

Original Article

Prevalence of Bowel Damage Assessed by Cross-Sectional Imaging in Early Crohn's Disease and its Impact on Disease Outcome

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Abstract

Background and Aims: Bowel damage in Crohn's disease [CD] is defined as the presence of intestinal strictures, fistulas or abscesses. Early disease may represent a window of opportunity for timely intervention. We evaluated disease activity and severity by the Lémann Index [LI] and the Magnetic Resonance Index of Activity [MaRIA] score, and their prognostic value in early CD.

Methods: All consecutive patients diagnosed with CD in two referral centres, assessed by magnetic resonance imaging or computerized tomography, were prospectively included. Disease activity and bowel damage in early CD, the correlation between the LI and the MaRIA score, and the value of cross-sectional imaging findings in predicting disease progression were assessed. Statistical analyses employed time-to-event methods.

Results: We included 142 consecutive CD patients. Median time from diagnosis to baseline imaging was 0.3 years; median follow-up time was 4.9 years. At diagnosis, 39.4% of CD patients had bowel damage. At multivariable analysis, bowel damage and the LI were independent prognostic factors for intestinal surgery (hazards ratio [HR]: 3.21 and 1.11, respectively, $p < 0.001$), and of CD-related hospitalization during patient follow-up [HR: 1.88, $p = 0.002$, and 1.08, $p < 0.001$, respectively]. Disease activity as expressed by the MaRIA score did not predict the disease course. The correlation between the LI and MaRIA score was weak [$\rho = +0.32$; $p < 0.001$].

Conclusion: Four out of ten CD patients have bowel damage at the time of the first imaging study. The presence of bowel damage, and not the MaRIA score, in early CD is associated with a worse outcome, with increased risks of surgery and hospitalization.



Key Words: Bowel damage; complications; early Crohn's disease; Lémann Index

1. Introduction

Crohn's disease [CD] is a chronic, disabling, progressive and destructive inflammatory bowel disease. The progression of chronic inflammation can lead to bowel damage [BD], which is defined as the presence of intestinal strictures, fistulas or abscesses that often require surgical resection of the bowel, with a consequent increase in BD. A cohort study found that up to 50% of CD patients experience complications up to 20 years after diagnosis.¹

Recently, the Lémann Index [LI] has been developed to quantify and measure cumulative BD in CD patients.^{2,3} Anti-tumour necrosis factor α [anti-TNF] agents are able to reverse BD in some CD patients.⁴ BD progression as measured by the LI may be predictive of subsequent major abdominal surgery in CD.⁴

Targeting early CD may be the best way to change disease course and patients' lives. The Paris definition of early CD, resulting from an expert discussion, comprises two components: disease duration ≤ 18 months and no previous use of disease-modifying agents.⁵ Unfortunately, CD patients often experience diagnostic delay, which is associated with an increased risk of BD over time.⁶

To achieve disease modification, an effective intervention must occur at the right time, i.e. before the development of BD and impaired intestinal functioning.⁷ Effective intervention before the onset of BD [stricture, fistula, abscess] may be required to optimize patient outcomes.⁷

Based on an analysis of 221 patients with CD using the LI, two-thirds had substantial mucosal damage 2–10 years after diagnosis.⁸ High LI scores at the first evaluation, time, persistent clinical activity and intestinal resection are associated with damage.⁸

Interestingly, treatment with immunomodulators or TNF antagonists within the first 2 years of CD diagnosis has been shown to be associated with reduced risk of developing bowel strictures, when compared to initiating these drugs >2 years after diagnosis.⁹ Furthermore, early immunomodulator treatment was associated with reduced risk of intestinal surgery, perianal surgery and any complication.⁹

Because computerized tomography [CT] is a technique that involves ionizing radiation, and accuracy of ultrasound is highly related to CD location, magnetic resonance imaging [MRI] is proposed as first choice for CD patients and for measurement of the LI.² MRI is accurate for assessing disease activity and complications of CD.¹⁰ The Magnetic Resonance Index of Activity [MaRIA] has been validated for assessing disease activity and severity in CD; it is a valid, responsive and reliable index for assessing response to therapy in patients with CD.¹¹

Perianal disease, stenosis and/or intra-abdominal fistulae at MRI independently predict an increased risk of resection surgery in patients with CD, whereas immunomodulators and/or anti-TNF therapy reduce this risk.¹²

In this prospective, observational, multicentre study, we evaluated for the first time damage activity and severity as measured by modified MaRIA and LI in early CD, and the prognostic value of these radiological findings.

2. Methods

This was a prospective observational cohort study conducted in two irritable bowel disease [IBD] referral centres [Humanitas Research

Hospital, Rozzano, Milan, Italy; CHU Nancy, Nancy France]. All consecutive patients diagnosed with CD in the two centres between January 1, 2006 and December 31, 2014 who underwent their first assessment by MRI or CT within 24 months of diagnosis were included. The disease activity assessed by MRI was scored according to the MaRIA score, assessed for each segment and then also summing the segmental scores, by using an automatic calculator used in both participating centres, as previously described.¹¹ The LI calculation was performed according to Pariente *et al.*,³ integrating data from pelvic MRI or colonoscopy, if required. Local ethics committee approval was obtained.

Patients were eligible for the study according to the following criteria: [1] age equal to or greater than 18 years; [2] ability to understand the study procedures and to sign an informed consent form; [3] referred to the participating centres for highly suspected or recent [<24 months] diagnosis of CD without any imaging performed earlier; [4] no previous surgery for CD; [5] no previous therapies for CD prior to inclusion into the study. Patients were excluded if they had an established diagnosis of CD [assessed also with adequate imaging technique], diagnosed in other centres, or were diagnosed after surgical intestinal resection, or were not able to comply or had contraindications to imaging procedures.

The primary outcome of this study was whether the LI calculated in newly diagnosed patients could be predictive of the disease course over time. Poor disease course was defined as the need for CD-related surgery, CD-related hospitalization, need for immunomodulators [IMMs], or anti-TNF therapy at any time since diagnosis. Secondary outcomes were: the proportion of subjects with BD at the time of the first assessment, defined as the presence of intestinal strictures, fistulas or abscess; the correlation between the MaRIA score and the LI at diagnosis; and the possible correlation between pre-defined baseline characteristics and the outcome of CD over time.

2.1. Imaging protocol

The imaging sessions were performed on a 1.5-T scanner [Siemens Symphony, Erlangen, Germany] or a 3-T scanner [Siemens Verio], with a combination of two surface coils, depending on the centre availability. Abdominal MRI did not require any bowel preparation. Fasting for 6 h prior to the session was required. All patients were given 1500 ml polyethylene glycol electrolyte solution, PEG [Colirei®, ABC Farmaceutici Spa, Torino, Italy], as biphasic contrast agent, by steady administration within 60 min before starting with MR sessions. Intravenous glucagon [GlucaGen® Hypokit, Novo Nordisk, Bagsvaerd, Denmark] 0.5 mg was administered intravenously. T2-weighted half Fourier acquisition single-shot turbo-spin-echo [HASTE] imaging was used in three planes [axial, coronal, sagittal], without fat suppression [in axial plane, TR 900 ms, TE 84 ms, flip angle 150°, breath held; in coronal plane TR 1000 ms, TE 73 ms, flip angle 150°, breath held; in sagittal plane TR 1000 ms, TE 75 ms, flip angle 150°]. True steady-state free precession [FISP] images were obtained, with fat suppression, in the coronal plane [TR 4.83 ms, TE 2.42 ms, flip angle 80°] and the axial plane [TR 4.85 ms, TE 2.43 ms, flip angle 70°]; a pre-contrast coronal T1-W volume interpolated gradient-echo [VIBE] sequence with fat suppression was performed [TR 6.86 ms, TE 2.44 ms, flip angle 10°], and this sequence was likewise repeated after intravenous administration of a gadolinium-based agent [gadobenate dimeglumine, Multihance,

Bracco, Milan, Italy] at a dose of 0.1 mmol/kg. After injection of the contrast agent, a T1-W VIBE sequence with fat suppression was performed in the axial plane [TR 5.16 ms, TE 2.57 ms, flip angle 10°] and an axial T1 fast low-angle shot [FLASH] [TR 316 ms, TE 36 ms, flip angle 120°].¹³

The CT scans were performed in supine position using a multi-slice scanner with a 16-detector row [MX8000 IDT, Philips, Best, Netherlands] after intravenous infusion of a bolus of non-iodinated contrast agent [2 ml/kg], in venous phase [70 s].¹⁴

An expert radiologist for each centre performed and read all the images. The MaRIA score and the LI was calculated by the radiologist and a gastroenterologist aware of both index calculations. MRI and CT images were used to calculate the LI for each patient, while only MR images in patients that had no upper disease location [98% of patients] were used for the MaRIA scoring process.

2.2. Statistical methods

Descriptive statistics are presented as medians and interquartile ranges [IQRs], or as percentages when appropriate. Because most variables were non-normally distributed, non-parametric statistical tests [Pearson's chi-squared, Fisher's exact and the two-sample Wilcoxon rank-sum test] were used for the comparisons between the 'early CD' sub cohort [patients without any complication at diagnosis, such as strictures, fistulas and abscesses] and the 'complicated CD' sub cohort [patients with BD at diagnosis]. The correlation between LI and MaRIA score was assessed using the Spearman rank correlation coefficient and the respective *p*-value. Four types of events were considered as endpoints: [i] the occurrence of surgery [intestinal resection], [ii] CD-related hospitalization, [iii] the need for IMMs and [iv] the need for anti-TNF agents. The effect of BD at diagnosis on the probability of events was evaluated using time-to-event [survival] methods for censored observations, because of the varying length of follow-up. Time to event was calculated from the date of diagnosis to the date of event or censoring. Kaplan-Meier estimates were used to draw the cumulative incidence curves, compared by log-rank tests, as well as by univariable and multivariable Cox's proportional hazards [PH] models of relevant prognostic factors. Different models were designed for each of the endpoints. Covariates included in the univariable and the multivariable analyses were either continuous [age at diagnosis, LI and MaRIA score] or categorical variables [BD at diagnosis, gender and localization of

disease]. We followed a standard approach for model selection.¹⁵ In the univariable Cox's PH analysis, a criterion of $p \leq 0.10$ was used to identify candidate predictors. We then fitted multivariable models and used a backwards selection procedure to eliminate variables not significant in the multivariate framework. A criterion of $p \leq 0.05$ was used for determining which variables to eliminate. After fitting the models, the proportional-hazards assumption was examined on the basis of Schoenfeld residuals.¹⁶ The hazards ratios or relative hazards [HR] derived from the Cox's PH models are presented with 95% confidence intervals [CIs] and the respective *p*-values. A ratio higher than 1.0 implies a higher probability of an event compared with the reference group. The *p*-values are two-tailed. For all tests, a *p*-value less than 0.05 indicates statistical significance. Stata software was used for all analyses [Stata Corp., College Station, TX, USA].

3. Results

Data from 142 consecutive eligible CD patients who were diagnosed with CD in two referral centres in Nancy [$n=72$] and Milan [$n=70$] were collected and analysed. Patient ages ranged from 15 to 84 years at diagnosis [median, 28.8 years]; 47% were males. The time from the date of diagnosis to the date of baseline imaging was relatively short (median, 0.3 years; interquartile range [IQR], 0.05–1.0 years). A total follow-up time of approximately 680 person-years [PY] was analysed [mean, 4.8 years per patient; median, 4.9 years].

Eighty-six patients [60.6%] formed the 'early CD' sub-cohort [subjects without any complications, such as strictures, fistulas and abscesses, at diagnosis], while the other 56 patients [39.4%] with BD at diagnosis formed the 'complicated CD' sub-cohort. At baseline, the two groups were different in terms of LI, MaRIA score, and Montreal classifications B and L. The baseline characteristics of the study population are presented in Table 1.

A weak positive correlation between LI and MaRIA score was identified [Spearman's ρ : +0.32; $p < 0.001$].

3.1. Risk of intestinal surgery

In the entire study population, 57 patients [40.1%] underwent surgery during the follow-up period. The overall incidence of intestinal surgery was 11.3 per 100 PY at risk, while the median time to surgery was 8.0 years [IQR, 1.7–9.4 years].

Table 1. Baseline characteristics of the study cohort.

	Total cohort [$n=142$]	'Early CD' [$n=86$]	'Complicated CD' [$n=56$]	<i>p</i> -value
Age [years], mean [range]	28.8 [20.5–41.5]	27.3 [20.3–42.4]	31.6 [22.5–41.1]	0.59
Time to imaging [years], mean [range]	0.3 [0.05–1.0]	0.4 [0.04–1.2]	0.3 [0.06–1.0]	0.56
Male gender	67/142 [47.2%]	41/86 [47.7%]	26/56 [46.4%]	0.88
Localization of disease:				
Upper disease	3/142 [2.1%]	2/86 [2.3%]	1/56 [1.8%]	0.99
Perianal disease	32/142 [22.5%]	20/86 [23.3%]	12/56 [21.4%]	0.80
Lémann Index	2.95 [1.3–6.1]	2.35 [1.0–5.3]	3.65 [2.3–6.65]	0.018
MaRIA score	18.5 [0.0–36.6]	6.2 [0.0–23.0]	31.5 [22.8–45.7]	<0.001
Montreal classification:				
A1/A2/A3	4/98/40	3/59/24	1/39/16	0.99
B1/B2/B3	80/39/22	65/14/6	15/25/16	<0.001
L1/L2/L3	54/23/64	29/20/36	25/3/28	0.013
Imaging [MRI/CT]	76/66	36/50	40/16	0.001
Stricture[s]	54/142 [38.0%]	0/86	54/56 [96.4%]	–
Fistula[s]	20/142 [14.1%]	0/86	20/56 [35.7%]	–
Abscess[es]	11/142 [7.8%]	0/86	11/56 [19.6%]	–

Among patients with BD at diagnosis, 35 events [i.e. surgeries] were reported [62.5%]. The incidence was 22.1 per 100 PY at risk, while the median time to surgery was 3.0 years. Interestingly, among patients who had no complications at diagnosis [‘early CD’ sub-cohort] only 22 events were reported [25.6%] with a corresponding incidence of 6.4 per 100 PY at risk, and a median time to surgery of 9.4 years.

Kaplan–Meier analysis demonstrated a higher cumulative probability of intestinal surgery in patients who had BD at diagnosis [‘complicated CD’ group] compared with those in the ‘early CD’ group [Figure 1; log-rank $p < 0.001$].

The Cox PH analysis identified BD and LI as independent prognostic factors for intestinal surgery. We found a statistically significant 3-fold increase in the risk of surgery among patients with BD at diagnosis compared with those in the ‘early CD’ sub-cohort (univariable analysis, HR: 3.33, 95% confidence interval [CI]: 1.93–5.73, $p < 0.001$; multivariable analysis, HR: 3.21, 95% CI: 1.87–5.53, $p < 0.001$) and an 11% risk increase per 1-unit increase of LI at baseline [univariable analysis, HR: 1.10, 95% CI: 1.05–1.15, $p < 0.001$; multivariable analysis, HR: 1.11, 95% CI: 1.05–1.16, $p < 0.001$; Table 2]. There was no evidence that the PH assumption was violated [global test of PH assumption, $p = 0.49$].

Finally, it is important to note that LI was significantly associated with the risk of surgery also when tested as a binary variable, as proposed in two previous studies^{4,8} [cut off: 2.0, HR: 3.81, 95% CI: 1.91–7.58, $p < 0.001$; cut off: 4.8, HR: 2.38, 95% CI: 1.38–4.13, $p = 0.002$].

3.2. Risk of CD-related hospitalization

In the entire study population, 95 patients [66.9%] experienced CD-related hospitalization during their follow-up. The overall incidence was 28.2 per 100 PY at risk, while the median time to hospitalization was 1.6 years [IQR, 0.1–7.7 years].

Among patients with BD at diagnosis, 47 events were reported [83.9%]. The incidence was 45.0 per 100 PY at risk, while the median time to hospitalization was 1.0 years. Among patients without any complication at diagnosis [‘early CD’ sub-cohort], 48 hospitalizations were reported [55.8%] with a corresponding incidence of 20.7 per 100 PY at risk, and a median time to hospitalization of 2.8 years.

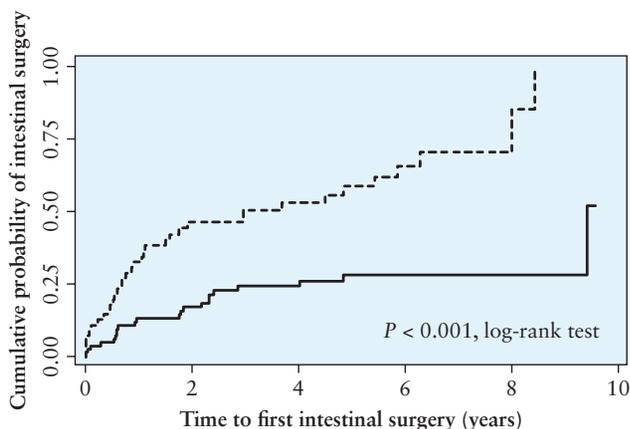


Figure 1. Kaplan–Meier curves for the cumulative probability of intestinal surgery in patients with bowel damage at diagnosis [‘complicated CD’ sub-cohort; dotted line] and patients without any complications at diagnosis [‘early CD’ sub-cohort; solid line].

Again, the Kaplan–Meier analysis demonstrated a higher cumulative probability of hospitalization in patients with BD at diagnosis [‘complicated CD’ group] compared with those in the ‘early CD’ group [Figure 2; log-rank $p = 0.001$].

The Cox PH analysis identified BD and LI as independent prognostic factors for hospitalization. We found a 90% increase in the risk of hospitalization among patients with BD at diagnosis compared with patients of the ‘early CD’ sub-cohort [univariable analysis, HR: 1.91, 95% CI: 1.27–2.87, $p = 0.002$; multivariable analysis, HR: 1.88, 95% CI: 1.25–2.83, $p = 0.002$], and an 8% rise in the risk per unit increase of LI [univariable analysis, HR: 1.08, 95% CI: 1.04–1.12, $p < 0.001$; multivariable analysis, HR: 1.08, 95% CI: 1.04–1.12, $p < 0.001$; Table 3].

There was no evidence that the PH assumption was violated [global test, $p = 0.40$].

It is important to note that LI was significantly associated with the risk of hospitalization also when tested as a binary variable [cut off: 2.0, HR: 2.28, 95% CI: 1.44–3.62, $p < 0.001$; cut off: 4.8, HR: 2.06, 95% CI: 1.34–3.17, $p = 0.001$].

3.3. Need for immunomodulators

Overall, 69 patients [48.6%] needed to start IMM during their follow-up [incidence of IMM initiation: 18.8 per 100 PY; median time to first IMM use: 4.2 years]. Among patients of the ‘complicated CD’ sub-cohort, 30 [53.6%] initiated IMM use [incidence: 23.9 per 100 PY at risk]. Among those of the ‘early CD’ sub-cohort, 39 [45.4%] initiated IMM use [incidence: 16.2 per 100 PY at risk].

Kaplan–Meier analysis indicated that the cumulative probabilities of IMM initiation for the ‘complicated CD’ group and the ‘early CD’ group were not statistically significantly different [Supplementary Figure 1; log-rank $p = 0.28$]. The respective univariable Cox’s PH analysis showed a non-significant increase in the risk of IMM use [HR: 1.30, 95% CI: 0.80–2.09, $p = 0.29$].

3.4. Need for anti-TNF agents

Eighty-four patients [59.2%] started anti-TNF drugs during their follow-up [incidence of anti-TNF drug initiation: 24.5 per 100 PY; median time to first use of anti-TNF drug: 2.1 years]. Among patients in the ‘complicated CD’ group, 35 [62.5%] started anti-TNF drugs [incidence of anti-TNF drug initiation: 26.0 per 100 PY at risk]. Among those of the ‘early CD’ group, 49 [57.0%] started using anti-TNF drugs [corresponding incidence: 23.5 per 100 PY at risk].

The cumulative probability of starting anti-TNF drug use did not differ between the ‘complicated CD’ and the ‘early CD’ sub-cohorts [Supplementary Figure 2; log-rank $p = 0.88$]. This was also shown by the respective univariable Cox’s PH analysis [HR: 1.04, 95% CI: 0.67–1.60, $p = 0.88$].

4. Discussion

This is the first study investigating the predictive role of disease activity and severity [BD] in early CD as measured by cross-sectional imaging. We found that the presence of BD at diagnosis was associated with a significantly higher risk of hospitalization and surgery during follow-up, compared with patients with a non-stricturing and non-penetrating pattern. We found also that the LI calculated at diagnosis was an independent predictor for disease progression and surgery. These data support the importance of a full evaluation of CD at diagnosis, both with endoscopy and with cross-sectional

Table 2. Influence of baseline parameters on the probability of surgery [intestinal resection]: results from time-to-event analysis.

Baseline parameter	Log-rank test		Univariable Cox PH model			Multivariable Cox PH model		
	Chi-squared [d.f.]	<i>p</i> -value	HR	[95% CI]	<i>p</i> -value	HR	[95% CI]	<i>p</i> -value
Age*	–	–	1.00	[0.98–1.02]	0.80	–	–	–
Gender	3.22 [1]	0.073	0.61	[0.36–1.05]	0.076	–	–	–
Upper disease	1.05 [1]	0.31	2.06	[0.50–8.47]	0.32	–	–	–
Perianal disease	1.94 [1]	0.16	1.50	[0.85–2.64]	0.17	–	–	–
Lémann Index**	–	–	1.10	[1.05–1.15]	<0.001	1.11	[1.05–1.16]	<0.001
MaRIA score**	–	–	1.00	[0.99–1.01]	0.50	–	–	–
Bowel damage	21.21 [1]	<0.001	3.33	[1.93–5.73]	<0.001	3.21	[1.87–5.53]	<0.001

Abbreviations: PH, proportional hazards; HR, hazard ratio; CI, confidence interval.

*per 1-year increase; **per 1-unit increase.

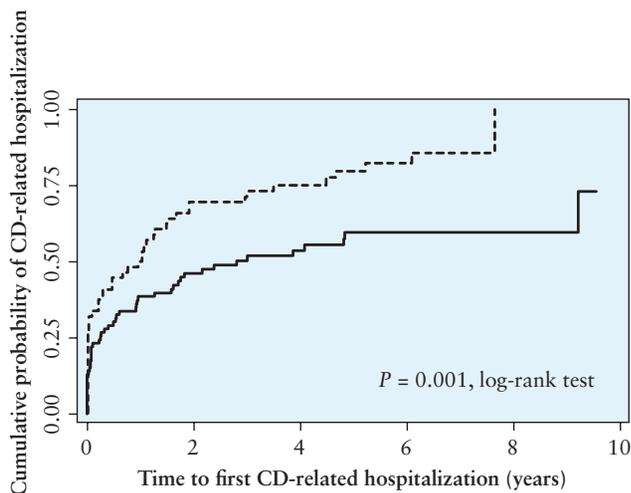


Figure 2. Kaplan-Meier curves for the cumulative probability of CD-related hospitalization in patients with bowel damage at diagnosis [‘complicated CD’ sub-cohort; dotted line] and patients without any complications at diagnosis [‘early CD’ sub-cohort; solid line].

imaging, as suggested by the ECCO Guidelines¹⁷ and relevant studies. The LI appears to be sensitive to assess and measure BD, and may also play a crucial role in predicting and monitoring disease progression overtime. Some cut-off values of the LI were proposed to discriminate patients with BD.¹⁸ Gilletta *et al.* found that an LI >2.0 at the first assessment indicated being more at risk of surgery.⁸ Fiorino *et al.* previously identified an LI >4.8 as a cut-off for the presence of BD in patients treated with anti-TNF.⁴ In our cohort, we also looked at the predictive role of both cut-offs, finding significant association with surgery and hospitalization. We found that any increase in the LI is associated with the risk of surgery, suggesting the hypothesis that the ideal cut-off for no BD should be 0.0, and that no increase or a decrease in BD over time may be a target for therapies in the near future.⁴ Moreover, our data suggest that any LI score >0.0 is always associated with a certain risk of disease progression, suggesting the importance of monitoring CD patients using cross-sectional imaging and endoscopy regularly,⁴ independent from clinical activity or biomarkers.

In our cohort, almost 40% of patients already had BD at diagnosis. Data from previous population-based cohort studies have shown that less than 20% of patients have complicated CD [stricturing or penetrating]. In a large population of CD patients [2002] evaluated retrospectively, with a consequent prospective

analysis on disease progression in a 5-year period [$n=646$], Cosnes *et al.*¹⁹ found that more than 80% of patients had non-stricturing and non-penetrating disease behaviour at diagnosis, but 60% of patients developed BD during the follow-up period. Thia *et al.*¹ showed more rapid progression than the French cohort since 18.6% developed BD within 90 days of diagnosis. Comparing the survival analysis in both studies, taking into account time from diagnosis to BD development, with our cohort, it appears that patients with BD at diagnosis had about 3-year-old disease at the time of the first assessment. These findings are in line with data on diagnostic delay in CD available in the literature. The IMPACT survey showed that up to 20% of subjects have to wait up to 5 years from the onset of symptoms in order to get an established diagnosis of CD.²⁰ More recently, Vavricka *et al.* showed that the median time-to-diagnosis for CD patients is >12 months from the onset of symptoms.²¹ The high rate of BD and the high LI score in our patients support the hypothesis of a delayed referral, in line with the data by Pariente *et al.* who found that the LI score increases with disease duration.² Diagnostic delay is actually associated with complications²² and delayed therapeutic strategies that could be ineffective and expensive if given at a late stage outside the ‘therapeutic window of opportunity’.⁶ Simple tools able to identify patients with high suspicion of CD, such as the recently developed ‘Red Flags’ questionnaire,²³ may play a key role in improving early referral and hopefully decrease the presence of complications at CD diagnosis, and the consequent risks for surgery and hospitalization.

MRI and CT are established as being complementary to endoscopy in assessing disease severity and complications. Recent data show that cross-sectional imaging can also predict the progression of CD over time. In a landmark single-centre, observational, prospective, longitudinal study enrolling 112 CD subjects with a median follow-up of 49 months, Jauregui-Amezaga *et al.*¹² found that MRI findings and, in particular, perianal disease, strictures and fistulas were significantly more associated with the risk of intestinal resection over time, with an odds ratio of 9.0 [95% CI 2–39, $p=0.003$], 3.4 [95% CI 1–11, $p=0.04$] and 10.6 [95% CI 2–46, $p=0.002$], respectively. More recently, Deepak *et al.*²⁴ showed that radiological response to treatments is associated with reduced risk of surgery, hospitalization and corticosteroid use in patients with small bowel CD. Although the LI was not calculated in these trials, our data are in line with these previous reports, since perianal disease, strictures and fistulas are integrated in the LI calculation,³ and, moreover, any decrease/lack of increase of the LI, which is mainly an MRI/CT-based index, may be associated with a lower risk of surgery over time.⁴

Table 3. Influence of baseline parameters on the probability of CD-related hospitalization: results from time-to-event analysis.

Baseline parameter	Log-rank test		Univariable Cox PH model			Multivariable Cox PH model		
	Chi-squared [d.f.]	<i>p</i> -value	HR	[95% CI]	<i>p</i> -value	HR	[95% CI]	<i>p</i> -value
Age*	–	–	1.01	[0.99–1.02]	0.24	–	–	–
Gender	0.39 [1]	0.53	1.13	[0.76–1.70]	0.54	–	–	–
Upper disease	0.00 [1]	0.95	0.96	[0.24–3.89]	0.95	–	–	–
Perianal disease	6.59 [1]	0.010	1.75	[1.13–2.72]	0.012	–	–	–
Lémann Index**	–	–	1.08	[1.04–1.12]	<0.001	1.08	[1.04–1.12]	<0.001
MaRIA score**	–	–	1.01	[1.00–1.02]	0.003	–	–	–
Bowel damage	10.33 [1]	0.001	1.91	[1.27–2.87]	0.002	1.88	[1.25–2.83]	0.002

Abbreviations: PH, proportional hazards; HR, hazard ratio; CI, confidence interval.

*per 1-year increase; **per 1-unit increase.

Interestingly and in contrast to BD, disease activity did not predict disease course in early CD, indicating that the presence of disease complications is an important risk factor for disease progression in these patients, whereas the presence of inflammation has no or little role in predicting disease course. The MaRIA index was developed to assess disease activity in the terminal ileum and in the colon,¹¹ while it has never been validated for upper disease. This could be an important limitation compared to the LI, which is able to assess BD in the entire digestive tract. Although such limitation may partially explain the poor correlation between the two indexes, the majority of our study population had ileal or ileo-colonic CD, allowing full assessment of disease activity by the MaRIA score, and suggesting that the LI is influenced, but is independent of, any grade of inflammation.

Our study has some limitations. First, the number of patients enrolled is small compared to all the patients screened [2997 during the study period]. This is because the vast majority of IBD patients are referred in our centres after receiving an established diagnosis. This may confirm that the majority of patients are late referred to IBD units, in line with the results of the IMPACT survey.²⁰ Second, we did not systematically collect data on smoking habits, need for corticosteroids or biomarkers of inflammation [such as C-reactive protein]. Third, variability was observed in the time elapsed from diagnosis to imaging, which is explained by the ‘real-life’ nature of the study. Furthermore, the median time to imaging was relatively short [0.3 years].

In conclusion, we found that four out of ten CD patients have BD at the time of the first cross-sectional imaging study performed within 24 months after diagnosis. Importantly, the presence of BD in early CD was associated with a worse outcome, with increased risks of surgery and hospitalization. These findings indicate that the LI calculation may play an important role in identifying patients at high risk of disease progression that would need more effective strategies and strict follow-up monitoring. Because too many patients are still diagnosed with complicated CD at the time of first assessment, the reduction of diagnostic delay and early referral remain the ultimate goals to significantly improve the quality of care of CD patients.

Conflict of Interest

GF served as a consultant and Advisory Board Member for MSD, AbbVie, Takeda, Pfizer, Mundipharma, Nikkiso, Otsuka. LP received consulting fees from Merck, AbbVie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly,

Pfizer, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis. Lecture fees from Merck, AbbVie, Takeda, Janssen, Takeda, Ferring, Norgine, Tillots, Vifor, Therakos, Mitsubishi, HAC-pharma. SD has served as a speaker, consultant, and advisory board member for Schering-Plough, Abbott Laboratories, Merck, UCB-pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Danone, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson. All the other authors have nothing to disclose.

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Author Contributions

Laurent Peyrin-Biroulet, Gionata Fiorino and Silvio Danese designed the study; Gionata Fiorino, Mathilde Morin, Cristiana Bonifacio, Valérie Laurent, Antonino Spinelli and Adeline Germain collected the data; Gionata Fiorino and Stefanos Bonovas performed the data analysis; Gionata Fiorino, Stefanos Bonovas, Mathilde Morin and Laurent Peyrin-Biroulet drafted the manuscript; Laurent Peyrin-Biroulet and Silvio Danese critically revised the manuscript; all the authors approved the final version of the manuscript.

Supplementary Material

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

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