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Original Article

Clinical Features and Long-term Prognosis of Crohn's Disease in Korea: Results from the Prospective CONNECT Study

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Background/Aims: The prospective Crohn's Disease Clinical Network and Cohort study is a nationwide multicenter cohort study of patients with Crohn's disease (CD) in Korea, aiming to prospectively investigate the clinical features and long-term prognosis associated with CD.

Methods: Patients diagnosed with CD between January 2009 and September 2019 were prospectively enrolled. They were divided into two cohorts according to the year of diagnosis: cohort 1 (diagnosed between 2009 and 2011) versus cohort 2 (between 2012 and 2019).

Results: A total of 1,175 patients were included, and the median follow-up duration was 68 months (interquartile range, 39.0 to 91.0 months). The treatment-free durations for thiopurines (p<0.001) and anti-tumor necrosis factor agents (p=0.018) of cohort 2 were shorter than those of cohort 1. Among 887 patients with B1 behavior at diagnosis, 149 patients (16.8%) progressed to either B2 or B3 behavior during follow-up. Early use of thiopurine was associated with a reduced risk of behavioral progression (adjusted hazard ratio [aHR], 0.69; 95% confidence interval [CI], 0.50 to 0.90), and family history of inflammatory bowel disease was associated with an increased risk of behavioral progression (aHR, 2.29; 95% CI, 1.16 to 4.50). One hundred forty-one patients (12.0%) underwent intestinal resection, and the intestinal resection-free survival time was significantly longer in cohort 2 than in cohort 1 (p=0.003). The early use of thiopurines (aHR, 0.35; 95% CI, 0.23 to 0.51) was independently associated with a reduced risk of intestinal resection.

Conclusions: The prognosis of CD in Korea appears to have improved over time, as evidenced by the decreasing intestinal resection rate. Early use of thiopurines was associated with an improved prognosis represented by a reduced risk of intestinal resection. **(Gut Liver, Published online March 24, 2022)**

Key Words: Cohort studies; Crohn disease; Prognosis; Multicenter study; Korea

INTRODUCTION

Crohn's disease (CD) is an idiopathic, chronic inflammatory disease of the gastrointestinal tract.[1,2] Traditionally, inflammatory bowel disease (IBD), including CD, has been considered a disease of high-income nations. However, recent epidemiologic studies have indicated that the incidence of IBD is stable or decreasing in North America and Europe but increasing in newly industrialized countries, including Korea.[3-9] In particular, the introduction of biologic therapy, including anti-tumor necrosis factor (TNF) agents, is expected to have a beneficial effect on the prognosis of patients with CD.[10,11] To date, however, there have been few studies on the clinical features and long-term prognosis of CD that reflect the clinical course of CD diagnosed after 2010 and its temporal changes.

The Crohn's Disease Clinical Network and Cohort (CONNECT) study is a nationwide multicenter cohort study of patients with CD in Korea.[12] The establishment of this study was led by the IBD research group of the Korean Association for the Study of Intestinal Diseases. The purpose of the CONNECT Study is to investigate the epidemiological and clinical characteristics of CD in Korea as well as its long-term prognosis.[12] The CONNECT study consists of a retrospective component and a prospective component, which was designed to enroll patients diagnosed with CD since 2009.[12] Clinical characteristics as well as prognosis and outcome predictors of retrospectively enrolled patients have been previously published.[13-16]

Here, we analyzed the data of the prospective component of the CONNECT study and investigated the clinical features at diagnosis, medical therapy, behavioral progression, intestinal resection rates, and mortality of patients diagnosed with CD since 2009. We were especially interested in the temporal changes of medical and surgical therapy as well as factors associated with intestinal resection. This is the first report of the prospective CONNECT study.

MATERIALS AND METHODS

1. Study design and data extraction

The CONNECT study is a nationwide multicenter study with 34 participating medical institutions in Korea. A web-based, electronic case registration system was developed in 2009; since then, the clinical data of patients diagnosed with CD have been prospectively collected (www.cdcohort.org).[12] Different from the retrospective CONNECT study, the prospective CONNECT study included clinical data of CD patients who have been enrolled through this system since 2009. The collected and registered clinical information by the participating researchers includes data collected

at the time of CD diagnosis: demographic data, smoking history, family history of IBD, endoscopic findings, radiologic findings, laboratory data, and disease location and behavior according to the Montreal classification.[17] During follow-up, the following information are supposed to be entered into the electronic case registration system: changes of disease location and behavior, medication, surgical treatment, hospitalization, pregnancy and associated outcomes, and mortality. We included the patients who were newly diagnosed with CD and registered in the CONNECT study from January 2009 through September 2019. During the study period, a total of 1,433 patients diagnosed with CD were registered. We excluded 258 patients whose data on smoking status (n=99), disease location (n=110), and/or family history of IBD (n=115) were uncertain or missing, and 1,175 patients were finally included in the analysis. This study was approved by the institutional review boards of all participating institutions, including Asan Medical Center (IRB No. 2008-0609, 2012-0862), and written informed consent was obtained from all enrolled patients. The CONNECT study is registered at ClinicalTrial.gov (NCT01554007).

2. Outcomes and definitions

CD diagnoses were made by combining conventional clinical, biochemical, endoscopic, radiologic, histopathological, and surgical findings.[3,18,19] The date of entry into the cohort was the date of diagnosis with CD. We investigated the following information at diagnosis of CD: demographics, smoking status, family history of IBD (i.e., first-degree relative [parents, offspring, and siblings] with IBD), disease location, and disease behavior. Age at diagnosis, disease location, and disease behavior were defined according to the Montreal classification.[17] Age at diagnosis was classified as A1 (≤16 years), A2 (17–40 years), or A3 (>40 years). Disease location was classified as L1 (ileum), L2 (colon), or L3 (ileocolon). Furthermore, involvement of the upper gastrointestinal tract only was noted as isolated L4 disease. Disease behavior was categorized as B1 (nonstricturing, nonpenetrating), B2 (stricturing), or B3 (penetrating).

After diagnosis, data on medications for CD, behavioral progression, intestinal resection, and mortality were collected and analyzed. Patients were defined as users of each medication for CD according to whether the drug was administered or not, irrespective of the duration of administration. Medication for CD was categorized as follows: oral 5-aminosalicylates, systemic corticosteroids (oral or intravenous corticosteroids), thiopurines (azathioprine or 6-mercaptopurine), and anti-TNF agents (infliximab [including biosimilar] or adalimumab). Early use of corticosteroids was defined as the commencement of corticosteroids within 3 months of diagnosis.[20,21] Early use of thiopurines or anti-TNF agents was defined as the commencement of each drug within 1 year of CD diagnosis and at least 6 months before behavioral progression or intestinal resection.[21-23] Early combined use of anti-TNF agent and thiopurine was defined as satisfying both of the above two conditions. Behavioral progression was defined as the development of B2 or B3 in patients with B1 at diagnosis.[24] The date of behavioral progression was defined as the date of development of behavior B2 or B3, whichever developed first.

We also investigated the clinical outcomes that included the cumulative probabilities of commencing each medication for CD, cumulative probability of behavioral progression, cumulative probability of intestinal resection, and mortality. Factors associated with behavioral progression and intestinal resection were also analyzed. We divided the enrolled patients into two cohorts according to the year of diagnosis to assess temporal changes in medication use, behavioral progression, and intestinal resection. The Korean National Health Insurance reimbursement criteria were amended to allow a lifetime reimbursement of infliximab and adalimumab for responders to induction therapy from October 2010 and May 2011, respectively, as a treatment of CD. Therefore, we assumed that ant-TNF agents were used for the treatment of CD without limitation from 2012 in Korea, and divided the patients into cohort 1 (diagnosed between 2009 and 2011) and cohort 2 (diagnosed between 2012 and 2019).

3. Statistical analysis

Continuous variables are expressed as medians with interquartile ranges (IQRs). Categorical variables are expressed as numbers with percentages. The differences in the characteristics between temporal cohorts were analyzed using the chi-square test or the Fisher exact test for categorical variables and the Mann-Whitney U test for continuous variables. The Kaplan-Meier method was used to calculate the cumulative probabilities of medication use (for each type), behavioral progression, intestinal resection, and death. The log-rank test was used to compare the cumulative probabilities of each medication use (for each type), behavioral progression, and intestinal resection between the temporal cohorts. To identify factors associated with behavioral progression and intestinal resection, the Cox proportional hazards regression modeling was applied. The variables with p-value <0.1 from the univariate model were included in the multivariable model. All results in the Cox regression model are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). A two-sided p-value <0.05 was considered statistically significant.

Table 1. Baseline Characteristics of 1,175 Patients with Crohn's Disease

Characteristics	Cohort			p-value
	Entire (2009–2019)	Cohort 1 (2009–2011)	Cohort 2 (2012–2019)	
No. of patients	1,175	515	660	
Male sex	876 (74.6)	377 (73.2)	499 (75.6)	0.384
Age at diagnosis, median (IQR), yr	22.0 (18.0–29.0)	21.0 (18.0–29.0)	22.0 (19.0–29.0)	0.003
Age at diagnosis				<0.001
≤16 yr (A1)	136 (11.5)	84 (16.3)	52 (7.9)	
17–40 yr (A2)	945 (80.4)	398 (77.3)	547 (82.9)	
>40 yr (A3)	94 (8.0)	33 (6.4)	61 (9.2)	
Follow-up duration, median (IQR), mo	68.0 (39.0–91.0)	92.0 (68.0–109.0)	52.0 (29.0–72.0)	<0.001
Smoking status at diagnosis				0.049
Never smoker	880 (74.9)	397 (77.1)	483 (73.2)	
Ex-smoker	102 (8.7)	33 (6.4)	69 (10.5)	
Current smoker	193 (16.4)	85 (16.5)	108 (16.4)	
Family history of IBD	29 (2.5)	15 (2.9)	14 (2.1)	0.498
Disease location at diagnosis				0.041
Ileum (L1)	337 (28.7)	132 (25.6)	205 (31.1)	
Colon (L2)	75 (6.4)	28 (5.4)	47 (7.1)	
Ileocolon (L3)	761 (64.8)	355 (68.9)	406 (61.5)	
Isolated upper gastrointestinal (L4)	2 (0.2)	0	2 (0.3)	
Perianal modifier at diagnosis	552 (47.0)	239 (46.4)	313 (47.4)	0.774
Disease behavior at diagnosis				0.064
Nonstricturing, nonpenetrating (B1)	887 (75.5)	372 (72.2)	515 (78.0)	
Stricturing (B2)	117 (10.0)	56 (10.9)	61 (9.2)	
Penetrating (B3)	171 (14.6)	87 (16.9)	84 (12.7)	
Medication use				
Oral 5-ASA	1,133 (96.4)	505 (98.1)	628 (95.2)	0.012
Systemic corticosteroids	619 (52.7)	289 (56.1)	330 (50.0)	0.043
Thiopurines	1,008 (85.8)	457 (88.7)	551 (83.5)	0.013
Anti-TNF agents	416 (35.4)	201 (39.0)	215 (32.6)	0.026

Data are presented as number (%) unless otherwise indicated.
IQR, interquartile range; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid; TNF, tumor necrosis factor.

All analyses were performed using R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

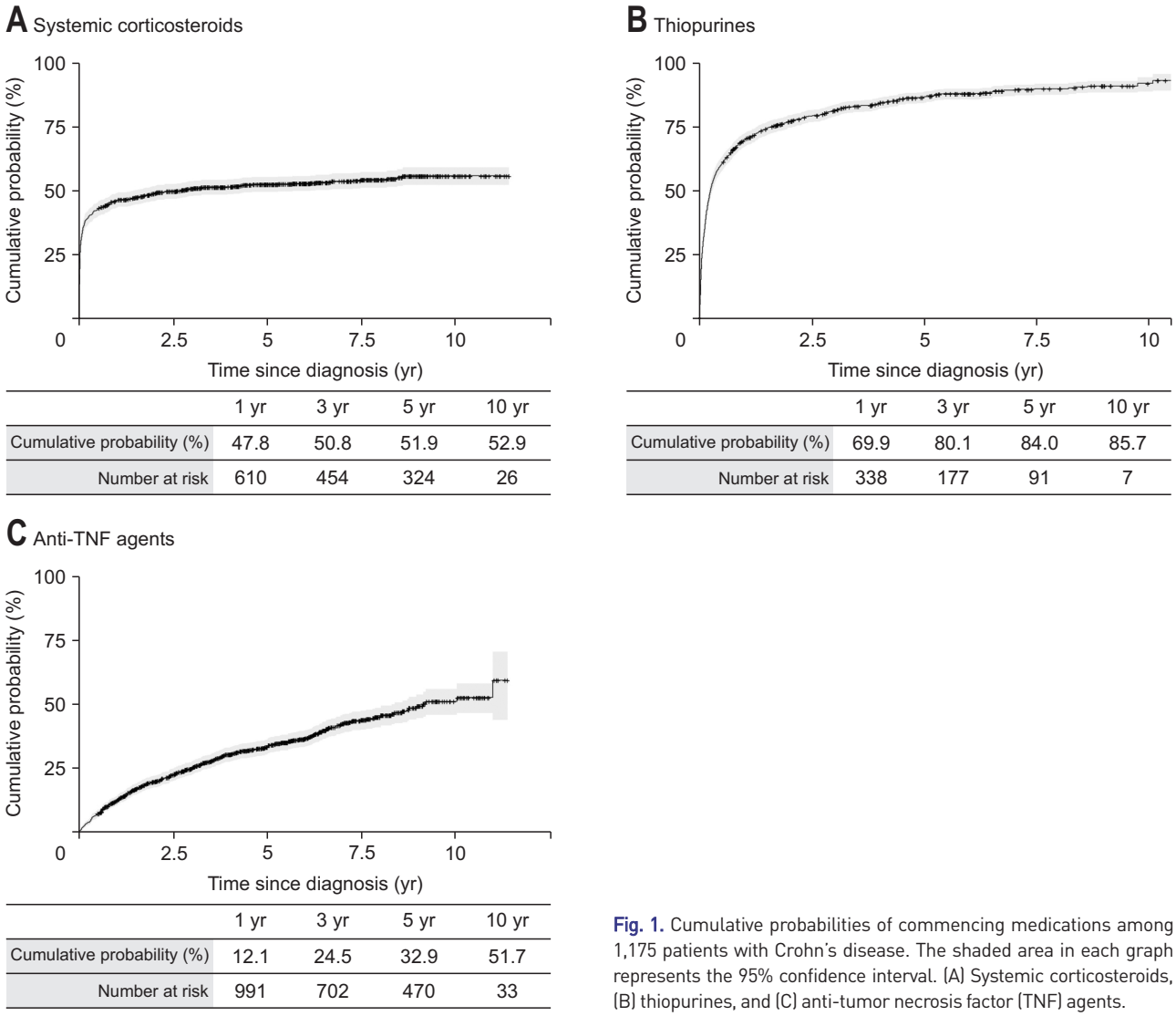
RESULTS

1. Baseline characteristics

A total of 1,175 patients were included in this analysis: 515 patients in cohort 1 (43.8%) and 660 patients in cohort 2 (56.2%). The baseline characteristics of the entire sample, cohort 1, and cohort 2 are summarized in Table 1. There were 876 males, accounting for 74.6% of the entire sample, and the median age at diagnosis was 22.0 years (IQR, 18.0 to 29.0). In the entire sample, 193 patients (16.4%) were current smokers, and 29 patients (2.5%) had a family history of IBD. Ileocolonic disease (L3, 64.8%) was the most common location at diagnosis, followed by ileal (L1, 28.7%) and colonic (L2, 6.4%) disease. A total of 887 patients (75.5%) had nonstricturing, nonpenetrating behavior at diagnosis. Overall, 552 patients (47.0%) had perianal disease at diagnosis.

2. Medical treatment

The median follow-up duration was 68.0 months (IQR, 39.0 to 91.0) for all patients, 92.0 months (IQR, 68.0 to 109.0) for cohort 1, and 52.0 months (IQR, 29.0 to 72.0) for cohort 2. After the diagnosis of CD, the numbers of patients ever treated with oral 5-aminosalicylates, systemic corticosteroids, thiopurines, and anti-TNF agents were 1,133 (96.4%), 619 (52.7%), 1,008 (85.8%), and 416 (35.4%), respectively (Table 1). The cumulative probabilities of using each medication type at 1, 3, 5, and 10 years after diagnosis were 47.8%, 50.8%, 51.9%, and 52.9%, respectively, for systemic corticosteroids; 69.9%, 80.1%, 84.0%, and 85.7%, respectively, for thiopurines; and 12.1%, 24.5%, 32.9%, and 51.7%, respectively, for anti-TNF agents (Fig. 1). The temporal changes between cohort 1 and cohort 2 in terms of the cumulative probabilities of commencing each type of medication are presented in Fig. 2. The treatment-free durations for thiopurines ($p<0.001$) and anti-TNFs ($p=0.018$) were significantly shorter in cohort 2 than in cohort 1, but there was no significant difference in the treatment-free duration for systemic cortico-



	1 yr	3 yr	5 yr	10 yr
Cumulative probability (%)	47.8	50.8	51.9	52.9
Number at risk	610	454	324	26

	1 yr	3 yr	5 yr	10 yr
Cumulative probability (%)	69.9	80.1	84.0	85.7
Number at risk	338	177	91	7

	1 yr	3 yr	5 yr	10 yr
Cumulative probability (%)	12.1	24.5	32.9	51.7
Number at risk	991	702	470	33

Fig. 1. Cumulative probabilities of commencing medications among 1,175 patients with Crohn's disease. The shaded area in each graph represents the 95% confidence interval. (A) Systemic corticosteroids, (B) thiopurines, and (C) anti-tumor necrosis factor (TNF) agents.

steroids between the two cohorts (p=0.500).

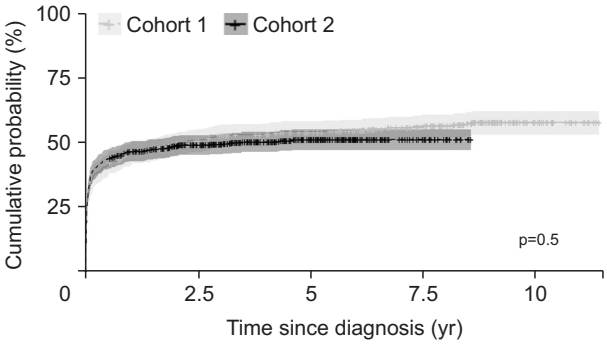
3. Behavioral progression

Among 887 patients with B1 behavior at diagnosis, 149 patients (16.8%) progressed to either B2 or B3 behavior during follow-up, and the median time from diagnosis to behavioral progression was 30.1 months (IQR, 11.9 to 60.7). The Kaplan-Meier curves presented in Fig. 3 depict the probabilities of remaining free of B2 or B3 complications for all 1,175 patients. For the 887 patients with initial B1 behavior, the cumulative probabilities of behavioral progression to either B2 or B3 at 1, 3, 5, and 10 years after diagnosis were 4.8%, 11.0%, 15.0%, and 27.1%, respectively (Fig. 4A). The behavioral progression-free survival for patients with initial B1 were not significantly different between cohort 1 and cohort 2 (p=0.191) (Fig. 4B). Multivariable Cox regression analysis showed that a family history of IBD at CD diagnosis was significantly associated with an increased risk of behavioral progression (adjusted HR [aHR], 2.29; 95% CI, 1.16 to 4.50), whereas early use of thiopurines was an independently associated with a reduced risk of behavioral progression (aHR, 0.69; 95% CI, 0.50 to 0.96) (Table 2).

4. Intestinal resection

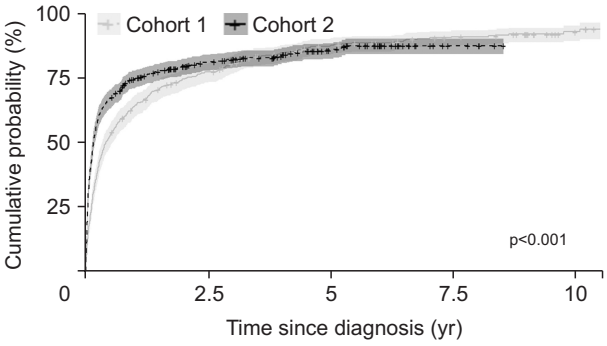
A total of 141 patients (12.0%) underwent intestinal resection during follow-up, and the median time from diagnosis to intestinal resection was 48.0 months (IQR, 8.3 to 205.1). The cumulative probabilities of intestinal resection at 1, 3, 5, and 10 years after diagnosis were 6.1%, 8.7%, 10.7%, and 19.3%, respectively (Fig. 5A). The intestinal resection-free survival was significantly longer in cohort 2 than in cohort 1 (p=0.003) (Fig. 5B). Multivariable Cox regression analysis revealed that stricturing behavior (B2) and penetrating behavior (B3) at diagnosis were significantly associated with an increased risk of intestinal resec-

A Systemic corticosteroids



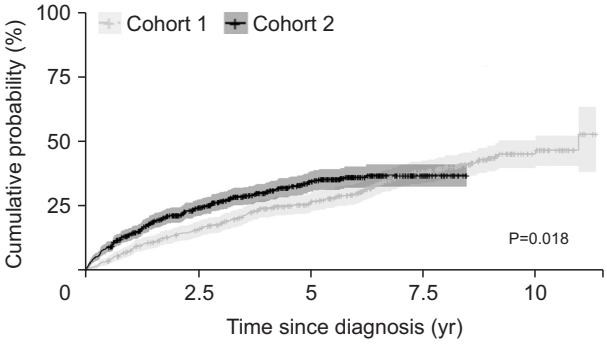
Cumulative probability	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	45.7%	52.4%	53.5%	55.7%
Cohort 2 (2012–2019)	46.4%	48.9%	49.9%	-
Number at risk	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	271	225	197	26
Cohort 2 (2012–2019)	339	229	127	-

B Thiopurines



Cumulative probability	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	64.3%	79.4%	85.6%	88.5%
Cohort 2 (2012–2019)	74.4%	80.8%	82.7%	-
Number at risk	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	180	93	49	7
Cohort 2 (2012–2019)	158	84	42	-

C Anti-TNF agents



Cumulative probability	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	8.2%	18.8%	26.8%	38.6%
Cohort 2 (2012–2019)	15.0%	27.0%	31.7%	-
Number at risk	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	464	382	296	33
Cohort 2 (2012–2019)	527	320	174	-

Fig. 2. Cumulative probabilities of commencing medications by temporal cohort, cohort 1 (2009–2011) versus cohort 2 (2012–2019). The shaded area in each graph represents the 95% confidence interval. (A) Systemic corticosteroids, (B) thiopurines, and (C) anti-tumor necrosis factor (TNF) agents.

tion (B2: aHR, 4.15; 95% CI, 2.61 to 6.61; B3: aHR, 5.05; 95% CI, 3.43 to 7.43) (Table 3). On the other hand, early use of thiopurines was independently associated with a reduced risk of intestinal resection (aHR, 0.35; 95% CI, 0.23 to 0.51) (Table 3).

5. Mortality

Eight patients (0.7%, four males and four females) died during follow-up. The median time from diagnosis to death was 54.0 months (IQR, 45.3 to 73.3). The causes of death were malignancies for three (hepatosplenic T cell lymphoma, lung, and breast for each), suicide for one, Alzheimer's disease for one, infection for one, and unknown but not related to CD for two. The cumulative survival rates at 1, 5, and 10 years after diagnosis were 100%, 99.8%, and 98.6%, respectively.

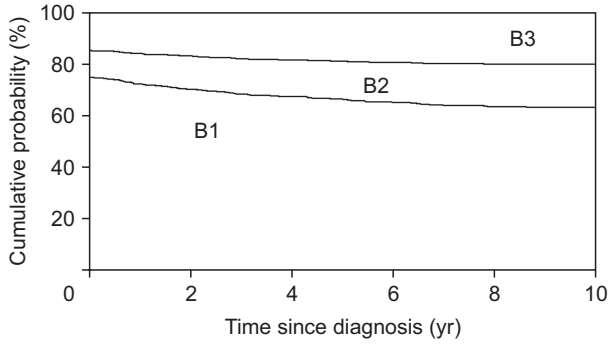
DISCUSSION

We investigated the clinical features and long-term prognosis of 1,175 patients with CD prospectively enrolled in the CONNECT study in Korea. Earlier use of thiopurines and anti-TNF agents was observed in the more

recently diagnosed cohort. Overall, 141 patients underwent intestinal resection during follow-up, and the risk of intestinal resection decreased among patients diagnosed with CD between 2012 and 2019 compared with those diagnosed with CD between 2009 and 2011. Early use of thiopurines was independently associated with a reduced risk of behavioral progression and intestinal resection.

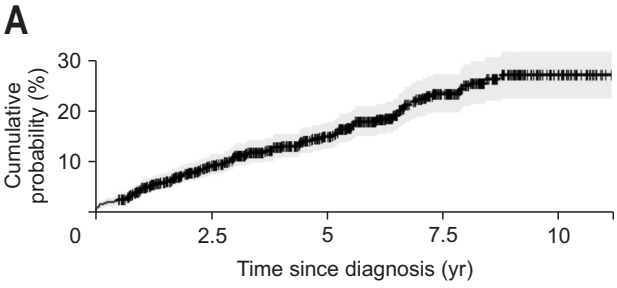
Similar to the present study, previous studies have shown that the clinical features of patients with CD in Asia differ from those of Western CD patients.[4,21,25-30] Prior studies have also reported that CD in Korea has a distinct epidemiologic pattern, including male predominance, a high frequency of ileocolonic (L3) disease, and frequent perianal disease at diagnosis.[21,26,29,31] Recently, the Songpa-Kangdong population-based study, including 418 patients diagnosed with CD between 1986 and 2015, corroborated these observations regarding the characteristic features of Korean patients with CD.[5] Among 275 CD patients from the Songpa-Kangdong district, diagnosed between 2006 and 2015, 76.0% were males, 64.7% had L3 disease, and 42.2% had perianal disease at diagnosis.[5] These findings are highly similar to the results of the present study, suggesting that our study sample is representative of patients with CD in Korea.

However, these findings contrast with those observed in Western studies. A European population-based inception cohort study, the Epi-IBD study, which included 488 patients diagnosed with CD in 2010 from 22 European countries, found that 50% were males, 29% had L3 disease, and only 9% had perianal disease at diagnosis.[24] Previous population-based Western studies also have observed lower proportions of males, L3 disease, and perianal disease compared with the present study.[20,22,32] The exact causes for these differences are still unclear. Genetics, epigenetic regulation of gene expression, microbiome factors, environmental factors, and other unrevealed factors might contribute to this phenomenon. For instance, *NOD2* genetic variants, which are established as strong CD-susceptible variants in Caucasians, are not associated with CD in Asian populations.[33-37] In contrast, the *TNFSF15* gene has a stronger association with CD in Korean and Japanese populations than in Western populations.[37-39] CD patients with these genetic variants showed distinct phenotypes and

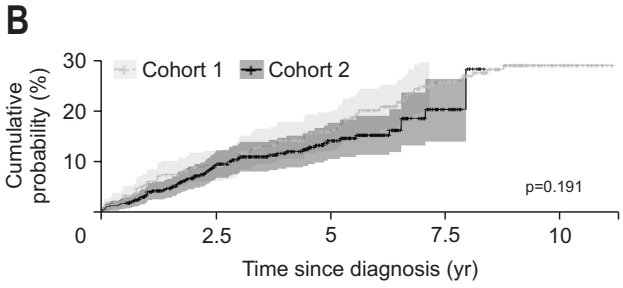


Proportion	0 yr	3 yr	5 yr	10 yr
B1	75.5%	68.0%	66.0%	62.9%
B2	10.0%	13.5%	14.8%	16.6%
B3	14.6%	18.5%	19.2%	20.5%

Fig. 3. Kaplan-Meier curves depicting the probabilities of remaining free of penetrating complications (upper curve) and free of stricturing or penetrating complications (lower curve) among 1,175 patients with Crohn's disease after diagnosis.
B1, nonstricturing, nonpenetrating; B2, stricturing; B3, penetrating.



	1 yr	3 yr	5 yr	10 yr
Cumulative probability (%)	4.8	11.0	15.0	27.1
Number at risk	806	605	429	38



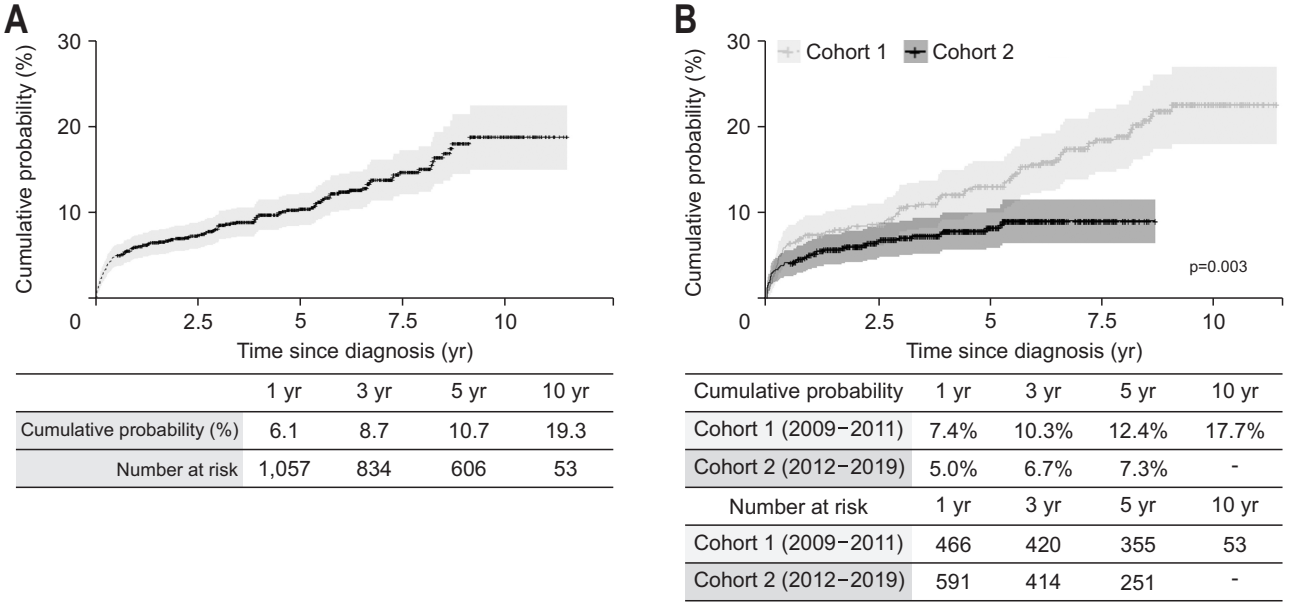
Cumulative probability	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	5.9%	11.0%	15.1%	22.8%
Cohort 2 (2012–2019)	3.9%	9.1%	10.9%	-
Number at risk	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	341	299	244	38
Cohort 2 (2012–2019)	465	306	185	-

Fig. 4. Cumulative probability of behavioral progression among 887 patients with nonstricturing, nonpenetrating behavior at diagnosis. The shaded area in each graph represents the 95% confidence interval. (A) Entire sample (2009–2019), (B) cohort 1 (2009–2011) versus cohort 2 (2012–2019).

Table 2. Factors Associated with Behavior Progression in Patients with Crohn's Disease

Variable	Patients with B1 behavior at diagnosis (n=887)			
	Univariate HR (95% CI)	p-value*	Multivariable HR (95% CI)	p-value
Sex			Not included	
Male	Reference			
Female	1.26 (0.89–1.79)	0.197		
Cohort			Not included	
2009–2011	Reference			
2012–2019	0.80 (0.57–1.12)	0.191		
Age at diagnosis			Not included	
≤16 yr (A1)	Reference			
17–40 yr (A2)	1.15 (0.72–1.82)	0.566		
>40 yr (A3)	0.81 (0.34–1.90)	0.627		
Family history of IBD				
No	Reference			
Yes	2.42 (1.23–4.76)	0.010	2.29 (1.16–4.50)	0.016
Smoking status at diagnosis			Not included	
Never smoker	Reference			
Ex-smoker	0.82 (0.43–1.57)	0.548		
Current smoker	1.09 (0.69–1.72)	0.712		
Disease location at diagnosis			Not included	
Ileum (L1)	Reference			
Colon (L2)	0.57 (0.24–1.35)	0.201		
Ileocolon (L3)	1.01 (0.70–1.46)	0.956		
Perianal modifier at diagnosis	0.81 (0.58–1.11)	0.192	Not included	
Early use of systemic corticosteroids	1.09 (0.79–1.51)	0.602	Not included	
Early use of thiopurines	0.64 (0.47–0.89)	0.008	0.69 (0.50–0.96)	0.026
Early use of anti-TNF agents	0.54 (0.22–1.31)	0.173	Not included	
Early combined use of anti-TNF agent and thiopurine	0.36 (0.11–1.13)	0.080	0.45 (0.14–1.42)	0.172

B1, nonstricturing, nonpenetrating behavior; HR, hazard ratio; CI, confidence interval; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.
*Variables with p<0.1 from the univariate model were included in the multivariable model.



	1 yr	3 yr	5 yr	10 yr
Cumulative probability (%)	6.1	8.7	10.7	19.3
Number at risk	1,057	834	606	53

Cumulative probability	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	7.4%	10.3%	12.4%	17.7%
Cohort 2 (2012–2019)	5.0%	6.7%	7.3%	-
Number at risk	1 yr	3 yr	5 yr	10 yr
Cohort 1 (2009–2011)	466	420	355	53
Cohort 2 (2012–2019)	591	414	251	-

Fig. 5. Cumulative probability of intestinal resection among 1,175 patients with Crohn's disease after diagnosis. The shaded area in each graph represents the 95% confidence interval. (A) Entire sample (2009–2019), (B) cohort 1 (2009–2011) versus cohort 2 (2012–2019).

Table 3. Factors Associated with Intestinal Resection in Patients with Crohn's Disease

Variable	Entire patients (n=1,175)			
	Univariate HR (95% CI)	p-value*	Multivariable HR (95% CI)	p-value
Sex			Not included	
Male	Reference			
Female	1.28 (0.76–1.60)	0.598		
Cohort				
2009–2011	Reference		Reference	
2012–2019	0.58 (0.41–0.83)	0.003	0.73 (0.51–1.04)	0.085
Age at diagnosis			Not included	
≤16 yr (A1)	Reference			
17–40 yr (A2)	1.26 (0.73–2.16)	0.404		
>40 yr (A3)	1.16 (0.52–2.57)	0.724		
Family history of IBD			Not included	
No	Reference			
Yes	1.13 (0.42–3.07)	0.805		
Smoking status at diagnosis				
Never smoker	Reference		Reference	
Ex-smoker	1.31 (0.73–2.32)	0.368	1.51 (0.83–2.74)	0.176
Current smoker	1.56 (1.03–2.33)	0.032	1.42 (0.93–2.16)	0.100
Disease location at diagnosis				
Ileum (L1)	Reference		Reference	
Colon (L2)	0.33 (0.12– 0.92)	0.034	0.48 (0.17–1.32)	0.155
Ileocolon (L3)	0.70 (0.49– 0.98)	0.040	0.94 (0.66–1.35)	0.736
Perianal modifier at diagnosis	0.66 (0.46– 0.92)	0.015	0.90 (0.63–1.28)	0.549
Disease behavior at diagnosis				
Nonstricturing, nonpenetrating (B1)	Reference		Reference	
Stricturing (B2)	4.55 (2.90–7.15)	<0.001	4.15 (2.61–6.61)	<0.001
Penetrating (B3)	6.70 (4.62–9.70)	<0.001	5.05 (3.43–7.43)	<0.001
Early use of systemic corticosteroids	0.74 (0.52–1.06)	0.098	1.10 (0.76–1.61)	0.616
Early use of thiopurines	0.27 (0.19–0.39)	0.014	0.35 (0.23–0.51)	<0.001
Early use of anti-TNF agents	0.41 (0.18–0.94)	0.035	0.67 (0.29–1.55)	0.349
Early combined use of anti-TNF agent and thiopurine	0.49 (0.18–1.32)	0.158	Not included	

HR, hazard ratio; CI, confidence interval; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.
*Variables with p<0.1 from the univariate model were included in the multivariable model.

prognoses. For example, in CD patients with *NOD2* variants, ileal disease, left colonic disease, right colonic disease, stenosing disease, fistulizing disease and intestinal resection have been reported to develop more frequently.[40,41] In Korean patients with CD, *TNFSF15* variants were independently associated with the development of stricture, nonperianal penetrating complications and perianal fistula.[42] Accordingly, differences in genetic characteristics might be associated with different phenotypes between Western and Korean CD patients. However, more studies are required to reveal the causes for different phenotypic characteristics between Korean and Caucasian CD patients.

In our study, a family history of IBD was independently associated with the risk of behavioral progression. This is in contrast to a population-based study from North America, which did not show an association between a family history of IBD and intestinal complications.[43] On the other hand, a population-based study from Denmark revealed that CD patients with a known CD family member had a significantly higher risk of major surgery after 2 years of disease duration than did patients with sporadic CD.[44] A hospital-based study from Korea showed that family history of IBD in CD patients was an independent factor for the time-to-first intestinal resection in patients with CD.[45] A recent population-based study on 418 patients with CD from Korea showed that a family history of IBD was significantly associated with an increased risk of behavioral progression.[46] Overall, family history of IBD is likely associated with the risks of intestinal complications and surgery, but further studies are required to reach a consistent and more reliable conclusion.

An intriguing finding of the present study was a relatively low intestinal resection rate compared with previous studies. In our study, the cumulative 5-year intestinal resection rate after diagnosis was 10.7% among all patients and 12.4% in cohort 1, compared with 22% in the aforemen-

tioned 2010 European population-based cohort,[24] 19.6% in a Danish cohort diagnosed between 2003 and 2011,[47] and 17.4% in a Dutch cohort diagnosed between 2006 and 2011.[32] It is not clear whether this difference in intestinal resection rates between Korean and Caucasian populations is due to difference in the natural course of CD or difference in treatment strategies by region. To clarify the issue, multi-regional, long-term cohort studies, including large sample sizes, are required.

Other remarkable findings of our study included the temporal change in the immunosuppressive medication initiation timing and in the frequency of intestinal resection. Over time, more patients received earlier thiopurines or anti-TNF therapy, and fewer patients underwent intestinal resection. Moreover, early use of thiopurines was independently associated with reduced risks of behavioral progression and intestinal resection. The previously reported retrospective CONNECT study also showed an independent association between immunomodulator use within 6 months of CD diagnosis and a lower risk of complications of CD (intestinal surgery, stricture, or fistula).[14] A retrospective study of 2,043 patients from Korea also showed that early azathioprine use (within the first year of diagnosis and at least 6 months before the first intestinal resection) was associated with a lower risk of intestinal resection.[21] This association between early thiopurine use and a lower likelihood of intestinal resection has also been observed in cohort studies conducted in the Western world.[20,22,24] However, in a prospective randomized trial by Cosnes *et al.*,[48] early azathioprine treatment within 6 months of CD diagnosis did not differ from conventional management in terms of the cumulative probability of intestinal resection at 36 months. A systemic review and meta-analysis of randomized controlled trials also did not find a reduced risk of CD-related surgery with azathioprine compared to placebo treatment.[10] However, the randomized controlled trial by Cosnes *et al.*[48] included a relatively small number of CD patients and the outcomes related to intestinal surgery were set as secondary outcomes. In addition, the follow-up period was only 3 years, which is too short to investigate the effect of early use of azathioprine on intestinal resection among patients with CD.[48] Given these limitations, the randomized controlled trial by Cosnes *et al.*[48] may fall short of fully addressing the long-term effects of early thiopurine therapy on the course of patients with CD. On the other hand, several large-scale, long-term, real-world studies have shown that the early use of thiopurine has a favorable effect on the course of CD, which is in line with our findings.[20-22] Collectively speaking, early use of thiopurines could have a positive effect on the natural course of CD.

In our study, early anti-TNF therapy was not associated with a reduced risk of intestinal resection, which was in line with previous studies.[24,32] In a recent study using health administrative data in Ontario, Canada, the marketplace introduction of infliximab did not produce a significant decline in the rate of intestinal resection.[49] However, in a systematic review and meta-analysis of randomized controlled trials, anti-TNF use significantly reduced the risk of surgery.[10] Therefore, currently, no definitive conclusions can be drawn regarding the contribution of anti-TNF therapy, especially early therapy, to reducing the risk of intestinal resection among patients with CD. Moreover, most related studies, including the present study, have not been designed to determine the causal relationship between medications and intestinal resection. Actually, the risk of intestinal resection could be influenced by several factors other than medication, such as improved access to diagnostic procedures, improved awareness of the disease, early CD diagnosis before development of bowel damage, and strict monitoring strategies.[50,51] Additionally, the clinical decision-making on intestinal resection for patients with CD can be influenced by multiple factors, including the preferences of patients and physicians, medical costs, and cultural differences. Hence, subsequent well-designed studies controlling multiple potential confounders and applying a consistent treatment algorithm for CD patients are required to prove the causal relationship between various drugs and intestinal resection.

This prospective cohort study showed that the prognosis of patients with CD has improved over time in Korea. The possible explanations for this improved prognosis are as follows. First, although the age at diagnosis was higher in cohort 2 compared with cohort 1, the proportion of ileal disease (L1) at diagnosis was also higher in cohort 2. Additionally, albeit without statistical significance, the proportion of patients with complicated behavior (B2 or B3) at diagnosis tended to be lower in cohort 2. This suggests that the awareness of CD could have improved over time, as evidenced by the detection of previously neglected ileal-only disease and the early diagnosis of CD prior to the development of intestinal complications. This improved awareness could have resulted in a better clinical outcome in cohort 2. Another possible reason for the better prognosis of cohort 2 is the timing of commencement of therapeutic agents for CD, considering that early use of thiopurines was associated with lower risks of behavioral progression and intestinal resection. Moreover, unmeasured factors such as the implementation of therapeutic and monitoring guidelines, and IBD-specific continuing medical education could have contributed to the improvements in the prognosis of CD patients over time.[50]

The main strength of this analysis was in its enrollment of over 1,000 patients across Korea and the analysis of CD patients diagnosed in recent years, which could fill the knowledge gap regarding the characteristics and prognosis of CD patients diagnosed in the 2010s. However, the present study also had several limitations. First, this study was not a population-based cohort study; it was a hospital-based cohort study. Since all of the medical institutions that participated in the CONNECT study were secondary or tertiary referral hospitals, there might have been selection bias favoring more severe disease. However, as mentioned, the highly similar baseline characteristics of patients included in this analysis and a previous Korean population-based study suggest that our sample could be representative of the general CD population in Korea.[5] Moreover, after referral from primary care clinics, almost all CD patients in Korea are continuously followed at secondary or tertiary centers and not referred back to the primary care clinics.[52] Therefore, the clinical outcomes of our study patients are likely not significantly biased. Second, there might have been differences in the treatment strategies or surgical indications among the participating hospitals because we did not provide a uniform therapeutic algorithm for the study centers. In particular, the timing of initiation of anti-TNF agents or surgery might have differed from center to center. This is an inherent issue of multicenter studies that could not be controlled. However, because Korean CD treatment guidelines have been widely distributed, and the therapeutic strategy of CD is universally based on the "step-up approach,"[53-56] and because therapeutic decisions are strictly regulated by the uniform and tight reimbursement system under the Health Insurance Review & Assessment Service of Korea, therapeutic algorithms would not have been significantly different among the participating centers. Third, because our study was not designed to investigate the causal relationship between treatment and outcomes, the significant association between early use of thiopurines and prognosis of CD patients might have been influenced by unmeasured confounders. As an example, patients who received earlier thiopurine therapy might have been managed with a tighter and closer disease monitoring, which might have been a confounder leading to a better prognosis. Finally, since this study enrolled CD patients who provided informed consent, there might have been a possibility of another selection bias. This concern can be settled indirectly through the difference in the numbers of enrolled patients in cohort 1 and cohort 2. Although the duration of enrollment to cohort 2 was nearly twice that of cohort 1, the number of patients in cohort 2 was smaller than that of cohort 1. When considering the steadily increasing incidence of CD in Korea,[5] more complete enrollment of consecutive patients newly diagnosed with CD could enhance the quality of the CONNECT study.

In conclusion, compared with Western patients, CD patients in Korea had different clinical features at the time of diagnosis. The prognosis of patients with CD in Korea appears to have improved over time, and early use of thiopurines was independently associated with reduced risks of behavioral progression and intestinal resection.

CONFLICTS OF INTEREST

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J.H.C., Y.S.K., J.P.I., and J.W.K. are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

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REFERENCES

1. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. Lancet 2017;389:1741-1755.
2. Mizoguchi E, Low D, Ezaki Y, Okada T. Recent updates on the basic mechanisms and pathogenesis of inflammatory bowel diseases in experimental animal models. Intest Res 2020;18:151-167.
3. Yang SK, Yun S, Kim JH, et al. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986-2005: a KASID study. Inflamm Bowel Dis 2008;14:542-549.
4. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017;390:2769-2778.
5. Park SH, Kim YJ, Rhee KH, et al. A 30-year trend analysis in the epidemiology of inflammatory bowel disease in the Songpa-Kangdong district of Seoul, Korea in 1986-2015. J Crohns Colitis 2019;13:1410-1417.
6. Yen HH, Weng MT, Tung CC, et al. Epidemiological trend in inflammatory bowel disease in Taiwan from 2001 to 2015: a nationwide populationbased study. Intest Res 2019;17:54-62.
7. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5:17-30.
8. Kaibullayeva J, Ualiyeva A, Oshibayeva A, Dushpanova A, Marshall JK. Prevalence and patient awareness of inflammatory bowel disease in Kazakhstan: a cross-sectional study. Intest Res 2020;18:430-437.
9. Sood A, Kaur K, Singh A, et al. Trends of inflammatory bowel disease at a tertiary care center in northern India. Intest Res 2021;19:282-290.
10. Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2017;45:3-13.
11. Frei R, Fournier N, Zeitz J, et al. Early initiation of anti-TNF is associated with favourable long-term outcome in Crohn's disease: 10-year-follow-up data from the Swiss IBD cohort study. J Crohns Colitis 2019;13:1292-1301.
12. Cheon JH, Kim YS, Ye BD, et al. Crohn's Disease Clinical Network and Cohort (CONNECT) Study: the first step toward nationwide multicenter research of Crohn's disease in Korea. Intest Res 2014;12:173-175.
13. Jung YS, Park DI, Ye BD, et al. Long-term clinical outcomes of urban versus rural environment in Korean patients with

Crohn's disease: results from the CONNECT study. J Crohns Colitis 2015;9:246-251.
14. Kim B, Cheon JH, Moon HJ, et al. Crohn's disease prognosis and early immunomodulator therapy: results from the CONNECT study. J Gastroenterol Hepatol 2016;31:126-132.
15. Kwon JH, Im JP, Ye BD, et al. Disease phenotype, activity and clinical course prediction based on C-reactive protein levels at diagnosis in patients with Crohn's disease: results from the CONNECT study. Gut Liver 2016;10:595-603.
16. Park Y, Cheon JH, Park YL, et al. Development of a novel predictive model for the clinical course of Crohn's disease: results from the CONNECT study. Inflamm Bowel Dis 2017;23:1071-1079.
17. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19 Suppl A:5A-36A.
18. Loftus EV Jr, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. Gastroenterology 1998;114:1161-1168.
19. Lee YJ, Yang SK, Byeon JS, et al. Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. Endoscopy 2006;38:592-597.
20. 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;59:1200-1206.
21. 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;20:488-494.
22. 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;107:579-588.
23. Noh SM, Oh EH, Park SH, et al. Association of faecal calprotectin level and combined endoscopic and radiological healing in patients with Crohn's disease receiving anti-tumour necrosis factor therapy. J Crohns Colitis 2020;14:1231-1240.
24. Burisch J, Kiudelis G, Kupcinskas L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. Gut 2019;68:423-433.
25. Oriuchi T, Hiwatashi N, Kinouchi Y, et al. Clinical course and longterm prognosis of Japanese patients with Crohn's disease: predictive factors, rates of operation, and mortality. J Gastroenterol 2003;38:942-953.
26. Ye BD, Yang SK, Cho YK, et al. Clinical features and long-term prognosis of Crohn's disease in Korea. Scand J Gastroenterol 2010;45:1178-1185.
27. Zeng Z, Zhu Z, Yang Y, et al. Incidence and clinical characteristics of inflammatory bowel disease in a developed region of Guangdong Province, China: a prospective population-based study. J Gastroenterol Hepatol 2013;28:1148-1153.
28. Kim HJ, Hann HJ, Hong SN, et al. Incidence and natural course of inflammatory bowel disease in Korea, 2006-2012: a nationwide population-based study. Inflamm Bowel Dis 2015;21:623-630.
29. Yang SK. How does the epidemiology of inflammatory bowel disease differ between east and west? A Korean perspective. Inflamm Intest Dis 2017;2:95-101.
30. Sood A, Kaur K, Mahajan R, et al. Colitis and Crohn's Foundation (India): a first nationwide inflammatory bowel disease registry. Intest Res 2021;19:206-216.
31. Moon CM, Park DI, Kim ER, et al. Clinical features and predictors of clinical outcomes in Korean patients with Crohn's disease: a Korean association for the study of intestinal diseases multicenter study. J Gastroenterol Hepatol 2014;29:74-82.
32. Jeuring SF, van den Heuvel TR, Liu LY, et al. Improvements in the long-term outcome of Crohn's disease over the past two decades and the relation to changes in medical management: results from the population-based IBDSL cohort. Am J Gastroenterol 2017;112:325-336.
33. Hampe J, Cuthbert A, Croucher PJ, et al. Association between insertion mutation in NOD2 gene and Crohn's disease in German and British populations. Lancet 2001;357:1925-1928.
34. Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001;411:603-606.
35. Economou M, Trikalinos TA, Loizou KT, Tsianos EV, Ioannidis JP. Differential effects of NOD2 variants on Crohn's disease risk and phenotype in diverse populations: a meta-analysis. Am J Gastroenterol 2004;99:2393-2404.
36. Ng SC, Tsoi KK, Kamm MA, et al. Genetics of inflammatory bowel disease in Asia: systematic review and meta-analysis. Inflamm Bowel Dis 2012;18:1164-1176.
37. Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet 2015;47:979-986.
38. Yang SK, Lim J, Chang HS, et al. Association of TNFSF15 with Crohn's disease in Koreans. Am J Gastroenterol 2008;103:1437-1442.
39. Yamazaki K, Umeno J, Takahashi A, et al. A genome-wide association study identifies 2 susceptibility Loci for Crohn's disease in a Japanese population. Gastroenterology

2013;144:781-788.
40. Abreu MT, Taylor KD, Lin YC, et al. Mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. Gastroenterology 2002;123:679-688.
41. Hampe J, Grebe J, Nikolaus S, et al. Association of NOD2 (CARD 15) genotype with clinical course of Crohn's disease: a cohort study. Lancet 2002;359:1661-1665.
42. Yang DH, Yang SK, Song K, et al. TNFSF15 is an independent predictor for the development of Crohn's disease-related complications in Koreans. J Crohns Colitis 2014;8:1315-1326.
43. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. Gastroenterology 2010;139:1147-1155.
44. Trier Moller F, Andersen V, Andersson M, Jess T. Hospital admissions, biological therapy, and surgery in familial and sporadic cases of inflammatory bowel disease: a population-based cohort study 1977-2011. Inflamm Bowel Dis 2015;21:2825-2832.
45. Hwang SW, Kwak MS, Kim WS, et al. Influence of a positive family history on the clinical course of inflammatory bowel disease. J Crohns Colitis 2016;10:1024-1032.
46. Ye BD, Hong SN, Seo SI, et al. Changes in the long-term prognosis of Crohn's disease between 1986 and 2015: the population-based Songpa-Kangdong inflammatory bowel disease cohort study. Gut Liver. Epub 2021 Jun 22. https://doi.org/10.5009/gnl210044.
47. Rungoe C, Langholz E, Andersson M, et al. Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979-2011. Gut 2014;63:1607-1616.
48. Cosnes J, Bourrier A, Laharie D, et al. Early administration of azathioprine vs conventional management of Crohn's disease: a randomized controlled trial. Gastroenterology 2013;145:758-765.
49. Murthy SK, Begum J, Benchimol EI, et al. Introduction of anti-TNF therapy has not yielded expected declines in hospitalisation and intestinal resection rates in inflammatory bowel diseases: a population-based interrupted time series study. Gut 2020;69:274-282.
50. Frolkis AD, Dykeman J, Negrón ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. Gastroenterology 2013;145:996-1006.
51. Beelen EM, van der Woude CJ, de Vries AC. Intestinal resection rates in Crohn's disease decline across two different epidemiological areas: a consistent observation not merely due to introduction of anti-TNFα. Gut 2020;69:1.
52. Seo H, Ye BD, Song EM, et al. Long-term outcomes of adalimumab treatment in 254 patients with Crohn's disease: a hospital-based cohort study from Korea. Dig Dis Sci 2017;62:2882-2893.
53. Hanauer SB. Crohn's disease: step up or top down therapy. Best Pract Res Clin Gastroenterol 2003;17:131-137.
54. Ye BD, Yang SK, Shin SJ, et al. Guidelines for the management of Crohn's disease. Korean J Gastroenterol 2012;59:141-179.
55. Park JJ, Yang SK, Ye BD, et al. Second Korean guidelines for the management of Crohn's disease. Intest Res 2017;15:38-67.
56. Ooi CJ, Hilmi I, Banerjee R, et al. Best practices on immunomodulators and biologic agents for ulcerative colitis and Crohn's disease in Asia. Intest Res 2019;17:285-310.