Index and Inflammatory	35 words — 1%

Bowel Disease Disability Index", Alimentary Pharmacology & Therapeutics, 2020
Crossref

7	Wong, D., M. Coenen, L. Derijks, C. van Marrewijk, S. Vermeulen, A. Verbeek, B. Franke, H.-J. Guchelaar, D. De Jong, L. Engels, and P. Hooymans. "DOP035 Early assessment of thiopurine metabolites predicts the occurrence of leukopenia in inflammatory bowel disease patients", Journal of Crohn s and Colitis, 2014. Crossref	34 words — 1%
8	www.wjgnet.com Internet	30 words — 1%
9	"ECR 2016 Book of Abstracts - B - Scientific Sessions and Clinical Trials in Radiology", Insights into Imaging, 2016. Crossref	23 words — < 1%
10	www.frontiersin.org Internet	22 words — < 1%
11	docplayer.net Internet	20 words — < 1%
12	gut.bmjjournals.com Internet	19 words — < 1%
13	"FESSH Abstracts", Journal of Hand Surgery (European Volume), 2021 Crossref	18 words — < 1%
14	Jordi Rimola, Agnès Fernàndez-Clotet, Nunzia Capozzi, Sònia Rojas-Farreras et al. "Pre-treatment magnetic resonance enterography findings predict	18 words — < 1%

the response to TNF-alpha inhibitors in Crohn's disease", Alimentary Pharmacology & Therapeutics, 2020
Crossref

15 Jordi Rimola, Joana Torres, Shankar Kumar, Stuart A Taylor, Torsten Kucharzik. "Recent advances in clinical practice: advances in cross-sectional imaging in inflammatory bowel disease", Gut, 2022 — 18 words — < 1%
Crossref

16 C. Gower-Rousseau, H. Sarter, D. Turck, M. Fumery et al. "DOP037 Long-term outcome of paediatric-onset ulcerative colitis: early years are shaping the future", Journal of Crohn's and Colitis, 2014 — 17 words — < 1%
Crossref

17 Dietmar J. Dinter, Anja Chakraborty, Joachim Brade, Walter Back, K. Wolfgang Neff, Manfred V. Singer, Ulrich Böcker. "Endoscopy and magnetic resonance imaging in patients with Crohn's disease: A retrospective single-centre comparative study", Scandinavian Journal of Gastroenterology, 2009 — 16 words — < 1%
Crossref

18 www.dovepress.com — 16 words — < 1%
Internet

19 www.irjournal.org — 16 words — < 1%
Internet

20 boris.unibe.ch — 15 words — < 1%
Internet

21 Mathilde Wagner, Huaibin Mabel Ko, Manjil Chatterji, Cecilia Besa et al. "Magnetic resonance imaging predicts histopathologic composition of ileal Crohn's disease", Journal of Crohn's and Colitis, 2018 — 14 words — < 1%
Crossref

22	assets.researchsquare.com Internet	13 words — < 1%
23	link.springer.com Internet	13 words — < 1%
24	www.panafrican-med-journal.com Internet	13 words — < 1%
25	f6publishing.blob.core.windows.net Internet	12 words — < 1%
26	ueaeprints.uea.ac.uk Internet	12 words — < 1%
27	medinfo.gsk.com Internet	11 words — < 1%
28	www.centerwatch.com Internet	10 words — < 1%
29	"ECR 2013 Book of Abstracts - B - Scientific Sessions", Insights into Imaging, 2013. Crossref	9 words — < 1%
30	docksci.com Internet	9 words — < 1%
31	www.ncbi.nlm.nih.gov Internet	9 words — < 1%
32	"Abstracts from the 2011 Advances in Inflammatory Bowel Diseases Crohn's & Colitis Foundation's National Clinical & Research Conference December 1-3, 2011 Hollywood, Florida", Inflammatory Bowel Diseases, 12/2011	8 words — < 1%

Crossref

33 Guillaume Pineton de Chambrun, Pierre Blanc, Laurent Peyrin-Biroulet. "Current evidence supporting mucosal healing and deep remission as important treatment goals for inflammatory bowel disease", Expert Review of Gastroenterology & Hepatology, 2016 — 8 words — < 1%
Crossref

34 W Reinisch. "A dose escalating, placebo controlled, double blind, single dose and multidose, safety and tolerability study of fontolizumab, a humanised anti-interferon antibody, in patients with moderate to severe Crohn's disease", Gut, 9/27/2005 — 8 words — < 1%
Crossref

35 dokumen.pub — 8 words — < 1%
Internet

EXCLUDE QUOTES	OFF	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	OFF