Ther Adv Gastroenterol
2018, Vol. 11: 1–9
DOI: 10.1177/1756284818777938

Different clinical outcomes in Crohn's disease patients with esophagogastroduodenal, jejunal, and proximal ileal disease involvement: is L4 truly a single phenotype?

Ren Mao*, Rui-Han Tang*, Yun Qiu*, Bai-Li Chen, Jing Guo, Sheng-Hong Zhang, Xue-Hua Li, Rui Feng, Yao He, Zi-Ping Li, Zhi-Rong Zeng, Rami Eliakim, Shomron Ben-Horin and Min-Hu Chen

Abstract

Background: The Montreal classification defines L4 Crohn's disease (CD) as any disease location proximal to the terminal ileum, which anatomically includes L4-esophagogastroduodenal (EGD), L4-jejunal, and L4-proximal ileal involvement. L4-jejunal disease was established to be associated with poor prognosis. However, the outcome of patients with L4-proximal ileal disease or L4-EGD remains to be clarified. Our study aimed to investigate whether the outcome differs among CD patients with L4-EGD, L4-jejunal, and L4-proximal ileal disease.

Methods: In our retrospective cohort study, 483 patients with confirmed CD were included. The primary outcome was intestinal surgery. Demographic features and outcomes were compared among L4-EGD, L4-jejunal, and L4-proximal ileal disease.

Results: Thirty-nine (8.1%) patients had isolated L4 disease, whereas 146 patients had L4 as well as concomitant L1, L2, or L3 disease. During a median follow up of 5.8 years, L4 patients were more likely to have intestinal surgeries compared to non-L4 patients (31% *versus* 16%, $p < 0.001$). The percentage of L4-jejunal patients who underwent surgery was higher than that of L4-proximal ileal (66% *versus* 28%, $p < 0.001$), and both of these subtypes of L4 were at higher risk for intestinal resection compared to L4-EGD patients (66% and 28% *versus* 9%, respectively, $p < 0.001$ and $p < 0.05$). On multi-variable analysis, L4-jejunal (HR 3.08; 95% CI 1.30–7.31) and L4-proximal ileal disease (HR 1.83; 95% CI 1.07–3.15) were independent predictors for intestinal resection.

Conclusions: L4 disease had worse prognosis compared to non-L4 disease. Within L4 disease, phenotype of L4-jejunal and L4-proximal ileal disease indicated higher risk for intestinal surgery. It might be justified to further characterize the L4 phenotype of the Montreal classification into three specific subgroups including L4-EGD, L4-jejunal, and L4-proximal ileal disease, similar to the Paris classification of pediatric patients.

Keywords: Crohn's disease, Montreal classification, proximal ileum, surgery

Received: 8 September 2017; revised manuscript accepted: 24 April 2018.

Correspondence to:
Ren Mao
Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, 58 Zhongshan II Road, Guangzhou, 510080, People's Republic of China
maoren2023@gmail.com

Rui-Han Tang
Yun Qiu
Bai-Li Chen
Jing Guo
Sheng-Hong Zhang
Rui Feng
Yao He
Zhi-Rong Zeng
Min-Hu Chen
Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China

Xue-Hua Li
Zi-Ping Li
Department of Radiology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China

Rami Eliakim
Department of Gastroenterology, Sheba Medical Center & Sackler School of Medicine, Tel-Aviv University, Israel

Shomron Ben-Horin
Department of Gastroenterology, Sheba Medical Center & Sackler School of Medicine, Tel-Aviv University, Israel
Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

*These three authors contributed equally to this study.

Introduction

Crohn's disease (CD) is a chronic disorder with relapsing inflammation of the gut and presents with variable manifestations that require individualized approaches to management.[1] Precise risk stratification of patients may facilitate tailoring of an optimal treatment, which remains a challenge in clinical practice.[2] Disease extent is associated with treatment response, complication development,

and risk for surgery and postoperative recurrence.[3–9] Thus, extent and location of involvement is a major determinant in phenotyping and risk stratification of CD patients.

In realizing the differences in outcomes between upper and different segments of lower gastrointestinal disease, the Vienna classification divided locations into ileal (L1), colonic (L2), ileocolonic (L3), or upper (L4) disease.[10] Recognizing the possibility of concurrent diseases, the Montreal classification made further modifications, in that L4 can be added to L1, L2, and L3.[11] This change was supported by mounting evidence that proximal disease is an important independent risk factor for stricturing and penetrating behavior even in patients with ileocolonic disease involvement, and is associated with an increased risk of disease relapse and hospitalizations among several ethnic groups.[6–9,12,13]

Upper gastrointestinal (GI) disease (L4) anatomically includes esophagogastroduodenal (EGD), jejunal, and proximal ileal disease. Recent studies showed that jejunal involvement portends unfavorable prognosis compared to L4-EGD, indicating that patients with jejunal disease should be distinguished as carrying a higher risk of surgery.[14,15] The Paris classification for pediatric CD patients was also modified by designating patients with upper gastrointestinal diseases into two more detailed subgroups of L4a (proximal to ligament of Treitz) and L4b (ligament of Treitz to above distal ileum).[16,17]

However, whether the outcome of L4-proximal ileal disease differs from that of L4-jejunal and L4-EGD disease has hitherto not been investigated. This is an important knowledge gap because identifying the phenotype of disease predicts prognosis and guides early aggressive treatment in patients. The aim of the present study was therefore to investigate whether the outcome differs among CD patients with L4-EGD, L4-jejunal, and L4-proximal ileal disease.

Methods

Population and study design

In this retrospective observational cohort study, all patients with confirmed CD between January 2008 and December 2014 in the First Affiliated Hospital of Sun Yat-sen University, a tertiary referral center, were included. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (No. 2015-47). There was a waiver of consent in the present retrospective study as this project meets the criteria according to Health & Human Services regulations (45 CFR 46).

The inclusion criteria were: (1) complete demographic and clinical information with regular clinic follow-up visits; (2) thorough evaluation of the entire gut – patients underwent gastroscopy, ileocolonoscopy, and CTE/MRE (computed tomography enterography and magnetic resonance enterography) at diagnosis.

The exclusion criteria included: (1) indeterminate colitis and other possible causes for small bowel disease, such as NSAIDS (nonsteroidal anti-inflammatory drugs) enteropathy or intestinal tuberculosis; (2) patients younger than 14 years old or older than 75 years old; (3) isolated ulcer, focal bowel wall edema, or focal stricture without concomitant typical findings in endoscopy.

The L4 disease was subdivided into EGD, jejunal, proximal ileal subgroups as per the imaging and endoscopic work-up according to the definitions outlined below. Phenotyping was performed according to the Montreal classification by at least two independent GI physicians who were experienced in CD management.

Data collection

The data were collected from our CD database of patients. Demographic and clinical parameters were retrieved, including gender, age, smoking habits, age at onset, duration of disease, family history of irritable bowel disease (IBD), prior appendectomy, surgical history, symptoms at presentation, extraintestinal manifestations, need for surgery, and hospitalization.

Definitions and outcomes

The small intestine was divided on CTE/MRE imaging into three segments including terminal ileum, proximal ileum, and jejunum, as previously reported.[18] The terminal ileum extended 10 cm from the ileocecal valve, and the proximal ileum was located in the left lower quadrant.[18,19] EGD was defined by lesions identified through upper endoscopy with biopsy histology.[20]

Lesions were defined as: (1) CTE/MRE findings included segmental mural thickening, perienteric infiltration, comb sign, perienteric fistula and/or abscess, segmental bowel stricture, etc.;[18] (2) multiple aphthous ulcers of >5 mm were the minimal requirement for endoscopic evidence of involvement. Mucosal erythema was considered insufficient as evidence of CD involvement.[15]

The primary outcome was the requirement for first intestinal resection during follow up. Perianal fistula surgery and percutaneous drainage of intraabdominal abscesses were not considered as a primary outcome.[15] The secondary outcome was hospitalizations defined as care in a hospital setting for at least 3 days for flare-ups or complications of CD. Hospitalizations for diagnostic work-up of disease or conditions not related to CD were excluded.[14]

Statistical analysis

Normal distributed continuous variables were expressed as mean ± standard deviation and were compared by analysis of variance (ANOVA) tests between three groups or student's *t* test between two groups. Non-normal distributed variables were compared by the Mann–Whitney *U* test. Discrete data were expressed as numbers and percentages. Chi-squared tests were utilized for categorical variables. Factors analyzed by univariate analysis with $p < 0.05$ were included in a multivariable analysis. Cox regression models were used to identify significant predictors of the cumulative probability of major surgery, and hospitalization between groups. Cox proportional hazards models were used to calculate their hazard ratios (HRs) and 95% confidence intervals (CIs). The Kaplan–Meier curve was used to estimate the cumulative possibilities of surgery in different groups. Statistical significance for all analyses was considered to be $p < 0.05$. All statistical analyses were performed using SPSS for Windows, version 23.0 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

There were 483 eligible CD patients according to inclusion/exclusion criteria outlined in the methods section. Demographic and clinical characteristics are shown in Table 1. In total, 39 (8.1%) patients had isolated L4 disease, whereas 146 (30.2%) patients had L4 concomitant disease in L1, L2, or L3 locations. Overall, 185 (38.3%) patients were diagnosed with the L4 phenotype at presentation and 75, 136, and 233 patients were diagnosed with the L1, L2, and L3 phenotypes, respectively.

The median interval between diagnosis and first surgery was 1.9 years (range: 0.1–20.6). In total, 104 of 483 (21.5%) patients underwent surgery, which demonstrated penetrating disease in 84 (80.8%) patients and stricturing disease in 20 (19.2%) patients. Small bowel resection with or without colonic resection was performed in 65 patients (62.5%), and the remaining 39 (37.5%) patients underwent colonic resection. In the 16 patients with L4-jejunal disease undergoing surgery, subsequent colonic resection was performed in 10 patients (10/16, 62.5%) compared with 35.8% (14/39) in patients with L4-proximal ileal disease undergoing colonic resection ($p = 0.07$), and 0% in patients with L4-EGD disease ($p = 0.10$). Regarding disease behavior, 30 of 39 (76.9%) patients with L4-proximal ileal disease undergoing surgery had penetrating disease, compared with 62.5% (10/16) in patients with L4-jejunal disease and 50% (1/2) in patients with L4-EGD lesions ($p = 0.28$, $p = 0.39$) (Supplementary Table 1). Of the 483 patients, 213 (44.1%) required one or more hospitalizations (Table 1).

Comparison between patients with different disease locations

Comparison of L4 versus *non-L4.* The baseline characteristics and clinical outcome of patients with and without L4 disease are shown in Table 1. L4 patients had higher male to female ratio (1.7:1). L1 involvement was more common in the L4 group than in the non-L4 group (23% *versus* 11%; $p < 0.001$), while the L4 patients were less likely to have concurrent L2 diseases (12% *versus* 38%; $p < 0.001$) (Table 1). Additionally, there were significantly higher proportions of patients who underwent intestinal resection in the L4 group than in the non-L4 group (31% *versus* 16%; $p < 0.001$). The cumulative probabilities of the first intestinal surgery were significantly higher in the L4 group than the non-L4 group ($p = 0.004$) (Figure 1).

Comparison of EGD, jejunal, and proximal ileal L4 disease. As shown in Supplementary Table 2, age at diagnosis, smoking, family history of CD,

Table 1. Characteristics of the patients.

	Total ***n*** **= 483**	**Non-L4 (*n* = 298) (%)**	**L4 (*n* = 185) (%)**	***p***
Male, *n* (%)	322 (66.7)	186 (62)	136 (74)	**0.012**
Smoker	57 (11.8)	33 (11)	24 (13)	0.689
Irritable bowel disease-related family history	10 (2.1)	7 (2)	3 (2)	0.387
Age at diagnosis, mean ± standard deviation	30.5 ± 12.3	30.3 ± 12.4	30.8 ± 12.1	0.392
Montreal classification of disease location, *n* (%)				
L1 (terminal ileal)	75 (15.5)	32 (11)	43 (23)	<**0.001**
L2 (colonic)	136 (28.2)	113 (38)	23 (12)	<**0.001**
L3 (ileocolonic)	233 (48.2)	153 (51)	80 (43)	0.083
L4 (isolated upper gastrointestinal disease)	39 (8.1)	NA	NA	
Montreal classification of disease behavior, *n* (%)				
B1 (nonstricturing, nonpenetrating)	257 (53.2)	157 (53)	100 (54)	0.769
B2 (stricturing)	160 (33.1)	94 (32)	66 (36)	0.348
B3 (penetrating)	66 (13.7)	47 (16)	19 (10)	0.087
P (perianal disease)	97 (20.1)	68 (22.8)	29 (15.7)	0.062
Abdominal surgery, *n* (%)	104 (21.5)	47 (16)	57 (31)	<**0.001**
Hospitalizations, *n* (%)	213 (44.1)	125 (42)	88 (48)	0.226

Note: Bold *p* values suggest that the differences were significant.

appendectomy history, disease behavior, and the duration from diagnosis to first surgery, distal disease location, and disease behavior were comparable between the L4-EGD and the L4-jejunal groups. There were significantly higher proportions of patients who underwent abdominal surgery (66% *versus* 9%; $p < 0.001$) as well as multiple surgeries (10% *versus* 0%; $p = 0.022$) in the L4-jejunal group than in the L4-EGD group (Figure 2).

Compared to L4-jejunal disease, patients with L4-proximal ileal disease were less likely to have concurrent L1 disease (28% *versus* 19%, respectively, $p = 0.023$), had more concurrent L2 disease (6% *versus* 12%, $p < 0.001$), and had lower rate of abdominal surgery (66% *versus* 28%, $p < 0.001$). In the EGD group, patients had less likelihood of undergoing intestinal resection and hospitalizations than the proximal ileal group (28% *versus* 9%, $p = 0.01$; 60% *versus* 38%, $p = 0.015$, respectively).

Independent predictors of intestinal surgery

As shown in Table 2, after including all variables found to be associated with the primary outcome on univariate analysis with a *p* value of <0.1, a multivariable analysis was performed for the primary outcome of intestinal surgery. The presence of penetrating (HR 12.27; 95% CI 6.38–23.59) or stricturing behavior (HR 6.58; 95% CI 3.48–12.45) compared with nonstricturing/nonpenetrating behavior, L4-jejunal (HR 3.082; 95% CI 1.30–7.31)

and L4-proximal disease (HR 1.83; 95% CI 1.07–3.15) at diagnosis were found to be independent significant risk factors for intestinal surgery after adjustment for covariates. Colonic, terminal ileal, and EGD locations were not independently predictive of intestinal surgery.

Discussion

The present study documented a relatively high rate of L4 disease and demonstrated that substantial difference in clinical outcome may exist among patients with subtypes of L4, namely L4-EGD, L4-jejunum, and L4-proximal ileum. Upper GI involvement in CD is common across ethnic groups. In some earlier reports, the prevalence of upper GI involvement was 4–5% among Western populations.[7,8,21] The higher rate of L4 disease in our study was in accordance with previous Asian cohort studies.[4] Indeed, a recent Japanese study also showed that ulcerative lesions were observed in 39 (39.8%) of 98 proximal ileal segments, and in 5 (12.5%) of 40 jejunal segments by small bowel enteroscopy.[18] The inconsistent rates of upper GI involvement in different studies could be ascribed to the different study population, but probably also reflect the advanced techniques in assessing the upper gastric tract and the utilization of different phenotyping methods. A recent prospective study showed that small bowel video capsule endoscopy and MRE could detect previously unrecognized disease locations in 51% and 25% of 79 patients, respectively. Both modalities combined thereby altered the original Montreal classification in 49 of 76 patients (64%).[22] As part of L4 disease, proximal ileal disease, which differs from L4-jejunal and L4-EGD disease, has been overlooked and not computed as an L4 phenotype in some studies.[13–15] This might also explain the higher rate of L4 disease in our study.

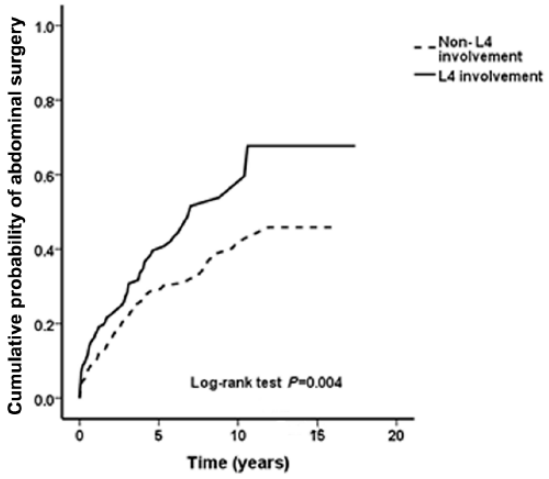

Figure 1. Kaplan–Meier estimation of the cumulative probabilities of intestinal surgery in CD patients with and without L4 disease.

Previous studies suggested that disease localization at diagnosis had a strong impact on the outcome of CD patients.[7–9,12,23–26] The L4 phenotype is associated with a higher risk of complications,[5,26–28] surgery,[3,4,13] postoperative recurrence,[6,29,30] further hospitalization,[13] and the need for higher dosages of steroids.[12] Our result also showed that patients with L4 disease were more likely to have abdominal surgeries and hospitalizations compared

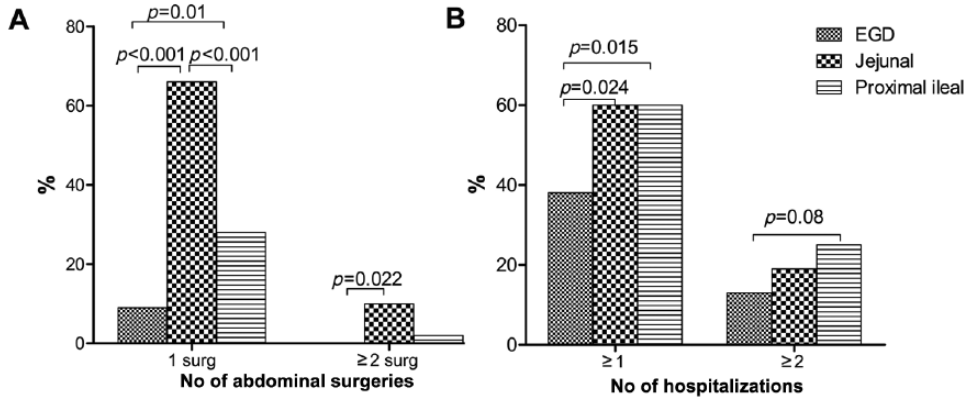

Figure 2. (a) Abdominal surgery rates in L4-EGD, L4-jejunal, and L4-proximal ileal disease; (b) hospitalization rates in L4-EGD, L4-jejunal, and L4-proximal ileal disease.
EGD, esophagogastroduodenal.

Table 2. Independent risk factors associated with abdominal surgery based on multivariable analysis.

	HR	HR 95% CI	*p* value
Penetrating (B3) disease	12.27	6.38–23.59	<0.001
Stricturing (B2) disease	6.58	3.48–12.45	<0.001
L4-jejunal	3.08	1.30–7.31	0.011
L4-proximal ileal	1.83	1.07–3.15	0.028
Colonic involvement	1.65	0.96–2.82	0.068
Terminal ileal involvement	0.71	0.45–1.10	0.124
Age at diagnosis	1.04	0.90–1.22	0.390
Smoker	1.17	0.65–2.11	0.596
Male	0.92	0.58–1.47	0.729
L4-EGD	0.96	0.29–3.17	0.952

EGD, esophagogastroduodenal.

to those with non-L4 disease. This supports the notion that CD patients with L4 disease should be potential candidates for close monitoring and earlier initiation of therapy and/or adopting top-down strategies to decrease or delay surgical interventions.[31]

Although both jejunal and EGD disease are considered parts of L4 disease, increasing evidence suggests that jejunal but not EGD involvement tends to be a more aggressive disease.[14,15,32,33] A landmark study showed that L4 patients with jejunal disease have a different disease course and outcome compared to those with L4-EGD disease.[14] Patients with L4-jejunal disease had higher risk of developing stricturing disease, and eventually had greater need for multiple abdominal surgeries compared to patients with L4-EGD disease.[14] A study from South Korea came to a similar conclusion that jejunal disease portends greater risk for surgery.[34] The findings in our study confirmed these prior observations by incriminating L4-jejunal but not L4-EGD as an independent predictor of abdominal surgeries. Nonetheless, given that L4-EGD is relatively less common, further studies with larger sample sizes are required to corroborate these findings.

According to the Montreal classification, ileal involvement proximal to the terminal ileal is also included in L4 disease designation.[11] However, currently there are no available studies focusing on the disease course and prognosis of patients with proximal ileal involvement compared to other L4 subtypes. To the best of our knowledge, our result is the first to show that although not as robust as L4-jejunal disease, L4-proximal ileal involvement itself is also independently predictive of abdominal surgery. The 10-year cumulative probability of abdominal surgeries in this proximal ileal subtype of L4 disease approached 60%. By distinguishing among the three possible localizations of L4 disease, our study showed that L4-jejunal disease portended the greatest risk of future surgery, followed by L4-proximal ileal disease, while L4-EGD was less prone to unfavorable disease outcomes. Based on the result, it might be justified to further characterize the L4 into three subtypes according to the herein described anatomical subdivision and their differential risk profiles.

Our study has certain limitations. First, the current study is a single-center retrospective study, and despite the relatively large number of patients included, the sample size of each subgroup is relatively small. Second, as in all studies on this topic, a possible predilection for medical therapy in patients with EGD involvement and reluctance of surgeons to operate on patients with disease proximal to the Trietz might be a confounder influencing lower rates of surgery in L4-EGD.

However, the fact that L4-proximal ileum and jejunal subtypes also had higher hospitalization rate compared to the EGD strongly argue in favor of the suggestion that these subtypes indeed portend a more aggressive disease, regardless of surgical considerations *per se*. Third, one may argue that proximal ileal disease might be a marker for more extensive small bowel disease, which could partly explain the worse outcome in such patients. However, there was no difference in number of segments resected among different disease subtypes (L4-EGD, L4-jejenal, and L4-proximal ileum) in our study. Nonetheless, prospective studies investigating the correlation between disease location and number, as well as length of segments resected, are needed. Finally, we did not employ capsule endoscopy or small bowel enteroscopy for detection of subtle mucosal inflammation in the small bowel for each patient. Only a small number of patients underwent capsule endoscopy or small bowel enteroscopy in our study (data not shown). The use of MRE/CTE in assessment of mural lesions could result in underestimation of proximal small bowel involvement in some patients. Future studies are needed to determine how capsule endoscopy or small bowel enteroscopy may impact the subclassification of L4 disease.

In conclusion, L4 disease had worse prognosis compared to non-L4 disease. Within L4 disease, the phenotype of L4-jejunal but also L4-proximal ileal disease at diagnosis are associated with more severe future disease course and higher risk for intestinal surgery. If corroborated by other studies, these observations indicate the need to consider a further modification of the Montreal classification by subdividing the L4 phenotype into three specific subgroups, including L4-EGD, L4-jejunal, and L4-proximal ileal disease.

Author contribution

Ren Mao and Rui-han Tang: study design, data collection, statistical analysis, interpretation, and manuscript drafting/revision. Min-hu Chen and Ren Mao: conception, design, and critical revision of the manuscript for important intellectual content and study supervision. Bai-li Chen, Yun Qiu, Jing Guo, Sheng-hong Zhang, Xue-hua Li, Rui Feng, Yao He, Zi-ping Li, Zhi-rong Zeng, Rami Eliakim, and Shomron Ben-Horin: study concept and critical revision of the manuscript for important intellectual content.

Funding

This work was supported by National Natural Science Foundation of China (Grant Nos. 81470821, 81270473, 81670607, and 81500501).

Conflict of interest statement

Min-Hu Chen has received speaker fees from Janssen, Falk, Takeda, and Ipson. Yao He has received speaker fees from Janssen, Falk, and Ipson. Shomron Ben-Horin has received consultancy fees and/or research support from AbbVie, Schering-Plough, Janssen, Celltrion, and Takeda. The other authors report no conflicts of interest.

References

1. Baumgart DC and Sandborn WJ. Crohn's disease. *Lancet* 2012; 380: 1590–1605.
2. Vermeire S, van Assche G and Rutgeerts P. Classification of inflammatory bowel disease: the old and the new. *Curr Opin Gastroenterol* 2012; 28: 321–326.
3. Peyrin-Biroulet L, Harmsen WS, Tremaine WJ, *et al*. Surgery in a population-based cohort of Crohn's disease from Olmsted County, Minnesota (1970–2004). *Am J Gastroenterol* 2012; 107: 1693–1701.
4. Song XM, Gao X, Li MZ, *et al*. Clinical features and risk factors for primary surgery in 205 patients with Crohn's disease: analysis of a South China cohort. *Dis Colon Rectum* 2011; 54: 1147–1154.
5. Thia KT, Sandborn WJ, Harmsen WS, *et al*. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology* 2010; 139: 1147–1155.
6. Wolters FL, Russel MG, Sijbrandij J, *et al*. Phenotype at diagnosis predicts recurrence rates in Crohn's disease. *Gut* 2006; 55: 1124–1130.
7. Nguyen GC, Torres EA, Regueiro M, *et al*. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort. *Am J Gastroenterol* 2006; 101: 1012–1023.
8. 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: 1274–1282.

9. Jiang L, Xia B, Li J, *et al*. Retrospective survey of 452 patients with inflammatory bowel disease in Wuhan city, central China. *Inflamm Bowel Dis* 2006; 12: 212–217.
10. Gasche C, Scholmerich J, Brynskov J, *et al*. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000; 6: 8–15.
11. Satsangi J, Silverberg MS, Vermeire S, *et al*. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; 55: 749–753.
12. Bernell O, Lapidus A and Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. *Ann Surg* 2000; 231: 38–45.
13. Chow DK, Sung JJ, Wu JC, *et al*. Upper gastrointestinal tract phenotype of Crohn's disease is associated with early surgery and further hospitalization. *Inflamm Bowel Dis* 2009; 15: 551–557.
14. Lazarev M, Huang C, Bitton A, *et al*. Relationship between proximal Crohn's disease location and disease behavior and surgery: a cross-sectional study of the IBD Genetics Consortium. *Am J Gastroenterol* 2013; 108: 106–112.
15. Park SK, Yang SK, Park SH, *et al*. Long-term prognosis of the jejunal involvement of Crohn's disease. *J Clin Gastroenterol* 2013; 47: 400–408.
16. Hyams JS. Standardized recording of parameters related to the natural history of inflammatory bowel disease: from Montreal to Paris. *Dig Dis* 2014; 32: 337–344.
17. Levine A, Griffiths A, Markowitz J, *et al*. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011; 17: 1314–1321.
18. Takenaka K, Ohtsuka K, Kitazume Y, *et al*. Comparison of magnetic resonance and balloon enteroscopic examination of the small intestine in patients with Crohn's disease. *Gastroenterology* 2014; 147: 334–342.
19. Yamagami H, Watanabe K, Kamata N, *et al*. Small bowel endoscopy in inflammatory bowel disease. *Clin Endosc* 2013; 46: 321–326.
20. Magro F, Langner C, Driessen A, *et al*. European consensus on the histopathology of inflammatory bowel disease. *J Crohns Colitis* 2013; 7: 827–851.
21. Trnka YM, Glotzer DJ, Kasdon EJ, *et al*. The long-term outcome of restorative operation in Crohn's disease: influence of location, prognostic factors and surgical guidelines. *Ann Surg* 1982; 196: 345–355.
22. Greener T, Klang E, Yablecovitch D, *et al*. Impact of magnetic resonance enterography and capsule endoscopy on the re-classification of disease in patients with known Crohn's disease: a prospective Israeli IBD Research Nucleus (IIRN) study. *J Crohns Colitis* 2016; 10: 525–531.
23. Dassopoulos T, Nguyen GC, Bitton A, *et al*. Assessment of reliability and validity of IBD phenotyping within the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) IBD Genetics Consortium (IBDGC). *Inflamm Bowel Dis* 2007; 13: 975–983.
24. Basson A, Swart R, Jordaan E, *et al*. The association between race and Crohn's disease phenotype in the Western Cape population of South Africa, defined by the Montreal Classification System. *PLoS One* 2014; 9: e104859.
25. Farmer RG, Hawk WA and Turnbull RJ. Clinical patterns in Crohn's disease: a statistical study of 615 cases. *Gastroenterology* 1975; 68: 627–635.
26. Staniland JR, Ditchburn J and de Dombal FT. Clinical presentation of diseases of the large bowel:.a detailed study of 642 patients. *Gastroenterology* 1976; 70: 22–28.
27. Louis E, Collard A, Oger AF, *et al*. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001; 49: 777–782.
28. Jess T, Riis L, Vind I, *et al*. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. *Inflamm Bowel Dis* 2007; 13: 481–489.
29. Cosnes J, Cattan S, Blain A, *et al*. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002; 8: 244–250.
30. Sampietro GM, Corsi F, Maconi G, *et al*. Prospective study of long-term results and prognostic factors after conservative surgery for small bowel Crohn's disease. *Clin Gastroenterol Hepatol* 2009; 7: 183–191.
31. Romberg-Camps MJ, Dagnelie PC, Kester AD, *et al*. Influence of phenotype at diagnosis and of other potential prognostic factors on the course

of inflammatory bowel disease. *Am J Gastroenterol* 2009; 104: 371–383.

32. Sato Y, Matsui T, Yano Y, *et al*. Long-term course of Crohn's disease in Japan: incidence of complications, cumulative rate of initial surgery, and risk factors at diagnosis for initial surgery. *J Gastroenterol Hepatol* 2015; 30: 1713–1719.
33. Freeman HJ. Long-term clinical behavior of jejunoileal involvement in Crohn's disease. *Can J Gastroenterol* 2005; 19: 575–578.
34. Keh C, Shatari T, Yamamoto T, *et al*. Jejunal Crohn's disease is associated with a higher postoperative recurrence rate than ileocaecal Crohn's disease. *Colorectal Dis* 2005; 7: 366–368.