*Journal of Crohn's and Colitis*, 2015, 633–639
doi:10.1093/ecco-jcc/jjv080
Advanced Access publication May 9, 2015
Original Article

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# Bowel Damage as Assessed by the Lémann Index is Reversible on Anti-TNF Therapy for Crohn's Disease

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**Conference presentations:** ECCO Congress, Copenhagen 2014; Digestive Disease Week, Chicago, IL, 2014.

## Abstract

**Background and aims:** Bowel damage [BD] will develop in the majority of Crohn's disease [CD] patients. Recently, the Lémann Index [LI] was developed to measure BD.

**Methods:** This was a prospective single-center cohort study. All included patients underwent full evaluation for bowel damage before starting anti-TNF therapy and every year thereafter. BD at baseline and during follow-up was measured using the LI. We assessed the impact of anti-TNF therapy on BD. We also assessed the sensitivity to change of the LI and the relationship between BD progression and disease outcomes, including the need for surgery.

**Results:** Thirty CD patients were enrolled [13 on infliximab, 17 on adalimumab]. Median baseline LI was 9.1 [range, 1.6–34.1]. Median follow up was 32.5 months [range, 10–64].

By a ROC curve analysis, a LI >4.8 defined CD subjects with BD. Any change >0.3 in the LI was related to BD change [AUC 0.98]. During follow-up, 83% of subjects had BD regression and 17% had BD progression. Anti-TNF therapy significantly reduced LI at 12 months [p=0.007]. Subjects with BD progression were more likely to undergo major abdominal surgery through the follow-up period [HR 0.19, p=0.005].

**Conclusion:** The LI has good sensitivity to change. Anti-TNFs agents are able to reverse BD in some CD patients. BD progression as measured by the LI may be predictive of major abdominal surgery in these patients.

**Keywords:** Crohn's disease; bowel damage; Lémann Index; anti-TNF; inflammatory bowel disease

## 1. Introduction

Crohn's disease [CD] is a chronic progressive, destructive and disabling condition.[1,2] In a population-based cohort study from Olmsted County involving 306 CD patients, 18.6% of patients had penetrating or stricturing complications within 90 days after diagnosis, and up to 50% developed intestinal complications within 20 years following diagnosis.[3]

In the same population-based cohort study, the cumulative probability of major abdominal surgery approached 60% after 20 years of disease, and many CD patients required more than one surgery. The

occurrence of bowel damage [BD], defined as the presence of strictures, fistulas and/or abscesses, was the main indication for surgery in CD.[4]

Preliminary data from a single-center cohort study suggested that 58% of patients have disease complications at diagnosis as assessed by magnetic resonance enterography [MRE].[5]

In rheumatoid arthritis, the Sharp score is used to assess joint damage,[6] and to evaluate the impact of disease-modifying agents in blocking or reversing damage and disability.[7–9] Recently, a panel of international experts developed the first index able to assess BD in CD, namely the Lémann index [LI].[10,11] Briefly, this index combines damage location, severity, extent, as measured by diagnostic imaging modalities, endoscopy, and history of surgical resection.[11] Diagnostic imaging modalities include magnetic resonance imaging [MRI] for small bowel and colon, and pelvic MRI for perianal disease. Endoscopy includes ileocolonoscopy for the assessment of ileal and/or colonic disease, and upper endoscopy for the assessment of CD located to the esophagus, stomach and duodenum. The entire digestive tract is divided in four segments [upper gastrointestinal tract, small bowel, colon and anus].[10] Very recently, the LI has been validated, showing that the unbiased correlation coefficients between predicted indexes and investigator damage evaluations are 0.85, 0.98, 0.90, 0.82 for upper tract, small bowel, colon/rectum, anus, respectively, and 0.84 overall.[11] However, the accuracy of this index in detecting changes in BD over time, and the evolution of BD in CD patients following anti-TNF treatment initiation are unknown. Furthermore, the impact of BD progression, as assessed by the LI, on disease outcomes such as the need for surgery has yet to be determined.

Cross-sectional imaging modalities, such as MRE, are increasingly used to assess disease activity and severity in CD.[12–14] MRE allows detection of CD activity and complications and is a valid tool for assessing response to therapies.[15]

Anti -Tumor Necrosis Factor-α [TNF] agents, including infliximab [IFX] and adalimumab [ADA], are able to induce and maintain mucosal healing in CD.[16–18] Whether BD as assessed by MRI and the LI may be reversible in some patients receiving anti-TNF therapy is unknown.

The aim of this study was therefore to assess the impact of anti-TNF on the bowel damage, and the sensitivity and specificity of the LI in the assessment of BD changes over time in a prospective observational cohort of patients with CD starting anti-TNF therapy.

## 2. Materials and methods

### 2.1. Study population

This was a prospective observational cohort pilot study on consecutive subjects with an established diagnosis of CD starting anti-TNF therapy monotherapy as follows: IFX administered as an induction regimen at 0, 2, 6 weeks, then every 8 weeks by intravenous injection at a dose of 5 mg/kg, as a scheduled maintenance regimen; ADA administered at a dose of 160 mg at week 0, then 80 mg after 2 weeks, then 40 mg subcutaneously every 2 weeks between January 2010 and January 2012. To be enrolled in the study, subjects should be in clinical remission [Harvey-Bradshaw Index <5] at the end of the induction phase, and then for at least 12 months after starting anti-TNF. The rationale for this inclusion criteria was to demonstrate the importance of regular monitoring bowel damage progression in subjects in clinical remission after successful induction with anti-TNF. Anti-TNF were administered as a monotherapy in order to investigate their efficacy on the study outcomes, without any confounding factor, such as additional therapy with thiopurines. Subjects were required to agree to be followed prospectively over the study period, in accordance with the scheduled follow-up required by the local guidelines. Based on the localization of the disease, according to the IPNIC protocol for the assessment of BD,[10,11] the subjects were to undergo an abdominal MRE, based on a previously described protocol.[19] In case of colonic localization, a colonoscopy with biopsies was required. In case of perianal disease, an additional pelvic MRE and a clinical evaluation of the perianal region was required. If patients had a recorded full evaluation before inclusion, from which calculation of the baseline score was possible, they were allowed to be enrolled in the study. An additional MRI was performed in case of disease relapse, change in therapy or indication to surgery, and the patient ended the follow-up period at that time. Moreover, endoscopic activity at each colonoscopy was scored according to the Simplified Endoscopic Score-Crohn's Disease [SES-CD]. The Magnetic Resonance Index of Activity [MaRIA] score was also calculated, as previously described,[12] when possible, in order to assess MRE-based activity of the disease.

The Crohn's Disease Digestive Damage Score [$CD_3S$, LI, Supplementary Table 1, (available as Supplementary data at ECCOJC online)] [10] was used to assess the grade of CD-related BD at baseline and at follow-up. The gastrointestinal tract was divided into different segments [esophagus, stomach, and duodenum; 20 tracts assumed to be 20-cm long for the small bowel; caecum-ascending colon, transverse colon, descending colon, sigmoid, rectum and anus]. Findings at MRE, colonoscopy and pelvic MRE were divided into stricturing and penetrating lesions, scored on a 4-grade scale. These scores were then adjusted for lesion and organ coefficients [Supplementary Table 2, (available as Supplementary data at ECCOJC online)], and the final index was used for the data analysis.

### 2.2. Study outcomes

The primary outcome was to investigate the impact of anti-TNFs on BD in a cohort of patients with active moderate-to-severe disease, that remained in stable clinical remission [defined as Harvey-Bradshaw Index <5].[20] We also assessed the sensitivity and specificity of the LI for the assessment of BD changes over time. Secondary outcomes included the need for surgery according to BD progression.

Because no previous studies had been performed on this specific outcome, sample size was not calculated. We planned to explore the impact of anti-TNF therapy on BD in 30 subjects enrolled in a pilot study.

To further determine the accuracy of this index in the assessment of the actual amount of intestinal damage, an independent gastroenterologist who was not aware of the LI calculation reviewed all the examinations and assessed BD progression using clinical judgment regarding the presence or absence of BD, taking into account previous intestinal resections, perianal damage, and CD-related complications. Then, a ROC analysis was performed to identify the cut-off value for BD and the minimal change in the LI able to assess BD progression.

The protocol was labeled as DAMCRO-01 and submitted to the Local Ethical Committee [registration number 730]. All patients provided written informed consent for participation in the study.

### 2.3. Statistical analysis

Because there are no data concerning the LI cut-off value to discriminate subjects with bowel damage, and also no data are available regarding the minimum change in the LI able to assess bowel damage progression, we performed a ROC curve analysis to identify both cut-off values, as a preliminary assessment to evaluate the primary outcome of the study.

A descriptive analysis was performed to assess the rate of BD progression, assessed by the LI, under therapy. The Spearman's correlation was used to investigate if there is a correlation between the LI and the validated indexes for clinical, endoscopic and radiological activity.[12,20,21] A Fisher's exact test was performed to determine if there were any statistically significant differences between IFX and ADA, and the paired t-test was used to assess the differences in the mean LI overtime. Logistic regression was also used to assess the predictive value of BD progression and the impact of therapies on the final outcome, which was the need for major surgery. Survival analysis by Kaplan-Meyer curves, Cox-regression, and the log-rank test were used to assess the percentage of subjects free of surgery, determined in accordance with the pre-defined parameters.

Any difference was considered statistically significant if $p<0.05$.

Statistical analysis was performed using SPSS®.

## 3. Results

### 3.1. Study population

Thirty subjects who met the inclusion criteria were enrolled. Baseline characteristics are summarized in Table 1. At baseline, 17 subjects [50%] had BD, according to the clinician's judgement. In particular, 14 subjects [56%] had inflammatory strictures at baseline, 3 subjects [10%] had fistulas, and none [0%] had an abscess. Seven subjects [23%] had previous intestinal resection at baseline. Thirteen subjects [43%] were treated with IFX monotherapy and 17 subjects [57%] with ADA monotherapy.

### 3.2. Cut-off values for the Lémann Index

As the LI includes some parameters that may be influenced by disease activity [such as inflammatory strictures, deep ulcers, or bowel wall thickening], we evaluated the correlation between the LI and the SES-CD and the MaRIA index at baseline. Since the purpose of the LI is to assess bowel damage independently from disease activity, we also performed the same analysis in subjects that achieved endoscopic remission [defined as a SES-CD<5], to evaluate the residual damage. Both LI scores at baseline and at 12 months were included in the ROC analyses, which were compared to determine the best-cut off for BD.

At baseline, the LI index was correlated to the MaRIA index [r=0.543, p=0.006], but not with the SES-CD [r=0.26, p=0.17]. The ROC curve analysis identified a LI cut-off of 3.1 to distinguish subjects with BD from those without BD, with AUC of 0.67, CI 95% 0.48–0.83, sensitivity of 0.91 [CI 95%, 0.73–0.98], specificity of 0.50 [0.12–0.87], positive and negative likelihood ratio [LR+ and LR-] of 1.83 and 0.17, respectively, and positive and negative predictive values of 0.88 and 0.60, respectively. The ROC curve analysis, based on subjects with clinical and endoscopic remission, identified a cut-off value of 4.8, as discriminating for bowel damage, with AUC 0.81 [CI 95%, 0.62–0.92], with sensitivity 0.76, specificity 0.89, LR+ 6.8, LR- 0.27, PPV and NPV of 0.94 and 0.61, respectively. The comparison between the two ROC curves resulted in a difference between the areas of 0.175 [SE= 0.08, 95% CI = 0.01–0.34, p=0.035, Figure 1].

The analysis of the minimal change in the LI overtime identified a cutoff of +0.3 as indicative for BD progression, with AUC > 0.98 [0.86–1.00], sensitivity 1.00, specificity 0.96, LR+ 27.00, LR- 0.0, PPV 0.75 and NPV of 1.00 [Figure 2].

Based on the ROC analysis results, the presence of damage was set as a LI >4.8, and the bowel damage progression was measured as an increase of >+ 0.3, compared to the previous assessment.

### 3.3. Impact of anti-TNF therapy on the Lémann index

The mean baseline LI in the overall study population was 9.2 [range, 3.1–34.1]. At baseline, all subjects had clinically active disease [median HBI=9.8], 27 [90%] subjects had endoscopic activity [defined as a SES-CD >5], and 13 subjects [56%] had radiological activity [defined as a global MaRIA index >50]. Bowel damage, as assessed by the LI, was present in 23 subjects [77%].

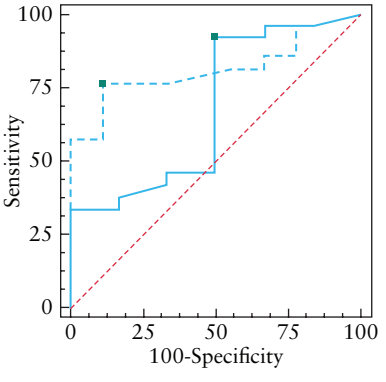


**Figure 1.** Receiver operating characteristic [ROC] analysis and comparison of ROC curves at baseline [bold line, cut-off 3.1] and after resolution of inflammation [dotted line] to assess the cut-off value for the LI [cut-off 4.8]. The cut-off values are indicated by black squares.

**Table 1.** Baseline characteristics of subjects.

| | Overall population [*n*=30] | Infliximab [*n*=13] | Adalimumab [*n*=17] |
|---|---|---|---|
| **Males** | 14 [47%] | 8 [61%] | 6 [35%] |
| **Median age [range] [years]** | 42 [18–67] | 35 [23–67] | 42 [18–61] |
| **Median disease duration [years]** | 5 [0–30] | 4 [0–30] | 6 [1–11] |
| **Montreal classification** | | | |
| ***L1*** | 10 [33%] | 4 [30%] | 6 [35%] |
| ***L2*** | 7 [23%] | 1 [8%] | 6 [35%] |
| ***L3*** | 13 [44%] | 8 [62%] | 5 [30%] |
| ***B1*** | 9 [30%] | 4 [30%] | 5 [29%] |
| ***B2*** | 10 [37%] | 3 [23%] | 8 [47%] |
| ***B3*** | 11 [33%] | 6 [47%] | 4 [24%] |
| **Perianal disease [%]** | 10 [33%] | 7 [54%] | 3 [18%] |
| **Active smokers** | 7 [23%] | 4 [31%] | 3 [18%] |
| **Previous surgery** | 7 [23%] | 5 [38%] | 2 [12%] |

At 12 months, 80% of subjects achieved endoscopic remission [defined as a SES-CD<5], and 66% achieved radiological response [global MaRIA <50]. Seven subjects [23%] had an increase in the LI, 5 [17%] had no change in the LI, while 18 [60%] had a reduction in the LI [p=0.008 compared to baseline]. The median change in the LI from baseline was -2.8 [-20.2–3.5, p=0.007]. Resolution of ileal and/or strictures was observed in 6 subjects [60%], while perianal fistula closure was observed in 3 subjects [30%]. No abdominal fistula closure was observed in the entire cohort. Bowel damage, assessed by the LI, was present in 17 subjects [56%].

Nineteen subjects entered in the 24-month follow-up period. Since the last observation, 4 subjects [20%] had bowel damage progression, with 5 subjects [26%] that showed any increase in the LI, 8 subjects [42%] that showed no changes, and 7 subjects [36%] that had a reduction in the LI. The mean variation of the LI was not statistically significant from the one at 12 months [p=0.57, Figure 3]. Bowel damage was present in 10 subjects [53%].

Six subjects were followed-up for 36 months, among them 2 subjects [32%] had bowel damage progression since month 24. The LI decreased only in 1 subject, while the rest had no change. Bowel damage was present in 3 subjects [50%, Figure 4]. Also at this time point, the mean LI did not differ significantly from the one measured at 24 months.

Between the baseline and last follow-up assessment, 83% of subjects treated with anti-TNF achieved bowel damage non-progression over a mean period of 32.5 months. However, an increase in the proportion of subjects with bowel damage progression was observed overtime, from 17% to 33% [Figure 5]. No differences were found between infliximab and adalimumab [p=0.31].

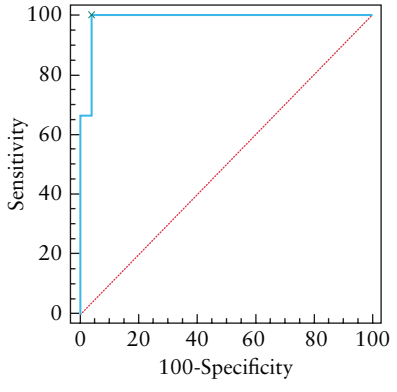


**Figure 2.** Receiver operating characteristic [ROC] curve analysis to identify the cut-off value for bowel damage progression [LI change >+ 0.3, black square].

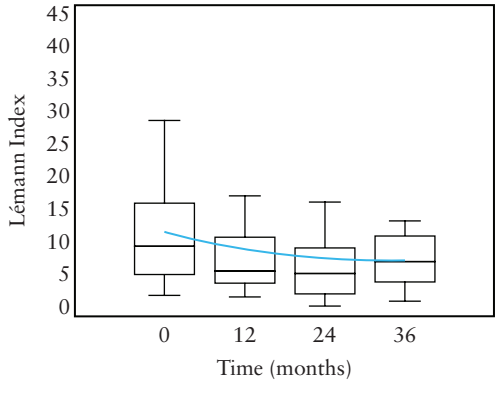


**Figure 3.** Mean differences in the LI between baseline and 12, 24, and 36 months.

### 3.4. Relationship between the Lémann index and disease outcomes

A total of 9 subjects [30%] underwent major bowel surgery due to symptomatic disease complications [IFX=4; ADA=6], 2 [23%] for stricturing disease and 7 [77%] for penetrating disease, during the follow-up period. Subjects with LI progression were more likely to undergo major surgery within the next 12 months [HR 0.19, p=0.005, Figure 6]. A total of 8 subjects [26%] needed a change or optimization in their anti-TNF therapy. No significant correlation was found with LI progression [HR 0.99, p=0.99].

Disease duration, age at diagnosis, age at baseline, smoking habits, perianal disease at baseline resulted not predictive for major surgery or change in therapy overtime [all p>0.05].

## 4. Discussion

CD is a chronic condition which can lead to progressive and irreversible BD.[2]

In rheumatoid arthritis, the Sharp score was developed to assess joint damage in both a real-life setting and in disease-modification trials.[22] It was demonstrated that the reliability for progression of the Sharp score ranges from 0.75 to 0.98, and the sensitivity to change ranges from 0.22 to 0.72.[22–24] Recent studies showed that disease-modifying agents [DMARDs], such as methotrexate and anti-TNF, are able to halt or even reverse joint damage.[25–27] In the ABRAB study, anti-TNF alone or in combination with methotrexate was found to be more effective than methotrexate alone in preventing disease progression.[26]

Recently, the LI was developed to assess and quantify CD-related intestinal damage.[10,11] This index takes into account bowel resection [that represents the maximum grade of BD], the number of damaged intestinal segments, and the presence of complications, such as strictures, fistulas and abscesses, and perianal disease. Recently, Pariente *et al.*[11] showed that the correlation coefficients between predicted indexes and investigators' evaluation were 0.85, 0.98, 0.90, 0.82 for upper tract, small bowel, colon/rectum, and anus, respectively, and 0.84 overall, concluding that the LI is highly sensitive for measuring cumulative structural BD in patients with CD. However, the utility of the LI for assessing changes in BD over time are unknown. It also remains to be determined whether BD may be reversible on anti-TNF therapy. This is a key step in assessing the potential of the biologics to be disease modifying in CD. Over the last decade, our attention has focused on the ability of anti-TNF agents to induce and maintain mucosal healing.[28,29] As CD is a transmural disease, data on the ability of anti-TNF therapy to reverse BD in CD are eagerly awaited.

At diagnosis, about 20% of CD patients have stricturing or penetrating disease and, within 20 years, half of all patients develop intestinal complications.[3] In our study, the mean disease duration was 4 years. Using the LI, we showed that subjects with a LI>4.8 had BD before starting anti-TNF, with a mean LI of 9.1.

We first demonstrated that the majority of subjects had BD non progression on anti-TNF therapy. Although this study is only a small cohort study, it does show that the LI might be able to detect change in BD and to assess response to therapies. A minimal change in terms of increase in the LI is correlated with progression, or regression or stability of BD.

Moreover, we found that disease activity may influence the LI score, but bowel damage progress independently from disease

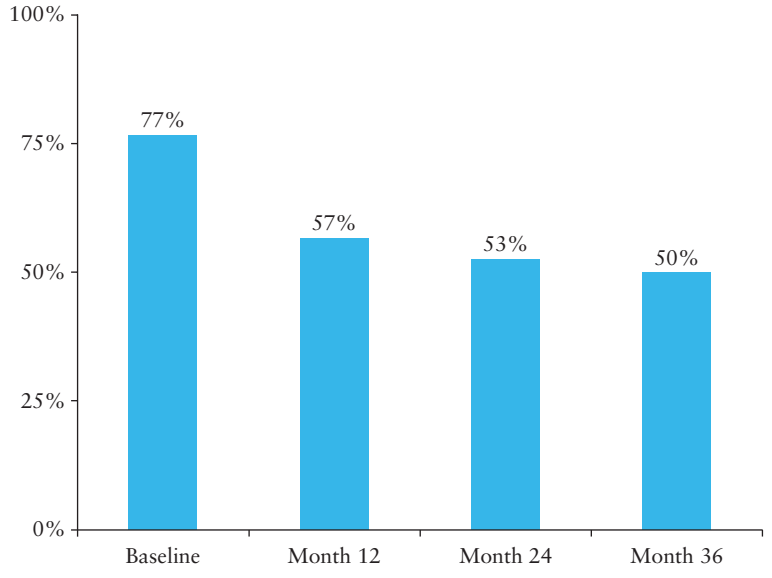


**Figure 4.** Efficacy of anti-tumour necrosis factors [TNFs] in decreasing bowel damage overtime [defined as a LI > 4.8].

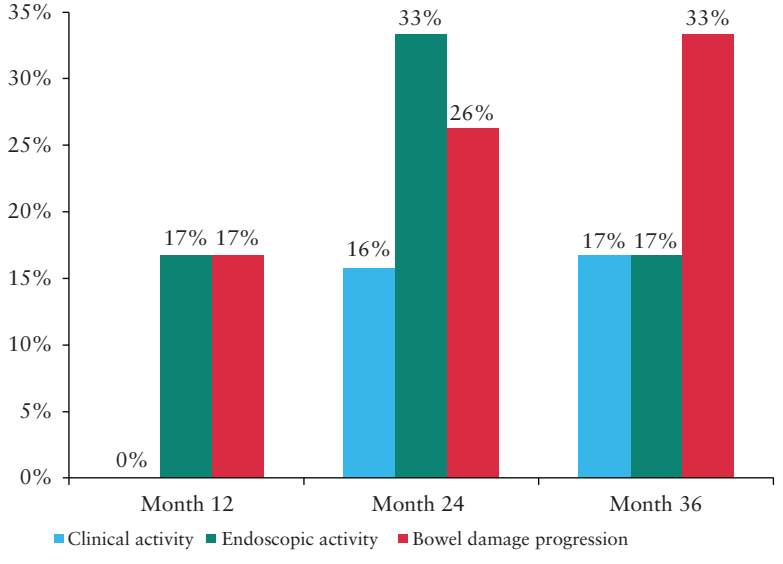


**Figure 5.** Progression of bowel damage overtime during anti-tumour necrosis factor [TNF] treatment [defined as a LI change >+ 0.3]. Bowel damage progression was observed in the minority of subjects, independently from clinical or endoscopic activity.

activity. In our cohort, we found that bowel damage slowly progressed overtime in a linear manner, with no direct correlation with clinical or endoscopic activity. The lack of correlation between endoscopic disease activity and the LI is likely explained by the fact that endoscopy only evaluates disease activity, whereas MRI evaluates both disease activity and complications [also called bowel damage].

BD is the main indication for surgery in CD.[4] Hence, it is not surprising that BD progression as assessed by the LI was associated with worse outcome, including an increased risk of CD-related surgery. Further data from a larger and prospective controlled study are needed to confirm their impact on modifying the natural history of CD in the long term, and if they are superior to conventional immunosuppressants such as thiopurines for this specific outcome. Indeed, we decided to focus on anti-TNF therapy as it is the most potent drug class in CD.[17] Two recent controlled trials made the potential for disease modification of thiopurines questionable in CD, at least in patients with early CD.[30,31] However, it would be interesting to compare changes in BD in patients treated with anti-TNF therapy to those in patients treated with azathioprine.

Our data show that the assessment of BD progression by the LI may be used to guide therapeutic decisions in CD patients. Subjects with BD progression were more likely to undergo surgery despite no direct correlation with the clinical disease activity and despite effective therapy in terms of symptom control. This confirms the disconnect between clinical symptoms and objective signs of inflammation in CD.[32] These data suggest that it may be necessary for patients to routinely undergo a global assessment of bowel damage with MRE and colonoscopy and, if BD is progressing, it may be necessary to step-up the treatment; this requires additional investigation. Moreover, since BD seems to be a function of time,[33] our data might suggest that early treatment with effective therapies, such as anti-TNF, may impact positively on the natural history of the disease

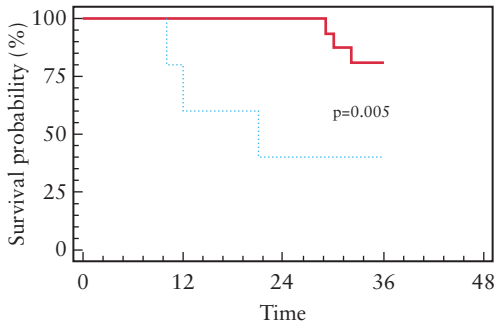


**Figure 6.** Bowel damage progression as assessed by the LI [dotted line] is predictive for CD-related major surgery within next 12 months compared with patients with no bowel damage progression [bold line].

overtime. This aspect needs to be evaluated in large prospective long-term trials.

Our study has some limitations. First, because this is a small pilot study, our conclusions need to be confirmed in large prospective studies. As it is unlikely that BD is spontaneously reversible, a control arm should not be considered necessary. However, to assess the real potential for disease modification of biologics and the magnitude of this benefit, that could be the ultimate endpoint to evaluate the efficacy of medications, controlled trials are needed.

Finally, there is no objective definition or measure of BD progression, Thus, further data are needed to clearly determine whether the LI changes and cut-offs are in fact closely related to actual changes in BD. Because of this limitation, our reference standard was arbitrarily chosen as a clinician's evaluation, which is currently the standard method of assessment. Moreover, the influence of disease activity on items included in the LI may justify the reduction of the LI from baseline, and should be taken into account in the serial evaluation of the LI overtime. However, this is the first study assessing changes in BD as assessed by the LI in CD subjects treated by anti-TNFs.

In conclusion, we showed for the first time that the LI might be able to provide an assessment of BD changes in CD. Anti-TNF therapy may allow BD regression in CD, although 30% of subjects required surgery in the follow-up period and some had BD progression. Hence, MRE may play a crucial role in assessing BD and its progression in CD, a transmural disease, and could be used to guide clinician's therapeutic decisions.

## Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

## Conflicts of interest

Gionata Fiorino served as a consultant and a member of Advisory Boards for MSD, Takeda Pharmaceuticals, and Janssen Pharmaceuticals; Mariangela Allocca received lecture fees from MSD, Takeda; Laurent Peyrin-Biroulet received consulting fees from Merck, Abbott, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Boerhinger-Ingelheim, Lilly. Lecture fees from Merck, Abbott, Janssen, Ferring, Norgine, Tillots, Vifor, Therakos, HAC-pharma; Silvio Danese has served as a speaker, consultant and advisory board member for Schering-Plough, Abbott Laboratories, Merck & Co, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson; the other Authors have no conflicts to declare.

## Acknowledgments

We gratefully thank Marie Cheeseman for her revision of the English in this manuscript.

**Author Contributions**: Gionata Fiorino and Silvio Danese conceived and designed the study protocol; Gionata Fiorino, Silvio Danese, Cristiana Bonifacio, Alessandro Repici and Luca Balzarini performed the study procedures; Gionata Fiorino and Mariangela Allocca independently performed the bowel damage assessment; Gionata Fiorino performed the data analysis and drafted the manuscript; Laurent Peyrin-Biroulet and Silvio Danese critically revised the manuscript; all the Authors approved the final version of the manuscript.

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