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ORIGINAL ARTICLE

Clinical Features and Prognosis of Crohn's Disease with Upper Gastrointestinal Tract Phenotype in Chinese Patients

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Abstract

Background The epidemiology of upper gastrointestinal (L4) Crohn's disease in China remains poorly characterized.

Aims We aimed to identify the clinical characteristics of L4 disease and clarify the relationship between disease characteristics at diagnosis and early outcomes.

Methods We retrospectively enrolled 246 patients diagnosed between 2013 and 2017 and followed up for > 1 year post-diagnosis. Primary outcomes included the 1-year rates of hospitalization and abdominal surgery according to disease location and behavior.

Results Of 80 patients with L4 disease (61, 25, and 18 with esophagogastroduodenal, jejunal, and proximal ileal involvement, respectively), none had granuloma, whereas 66.7%, 50%, 46.9%, 75%, and 70% had disease-specific endoscopic lesions in the esophagus, stomach, duodenum, jejunum, and proximal ileum, respectively. Compared to non-L4 disease, L4 disease was associated with higher rates of abdominal surgery (41.3% vs. 11.4%, $P < 0.001$) but similar rates of hospitalization within 1 year post-diagnosis. In L4 disease, jejunal and proximal ileal involvement was associated with stricturing behavior ($P = 0.034$, $P < 0.001$) and higher abdominal surgery rate (both: $P < 0.001$). Risk factors for abdominal surgery within 1 year post-diagnosis included age ≥ 40 years (OR 1.920; 95% CI 1.095–3.367), L4 phenotype (OR 6.335; 95% CI 3.862–10.390), stricturing disease (OR 3.162; 95% CI 1.103–9.866), and penetrating disease (OR 11.504; 95% CI 3.409–38.825), whereas the protective factor was female sex (OR 0.214; 95% CI 0.123–0.373).

Conclusions Early outcomes are worse for L4 than for non-L4 disease. Jejunoileum involvement predicts stricturing disease and early surgery. More aggressive initial therapy is needed to improve L4-disease prognosis.

Keywords Crohn's disease · Upper gastrointestinal tract phenotype · Clinical feature · Prognosis

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Introduction

Crohn's disease (CD) is a chronic and relapsing disease manifesting as transmural inflammation of the gut and involving the whole gastrointestinal tract. In an effort to help doctors assess the prognosis and choose the most appropriate therapy, the Montreal classification categorizes CD into four phenotypes according to lesion location: ileal (L1), colonic (L2), ileocolonic (L3), and upper gastrointestinal (L4) disease. The L4 phenotype may occur independently or concomitantly with other phenotypes. In addition, CD phenotypes are classified according to disease behavior: non-stricturing and non-penetrating (B1), stricturing (B2), penetrating (B3), or perianal disease (P). The P phenotype may occur concomitantly with B1–B3 [1].

Numerous studies have showed that L4 disease predicts disease relapse and the need for surgery [2–4]. L4 disease can be further divided anatomically into esophagogastroduodenal (EGD), jejunal, and proximal ileal disease. Recent studies indicated that the L4-jejunal and L4-proximal ileal phenotypes are associated with higher risk for worse prognosis [5–8]. Disease behavior at diagnosis is also a risk factor for aggressive disease activity and worse CD prognosis [3, 9, 10]. Regarding the outcome, disease behavior changes significantly as early as 1 year after diagnosis [11], as reflected in the fact that the rate of CD-related abdominal surgery is highest in the first year post-diagnosis, with a gradual fall during the subsequent 4 years [12, 13]. It remains unclear whether early initiation of immunomodulatory or antitumor necrosis factor (anti-TNF) therapy is superior to the current stepwise approach regarding the need for surgery and the effectiveness of symptom control in patients with L4 disease. It is thus useful to gather early outcome data, as these could have a meaningful impact on the development and adoption of new therapeutic strategies to maintain CD remission and prevent or delay the first surgery in patients with L4 disease.

While it is recognized that the L4 phenotype is associated with worse prognosis, there are no definite diagnostic criteria, which makes it challenging to adequately identify upper gastrointestinal lesions. Non-caseating granulomas are still considered the histological hallmark of L4 disease, but such findings are very difficult to detect in biopsy specimens [14, 15]. Longitudinal/irregular erosions and ulcers, bamboo joint-like appearance, stricture, and fistula are considered specific findings of L4 CD [14, 16]. However, the prevalence of such lesions in the jejunum and proximal ileum remains unclear.

The aim of this study was to evaluate the clinical characteristics of L4 CD at diagnosis, as well as to clarify the relationship between disease characteristics at diagnosis and the rates of disease-related hospitalization and surgery during the first year after diagnosis.

Methods

Patients and Study Design

This retrospective, observational, cohort study included patients managed at the General Hospital of the Eastern Theater Command, who, between January 2013 and December 2017, were diagnosed as having CD. The inclusion criteria were: (1) complete follow-up data for over 1 year after diagnosis; (2) complete data on the entire gut, including endoscopy (gastroscopy, ileocolonoscopy), imaging (barium studies, computer tomography, and magnetic resonance imaging), and operative reports at diagnosis. The exclusion criteria were: (1) ulcerative colitis, indeterminate colitis, intestinal tuberculosis, infective enterocolitis, or other possible causes for gastrointestinal disease, such as nonsteroidal anti-inflammatory drug-induced enteropathy or Behcet disease; (2) age < 14 years or > 75 years. Disease phenotype was assessed independently by two experienced gastroenterologists, who examined the findings reported at the time of diagnosis and established the CD phenotype according to the Montreal classification system. The patients were classified according to disease location (L1–L4) and according to disease behavior (B1–B3, P). Additionally, the L4 group was divided into subgroups according to lesion location (EGD, jejunal, and proximal ileal) [8]. This study was approved by the institutional review board of the General Hospital of the Eastern Theater Command. All patients provided written informed consent to have their data stored and analyzed for research purposes.

Data Collection

Demographic information and clinical data were collected from our hospital's database and included sex, age at diagnosis, duration of disease, family history of inflammatory bowel disease, smoking history, disease location, disease behavior, perianal disease, extraintestinal manifestations, upper gastrointestinal endoscopic features, and history of surgery and hospitalization.

Definitions

The diagnostic criteria for L4 CD included: (1) distinctive histology with non-caseating granulomas, with or without CD elsewhere in the upper gastrointestinal tract, in absence of a systemic granulomatous condition; or (2) radiologic or endoscopic evidence of diffuse inflammation consistent with CD, in addition to diagnosed CD elsewhere in the upper gastrointestinal tract [17].

EGD lesions were defined based on the findings of gastroscopy with biopsy: (1) erythema, vascular changes,

edema, erosions, ulcers, aphthous lesions, and strictures as macroscopic findings on gastroscopy; (2) focal (discontinuous) and patchy chronic inflammation (lymphocyte and plasma cell infiltration), focal crypt irregularity (discontinuous crypt distortion), granulomas, and irregular villous architecture as microscopic findings on biopsy [16]. Jejunal and proximal ileal lesions were defined based on: (1) relevant findings on computed tomography enterography and magnetic resonance enterography, including segmental mural thickening, perienteric infiltration, comb sign, perienteric fistula and/or abscess, segmental bowel stricture, etc.; (2) specific endoscopy findings such as multiple aphthous ulcers measuring > 5 mm in diameter [8].

Within the first year post-diagnosis, most patients received step-up therapy. Patients with mild disease received 5-aminosalicylates. Symptom worsening was considered failure to respond to treatment for mild disease, and the patients were switched to corticosteroids during episodes of moderate-to-severe CD. Second-line agents including thiopurines were used for corticosteroid-dependent or refractory disease. Corticosteroid dependence was defined as failure to reduce prednisolone below 10 mg/day within 3 months of starting steroid treatment, or relapse within 3 months of stopping steroid treatment. Corticosteroid-refractory disease was defined in patients who showed no remission after using prednisone at 0.75 mg/kg/day for > 4 weeks. Infliximab was used in patients with corticosteroid- and/or immunomodulator-refractory CD. Patients refractory to medical treatment, as well as those who developed severe complications such as intestinal obstruction, bowel perforation, massive gastrointestinal bleeding, or bowel cancer were indicated for surgery.

The outcomes of this study included the rates of disease-related hospitalization and abdominal surgery within 1 year post-diagnosis. Abdominal surgery included bowel resection or strictureplasty. Procedures such as perianal fistula surgery, percutaneous drainage of an intra-abdominal abscess, and balloon dilatation of strictures were not considered disease-related surgeries. Relapse was defined as a flare of symptoms in a patient with established CD in clinical remission, either spontaneously or after medical treatment. Hospitalization was defined as care in a hospital setting for at least 3 days for CD relapse, complications, or relapse after surgery [18]. Hospitalizations for diagnostic work-up for CD or for conditions not related to CD were not considered disease-related hospitalizations [2, 6].

Statistical Analysis

Continuous variables were expressed as medians with ranges, while discrete data were expressed as numbers and percentages. Chi-squared tests were used to compare categorical data. Multivariate logistic regression modeling was performed to evaluate the association between potential risk factors (age, sex, smoking status at diagnosis, history of inflammatory bowel disease in the parents, disease duration, disease location, disease behavior, and initial therapy) and the rate of abdominal surgery or hospitalization, with results expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS version 19.0, for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

Of the 1237 consecutive patients screened in the Nanjing General Hospital between January 2013 and December 2017, 246 CD patients were included in this study. A total of 991 patients were excluded owing to lack of complete data on the entire gut, disease duration < 1 year, concomitant other gastrointestinal diseases, and other such factors. The demographic and clinical characteristics are summarized in Table 1 and Fig. 1. In total, 80 (32.5%) patients had L4 phenotype concomitant with the L1, L2, or L3 phenotype, and no patients had isolated L4 disease.

The proportion of male patients was greater in the L4 group than in the non-L4 group (71.3% vs. 55.4%; $P = 0.017$). Within L4 disease, stricturing behavior was more common for the jejunal (48% vs. 24.6%; $P = 0.034$) and proximal ileal (66.7% vs. 24.6%; $P < 0.001$) phenotypes than for the EGD phenotype.

Additionally, the rate of complications (intestinal obstruction, fistula, intra-abdominal abscess, hemorrhea, and intestinal perforation; 20% vs. 8.4%; $P = 0.007$) and abdominal surgery within the first year post-diagnosis (41.3% vs. 11.4%; $P < 0.001$) were significantly higher in the L4 group than in the non-L4 group. Moreover, there was a notable difference between the L4 group and the non-L4 group regarding the surgical rate at diagnosis (21.3% vs. 6%; $P < 0.001$) and at 1 year after diagnosis (20% vs. 5.4%; $P < 0.001$). Finally, there was no significant difference between the two groups regarding the rate of hospitalization within the first year post-diagnosis.

Endoscopic Findings in the Upper Gastrointestinal Tract

In total, 73 patients underwent upper gastrointestinal endoscopy. The most common endoscopic findings of the upper gastrointestinal tract included erosions and ulcers, followed by stricture, protruded lesions, and other lesions (Table 2 and Fig. 2). While erosions and ulcers, especially longitudinal, were more commonly noted in the esophagus, stricturing lesions were more commonly detected in the jejunum and

Table 1 Characteristics of patients with Crohn's disease

Characteristic	All patients $N=246$	Non-L4 group $N=166$	L4 group $N=80$	P value[a]
Sex				
Male	149 (60.6%)	92 (55.4%)	57 (71.3%)	0.017
Female	97 (39.4%)	74 (44.6%)	23 (28.7%)	
Age at diagnosis				
≤ 16 years	21 (8.5%)	13 (7.8%)	8 (10.0%)	0.569
17–40 years	163 (66.3%)	112 (67.5%)	51 (63.8%)	0.563
≥ 40 years	62 (25.2%)	41 (24.7%)	21 (26.2%)	0.793
Mean age at diagnosis (years)	31.6	30.5	32.6	0.734
Smoking history				
Non-smoker	213 (86.6%)	148 (89.2%)	65 (81.3%)	0.088
Ever smoker	33 (13.4%)	18 (10.8%)	15 (18.7%)	
Family history of CD				
No	243 (98.8%)	164 (98.8%)	79 (98.8%)	1.000
Yes	3 (1.2%)	2 (1.2%)	1 (1.2%)	
Disease phenotype by location				
Ileal (L1)	74 (30.1%)	56 (33.7%)	18 (22.5%)	0.072
Colonic (L2)	22 (8.9%)	15 (9.0%)	7 (8.8%)	0.941
Ileocolonic (L3)	150 (61.0%)	95 (57.2%)	55 (68.7%)	0.083
Upper GI (L4)	80 (32.5%)	0	80	
Disease behavior				
Non-stricturing and non-penetrating (B1)	87 (35.4%)	55 (33.1%)	32 (40.0%)	0.291
Stricturing (B2)	108 (43.9%)	73 (44.0%)	35 (43.8%)	0.973
Penetrating (B3)	51 (20.7%)	38 (22.9%)	13 (16.3%)	0.229
Perianal (P)	71 (28.9%)	47 (28.3%)	24 (30.0%)	0.784
Involvement of the upper gastrointestinal tract				
Esophagus			8 (10%)	
Stomach			19 (23.75%)	
Duodenum			52 (65%)	
Jejunum			25 (31.25%)	
Proximal ileum			18 (22.5%)	
Initial treatment in the first year post-diagnosis				
5-aminosalicylate	220 (89.4%)	152 (91.6%)	68 (85%)	0.117
Corticosteroids	14 (5.7%)	8 (4.8%)	6 (7.5%)	0.393
Azathioprine or tripterygium	13 (5.3%)	6 (3.6%)	7 (8.75%)	0.126
Infliximab	2 (0.8%)	2 (1.2%)	0 (0%)	1.000
Clinical course within the first year post-diagnosis				
Complications	30 (12.2%)	14 (8.4%)	16 (20.0%)	**0.009**
Intestinal obstruction		5 (3.0%)	9 (11.3%)	**0.016**
Abdominal abscess		3 (1.8%)	0	0.553
Intestinal fistula		4 (2.4%)	3 (3.8%)	0.685
Bowel perforation		2 (1.2%)	4 (5.0%)	0.09
Relapse	83 (33.7%)	54 (32.5%)	29 (36.3%)	0.563
Abdominal surgery	52 (21.1%)	19 (11.4%)	33 (41.3%)	**< 0.001**
Bowel resection/strictureplasty (duodenum/jejunum/proximal ileum)		6 (3.6%)	22 (27.5%)	**< 0.001**
Bowel resection (terminal ileum/colon)		13 (7.8%)	11 (13.8%)	0.143
Surgery at diagnosis	27 (11.0%)	10 (6.0%)	17 (21.3%)	**< 0.001**
Surgery at 1 year after diagnosis	25 (10.2%)	9 (5.4%)	16 (20.0%)	**< 0.001**

Bold values are statistically significant

CD Crohn's disease, *GI* gastrointestinal

[a]*P* values refer to the differences in proportions between patients with L4 disease and those without L4 disease

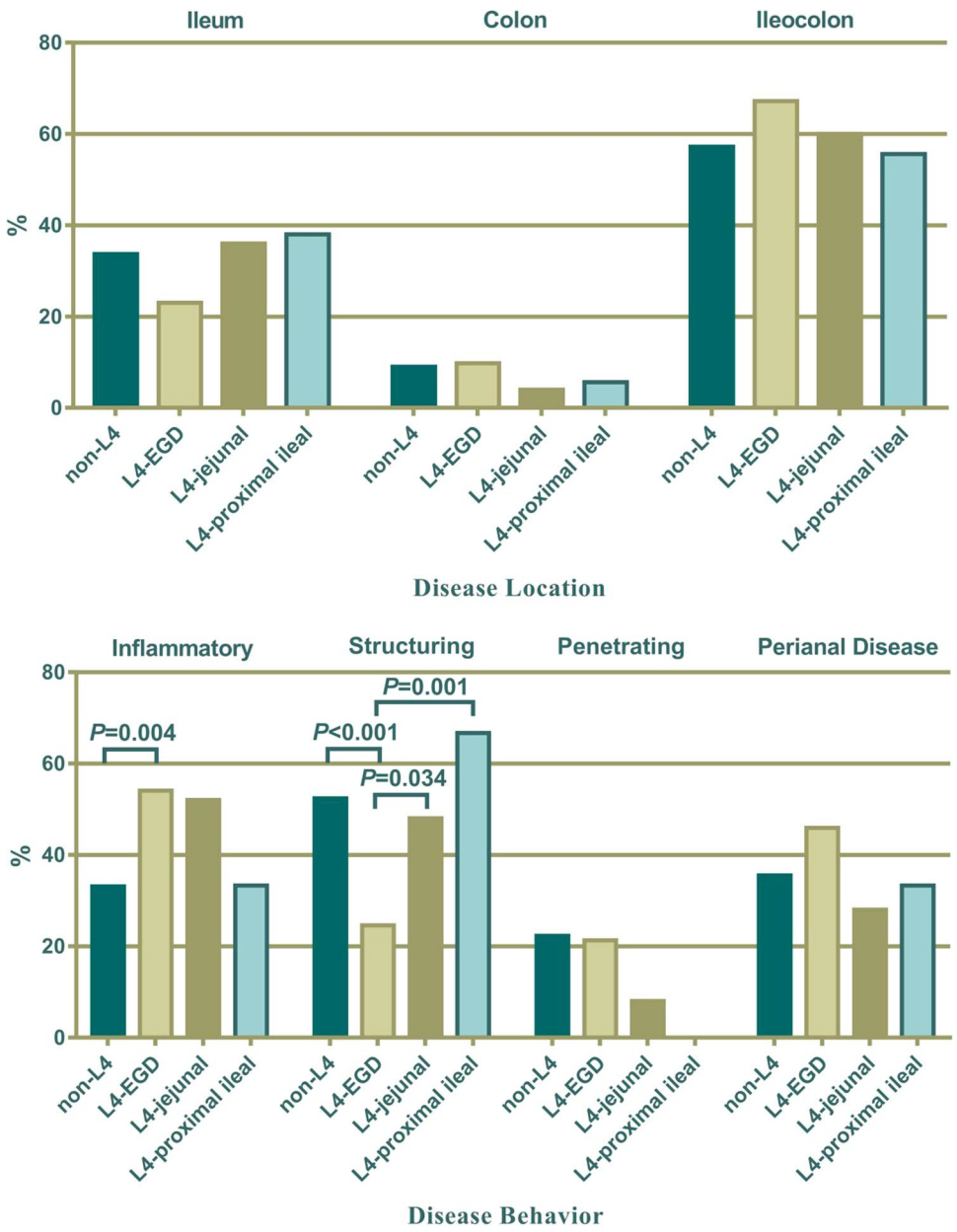

Fig. 1 Disease characteristics. Abbreviations: EGD, esophagogastroduodenal

Table 2 Endoscopic findings in the upper gastrointestinal tract

Location	Erosions and ulcers	Bamboo joint appearance	Longitudinal erosions and ulcers	Protruded lesions	Stricture	Fistula
Esophagus	4 (50%)	0	3 (37.5%)	2 (25%)	1 (12.5%)	0
Stomach	8 (53.3%)	1 (6.7%)	1 (6.7%)	5 (33.3%)	2 (13.3%)	1 (6.7%)
Duodenum	26 (53.1%)	0	1 (2%)	8 (16.3%)	11 (22.4%)	9 (18.4%)
Jejunum	5 (41.7%)	0	2 (16.7%)	2 (16.7%)	6 (50%)	0
Proximal ileum	9 (90%)	0	2 (20%)	0	9 (90%)	0
Total	52 (71.2%)	1 (1.4%)	9 (12.3%)	17 (23.3%)	29 (39.7%)	10 (13.7%)

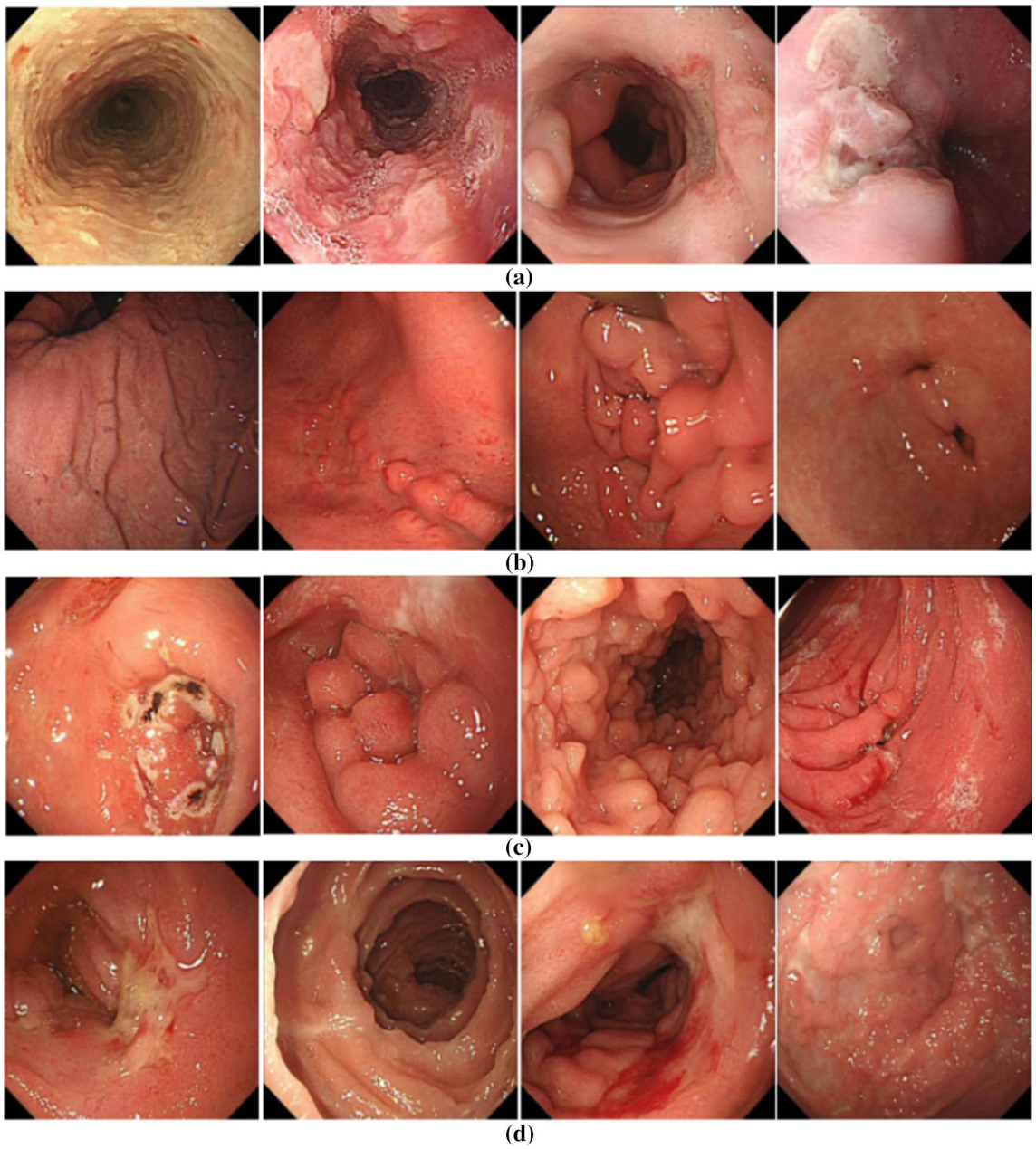

Fig. 2 Specific endoscopic findings of upper gastrointestinal lesions. **a** Esophagus, **b** stomach, **c** duodenum, **d** jejunum and proximal ileum. EGD—esophagogastroduodenal

proximal ileum. Various endoscopic findings were noted in patients with stomach and duodenum involvement, but bamboo joint-like appearance and fistula, respectively, tended to occur preferentially in these locations. No granuloma was detected.

Effect of Disease Location in L4 Disease

Among the 80 patients with L4 phenotype, CD most commonly exhibited EGD involvement (76.25%), followed by jejunal (31.3%) and proximal ileal (22.5%) involvement. The rate of hospitalization within the first year post-diagnosis was significantly higher for proximal ileal disease than for EGD disease (55.6% vs. 32.8%; $P = 0.012$). The rate of abdominal surgery within the first year post-diagnosis was significantly higher for proximal ileal and jejunal disease than for EGD disease (72.2% vs. 37.7%, $P < 0.001$; 52% vs. 37.7%, $P = 0.036$; respectively).

Effect of Disease Behavior in L4 Disease

Of the 80 patients with L4 phenotype, 34 (42.5%) had non-stricturing and non-penetrating disease, 35 (43.75%) had

stricturing disease, and 13 (16.25%) had penetrating disease of the upper gastrointestinal tract. Penetrating disease occurred in the duodenum (100%), jejunum (15.4%), and stomach (7.7%), whereas stricturing disease occurred in 66.7% (12/18) of patients with jejunal disease, 48% (12/25) of patients with proximal ileal disease, and 24.6% (15/61) of patients with EGD disease. There was no significant difference across the three groups regarding the rate of hospitalization within the first year post-diagnosis.

Independent Predictors of Abdominal Surgery Post-diagnosis

The significant independent risk factors for abdominal surgery within the first year post-diagnosis included age ≥ 40 years (OR 1.920; 95% CI 1.095–3.367), L4 phenotype (OR 6.335; 95% CI 3.862–10.390), stricturing disease (OR 3.162; 95% CI 1.103–9.866), and penetrating disease (OR 11.504; 95% CI 3.409–38.825), whereas the protective factor was female sex (OR 0.214; 95% CI 0.123–0.373). However, the treatment variable (5-aminosalicylate vs. more aggressive treatment) was not in the regression equation (Table 3).

Discussion

Since the adoption of routine upper gastrointestinal tract evaluation in CD, the rate of detection of upper gastrointestinal involvement (L4 phenotype) has been increasing. Among Western populations, the prevalence of upper gastrointestinal involvement was reported at 4.2%–15.8% [3, 19, 20]. In our study, the prevalence of L4 phenotype at diagnosis was substantially higher (32.5%), in accordance with values previously reported in Asian patients (19%–30.7%) [2, 13, 21]. There are two possible reasons for the increased prevalence of upper gastrointestinal involvement. On the one hand, although most patients with L4 disease are asymptomatic [16], upper gastrointestinal assessment is becoming a routine procedure. In our study, 47.5% of patients with L4 disease were asymptomatic. On the other hand, in the past, the definition of L4 disease was limited to EGD involvement. With the development of imaging and diagnostic technologies, it has become clear that involvement of the jejunum and proximal ileum also represents a risk factor for worse prognosis [5, 6, 8]. We found that age ≥ 40 years at diagnosis was a significant and independent risk factor for abdominal surgery, which is in agreement with previous reports, indicating that the increased risk of stricturing lesions is higher in older individuals [5].

Diagnostic and monitoring strategies involving routine endoscopy and biopsy are important in the diagnosis of L4 disease [1]. Most endoscopic findings in the upper gastrointestinal tract are non-specific and include erythema, erosion, and ulcer. However, some CD-related endoscopic findings may be specific when detected in certain locations. Such CD-specific findings include aphthae, erosions, and ulcers in the esophagus [14], bamboo joint-like appearance in the stomach [22], notch-like appearance and nodular folds in the duodenum [23, 24], and nodular lymphoid hyperplasia, abnormal mucosal folds, villous pattern, and cobblestone pattern in the small bowel [25]. Longitudinal ulcers, fistula, and stricture are considered CD-specific findings irrespective of location. In our study, the prevalence of CD-specific lesions in the esophagus, stomach, duodenum, jejunum, and proximal ileum was 66.7%, 50%, 46.9%, 75%, and 70%, respectively. However, biopsy-confirmed granuloma is considered suitable for a definite diagnosis. No granuloma was found in the biopsy specimens collected from our patients, which is below the detection rate reported in previous studies (9%–19.5%) [14, 26, 27]. This may be due to the fact that only single biopsies were obtained in each of our patients. Key factors known to affect the detection rate of granuloma include the number of biopsies taken, the number of serial sections examined for each biopsy specimen, and the patients' age [26].

Previous studies have suggested that L4 disease is associated with worse long-term prognosis such as prolonged or repeated hospitalization [2, 3], increased need for surgery [2, 13, 28], and postoperative relapse [29]. Few studies have examined the early prognosis of L4 disease, especially within the first year post-diagnosis. In the present study, the rate of abdominal surgery within the first year post-diagnosis was significantly higher in the L4 group than in the non-L4 group, whereas the rate of hospitalization did not differ significantly between the two groups. This finding suggests that L4 phenotype is associated with a higher risk of relapse. In addition, the need for surgery at diagnosis was more common in the L4 group than in the non-L4 group (21.3% vs. 6%; $P < 0.001$). One potential explanation is that patients with L4 phenotype had higher disease activity at diagnosis and were more likely to have severe complications at early

Table 3 Predictors of abdominal surgery within the first year after Crohn's disease diagnosis

Predictor	OR	95% CI	*P* value
Age ≥ 40 years	1.920	1.095–3.367	**0.023**
L4 phenotype	6.335	3.862–10.390	**< 0.001**
Stricturing disease (B2)	3.162	1.013–9.866	**0.047**
Penetrating disease (B3)	11.504	3.409–38.825	**< 0.001**
Female sex	0.214	0.123–0.373	**< 0.001**

Data were obtained using multivariable logistic regression analysis

Bold values are statistically significant

95% CI—95% confidence interval, OR—odds ratio

relapse. Indeed, in our study, the rate of complications, especially intestinal obstruction, was significantly higher in the L4 group ($P = 0.009$).

Among patients with L4 phenotype, the prevalence of stricturing disease, as well as the rates of relapse and abdominal surgery within the first year post-diagnosis, was higher for jejunal and proximal ileal involvement than for EGD involvement. This finding is similar to observations from previous studies [5, 6, 8]. Although the jejunoileum is recognized as the most common site of stricture in CD, the pathophysiology of CD-related intestinal stricture remains unclear [5, 30, 31]. On the other hand, we found that, among patients with L4 phenotype, penetrating disease occurred mainly in the duodenum. Gastroduodenal fistula is rare and almost always results from involvement of adjacent disease in the transverse colon or from an ileocolonic anastomosis adherent to the stomach or duodenum [32]. In the present study, 10 patients had duodenocolic fistula, two had duodenojejunal fistula, and one had gastroduodenal fistula; of these patients, only two had fistula originating from primary duodenal disease.

Our study is important for two reasons. First, our findings support recent proposals that the Montreal classification of the L4 phenotype should be expanded according to the Paris classification of pediatric CD [5, 8, 33]. Specifically, the present study confirmed that, compared to EGD involvement, jejunoileum involvement is associated with worse prognosis in patients with L4 disease. Second, our study revealed that 41.3% of patients with L4 disease required abdominal surgery within a year post-diagnosis, strongly suggesting that the therapies offered to patients upon diagnosis may not be effective enough to suppress inflammation and to prevent the complications that may necessitate surgery. These findings highlight the critical impact of more aggressive therapies in the early period after diagnosis, potentially delaying the first surgery or maintaining remission. The European evidence-based consensus suggests that patients with L4 disease may require systemic corticosteroids or anti-TNF therapy sooner [18]. In patients with poor prognosis, early initiation of biologic treatment is recommended [34]. However, further randomized controlled studies are required to clarify the optimal timing of biologic treatment after CD diagnosis.

Our study has the following limitations. First, this was a single-center, retrospective study, and we could not exclude selection bias toward patients with more severe disease than that expected in population-based cohorts. Second, the analysis did not take into account the levels of relevant serological markers. Third, we could not rule out the contribution of inflammation related to *Helicobacter pylori* infection, as such information was not included in the medical records. Although the prevalence of *H. pylori* infection is significantly lower in inflammatory bowel disease patients than in healthy individuals [35, 36], *H. pylori*-induced lesions may contribute to overestimating the incidence of L4 disease.

Despite its limitations, our study brings strong evidence that L4 phenotype is associated with worse prognosis within the first year after CD diagnosis. Moreover, among patients with L4 phenotype, jejunoileum involvement is associated with stricturing disease and early surgery. More aggressive initial therapy is needed to improve the prognosis of L4 disease.

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Author's contribution X-WS, JW, and F-YW are the guarantors of the article, having initiated and designed the study; X-WS, X-XJ, H-JW, and B-SY collected the data; X-WS and ZY performed the data analysis; X-WS and JW drafted the manuscript; M-FY, JL, and F-YW critically revised the manuscript; all authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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