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Clinical Characteristics and Long-Term Outcomes of Paediatric Crohn's Disease: A Single-Centre Experience

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Abstract

Background and Aims: Although paediatric Crohn's disease [CD] has a different phenotype and clinical course to adult CD, its clinical features and surgical risks are poorly defined, especially in Asian countries. The aim of this study was to investigate the clinical features and long-term outcomes of paediatric CD in a Korean population.

Methods: We retrospectively analysed 594 patients who were younger than 18 years of age at CD diagnosis between 1987 and 2013. Patient characteristics at diagnosis according to the Paris classification and clinical courses were analysed.

Results: The male-to-female ratio was 2.4:1 and the median age at CD diagnosis was 15 years [range, 2–17 years]. A positive first-degree family history of inflammatory bowel disease was present in 30 patients [5.1%]. Sixty-seven patients [11.3%] showed growth impairment. The cumulative probabilities of perianal fistula at 1, 5 and 10 years after diagnosis were 50.3%, 54.9% and 57.6%, respectively. The cumulative probabilities of anti-tumour necrosis factor treatment at 1, 5, 10 and 20 years after diagnosis were 10.7%, 25.8%, 41.8% and 76.3%, respectively. The cumulative probabilities of intestinal resection at 1, 5, 10 and 20 years after diagnosis were 4.5%, 17.2%, 33.9% and 62.9 %, respectively. In multivariate analysis, complicated behaviour and isolated colonic location [L2] at diagnosis were associated with an increased and decreased risk of intestinal resection, respectively.

Conclusions: Our study is the largest Asian paediatric study which applied the Paris classification to patients. This study provides detailed information on disease phenotype and long-term clinical outcomes in a large cohort of Asian children with CD.

Key Words: Pediatric; Crohn's disease; Korea

1. Introduction

Crohn's disease [CD] is a chronic relapsing inflammatory disorder.[1] The factors involved in its pathogenicity, such as genetic predisposition, environmental changes and enteric flora, are still unknown in both adult and paediatric patients.[2–4] As in adults with inflammatory bowel disease [IBD], the incidence of CD in children

is rising worldwide,[5] and Korea is also one of the new populations showing an exponential increase in the incidence of paediatric CD.[6]

The clinical features of paediatric CD are distinct from those of adult patients in some respects.[7–10] Paediatric CD is likely to have a more extensive and complicated phenotype, resulting in high severity.[7,11] Children who are younger than 10 years at diagnosis are likely to have isolated colic disease [L2 location] and upper gastrointestinal involvement,[7,9] while ileocolonic diseases [L3 location] are predominantly seen in adolescents and adults.[12] Furthermore, patients with very early-onset CD [onset <6 years of age] are more likely to have severe colitis refractory to conventional treatments and are of particular interest to IBD geneticists.[13] The CD may present with primary immune deficiencies showing Mendelian inheritance such as chronic granulomatous disease, Wiskott–Aldrich syndrome, interleukin-10 deficiency and X-linked inhibitor of apoptosis deficiency.[13,14] In addition, nutritional issues and failure to thrive are common and significant clinical issues that can lead to growth failure.[15,16] For example, prepubertal patients in the <3 percentile group for height showed no catch-up growth and had an early relapse of the disease after surgery.[17]

Therefore, the international group of IBD experts presented a new classification, the Paris classification, for paediatric patients with IBD.[18] Important modifications included classification of age at diagnosis as A1a [0 to <10 years], A1b [10 to <17 years] and A2 [17 to 40 years]. The classification of upper gastrointestinal involvement was also changed: the region proximal to the ligament of Treitz [L4a location] has been separated from the area distal to the ligament of Treitz [L4b location]. The new system allows for the classification of both stenosing and penetrating disease in the same patient [B2B3], and denotes the presence of growth failure in the patient at any time as G1 versus G0.

Surgical risks are 17–35% at 5 years after the diagnosis of paediatric CD.[19–21] Due to the longevity of this chronic disease, children may be more vulnerable to cumulative mucosal injuries. In fact, childhood-onset CD has shown a three times higher cumulative risk of complicated CD than adulthood-onset CD.[22] Few risk factors for intestinal surgery have been identified and those identified are still controversial.[19,22–24] Not only demographic factors [age and sex], but also the phenotype at the time of diagnosis [complicated behaviour, small bowel and ileocecal involvement, and perianal fistula] have been discussed in the literature. Treatment modalities such as azathioprine and infliximab also reduce the surgical risks of paediatric CD.[19,21] Therefore, recognition of the risk factors for intestinal resection is important to determine the appropriate top-down or early aggressive strategy for higher-risk children.

Because there are few data on the clinical characteristics and natural history of paediatric CD, especially in Eastern countries, we investigated the clinical characteristics and long-term outcomes of CD patients who were diagnosed at a single tertiary hospital in Korea.

2. Materials and Methods

2.1. Patients

Patients with CD who were diagnosed before 18 years of age between March 1987 and December 2013 were enrolled. They were registered at the IBD Center and Children's Hospital of the Asan Medical Center, a tertiary-care referral hospital. Six of monogenic IBD patients were excluded from the study. A diagnosis of CD was based on conventional clinical, upper and lower endoscopic, radiological and histological criteria, and indeterminate colitis, infections or other recognized causes of intestinal inflammation were excluded by appropriate investigations.[25] A total of 235 patients were first diagnosed at the Asan Medical Center and 359 patients were diagnosed and referred from other hospitals or primary clinics [see Supplementary data, available at *ECCO-JCC* online].

2.2. Study design

All data were collected from the IBD registry of the Asan Medical Center or obtained by retrospective review of the medical records. Medical information prior to the first visit to the Asan Medical Center was retrospectively obtained by interviewing the patients at their first visit or by reviewing the medical records provided by the referring physicians.

Baseline demographic and clinical characteristics of patients, including gender, age at diagnosis, interval from onset of symptoms to diagnosis, family history of IBD, extraintestinal manifestations, disease behaviour and location, presence of perianal fistula and growth failure, were evaluated. To determine the long-term outcomes of the disease, we evaluated the initiation of various medications, changes in disease behaviour and cumulative probability of surgery. We also analysed the risk factors for intestinal resection. In addition, to evaluate the changes in baseline characteristics, treatment policies and prognosis of CD, we divided the patients into three consecutive cohorts based on the date of diagnosis [cohort 1, 1987–2000; cohort 2, 2001–2005; cohort 3, 2006–2013].

Age at diagnosis, disease location and behaviour of CD were categorized according to the Paris classification.[18] Growth impairment was defined when height z-score at diagnosis or subsequently was significantly less than the expected height z-score.[18] Our treatment policy is the same as that of Western countries. We used more aggressive therapies when patients became unresponsive to first-line agents.[26] Early corticosteroids use was defined as the initiation of therapy within 3 months of diagnosis. In the case of thiopurines or anti-tumour necrosis factor [TNF] agents, early use was defined as treatment starting within 6 months before the intestinal surgery and within the first year of diagnosis.[27] This retrospective analysis was approved by the Institutional Review Board of Asan Medical Center [IRB number: 2014-1064].

2.3. Statistics

Continuous data were expressed as medians with ranges and discrete data as numbers and percentages. We used chi-square or Fisher's exact tests to compare binominal variables. The cumulative probabilities of medication use, perianal fistula and intestinal resection were calculated using the Kaplan–Meier method. Differences between Kaplan–Meier curves were compared using a log-rank test. To quantify risk, we used the hazard ratios [HRs] of the Cox proportional hazards models. All prognostic variables with a p value < 0.1 in univariate analysis were included in the multivariate analysis. A p value < 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS version 18.0 [IBM].

3. Results

3.1. Baseline characteristics of the study subjects

Of the 594 patients included in the present study, 421 [70.9%] were males and 173 [29.1%] were females. The male-to-female ratio was 2.4:1 and the median age at CD diagnosis was 15 years [range, 2–17 years]. The median interval from onset of symptoms to diagnosis was 13 months [range, 0–121 months]. Anti-tuberculosis medication prior to CD diagnosis had been taken by 102 patients [17.2%] with clinical suspicion of intestinal tuberculosis, but the treatment failed in all patients and all 102 patients were finally confirmed to have CD.

There were 75 patients in cohort 1 [diagnosed from 1987 to 2000], 125 in cohort 2 [diagnosed from 2001 to 2005] and 394 in cohort 3 [diagnosed from 2006 to 2013]. The proportion of males [$p < 0.001$] and history of perianal fistula at diagnosis [$p = 0.046$] increased significantly from cohort 1 to cohort 3. However, the time from onset of symptoms to CD diagnosis and the proportion of patients who received anti-tuberculosis medication prior to diagnosis of CD decreased significantly from cohort 1 to cohort 3 [$p < 0.001$]. The median age, disease location and disease behaviour at diagnosis were not different among the three cohorts. The baseline characteristics at diagnosis of CD in all patients and in the three cohorts are separately summarized in Table 1.

When analysed according to the place of first diagnosis, the proportions of A1a group [0 to <10 years of age at diagnosis] at diagnosis [3.8% vs. 1.4%] and growth impairment [18.3% vs 6.7%] were significantly higher in the Asan Medical Center [$p < 0.001$] [see Supplementary data, available at *ECCO-JCC* online].

When analysed according to age groups at diagnosis, the proportion of isolated colonic location [L2] at diagnosis was higher significantly in the A1a group [0 to <10 years of age at diagnosis] than in the older age groups [$p < 0.001$]. In addition, at diagnosis of CD, patients in the A1a group tended to show lower rates of complicated behaviour and perianal fistula than those in the older age groups, although the differences were not statistically significant. The clinical characteristics of CD at diagnosis according to age at diagnosis are summarized in Table 2.

3.2. Medical treatment

The proportions of patients who used systemic corticosteroids, thiopurines and anti-TNF agents at diagnosis and/or during the follow-up were 58.2% [346/594], 78.1% [464/594] and 33.5% [199/594], respectively. The cumulative probabilities of medication use at 1, 5 and 10 years after diagnosis were 49.0%, 60.1% and 65.7%, respectively, for corticosteroids; 42.8%, 71.1% and 85.7%, respectively, for thiopurines; and 10.7%, 25.8% and 41.8%, respectively, for anti-TNF agents [Figure 1]. The median intervals from CD diagnosis to start of medication were 11 months [range, 0–200 months] for corticosteroids, 28 months [range, 2–221 months] for thiopurines and 53 months [range, 5–281 months] for anti-TNF agents.

The cumulative probability of corticosteroids prescription decreased from cohort 1 to cohort 3, whereas that of thiopurines and anti-TNF agents prescription increased from cohort 1 to cohort 3 [Figure 1]. The 1- and 5-year cumulative probabilities of receiving corticosteroids decreased from 54.2% and 67.7%, respectively, in cohort 1 to 47.2% and 57.4%, respectively, in cohort 3 [$p < 0.001$]. The median interval from CD diagnosis to the start of corticosteroids decreased from 2.8 years in cohort 1 to 0.7 years and 0.4 years in cohorts 2 and 3, respectively [$p < 0.001$]. The 1- and 5-year

Table 1. Baseline characteristics of the 594 paediatric patients with Crohn's disease [CD] according to the year of diagnosis.

	Total 1987–2013	Cohort 1 1987–2000	Cohort 2 2001–2005	Cohort 3 2006–2013	*p*-Value
No. of patients	594	75	125	394	
Male	421 [70.9]	38 [50.7]	90 [72.0]	293 [74.4]	< 0.001
Median age at diagnosis [range], years	15 [2–17]	15 [9–17]	15 [2–17]	15 [4–17]	0.592
Median interval from onset to diagnosis [range], months	13 [0–121]	21 [0–121]	13 [0–80]	11 [0–83]	< 0.001
Anti-tuberculosis medication prior to CD diagnosis	102 [17.2]	22 [29.3]	32 [25.6]	48 [12.2]	< 0.001
Age at diagnosis, years					0.226
A1a	14 [2.4]	1 [1.3]	4 [3.2]	9 [2.3]	
A1b	438 [73.7]	49 [65.3]	97 [77.6]	292 [74.1]	
A2	142 [23.9]	25 [33.4]	24 [19.2]	93 [23.6]	
Location at diagnosis					0.393
L1	63 [10.7]	8 [10.8]	14 [11.3]	41 [10.4]	
L2	48 [8.2]	5 [6.8]	9 [8.1]	34 [9.3]	
L3	466 [79.3]	61 [82.4]	100 [80.6]	305 [77.5]	
L4 only	11 [1.8]	0 [0.0]	0 [0.0]	11 [2.8]	
Upper disease at diagnosis	153 [25.8]	15 [20.0]	17 [13.6]	121 [30.7]	0.002
L4 only	11 [1.9]	0 [0.0]	0 [0.0]	11 [2.8]	
+L4a*	41 [6.9]	0 [0.0]	4 [3.2]	37 [9.4]	
+L4b*	101 [17.0]	15 [20.0]	13 [10.4]	73 [18.5]	
Behaviour at diagnosis					0.304
B1	511 [88.9]	63 [86.2]	109 [89.4]	339 [89.2]	
B2	54 [9.4]	8 [11.0]	11 [9.0]	35 [9.2]	
B3	9 [1.6]	1 [1.4]	2 [1.6]	6 [1.6]	
B2B3	1 [0.1]	1 [1.4]	0 [0.0]	0 [0.0]	
Perianal fistula at diagnosis	280 [47.1]	26 [34.7]	57 [45.6]	197 [50.0]	0.046
Growth impairment					0.978
G0	527 [88.7]	66 [88.0]	111 [88.8]	350 [88.8]	
G1	67 [11.3]	9 [12.0]	14 [11.2]	44 [11.2]	

Data are presented as a mean [range] or number [%].

*L4a/L4b may coexist with L1, L2, and L3, respectively.

Age at diagnosis, disease location, behaviour and growth impairment were categorized according to the Paris classification.

Table 2. Clinical characteristics of the 594 paediatric patients with Crohn's disease according to the age at diagnosis.

Characteristics	A1a	A1b	A2	*p*-Value
No. of patients	14 [2.4]	438 [73.7]	142 [23.9]	
Male	9 [64.3]	307 [70.1]	105 [73.9]	0.394
Location at diagnosis				< 0.001
L1	1 [7.1]	40 [9.3]	22 [15.6]	
L2	4 [28.6]	39 [9.0]	5 [3.6]	
L3	9 [64.3]	344 [79.4]	113 [80.1]	
L4 only	0 [0.0]	10 [2.3]	1 [0.7]	
Upper disease at diagnosis	5 [35.7]	120 [27.4]	28 [19.7]	0.183
L4 only	0 [0.0]	10 [2.3]	1 [0.7]	
+L4a*	0 [0.0]	35 [8.0]	6 [4.2]	
+L4b*	5 [35.7]	75 [17.1]	21 [14.8]	
Behaviour at diagnosis				0.188
B1	13 [92.9]	386 [90.6]	112 [83.0]	
B2	1 [7.1]	34 [8.0]	19 [14.1]	
B3	0 [0.0]	6 [1.4]	3 [2.2]	
B2B3	0 [0.0]	0 [0.0]	1 [0.7]	
Perianal fistula at diagnosis	3 [21.4]	210 [47.9]	67 [47.2]	0.145
Growth impairment				0.256
G0	13 [92.9]	383 [87.4]	131 [92.3]	
G1	1 [7.1]	55 [12.6]	11 [7.7]	

Data are presented as a number [%].
*L4a/L4b may coexist with L1, L2 and L3, respectively.
Age at diagnosis, disease location, behaviour and growth impairment were categorized according to the Paris classification.

cumulative probabilities of receiving thiopurines increased from 2.3% and 26.2%, respectively, in cohort 1 to 55.8% and 85.1%, respectively, in cohort 3 [$p = 0.002$]. The median interval from CD diagnosis to the start of thiopurines decreased from 7.9 years in cohort 1 to 2.8 years and 0.8 years in cohorts 2 and 3, respectively [$p < 0.001$]. Similarly, the 1- and 5-year cumulative probabilities of receiving anti-TNF agents increased from 0.0% and 1.3%, respectively, in cohort 1 to 15.2% and 35.2%, respectively, in cohort 3 [$p < 0.001$]. The median interval from CD diagnosis to the commencement of anti-TNF agents decreased significantly from 12.3 years in cohort 1 to 5.3 years and 1.7 years in cohorts 2 and 3, respectively [$p < 0.001$].

3.3. Clinical course

The median duration of follow-up was 6.8 years [range, 1 month to 27 years]. A positive family history of IBD was seen at diagnosis and/or during the follow-up in 40 patients [6.7%], 30 of whom [5.1%] had a positive family history of IBD among first-degree relatives. Six and four patients had a positive family history of IBD among second- and third-degree relatives, respectively.

Regarding disease behaviour at diagnosis, 89.5% had B1 disease, 9.4% had B2 and 1.1% had B3 or B2B3. At 5 years after diagnosis, these proportions were 68.0% with B1 disease, 23.8% with B2 and 8.2% with B3 or B2B3. At 10 years after diagnosis, these proportions were 50.0% with B1 disease, 32.9% with B2 and 17.1% with B3 or B2B3. At 20 years after diagnosis, the proportion of patients according to disease behaviour was 18.7% with B1 disease, 36.9% with B2 and 44.4% with B3 or B2B3 [Figure 2].

Perianal fistula occurred at least once in 329 patients [55.4%]. The cumulative probabilities of perianal fistula were 46.7% at diagnosis, 50.3% at 1 year, 54.9% at 5 years and 57.6% at 10 years after diagnosis.

Intestinal resections were performed in 135 patients [22.7%]. The cumulative probabilities of intestinal resection were 1.7% at diagnosis, 4.5% at 1 year, 17.2% at 5 years, 33.9% at 10 years and 62.9% at 20 years after diagnosis [Figure 3]. Kaplan–Meier curves showed the cumulative probabilities of intestinal resection according to possible risk factors [see Supplementary data, available at *ECCO-JCC* online]. The results of univariate and multivariate Cox analysis of possible risk factors for intestinal resection are presented in Table 3. Stricturing behaviour (HR: 2.78, 95% confidence interval [CI] = 1.77–4.35, $p < 0.001$) and penetrating behavior [HR: 6.97, 95% CI = 2.81–17.30, $p < 0.001$] at diagnosis were associated with increased risk of intestinal resection compared with patients with non-stricturing and non-penetrating behavior. Isolated colonic location [HR: 0.10, 95% CI = 0.01–1.78, $p = 0.028$] at diagnosis was associated with decreased risk of intestinal resection compared with patients with distal one-third ileum with or without limited caecal disease. Early use of thiopurines induced a lower probability of intestinal resection with a relative risk of 0.65 [95% CI = 0.42–1.01, $p = 0.060$]. Early use of anti-TNF agents also induced a lower probability of intestinal resection with a relative risk of 0.54 [95% CI = 0.22–1.32, $p = 0.181$]. However, the difference was not significant.

The risk of intestinal resection was not different among the three temporal cohorts and the place of first diagnosis.

4. Discussion

This large single-centre study, which applied the Paris classification for the first time to an Asian paediatric population with CD, provides detailed information on the disease phenotype and long-term course. In this study, the predominance of males, as observed in Western studies, was evident and perianal disease appeared more common at diagnosis.

Similar to other paediatric studies, a male predominance was noted. However, the male-to-female ratio of 2.4:1 was higher than the 1.8:1 ratio of a Japanese nationwide survey[10] and much higher than the 1.6:1 ratio of two Western population-based studies.[28,29] A greater predominance of Asian male adult patients can be postulated to be due to cigarette smoking, an important environmental risk factor for CD.[30] However, the male predominance in paediatric patients, who are unlikely to be exposed to smoking, weakens the hypothesized association between male predominance and smoking.

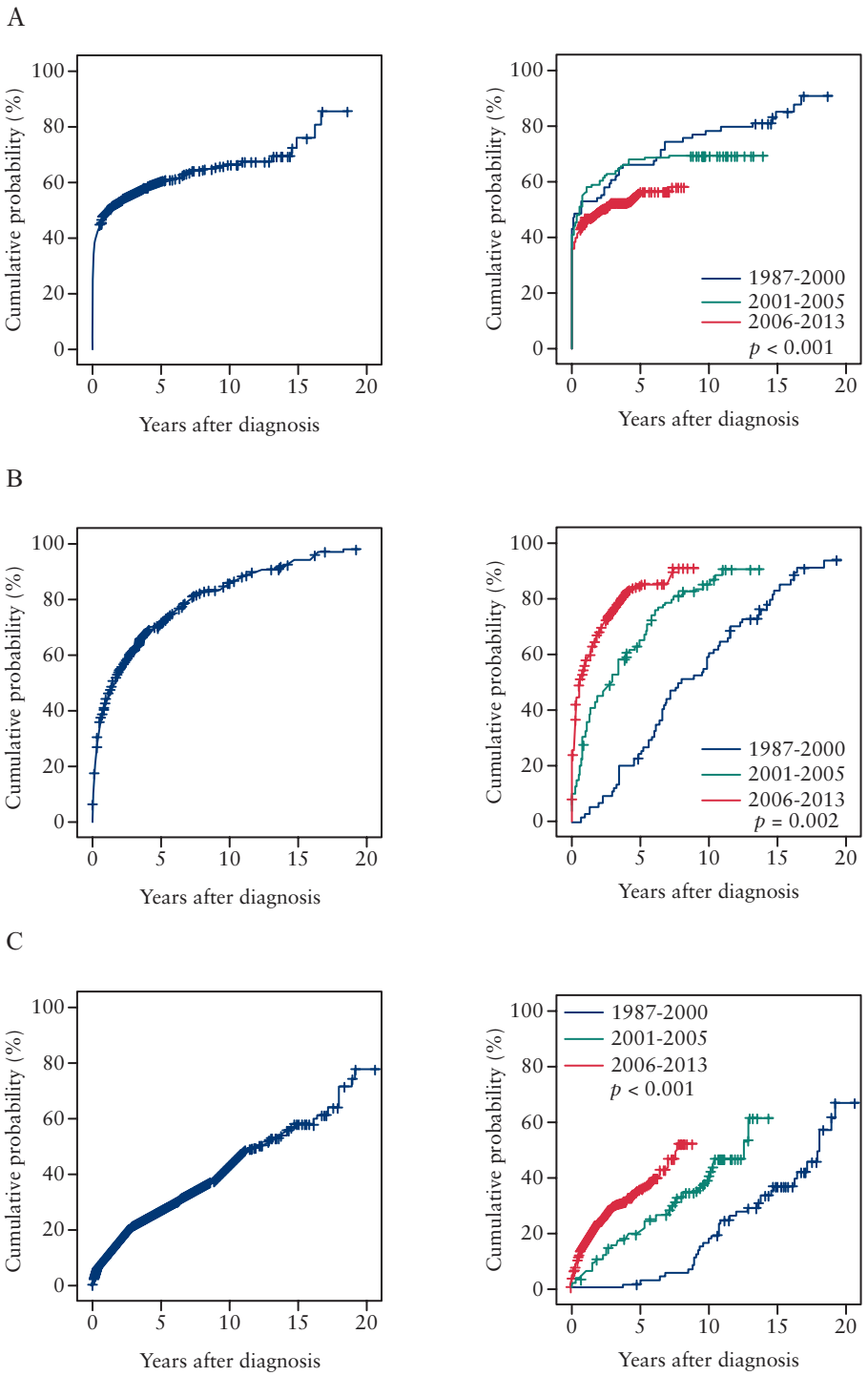

Figure 1. Cumulative probability of medication use in all 594 paediatric patients with Crohn's disease [left] and in the three cohorts [right] from the time of diagnosis. A, corticosteroids; B, thiopurines; C, anti-tumor necrosis factor agents.

In contrast to Western studies, approximately half of the children with CD in this study had perianal fistula. The incidence of perianal fistula in Western paediatric groups was much lower than in present study [9–18%].[31,32] One Asian adult study and our paediatric study reported the association between *tumour necrosis factor superfamily member 15* polymorphisms and perianal lesion.[33,34] Different genetic features may be influencing this, but a definite explanantion is lacking and more studies may be needed to resolve this. The results of our present study did not reflect a referral bias, because the patients diagnosed at our hospital initially also had a high incidence of perianal fistula at diagnosis [47.2%].

Different disease location-related findings were seen in this paediatric cohort. Ileocolonic [L3] disease [79.3%] was frequently noted in this study, whereas isolated colonic [L2] disease [8.2%] was less common than in Western countries.[35,36] Considering the tendency of younger children to have more isolated colonic disease,[36] the lower proportion of A1a patients in this cohort may be partly related to the lower incidence of L2 disease. The number of children younger than 10 years may have been underestimated in our study.

Disease behaviours in our present study series were monitored during a median follow-up of 6.8 years. As shown in Figure 2, the

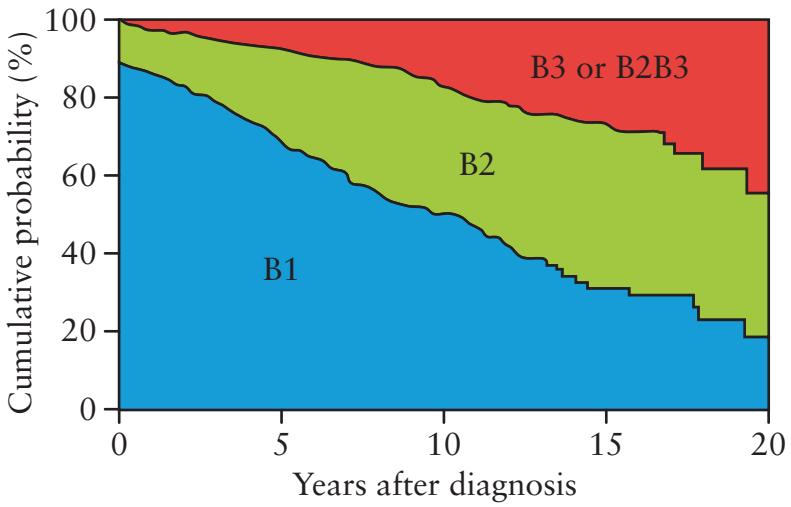

Figure 2. Temporal distribution of behaviour B1 [lower curve], B2 [middle curve], and B3 or B2B3 [upper curve] in 594 paediatric patients with Crohn's disease after diagnosis. [B1, non-stricturing and non-penetrating; B2, stricturing; B3, penetrating; B2B3, both penetrating and stricturing].

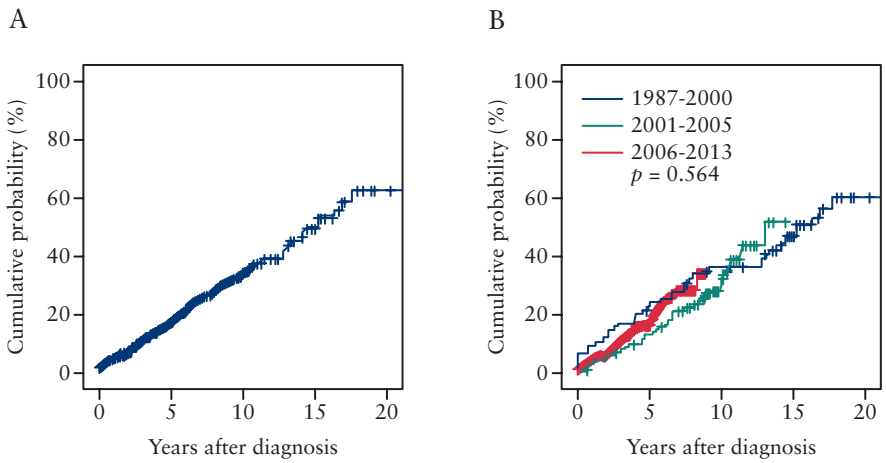

Figure 3. Cumulative probability of intestinal resection in 594 paediatric patients with Crohn's disease. A, in all patients; B, in the three temporal cohorts.

cumulative probabilities of B2 and B3/B2B3 disease increased from 9.4% and 1.1% to 23.8% and 8.2% at 5 years, respectively, and to 36.9% in B2 and 44.4% in B3/B2B3 at 20 years. Compared with a recent Korean adult study [10.1% in B2 and 12% in B3 at diagnosis; 17.4% in B2 and 28.2% in B3 at 5 years],[24] the proportion of patients with complicated behaviour at diagnosis was lower in our study. Furthermore, intestinal resection was performed more commonly for adult-onset CD [35.5% in adults,[24] vs 22.7% in the present study] and the cumulative probability of surgery was lower in paediatric-onset CD patients. The cumulative probabilities of intestinal resection at 10 and 20 years after diagnosis were 33.9% and 62.9% in our study, respectively, compared with previously reported cumulative probabilities for adult-onset CD patients of 43.5% and 70.0% at 10 and 20 years after diagnosis.[24] Van Limbergen *et al.*[11] reported that 20.2% of paediatric-onset CD patients had undergone surgery at 5 years after diagnosis versus 42.8% of adult-onset CD patients, although paediatric-onset CD is characterized by extensive intestinal involvement. A population-based study by Vernier-Massouille *et al.*[21] reported the cumulative probability of intestinal resection at 5 years was 35%, whereas that of our present study was 17.2%. Therefore, Korean children with paediatric CD seem to experience a more benign clinical course.

The increased incidence of CD has favoured its early detection and proper treatment. The median time from symptom appearance to diagnosis and prescription of anti-tuberculosis medication has decreased. Moreover, immunomodulators and biologics are increasingly being used and at an earlier stage. However, the increasing use of these medications has not reduced the cumulative probability of surgery over time and we also could not find a significant impact of early or ever use of anti-TNF agents and immunomodulators on the rate of surgery. Gupta *et al.*[19] reported that treatment with infliximab was associated with a decreased risk for surgery. Another adult population study by Lakatos *et al.*[37] reported that early treatment with immunomodulators reduced the rate of surgery. However, it is difficult to confirm the effect of these medications on decreasing the rate of surgery, because immunomodulators or anti-TNF agents are used in patients with a more severe disease.

Table 3. Univariate and multivariate Cox analysis: risk factors of intestinal resection in 594 paediatric patients with Crohn's disease.

	Univariate analysis	*p*-Value	Multivariate analysis	*p*-Value
	HR, 95% CI		HR, 95% CI	
Sex				
Male	Reference			
Female	1.19, 0.84–1.69	0.322		
Family history of IBD				
No	Reference			
Yes	1.13, 0.53–2.42	0.746		
Age at diagnosis				
1–9 years	Reference			
10–17 years	4.05, 0.56–29.01	0.163		
Location at diagnosis				
L1	Reference			
L2	0.14, 0.03–1.61	0.009	0.10, 0.01–1.78	0.028
L3	0.78, 0.46–1.33	0.371		
Upper disease at diagnosis				
No	Reference			
Yes	0.89, 0.48–1.19	0.342		
Behavior at diagnosis				
B1	Reference		Reference	
B2	2.77, 1.77–4.33	< 0.001	2.78, 1.77–4.35	< 0.001
B3	7.11, 2.86–17.64	< 0.001	6.97, 2.81–17.30	< 0.001
Perianal fistula at diagnosis				
No	Reference			
Yes	0.88, 0.62–1.25	0.504		
Growth impairment				
No	Reference			
Yes	1.05, 0.56–1.66	0.810		
Diagnosis period				
1987–2000	Reference			
2001–2005	0.97, 0.60–1.58	0.920		
2006–2013	1.08, 0.65–1.80	0.745		
Early use of medications				
Corticosteroids	0.82, 0.57–1.16	0.272		
Thiopurines	0.66, 0.44–1.01	0.053	0.65, 0.42–1.01	0.060
Anti-TNF agents	0.54, 0.22–1.32	0.181		
Place of first diagnosis				
Other hospitals	Reference			
Asan Medical Center	0.71, 0.49–1.03	0.125		

Abbreviations: CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; anti-TNF, anti-tumor necrosis factor.

In the present study, we applied the Paris classification to a large group of Asian patients and found a higher proportion of patients with isolated colonic-type CD [28.6% vs 9%, $p < 0.001$] in the A1a group than in the A1b group, which was also shown in previous studies.[36,38] However, in contrast to a previous study that reported a poor prognosis of L4b disease,[39] separation of the upper location [L4a/L4] did not affect the natural history of the disease in our study. The number of patients who had B2B3 was small and it was not associated with any specific findings. Thus, more studies may be needed to determine the appropriateness of the revision to the Montreal classification.

There were several limitations to our study. First, the study patients were from a single referral centre, which may not reflect the general prevalence and prognosis of Korean paediatric CD. Also, the retrospective design may have introduced a bias. Second, although a large number of patients were included, because of the small proportion of patients in the A1a group, we could not find an association between age at diagnosis and risk of surgery in univariate analysis.

In conclusion, our current study provides detailed information on disease phenotype according to the Paris classification and long-term course in a large cohort of Asian children with CD. By comparing our results with those of previous studies, characteristic findings were noted regarding disease phenotype and clinical course. The prevalence of perianal fistula at diagnosis was higher than reported from other Western studies. Behaviour and location at the time of diagnosis were risk factors for intestinal resection, suggesting the need for a modified strategy for children with surgical risks. The potential controversies caused by a referral bias in this study could be resolved by a future population-based study.

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Conflict of Interest

The authors declare no conflicts of interest.

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Supplementary Data

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

References

1. Hyams JS, Markowitz JF. Can we alter the natural history of Crohn disease in children? *J Pediatr Gastroenterol Nutr* 2005;**40**:262–72.
2. Lees CW, Barrett JC, Parkes M, Satsangi J. New IBD genetics: common pathways with other diseases. *Gut* 2011;**60**:1739–53.
3. Jostins L, Ripke S, Weersma RK, *et al*. Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012;**491**:119–24.
4. Imielinski M, Baldassano RN, Griffiths A, *et al*. Common variants at five new loci associated with early-onset inflammatory bowel disease. *Nat Genet* 2009;**41**:1335–40.
5. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011;**17**:423–39.
6. Kim BJ, Song SM, Kim KM, *et al*. Characteristics and trends in the incidence of inflammatory bowel disease in Korean children: a single-center experience. *Dig Dis Sci* 2010;**55**:1989–95.
7. Polito JM, 2nd, Childs B, Mellits ED, Tokayer AZ, Harris ML, Bayless TM. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. *Gastroenterology* 1996;**111**:580–6.
8. Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol* 2004;**18**:509–23.
9. Heyman MB, Kirschner BS, Gold BD, *et al*. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr* 2005;**146**:35–40.
10. Ishige T, Tomomasa T, Takebayashi T, *et al*. Inflammatory bowel disease in children: epidemiological analysis of the nationwide IBD registry in Japan. *J Gastroenterol* 2010;**45**:911–7.
11. Van Limbergen J, Russell RK, Drummond HE, *et al*. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008;**135**:1114–22.
12. Moum B, Vatn MH, Ekbom A, *et al*. Incidence of Crohn's disease in four counties in southeastern Norway, 1990–93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists. *Scand J Gastroenterol* 1996;**31**:355–61.
13. Uhlig HH, Schwerd T, Koletzko S, *et al*. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology* 2014;**147**:990–1007.e3.
14. Oh SH, Baek J, Kim KM, *et al*. Is whole exome sequencing clinically pratical in the management of pediatric Crohn's disease. *Gut Liver* 2015;**9**:767–75.
15. Sentongo TA, Semeao EJ, Piccoli DA, Stallings VA, Zemel BS. Growth, body composition, and nutritional status in children and adolescents with Crohn's disease. *J Pediatr Gastroenterol Nutr* 2000;**31**:33–40.
16. Song SM, Kim Y, Oh SH, Kim KM. Nutritional status and growth in Korean children with Crohn's disease: a single-center study. *Gut Liver* 2014;**8**:500–7.
17. Homer DR, Grand RJ, Colodny AH. Growth, course, and prognosis after surgery for Crohn's disease in children and adolescents. *Pediatrics* 1977;**59**:717–25.
18. 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**:1314–21.
19. Gupta N, Cohen SA, Bostrom AG, *et al*. Risk factors for initial surgery in pediatric patients with Crohn's disease. *Gastroenterology* 2006;**130**:1069–77.
20. Patel HI, Leichtner AM, Colodny AH, Shamberger RC. Surgery for Crohn's disease in infants and children. *J Pediatr Surg* 1997;**32**:1063–7; discussion 7–8.
21. Vernier-Massouille G, Balde M, Salleron J, *et al*. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008;**135**:1106–13.
22. Pigneur B, Seksik P, Viola S, *et al*. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis* 2010;**16**:953–61.
23. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. *Ann Surg* 2000;**231**:38–45.
24. Park SH, Yang SK, Park SK, *et al*. Long-term prognosis of Crohn's disease and its temporal change between 1981 and 2012: a hospital-based cohort study from Korea. *Inflamm Bowel Dis* 2014;**20**:488–94.
25. Levine A, Koletzko S, Turner D, *et al*. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014;**58**:795–806.
26. Hanauer SB. Crohn's disease: step up or top down therapy. *Best Pract Res Clin Gastroenterol* 2003;**17**:131–7.
27. Ramadas AV, Gunesh S, Thomas GA, Williams GT, Hawthorne AB. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986–2003): a study of changes in medical treatment and surgical resection rates. *Gut* 2010;**59**:1200–6.
28. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Arch Dis Child* 2003;**88**:995–1000.
29. Kugathasan S, Judd RH, Hoffmann RG, *et al*. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr* 2003;**143**:525–31.
30. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc* 2006;**81**:1462–71.
31. Short SS, Dubinsky MC, Rabizadeh S, Farrior S, Berel D, Frykman PK. Distinct phenotypes of children with perianal perforating Crohn's disease. *J Pediatr Surg* 2013;**48**:1301–5.
32. Gupta N, Bostrom AG, Kirschner BS, *et al*. Incidence of stricturing and penetrating complications of Crohn's disease diagnosed in pediatric patients. *Inflamm Bowel Dis* 2010;**16**:638–44.
33. Kakuta Y, Kinouchi Y, Negoro K, Takahashi S, Shimosegawa T. Association study of *TNFSF15* polymorphisms in Japanese patients with inflammatory bowel disease. *Gut* 2006;**55**:1527–8.
34. Lee YJ, Kim KM, Jang JY, Song K. Association of *TNFSF15* polymorphisms in Korean children with Crohn's disease. *Pediatr Int* 2015;**57**:1149–53.
35. Muller KE, Lakatos PL, Arato A, *et al*. Incidence, Paris classification, and follow-up in a nationwide incident cohort of pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2013;**57**:576–82.
36. de Bie CI, Paerregaard A, Kolacek S, *et al*. Disease phenotype at diagnosis in pediatric Crohn's disease: 5-year analyses of the EUROKIDS Registry. *Inflamm Bowel Dis* 2013;**19**:378–85.
37. Lakatos PL, Golovics PA, David G, *et al*. Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from Western Hungary between 1977–2009. *Am J Gastroenterol* 2012;**107**:579–88.
38. Mamula P, Telega GW, Markowitz JE, *et al*. Inflammatory bowel disease in children 5 years of age and younger. *Am J Gastroenterol* 2002;**97**:2005–10.
39. 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**:106–12.