

Efficacy of Early Intervention on the Bowel Damage and Intestinal Surgery of Crohn's Disease, Based on the Lémann Index

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Abstract

Background: Clinicians aim to prevent progression of Crohn's disease (CD); however, many patients require surgical resection because of cumulative bowel damage. The aim of this study was to evaluate the impact of early intervention on bowel damage in patients with CD using the Lémann Index and to identify bowel resection predictors.

Methods: We analyzed consecutive patients with CD retrospectively. The Lémann Index was determined at the point of inclusion and at follow-up termination. The Paris definition was used to subdivide patients into early and late CD groups.

Results: We included 154 patients, comprising 70 with early CD and 84 with late CD. After follow-up for 17.0 months, more patients experienced a decrease in the Lémann Index (61.4% vs. 42.9%), and fewer patients showed an increase in the Lémann Index (20% vs. 35.7%) in the early compared with the late CD group. Infliximab and other therapies reversed bowel damage to a greater extent in early CD patients than in late CD patients. Twenty-two patients underwent intestinal surgery, involving 5 patients in the early CD group and 17 patients in the late CD group. Three independent predictors of bowel resection were identified: baseline Lémann index ≥ 8.99 , disease behavior B1, and history of intestinal surgery.

Conclusions: Early intervention within 18 months after CD diagnosis could reverse bowel damage and decrease short-term intestinal resection. Patients with CD with a history of intestinal surgery, and/or a Lémann Index > 8.99 should be treated aggressively and monitored carefully to prevent progressive bowel damage.

Introduction

Crohn's disease (CD) is a chronic, destructive, and progressive disease of the gastrointestinal tract. In recent years, the prevalence of CD has increased in both Asian and Western countries¹⁻³. Current data shows that in China, the estimated incidence of CD is 0.51–1.09 cases per 100,000 persons^{4,5}.

At diagnosis, most patients with CD show chronic inflammatory behavior.⁶ However, during the course of the disease, CD can cause structural bowel damage (BD) over time, such as fibrostenotic or penetrating complications^{7,8}. Preventing the progression of BD has become a key goal to improve the long-term prognosis of patients with CD⁹.

Recently, to quantify and measure cumulative BD in patients with CD, the Lémann index (LI), which is based on small bowel imaging, endoscopy, previous surgery and perianal assessment, was developed.¹⁰ The LI has been used to evaluate the progression of CD and the efficacy of treatment.^{11,12}

Earlier use of biological agents tended to slow down the progression of BD.¹³ Targeting early CD might be the best way to change the disease course and maximize patient benefit. Unfortunately, patients with CD often experience a delay in diagnosis, which is associated with an increased risk of BD over time.^{7,8} The

Paris definition describes early CD as having a disease duration less than or equal to 18 months, without a history of previous treatment using disease-modifying agents (e.g., biologics, immunomodulators).¹⁴ Among the anti-tumor necrosis factor (TNF) agents currently available to treat CD, only infliximab (IFX) is approved in China. However, data supporting the effectiveness of IFX on BD in patients with CD are limited in China, because of the lower infusion rate of IFX and lower incidence of CD. Therefore, the main objective of this study was to determine the effect of early intervention on short-term outcomes of BD using LI, based on magnetic resonance enterography (MRE), and to identify predictors of short-term bowel resection in a series of patients with CD.

Materials And Methods

Participants and protocols

In our center, we conducted a retrospective, single-center study in patients with CD between July 2013 and October 2018. Criteria for inclusion in this study were patients older than 16 years and were diagnosed with CD according to histological, endoscopic, clinical, and pathological examinations. Patients involved in the study underwent MRE and endoscopy and/or pelvic magnetic resonance imaging (MRI) after surgical drainage if needed, within 4 weeks at baseline and at the end of follow-up. Different treatments were selected by the physician according to the patients' condition, including infliximab (5 mg/kg at weeks 0, 2, and 6, followed 5 mg/kg every 8 weeks), azathioprine (1.5 or 2.0 mg/kg/d) combined with steroids,¹⁵ other immunomodulators (tacrolimus or methotrexate), enteral nutrition, or mesalazine (3.0–4.0 mg/day) therapy.

The exclusion criteria included aged < 16 years, absence of two serial MRE data, incomplete follow-up data, history of treatment with biological agents within 12 months, history of intestinal surgery within 12 months, and less than 12 months' of follow-up.

The patients were subdivided into an early CD group and a late CD group according to the Paris definition. The early CD group comprised patients whose disease duration was less than or equal to 18 months and who had no previous history of the use of disease-modifying agents, which is independent of BD.¹⁴ The remaining patients whose disease duration was longer than 18 months and/or had started treatment with diseasemodifying agents were defined as the late CD group.

From the patients' medical records, the following data were extracted: Age; sex; smoking history; disease duration; age at CD diagnosis; age at enrollment; basic laboratory tests; clinical disease activity scores (CDAI); previous medical and surgical interventions; and time between initial and follow-up MRE (months).

Calculation of Lémann Index

For each patient, MRE-based LIs were calculated by scoring the following factors: endoscopy data, previous surgery, extension, location, and intestinal complications, according to Pariente et al.¹⁰

Endoscopic data, MRE of the small bowel, and pelvic MRI were reviewed by senior radiologists and gastroenterologists who were blinded to the other procedures of this study and had more than 10 years of experience.

The LI score was calculated by conceptually dividing the gastrointestinal tract into four segments. 1) The upper digestive tract, comprising the duodenum, stomach, and esophagus; 2) the small bowel tract, which was further subdivided into 20 segments each of 20-cm in length; 3) the colon and rectum, including sigmoid colon, descending colon, transverse colon, ascending colon, cecum, and rectum; 4) the anus. Investigators scored the information on previous operations, stricturing and/or penetrating lesions of maximal severity for each segment (grades 1–3). A known coefficient for each segment and the overall level of organ damage were calculated.¹⁰

Patients whose LI was unchanged were defined as “stabilized”, those with a decreased LI as “Improved”, and those with an increased LI as “Deteriorated”.

Statistical analysis

To summarize continuous variables, medians with the interquartile range (IQR) were used. For discrete data, percentages were computed. A chi-squared test or Fisher's exact test were used to compare categorical variables, and the Mann-Whitney U-test was used to compare the differences between independent groups. To determine the ideal cut-off value of LI to predict the risk factors of bowel surgery, analysis using receiver operating characteristic (ROC) curves analysis was used. We also calculated the area under the curve (AUC) with 95% confidence intervals (CIs), sensitivity, and specificity. Univariate logistic regression was performed to identify significant predictors of increase in short-term intestinal resection. Multivariate analysis was then performed on the variables with a *P* value < 0.10 from the univariate analysis. IBM SPSS Statistics 21.0 software (IBM Corp., Armonk, NY, USA) was used to perform all the statistical analyses. Statistical significance was accepted at a two-sided *P*-value of < 0.05.

Results

Baseline Characteristics of the Patients

A total of 209 patients with data from at least two serial MREs and endoscopic data w

ere potentially eligible. Finally, 154 patients with at least two serial MRE examinations met the inclusion criteria and were included, whereas 55 patients were excluded (aged < 16 years, *n* = 8, MRE performed less than 12 months apart, *n* = 21, incomplete follow-up data, *n* = 15, history of intestinal surgery within 12 months, *n* = 11).

The baseline characteristics of the included patients are summarized in Table 1. Approximately two-thirds of the population was male, and the median age at CD diagnosis was 24.5 years [IQR: 17.0–29.0]. Seventy (45.5%) patients received an early CD diagnosis. Ninety-four (61.0%) patients were without complicated behavior (B1), while 40 (26.0%) patients showed at least one stricture (B2), and 26 (16.9%)

patients presented with penetrating CD (B3) at the time of inclusion. Regarding CD location, 72 (47.1%) had ileal disease (L1), 9 (5.8%) had isolated colonic disease (L2), 71 (46.1%) had ileocolonic disease (L3), and 31 (20.1%) showed an upper gastrointestinal tract CD location (L4). Sixty-nine (44.8%) patients had perianal involvement in our IBD center, while 27 (17.5%) of the included patients had received previous intestinal surgery.

Table 1
Demographic and clinical characteristics-grouped by disease duration

Variable	Total patients (n = 154)	Early CD(n = 70)	Late CD(n = 84)	P value
Gender(Male: Female)	103: 51	44: 26	58: 26	0.42
Median age on set of CD, years	24.5 [17.0–29.0]	25.0 [17.0–28.0]	24.0 [15.5–31.0]	0.56
Median age at enrollment, years	29.0 [23.0–36.0]	26.0 [19.8–30.5]	33.0 [27.00–39.8]	< 0.001
Median disease duration, years	4.5 [1.0–7.0]	1.0 [0.5–2.0]	7.0 [4.0–9.0]	< 0.001
Montreal (Age)				
A1 (16 years or younger)	16 (10.4%)	8 (11.4%)	8 (10.7%)	0.43
A2 (17–40 years)	114 (74.0%)	53 (75.7%)	61 (72.6%)	0.42
A3 (more than 40 years)	24 (15.6%)	9 (12.9%)	15 (17.9%)	0.36
Montreal L (location)				
L1 (ileal)	72 (47.1%)	38 (54.3%)	32 (38.1%)	0.43
L2 (colonic)	9 (5.8%)	3 (4.3%)	6 (7.1%)	0.19
L3 (ileocolonic)	71 (46.1%)	26 (37.1%)	45 (53.6%)	0.16
L4 (upper GI)	31 (20.1%)	13 (18.6%)	19 (22.6%)	0.60
Montreal B (Behavior)				
B1	94 (61.0%)	46 (65.7%)	48 (57.1%)	0.26
B2	40 (26.0%)	17 (24.3%)	23 (27.4%)	0.51
B3	26 (16.9%)	9 (12.9%)	17 (20.2%)	0.53
Perianal disease	69 (44.8%)	37 (52.9%)	32 (38.1%)	0.07
Previous surgical resection	27 (15.5%)	7 (10.0%)	20 (23.8%)	0.02
Previous medical treatments				
Steroids	24 (15.6%)	9 (12.9%)	15 (17.9%)	0.08

Data are expressed as number (%) or median[IQR].

B1, nonstricturing nonpenetrating; B2, stricturing; B3, penetrating; 5-ASA, 5-aminosalicylic; CRP, C-reactive protein; ESR, erythrocyte sedimentation; ALB, Albumin; HB, Hemoglobin; PLT, Platelet; LI, Lémann index.

Variable	Total patients (n = 154)	Early CD(n = 70)	Late CD(n = 84)	P value
Immunomodulators	43 (27.9%)	0 (0%)	43 (51.2%)	< 0.001
5-ASA	41 (26.7%)	18 (25.7%)	23 (27.4%)	0.62
Smoking habit	12 (7.8%)	4 (5.7%)	8 (9.5%)	0.23
Baseline serological markers				
CRP, mg/L	4.3 [0.5–15.3]	6.16 [0.4–24.9]	5.2 [0.5–13.1]	0.12
ESR, mm/h	22.0 [12.0–45.0]	19.0 [12.0–42.0]	24.0 [13.0–49.0]	0.10
ALB, g/L	38.6 [31.5–43.6]	38.7 [32.1–42.6]	38.4 [30.6–44.7]	0.70
HB, g/L	125.0 [101.0-141.3]	126.5 [105.0-140.3]	124.0 [95.25–142.0]	0.24
PLT, × 10 ⁹ /L	240.0 [196.0-314.3]	247.0 [197.0-342.0]	229.0 [193.8-297.3]	0.12
Current serological markers				
CRP, mg/L	0.6 [0.2-3.0]	0.55 [0.2–2.2]	0.57 [0.17–3.4]	0.61
ESR, mm/h	14.0 [3.0–22.0]	12.0 [2.0–20.0]	15.0 [3.0–24.0]	0.16
ALB, g/L	42.0 [32.7–46.0]	42.6 [33.4–46.3]	41.05 [30.28–45.6]	0.27
HB, g/L	132.0 [113.0-147.0]	136.0 [122.0-149.3]	126.5 [111.0-146.8]	0.27
PLT, × 10 ⁹ /L	225.5 [199.0-286.0]	225.0 [198.0-283.0]	228.0 [199.0-300.0]	0.73
Inclusion LI	6.2 [2.4–10.7]	6.3 [1.7–10.5]	5.9 [3.0–11.0]	0.67
Follow up LI	4.5 [1.7–9.4]	3.4 [1.6–7.5]	5.2 [2.0-10.5]	0.02
Follow up time (months)	17.0 [13.2–23.3]	15.0 [13.0–25.0]	18.5 [13.5–24.0]	0.18
CD-related bowel surgery	22 (14.3%)	5 (7.1%)	17 (20.2%)	0.001
Stabilized	31 (20.1%)	13 (18.6%)	18 (21.4%)	0.29
Improved	79 (51.3%)	43 (61.4%)	36 (42.9%)	< 0.001

Data are expressed as number (%) or median[IQR].

B1, nonstricturing nonpenetrating; B2, stricturing; B3, penetrating; 5-ASA, 5-aminosalicylic; CRP, C-reactive protein; ESR, erythrocyte sedimentation; ALB, Albumin; HB, Hemoglobin; PLT, Platelet; LI, Lémann index.

Variable	Total patients (n = 154)	Early CD(n = 70)	Late CD(n = 84)	P value
Deteriorated	44 (28.6%)	14 (20%)	30 (35.7%)	< 0.001
Data are expressed as number (%) or median[IQR].				
B1, nonstricturing nonpenetrating; B2, stricturing; B3, penetrating; 5-ASA, 5-aminosalicylic; CRP, C-reactive protein; ESR, erythrocyte sedimentation; ALB, Albumin; HB, Hemoglobin; PLT, Platelet; LI, Lémann index.				

On the basis of the Paris definition, the study population was subdivided the early CD group (n = 70, 45.5%), and the late CD group (n = 84, 54.5%). In terms of median follow-up time, the two groups showed no statistically significant difference ($P = 0.18$): 15.0 months [13.0–25.0] and 18.5 months [13.5–24.0]. The median disease duration in the two groups were 1.0 year [0.5–2.0] and 7.0 years [4.0–9.0], respectively, $P < 0.001$. The two groups showed a significant difference in terms of median age at enrollment (26.0 years [19.8–30.5] vs. 33.0 years [27.0–39.8], $P < 0.001$, whereas between the two groups, there was no statistically significant difference for median age on set of CD, disease location, perianal involvement, and behavior. (Table 1).

Comparison of the Lémann Index in patients with different disease durations

At the time of inclusion, the median LI was calculated as 6.2 [2.4–10.7]. There was no significant difference in the LI score between the early CD group (6.3 [1.7–10.5]) and the late CD group (5.9 [3.1–11.0], $P = 0.67$).

Among the 154 patients, at the end of follow-up, the LI decreased to a median of 4.5 [1.7–9.4], $P = 0.001$. The LI score decreased in 79 (51.3%) patients, remained unchanged in 31 (20.1%) patients, and increased in 44 (28.6%) patients. When subgroup analysis was performed, we found that the median LI score decreased significantly from 6.3 [1.7–10.5] to 3.4 [0.6–7.5] in the early CD group ($P = 0.001$), whereas it remained unchanged in the late CD group (from 5.9 [3.1–11.0] to 5.2 [2.0–10.5], $P = 0.34$). At follow up termination, 43 (61.4%) patients and 36 (42.9%) patients experienced a decrease in LI in the early and late CD group, respectively, $P < 0.001$. Fourteen (20.0%) patients and 30 (35.7%) patients showed an increased LI score, respectively, $P < 0.001$, whereas there was no significant difference in proportion of patients with a stable LI score between the two groups (18.6% vs. 21.4%), $P = 0.29$. (Fig. 1)

Comparison of the effect of different therapies on the Lémann Index

Among the patients included in the early CD group, 42 patients received IFX therapy and 28 patients underwent other treatments, including azathioprine combined with steroids (n = 11), other immunomodulators (n = 9), enteral nutrition (n = 2), or mesalazine (n = 6). We found that IFX and other

therapy could both reverse bowel damage in the early CD group (LI decreased from 5.5 [1.3–12.3] to 2.8 [0.3–7.4], $P=0.01$ and from 6.9 [2.8–8.8] to 4.1 [1.4–8.0], $P=0.02$, respectively). Twenty-five patients (59.5%) who received IFX and 18 patients (64.3%) who received other therapies experienced a decrease in LI during follow up. ($P=0.59$, Fig. 2). However, IFX induced a lower decrease in the LI score than other therapies (16.7% vs. 25.0%, $P=0.03$)

In the late CD group, 38 patients received IFX treatment and 46 patients were treated with other drugs, including AZA combined with steroid ($n=14$), other immunomodulators ($n=22$), enteral nutrition ($n=7$), or mesalazine ($n=3$). Compared with other treatments, IFX did not present a major effect of improving BD (42.1% vs. 43.5%, $P=0.91$), and more patients on IFX therapy experienced an increase in LI score compared with patients receiving other therapies (42.1% vs. 30.4%, $P=0.06$, Fig. 2). The median LI scores were relatively stable in patients treated with IFX and in those treated with other drugs (LI from 6.6 [2.7–13.6] to 6.7 [2.0–12.5], $P=0.93$ and from 5.5 [3.2–10.3] to 4.3 [2.0–9.4], $P=0.20$, respectively) (Table 2).

Table 2
Different therapy in patients with early CD and late CD

	Medical treatments	N	Inclusion LI	Follow up LI	P value
Early CD	Total	70	6.3 [1.7–10.5]	3.4 [0.6–7.4]	0.001
	IFX	42	5.5 [1.3–12.3]	2.8 [0.3–7.4]	0.01
	Other therapy	28	6.9 [2.8–8.8]	4.1 [1.4-8.0]	0.02
	Steroids + AZA	11	8.1 [6.5–12.8]	4.4 [1.8–11.0]	0.02
	Immunomodulator	9	4.3 [1.8–7.2]	3.0 [1.8–6.3]	0.61
	Enteral nutrition	2	11.0 [6.8–11.0]	7.4 [1.3–7.4]	0.18
	Mesalazine	6	4.9 [0.3–8.1]	3.6 [0.3–7.5]	0.50
	Late CD	Total	84	6.0 [3.1–11.0]	5.2 [2.0-10.5]
IFX		38	6.6 [2.7–13.6]	6.7 [2.0-12.5]	0.93
Other therapy		46	5.5 [3.2–10.3]	4.3 [2.0-9.4]	0.20
Steroids + AZA		14	5.0 [3.7–6.5]	3.3 [2.3–8.4]	0.39
Immunomodulator		22	6.3 [2.9–11.4]	4.9 [2.3–9.3]	0.09
Enteral nutrition		7	10.6 [2.0-18.3]	2.4 [1.3–11.9]	0.71
Mesalazine		3	3.2 [1.0-4.9]	9.0 [1.0-13.2]	0.18

Data are expressed as median[IQR].

Predictors of short-term intestinal resection in patients with CD

During the follow-up period, 22 patients (14.3%) underwent intestinal surgery, including 5 patients (7.1%) in the early CD group and 17 patients (20.2%) in the late CD group, respectively ($P= 0.001$). For patients receiving IFX therapy and other treatment, intestinal resection rates were not significantly different the early CD group (7.1% vs. 7.1%) and late CD group (21.1% vs. 19.6%).

The relationship between the LI score and short-term intestinal resection rates was assessed by dividing LI into quartiles, and a significant LI level-dependent effect was observed on intestinal resection rates (5.3%, 10.3%, 12.8%, and 28.9%; $P < 0.001$) (Fig. 3). The cut-off value of the LI score to predict early bowel resection was determined using ROC analysis, which showed that the optimal cut-off threshold for the LI score was 8.99 (AUC, 0.75, 95% CI, 0.63–0.87; $P < 0.001$) to discriminate the presence and absence of bowel resection, with a sensitivity of 68.2% and a specificity of 81.1% (Fig. 4).

The relationship between baseline LI levels and short-term bowel resection was further analyzed by dividing the LI scores into two groups ($LI \geq 8.99$ and $LI < 8.99$). Univariate logistic regression analysis showed that, age at CD diagnosis ($P = 0.09$), disease duration ($P = 0.03$), early CD duration ($P = 0.04$), disease behavior B1 ($P = 0.01$), baseline $LI > 8.99$ ($P = 0.008$), and history of intestinal surgery ($P = 0.001$) were associated significantly with the early bowel resection in patients with CD. However, upon multivariate logistic regression analysis, only baseline $LI > 8.99$ (OR, 2.86; 95% CI: 1.05–7.83; $P = 0.03$), disease behavior B1 (OR, 0.20; 95% CI: 0.07–0.90; $P = 0.04$), and history of intestinal surgery (OR, 4.09; 95% CI: 1.43–11.74; $P = 0.01$), remained as significant independent risk factors for short-term bowel resection (Table 3).

Table 3
Predictors of the early bowel resection in patients with CD

Factors	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age at CD diagnosis	1.03 (0.99–1.06)	0.09	1.01(0.96–1.06)	0.72
Disease duration, year	1.12 (1.01–1.24)	0.03	0.87 (0.45–1.68)	0.68
Early CD duration	0.40 (0.15–0.88)	0.04	0.67 (0.17–2.90)	0.39
Disease behavior (B1)	0.22 (0.07–0.72)	0.01	0.20 (0.07–0.90)	0.04
Baseline $LI > 7.99$	3.55 (1.40–9.02)	0.008	2.86 (1.05–7.83)	0.03
History of intestinal surgery	5.64 (2.11–15.04)	0.001	4.09 (1.43–11.74)	0.01

Discussion

In recent years, the Lémann index has been used frequently as a valid tool to monitor BD progression^{11–13,16}. The present study is the first to investigate the influence of different medical therapies on the LI score in consecutive patients with early CD, and identified predictors for short-term bowel resection. We included patients with data for at least two serial MREs and subdivided these patients into early and late CD groups according to the Paris classification. At present, the Paris classification is the most accurate method to define patients with early CD. We found no statistically significant difference in baseline LI scores between the two groups. After a median follow up of 17.0 months, in the early CD group, more patients experienced a decrease in the LI score (61.4% vs. 42.9%), whereas fewer patients showed an

increase in the LI score (20% vs. 35.7%) compared with those in the late CD group. These findings indicated that patients with a shorter disease duration were less likely to have undergone BD progression compared patients with longer disease duration after medical treatment.

Recently, several cohort studies have been published that investigated the impact of early therapy on BD in patients with CD.¹⁷⁻²⁰ One study from Switzerland showed that early use of anti-TNF and/or immunomodulators in patients with CD within 24 months after diagnosis was related to a reduced risk of intestinal surgery and bowel strictures.¹⁷ Another cohort study found that within 16 months after diagnosis, patients using anti-TNF and conventional therapy had similar levels of IBD-related complications.¹⁸ However, these studies did not use the LI to evaluate the BD. The present study evaluated the effect of IFX and conventional therapy on BD using the LI score in patients with CD with different disease durations. We observed that IFX and other therapies both reversed BD in early CD patients (disease duration < 18 months). However, IFX was not more effective at improving BD for patients with longer disease duration. This result demonstrated the presence of a therapeutic window of opportunity to avoid irreversible BD, even though increasing evidence indicates that anti-TNF therapy could achieve higher mucosal healing and deep remission rates.²¹⁻²³

In this study, previous different previous intestinal surgery rates did not seem to affect baseline LI, whereas intestinal resection was one of the most decisive and scoring items in LI. During the follow-up period, the CD-related bowel resection rate was 14.3%, which was similar to certain previous studies,^{24,25} but lower than that in other studies.^{26,27} Patients with longer disease duration tended to have a higher intestinal surgery rate than patients with early CD (20.2% vs. 7.1%, $P = 0.001$). More importantly, patients receiving IFX did not suffer fewer CD-related intestinal resections compared with patients treated with other therapies. Then ROC analysis identified that an LI value of 8.99 was the optimal threshold to predict the risk of early intestinal resection. Other predictive factors for short-term intestinal resection were also assessed. We found that a higher risk of bowel surgery for CD was associated with a history of intestinal surgery, whereas disease behavior B1 could negatively predict the possibility of early bowel resection.

Several limitations of the present study should be acknowledged. First, its retrospective design might have the potential for selection bias and some possible confounders. Second, the choice of therapeutic strategies was affected partly by the patient's ability to pay. IFX, as the only biologic is approved in China, is not covered by the basic health insurance, which has led to a lower rate of IFX use²⁸. Third, the duration of follow-up varied in this study and the median follow-up was only 17.0 months, which might have been insufficient for some subjects to develop to BD complications.^{29,30} We recommend that long-term outcomes be measured using the LI in further prospective study, even though several studies showed that BD may occur quite early.^{6,31}

In conclusion, early intervention in CD could reverse BD, decrease the need for short-term intestinal resection, and change the natural history of the disease. In patients with CD, the LI is an effective and ideal measure to assess BD outcome. Moreover, patients with CD with a history of intestinal surgery at

diagnosis, and/or a baseline LI > 8.99 should be treated aggressively and monitored carefully to prevent or block BD progression.

Abbreviations

CD

Crohn's disease

BD

bowel damage

LI

Lémann index

TNF

anti-tumor necrosis factor

IFX

infliximab

MRE

magnetic resonance enterography

CDAI

clinical disease activity scores

IQR

the interquartile range

ROC

receiver operating characteristic

AUC

area under the curve

CI

confidence interval

Declarations

Acknowledgements:

Not applicable.

Authors' contributions

MMZ and QF designed the research study, prepared the manuscript, and analyzed data. MMZ, XTX, YQQ, ZC, and TRW contributed to acquisition and interpretation of data. QF, analyzed and calculated the MRI data. YQY provided partial MRI data. ZHR contributed to the study design, revising it critically for important intellectual content, and gave final approval of the version to be submitted. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Research Ethics Committee of Renji Hospital approved the present study. Individual consent was not necessary according to local ethical regulation in a retrospective investigation based on the hospital data management system as performed here.

Consent for publication

Not applicable.

Declaration of conflict of interest

All authors declare that they have no conflict of interests.

References

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142:46–54.
2. Jangi S, Ruan A, Korzenik J, et al. South Asian Patients With Inflammatory Bowel Disease in the United States Demonstrate More Fistulizing and Perianal Crohn Phenotype. *Inflamm Bowel Dis*. 2020 Mar 2. doi: 0.1093/ibd/izaa029.
3. Park SH, Kim YJ, Rhee KH, et al. A 30-year Trend Analysis in the Epidemiology of Inflammatory Bowel Disease in the Songpa-Kangdong District of Seoul, Korea in 1986–2015. *J Crohns Colitis*. 2019;13:1410–7.
4. Zhao J, Ng SC, Lei Y, et al. First prospective, population-based inflammatory bowel disease incidence study in mainland of China: the emergence of "western" disease. *Inflamm Bowel Dis*. 2013;19:1839–45.
5. Zeng Z, Zhu Z, Yang Y, et al. Incidence and clinical characteristics of inflammatory bowel disease in a developed region of Guangdong Province, China: a prospective population-based study. *J Gastroenterol Hepatol*. 2013;28:1148–53.
6. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, et al. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol*. 2010;105:289–97.

7. Roda G, Chien Ng S, Kotze PG, et al. Crohn's disease. *Nat Rev Dis Primers*. 2020;6:22.
8. Schoepfer A, Santos J, Fournier N, et al. Systematic Analysis of the Impact of Diagnostic Delay on Bowel Damage in Paediatric Versus Adult Onset Crohn's Disease. *J Crohns Colitis*. 2019;13:1334–42.
9. Fiorino G, Bonifacio C, Peyrin-Biroulet, et al. Preventing collateral damage in Crohn's disease: the Lémann index. *J Crohns Colitis*. 2016;10:495–500.
10. Pariente B, Mary JY, Danese S, et al. Development of the Lemann index to assess digestive tract damage in patients with Crohn's disease. *Gastroenterology*. 2015;148:52–63.
11. Lauriot D, Prevost C, Azahaf M, Nachury M, et al. Bowel damage and disability in Crohn's disease: a prospective study in a tertiary referral centre of the Lemann Index and Inflammatory Bowel Disease Disability Index. *Aliment Pharmacol Ther*. 2020;51:889–98.
12. Bodini G, Giannini EG, De Maria C, et al. Anti-TNF therapy is able to stabilize bowel damage progression in patients with Crohn's disease. A study performed using the Lemann Index. *Dig Liver Dis*. 2017;49:175–80.
13. Panchal H, Wagner M, Chatterji M, et al. Earlier Anti-Tumor Necrosis Factor Therapy of Crohn's Disease Correlates with Slower Progression of Bowel Damage. *Dig Dis Sci*. 2019;64:3274–83.
14. Peyrin-Biroulet L, Billioud V, D'Haens G, et al. Development of the Paris definition of early Crohn's disease for disease-modification trials: results of an international expert opinion process. *Am J Gastroenterol*. 2012;107:1770–6.
15. Qian X, Wang T, Shen J, et al. Low dose of azathioprine is effective to induce and maintain remission in active Crohn disease: A prospective observational study. *Medicine*. 2018;97:e11814.
16. Rispo A, Imperatore N, Testa A, et al. Bowel Damage in Crohn's Disease: Direct Comparison of Ultrasonography-based and Magnetic Resonance-based Lemann Index. *Inflamm Bowel Dis*. 2017;23:143–51.
17. Safroneeva E, Vavricka SR, Fournier N, et al. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. *Aliment Pharmacol Ther*. 2015;42:977–89.
18. Nuij V, Fuhler GM, Edel AJ, et al. Benefit of Earlier Anti-TNF Treatment on IBD Disease Complications? *J Crohns Colitis*. 2015;9:997–1003.
19. Kim B, Cheon JH, Moon HJ, et al. Crohn's disease prognosis and early immunomodulator therapy: Results from the CONNECT study. *J Gastroenterol Hepatol*. 2016;31:126–32.
20. Kwak MS, Kim DH, Park SJ, et al. Efficacy of early immunomodulator therapy on the outcomes of Crohn's disease. *BMC Gastroenterol*. 2014;14:85.
21. Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: towards disease modification trials. *Gut*. 2017;66:2179–87.
22. Cholakpranee A, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther*. 2017;45:1291–302.

23. Barnes EL, Allegretti JR. Are Anti-Tumor Necrosis Factor Trough Levels Predictive of Mucosal Healing in Patients With Inflammatory Bowel Disease?: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol*. 2016;50:733–41.
24. Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol*. 2006;101:1274–82.
25. Qiu Y, Chen BL, Feng R, et al. Prolonged azathioprine treatment reduces the need for surgery in early Crohn's disease. *J Gastroenterol Hepatol*. 2018;33:664–70.
26. Ng SC, Leung WK, Shi HY, et al. Epidemiology of Inflammatory Bowel Disease from 1981 to 2014: Results from a Territory-Wide Population-Based Registry in Hong Kong. *Inflamm Bowel Dis*. 2016;22:1954–60.
27. Liu W, Zhou W, Xiang J, et al. Lemann Index at Diagnosis Predicts the Risk of Early Surgery in Crohn's Disease. *Dis Colon Rectum*. 2018;61:207–13.
28. Zhu M, Xu X, Feng Q, et al. Effectiveness of Infliximab on Deep Radiological Remission in Chinese Patients with Perianal Fistulizing Crohn's Disease [published online ahead of print, 2020 Jun 10]. *Dig Dis Sci*. 2020. 10.1007/s10620-020-06398-w. doi:10.1007/s10620-020-06398-w.
29. Peyrin-Biroulet L, Cieza A, Sandborn WJ, et al. Development of the first disability index for inflammatory bowel disease based on the international classification of functioning, disability and health. *Gut*. 2012;61:241–7.
30. Nahon S, Lahmek P, Paupard T, Lesgourgues B, Chaussade S, Peyrin-Biroulet L, et al. Diagnostic Delay Is Associated with a Greater Risk of Early Surgery in a French Cohort of Crohn's Disease Patients. *Dig Dis Sci*. 2016;61:3278–84.
31. Fiorino G, Morin M, Bonovas S, Bonifacio C, Spinelli A, Germain A, et al. Prevalence of Bowel Damage Assessed by Cross-Sectional Imaging in Early Crohn's Disease and its Impact on Disease Outcome. *J Crohns Colitis*. 2017;11:274–80.

Figures

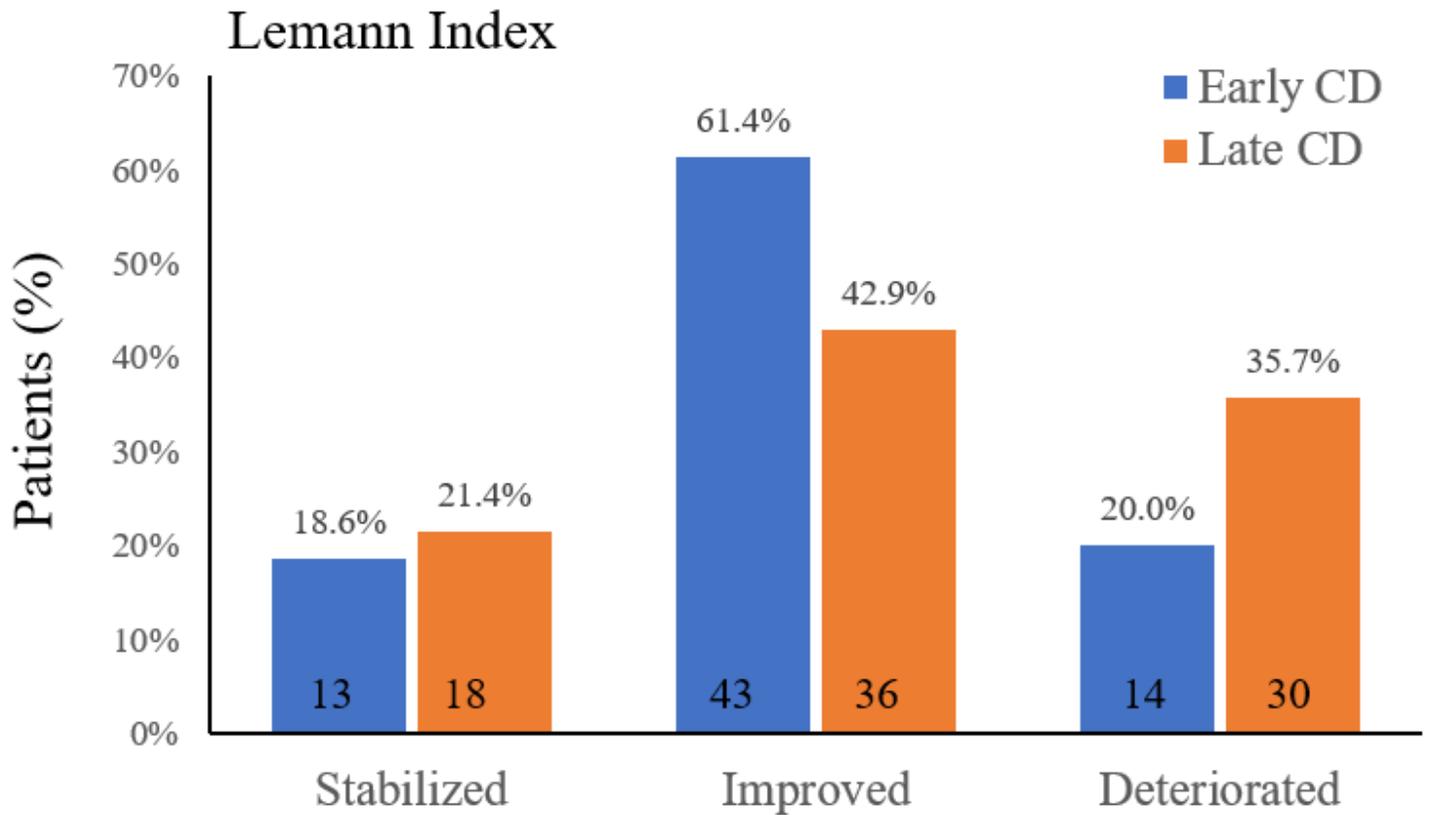


Figure 1

The changes of Lemann Index (LI) at follow-up termination in the early Crohn's disease (CD) and late CD groups. Patients whose LI was unchanged were defined as "stabilized", those with a decreased LI as "Improved", and those with an increased LI as "Deteriorated".

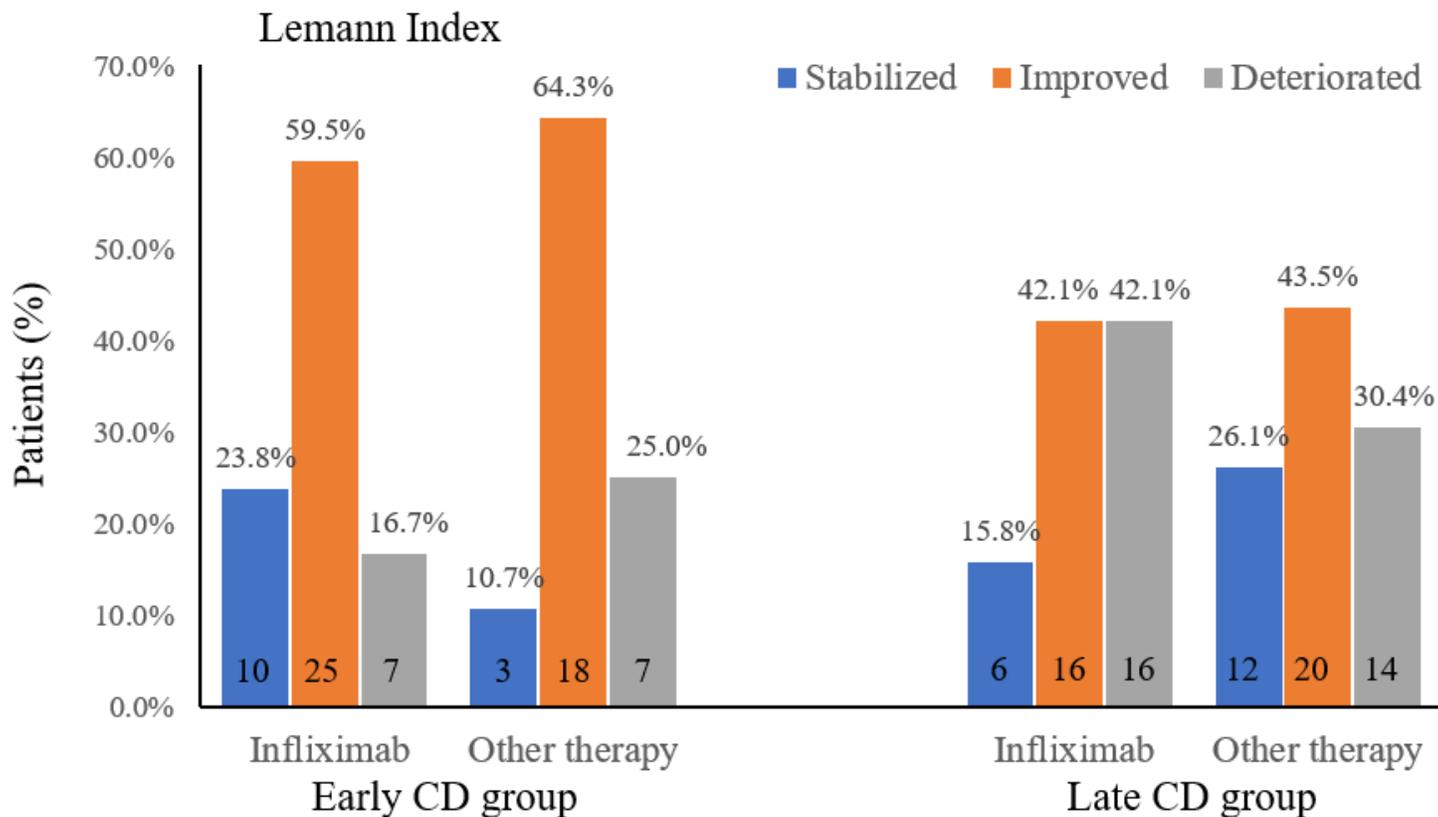


Figure 2

The effects of Infliximab and other therapy on Lémann Index (LI) of patients with different duration. Patients whose LI was unchanged were defined as “stabilized”, those with a decreased LI as “Improved”, and those with an increased LI as “Deteriorated”.

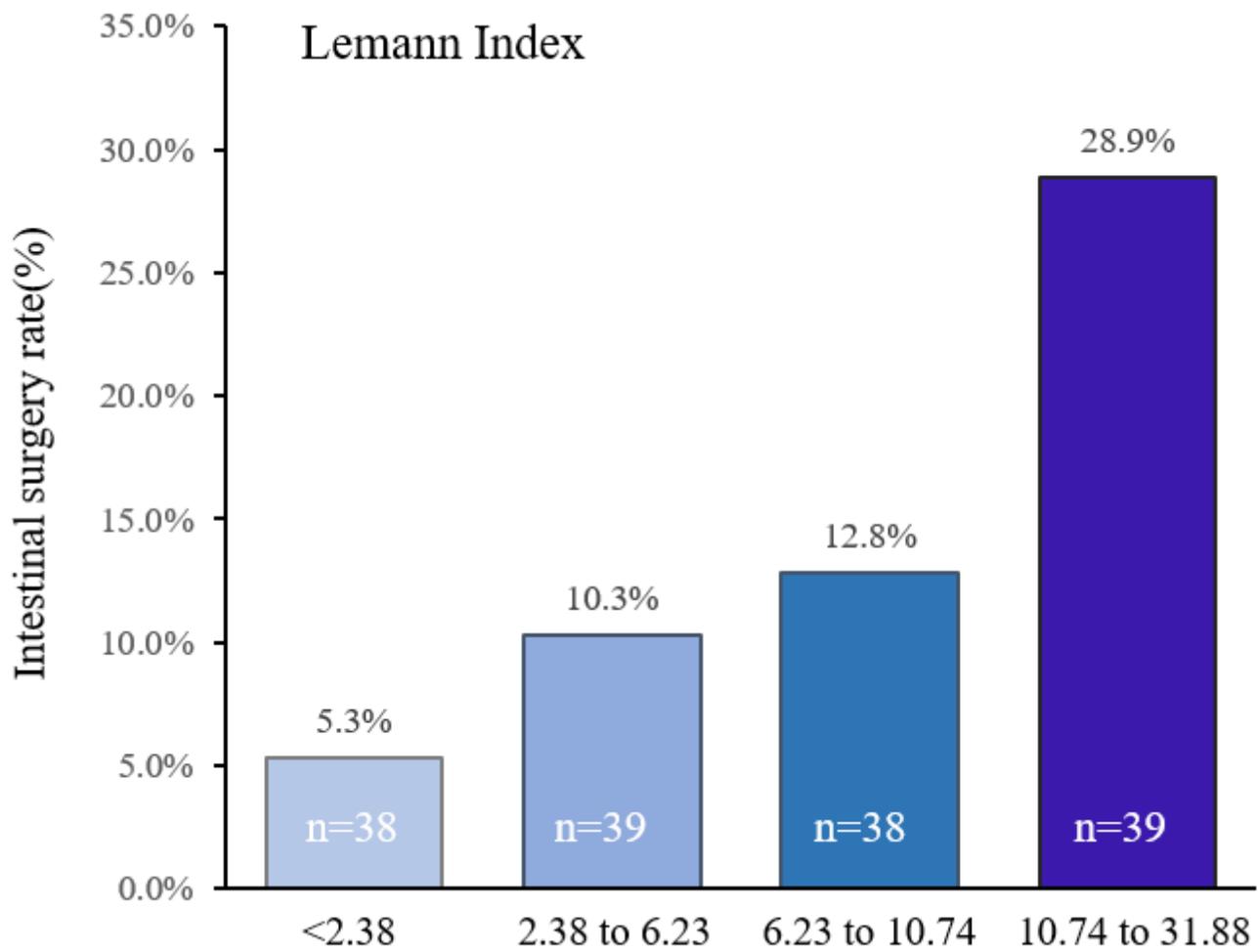


Figure 3

Quartile analysis of the L emann Index level for the rates of short-term intestinal resection in patients with Crohn’s disease.

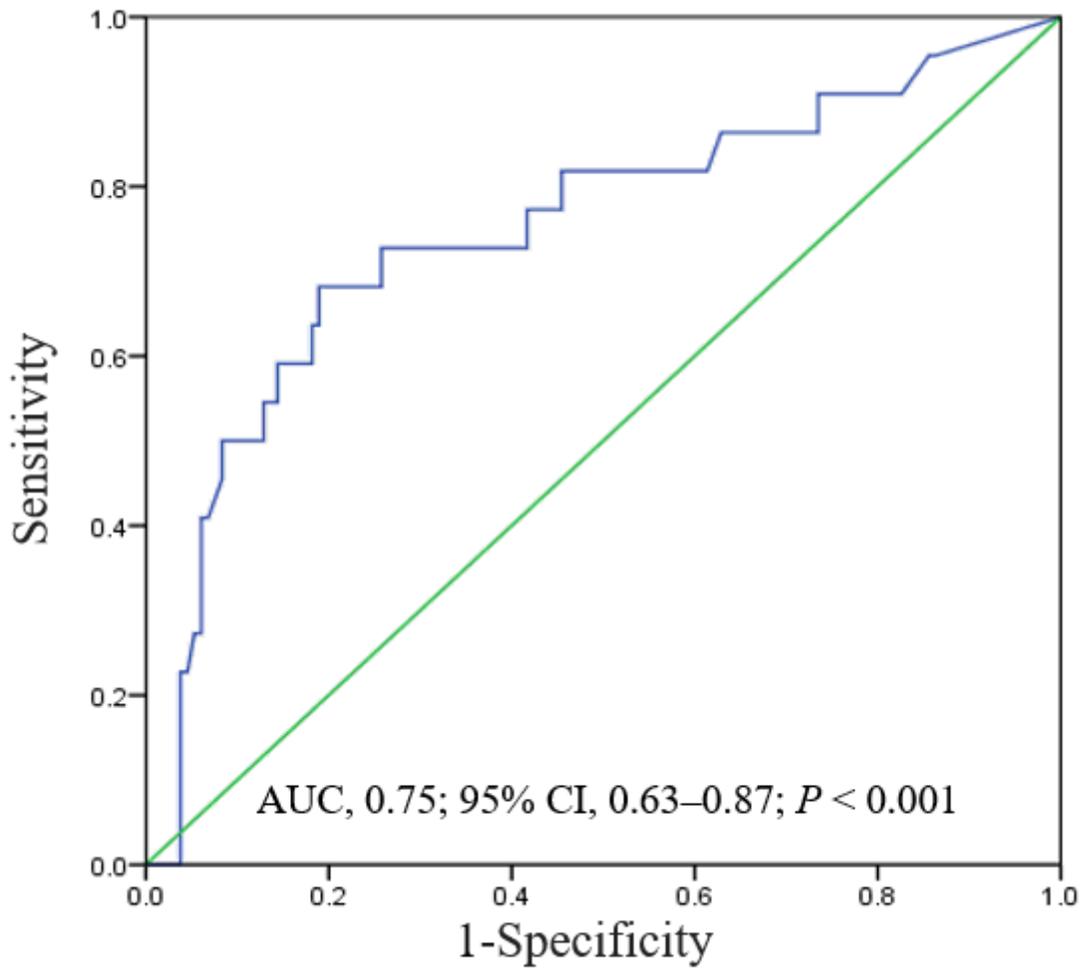


Figure 4

The receiver operating characteristic (ROC) analysis of the Lémann Index level to predict the risk of bowel resection in patients with Crohn's disease. AUC: Area under the curve, 95% CI: 95% confidence interval.