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Influence of age at diagnosis on the clinical characteristics of Crohn's disease in Korea: Results from the CONNECT study

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Abstract

Background and Aim: The present study evaluated the clinical characteristics of Korean patients with Crohn's disease (CD) according to their age at diagnosis in a nationwide multicenter cohort study.

Methods: A total of 1224 patients diagnosed with CD between 1982 and 2008 in 32 hospitals were included, and age at diagnosis was categorized as ≤ 16 (G1), 17–40 (G2), 41–59 (G3) and ≥ 60 (G4) years old. The baseline characteristics, medication, and intestinal resection were compared according to the age at diagnosis.

Results: The number of patients in each age group was 155 (G1; 12.7%), 919 (G2; 75.1%), 120 (G3; 9.8%), and 30 (G4; 2.5%). The frequencies of ileocolonic disease in the late adult onset and elderly onset groups were lower than those in the other groups ($P < 0.001$). The cumulative probabilities of thiopurine and anti-tumor necrosis factor use in late adult onset and elderly onset groups were significantly reduced compared with those of the other groups ($P < 0.01$). However, the risk of the first intestinal resection was not different among the age groups. The ileal location (hazard ratio [HR]: 1.59; 95% confidence interval [CI]: 1.11–2.27), complicated behavior (HR: 3.35; 95% CI: 2.63–4.27), and early thiopurine use (HR: 0.27; 95% CI: 0.17–0.43) were associated with the first intestinal resection, whereas the age at diagnosis was not a risk factor.

Conclusions: Elderly onset CD may be related to favorable outcomes in Korea. Thus, the heterogeneity of this disease should be considered when developing a tailored strategy for the treatment of CD.

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract, and the cause of CD has not been fully elucidated.[1–4] The incidence of CD is increasing worldwide, and a recent study reported rapidly increasing incidence rates in Asia, including Korea, over the past two decades,[5] although still being lower than that in Western countries.[6] Some differences in genetic susceptibility and clinical characteristics between Western and Asian populations have been reported.[5,7]

The clinical presentation, disease course and treatment for elderly onset CD have not been well established. Even in Western countries, most data regarding elderly patients with CD have typically originated from referral centers and/or small size series,[8–10] and few epidemiological studies have provided clinical information across the age spectrum in developing countries. With the worldwide aging of the population, especially in East Asian countries,[10,11] the number of elderly onset CD cases is expected to increase accordingly.[8,9] Thus, a better understanding of the clinical features across the age spectrum is strongly needed to manage patients with CD.

The aim of the present study was to evaluate the clinical characteristics of patients with CD at diagnosis and during follow up according to the age at diagnosis in a nationwide multicenter cohort study of Korean patients with CD. Therapeutic management and

clinical outcomes with a focus on the risk of surgery were also evaluated.

Methods

Study population. A total of 1382 patients diagnosed with CD between 1982 and 2008 in 30 university hospitals and 2 local hospitals, which cover the majority of referral hospitals in Korea, were included in the CrOhn's disease cliNical NEtwork and CohorT (CONNECT) study.[12] This retrospective multicenter cohort study was conducted nationwide in Korea and performed by the Korean Association for the Study of Intestinal Diseases. This cohort study was supported by the Ministry for Health, Welfare and Family Affairs and Center for Disease Control in Korea. A diagnosis of CD was based on clinical, radiological, endoscopic, and histopathologic criteria,[6,13,14] and all patients were diagnosed and treated by gastroenterologists who are members of Korean Association for the Study of Intestinal Diseases. Patients with the following were excluded: (i) condition diagnosed or suspected as indeterminate colitis, intestinal Behcet's disease, intestinal tuberculosis, or infectious disease; (ii) follow-up period of less than 1 year (regardless of the date of diagnosis); and (iii) incomplete medical records. Because the CONNECT study originally recruited Koreans only, all participants were of Korean ethnicity.[12] The study protocol was approved by the Ethics Committee of Seoul National University Hospital.

Study design. Data were retrospectively collected from each hospital, and the study coordinators monitored the submission and quality of the data.[12] The age at diagnosis, location, and behavior of CD were classified according to the Montreal classification.[15,16] The age at diagnosis was categorized as ≤ 16 (G_1), 17–40 (G_2), 41–59 (G_3) and ≥ 60 years old (G_4). Regarding the disease location, L1 was defined as ileal disease and L2 and L3 were defined as colonic and ileocolonic disease, respectively. Because the information on upper endoscopy during the follow-up in the database was not considered sufficient, the evaluation of upper gastrointestinal disease (L4) was not included in the analysis. Regarding behavior, B1 was inflammatory (non-stricturing, non-penetrating), B2 was stricturing, and B3 was penetrating disease. Stricturing and penetrating together were defined as a complicated behavior (B2 + B3). The location and behavior were evaluated at diagnosis and at the maximal follow up.

The use of 5-aminosalicylic acid, thiopurine (azathioprine and 6-mercaptopurine), and anti-tumor necrosis factor (TNF) (infliximab and adalimumab) drugs were recorded. Other immunosuppressants and anti-TNF drugs, such as methotrexate and certolizumab, are rarely used for patients with CD in Korea. If the medication was initiated at any time during the follow-up period, the use of the medication was considered positive. The early use of thiopurine was defined as initiation within the first year of diagnosis and at least 6 months before the first intestinal resection.[17,18] Regarding CD-related surgery, the first intestinal resection was considered the primary outcome. Appendectomy, stricturoplasty, or surgeries for perianal disease were excluded.

Statistical analysis. Continuous variables were expressed as median and interquartile range values, and categorical variables were expressed as percentages (%). The Chi-squared or Fisher's exact test were used to compare the categorical variables, and the Mann–Whitney *U*-test or Kruskal–Wallis test was used to compare the continuous variables among the groups. The cumulative probabilities of the use of thiopurine/anti-TNF drugs or first intestinal resection were calculated using the Kaplan–Meier method. Log-rank tests were used to evaluate significant differences among the age-at-diagnosis groups. A Cox proportional hazards model was used to assess whether age at diagnosis was an independent predictor for surgical intervention. Variables with $P < 0.2$ in the univariate analysis were included in the multivariate analysis. The results were reported as hazard ratio (HR) with 95% confidence interval (CI). The analyses were performed using the IBM SPSS version 21.0 for Windows (IBM Co., Armonk, NY, USA). A value of $P < 0.05$ was considered significant.

Results

Baseline clinical characteristics. Among the total of 1382 patients, finally, 1224 Korean patients with CD were included in the analysis; 853 (69.7%) were male, the median age at diagnosis of CD was 23 years old (interquartile range, 19–31), the median time from symptom onset to CD diagnosis was 3 months (0–14), and the median duration of follow-up was 96 months (71–132).

The patients were categorized according to the age at diagnosis as described previously, and the number of patients in each age group was 155 (G_1; 12.7%), 919 (G_2; 75.1%), 120 (G_3; 9.8%), and 30 (G_4; 2.5%). The baseline clinical characteristics are summarized in Table 1. In the elderly onset group (G_4), a predominance of female subjects (66.7%) was observed (G_{1+2+3} *vs* G_4, $P < 0.001$). In the pediatric onset group, the median time from symptom onset to diagnosis was shorter and the familial history of inflammatory bowel disease was more frequent than those in the other groups. The presence of perianal fistula at diagnosis and during follow up in the pediatric and young adult onset groups was more frequent than that in the other groups (G_1 *vs* G_{3+4} and G_2 *vs* G_{3+4}, all $P < 0.001$). The duration of follow-up treatment in the elderly onset group was shorter than that in the other groups (G_{1+2+3} *vs* G_4, $P < 0.001$).

Disease location and behavior at diagnosis and follow up. Regarding the disease location at diagnosis, 282 (23.0%) patients had L1, and 248 (20.3%) patients and 694 (56.7%) patients had L2 and L3 disease, respectively. Regarding the location at maximal follow up, 273 (22.3%) patients had L1, 190 (15.5%) had L2, and 761 (62.2%) had L3. When the disease location at diagnosis was assessed according to the age at diagnosis, the frequency of L1 in the late adult onset and elderly onset groups (38.3% in G_3 and 36.7% in G_4) was higher than that in the other groups (14.2% in G_1 and 22.1% in G_2), whereas the frequency of L3 in the late adult onset and elderly onset groups (40.8% in G_3 and 33.3% in G_4) was lower than that in the other groups (61.9% in G_1 and 58.7% in G_2) (Fig. 1a; overall $P < 0.001$). During follow up, the frequency of L3 increased in each age group compared with the disease location at diagnosis (72.9%, 62.7%, 47.5%, and 50.0%; Fig. 1b), and the prevalence of the L1 location in the late adult onset and elderly onset groups (35.0% and 30.0%, respectively) remained higher than that in the pediatric onset and young adult onset groups (14.2% and 21.8%, respectively) (Fig. 1b; overall $P = 0.001$).

Table 1 Baseline clinical characteristics according to the age at diagnosis in patients with CD

Age at diagnosis	≤ 16 years old	17–40 years old	41–59 years old	≥ 60 years old	*P* value
n (%)	155 (12.7)	919 (75.1)	120 (9.8)	30 (2.5)	—
Age at diagnosis, median years (IQR)	15 (14–16)	23 (19–28)	48 (43–53)	66 (62–68)	—
Male, *n* (%)	97 (62.6)	665 (72.4)	81 (67.5)	10 (33.3)	< 0.001
Duration from symptom onset to diagnosis, median months (IQR)	2 (0–6)	3 (0–15)	3 (0–32)	3 (0–8)	< 0.05
Familial history of IBD, *n* (%)	8 (5.2%)	22 (2.4%)	2 (1.7%)	0 (0%)	< 0.05†
Previous anti-Tb treatment, *n* (%)	25 (16.1%)	218 (23.7%)	26 (21.5%)	8 (26.7%)	0.194
Smoking status at diagnosis, *n* (%)					
Current	3 (1.9)	111 (12.1)	17 (14.2)	1 (3.3)	< 0.001
Never/Ex-	152 (98.1)	808 (87.9)	103 (85.8)	29 (96.7)	
Perianal fistula, total, *n* (%)	74 (47.7%)	387 (42.1%)	20 (16.7%)	1 (3.3%)	< 0.001
at diagnosis	47 (30.3%)	272 (29.6%)	14 (11.7%)	1 (3.3%)	< 0.001
Number of CD-related admission, median (IQR)	2 (1–5)	2 (1–4)	1 (0–3)	2 (1–5)	0.186
Duration of follow-up, median month (IQR)	96 (77–130)	99 (71–135)	92 (71–127)	75 (49–94)	0.001

CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile range; Tb, tuberculosis.
†Linear-by-linear association

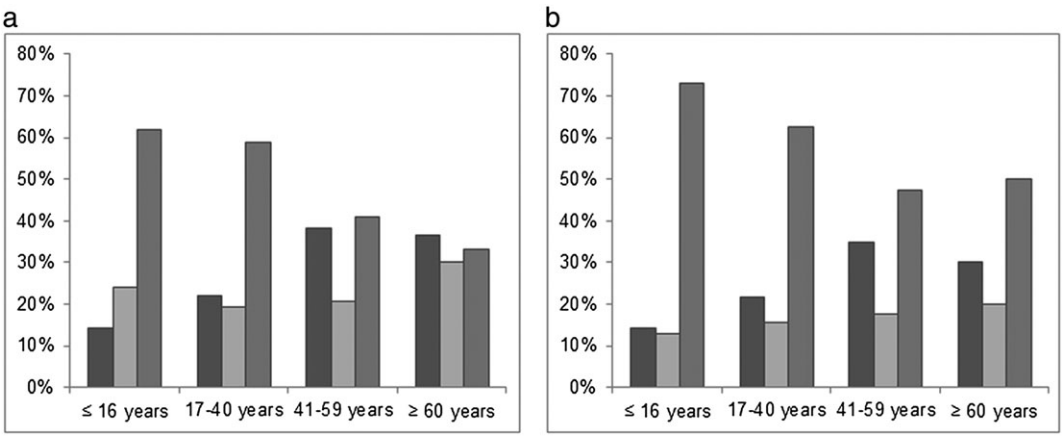

Figure 1 Disease location at diagnosis and the maximal follow up according to the age at diagnosis in patients with Crohn's disease. (a) Disease location at diagnosis (overall, $P < 0.001$). (b) Disease location at maximal follow up (overall, $P = 0.001$). ■, L1 (ileal); ■, L2 (colonic); ■, L3 (ileocolic).

Regarding the behavior at diagnosis, 723 (59.1%) patients presented B1, 208 (17.0%) patients presented B2, and 293 (23.9%) patients presented B3. The behavior at maximal follow up was B1 in 663 (54.2%) patients, B2 in 210 (17.2%) patients and B3 in 351 (28.7%) patients. When the disease behavior at diagnosis was assessed according to the age at diagnosis, the frequency of complicated behavior in the pediatric and elderly onset groups (32.9% in G_1 and 33.3% in G_4) was lower than that in the other groups (42.9% in G_2 and 38.3% in G_4) (Fig. 2a). During follow up, the frequency of complicated behavior in the pediatric and elderly onset groups remained lower than that in the other groups (Fig. 2b). However, a statistically significant difference was not observed among the age groups regarding the behavior at diagnosis and at follow up. In addition, the progression rate to complicated behavior according to the age at diagnosis was not significantly different.

Medications. 5-aminosalicylic acid, thiopurine, and anti-TNF drugs were administered to 1201 (98.1%), 907 (74.1%), and 406 (33.2%) patients, respectively, during the follow-up period. When the medications were assessed according to the age at diagnosis (Fig. 3a), the use of thiopurine and anti-TNF drugs was significantly lower in the late adult and elderly onset groups compared to the pediatric and young adult onset groups (both $P < 0.001$).

The cumulative probability of receiving thiopurine was 35.1% at 1 year, 54.4% at 5 years, 75.7% at 10 years, and 89.1% at 20 years (Fig. 3b). The cumulative probability of receiving anti-TNF drugs was 3.2% at 1 year, 19.6% at 5 years, 34.2% at 10 years, and 65.8% at 20 years (Fig. 3c). When assessed according to the age at diagnosis, the cumulative probability of receiving thiopurine in the late adult and elderly onset groups was significantly lower than that in the other groups (Fig. 3b; G_{1+2} *vs* G_{3+4}, $P < 0.001$). The cumulative probability of receiving anti-TNF drugs in the late adult and elderly onset groups was also lower than that in the other groups (Fig. 3c; G_{1+2} *vs* G_{3+4}, $P = 0.005$).

Intestinal resection. Among the 1224 patients, the operative status of 1190 patients (97.2%) was properly assessed in the

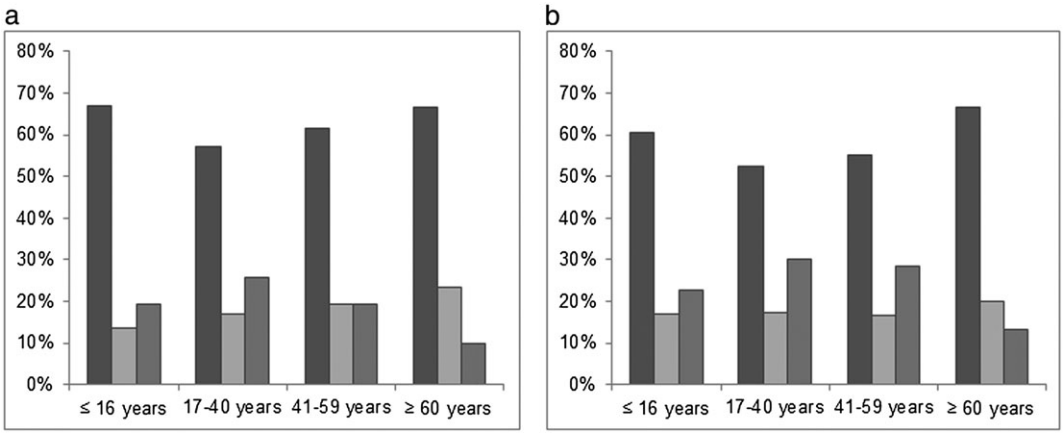

Figure 2 Disease behavior at diagnosis and at maximal follow up according to the age at diagnosis in patients with Crohn's disease (a) Disease behavior at diagnosis (overall, $P = 0.085$). (b) Disease behavior at maximal follow up (overall, $P = 0.241$). ■, B1 (non-stricturing, non-penetrating); ■, B2 (stricturing); ■, B3 (penetrating).

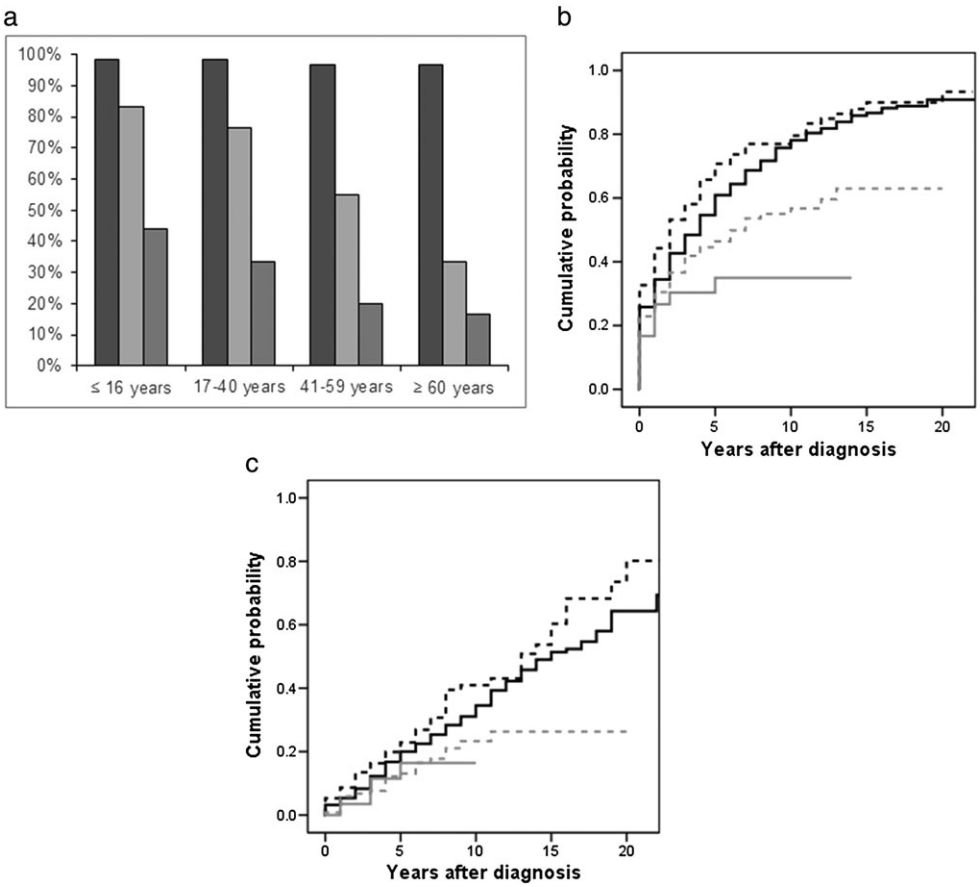

Figure 3 Medication according to the age at diagnosis in patients with Crohn's disease (a) Medication use during follow-up. ■, 5-aminosalicylic acid; ■, Azathioprine/6-mercaptopurine; ■, Anti-tumor necrosis factor. (b) Cumulative probability of receiving thiopurine (overall, $P < 0.001$). (c) Cumulative probability of receiving anti-tumor necrosis factor drugs (overall, $P = 0.007$). - - -, ≤ 16; ——, 17–40; - - -, 41–59; ——, ≥ 60.

database, and 320 patients (26.9%) were reported to have undergone intestinal resection related to CD. The cumulative probability of first intestinal resection was 14.6% at 1 year, 22.3% at 5 years, 31.0% at 10 years, and 42.9% at 20 years after the diagnosis of CD. Among all age groups, the cumulative probability of the first intestinal resection did not significantly differ (Fig. 4a). Although the cumulative probability of first intestinal resection was reanalyzed after excluding patients who underwent intestinal

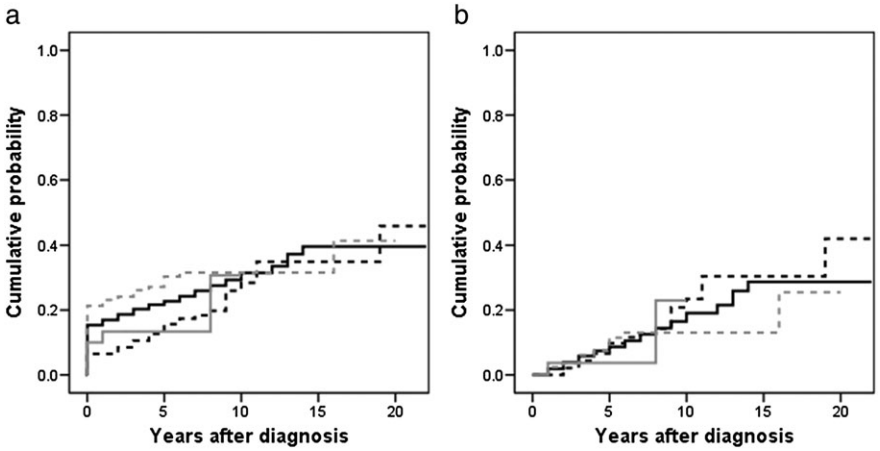

Figure 4 Cumulative probability of first intestinal resection according to the age at diagnosis in patients with Crohn's disease (CD). (a) Cumulative probability of first intestinal resection in all patients with CD (overall, $P = 0.195$). (b) Cumulative probability of first intestinal resection in the patients with CD after excluding the cases with intestinal resection within 1 year of diagnosis (overall, $P = 0.877$). ▬ ▬, ≤ 16; ▬, 17–40; ▬ ▬, 41–59; ▬, ≥ 60.

Table 2 Predictive factors associated with the first intestinal resection in Crohn's disease

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex						
Male	Reference			Not included		
Female	1.06	0.84–1.34	0.630	—	—	—
Age at diagnosis						
17–40	Reference			Reference		
≤ 16	0.76	0.53–1.09	0.137	0.90	0.63–1.30	0.578
41–59	1.20	0.84–1.72	0.322	1.22	0.85–1.75	0.292
≥ 60	0.69	0.28–1.67	0.408	0.74	0.31–1.81	0.512
Smoking status at diagnosis						
Never	Reference			Reference		
Ex	0.92	0.53–1.61	0.772	0.99	0.56–1.73	0.968
Current	1.35	0.98–1.86	0.070	1.36	0.98–1.88	0.067
Disease location at diagnosis						
L2	Reference			Reference		
L3	1.49	1.08–2.07	0.015	1.23	0.89–1.70	0.217
L1	2.04	1.43–2.91	< 0.001	1.59	1.11–2.27	0.012
Disease behavior at diagnosis						
B1	Reference			Reference		
B2	2.92	2.15–3.95	< 0.001	2.78	2.05–3.76	< 0.001
B3	4.31	3.33–5.56	< 0.001	3.76	2.90–4.88	< 0.001
Early use of thiopurines						
No	Reference			Reference		
Yes	0.22	0.14–0.34	< 0.001	0.27	0.17–0.43	< 0.001

CI, confidence interval, HR, hazard ratio.

resection within 1 year of diagnosis,[17–19] the results were not significant (Fig. 4b).

To further evaluate the independent predictors for intestinal resection in CD, we performed a multivariate Cox regression analysis(Table 2). In the multivariable analysis, ileal location (L1 *vs* L2; HR 1.59, 95% CI 1.11–2.27; $P = 0.012$) and complicated behavior (B2 + 3 *vs* B1; HR 3.35, 95% CI 2.63–4.27; $P < 0.001$) were associated with an increased risk for first intestinal resection, whereas early use of thiopurine (HR 0.27, 95% CI 0.17–0.43; $P < 0.001$) was associated with a decreased risk. However, the age at diagnosis was not an independent risk factor of intestinal resection.

Discussion

We investigated the influence of age at diagnosis on the baseline characteristics and disease course in a nationwide multicenter cohort of Korean patients with CD. The proportions of pediatric and elderly onset patients in the cohort were 12.7% and 2.5%, respectively. In the late adult and elderly onset groups, a higher frequency of ileal disease and a lower frequency of ileocolic disease were observed compared with the other groups, whereas the disease behavior did not significantly differ among the age groups. The cumulative probabilities of thiopurine and anti-TNF use in the late adult and elderly onset groups were significantly lower than

those in the other groups. However, the cumulative probability of first intestinal resection was not different among the age groups. To the best of our knowledge, our present study is the first to evaluate the influence of age at diagnosis on the baseline characteristics and long-term clinical course of CD in a large cohort of non-Caucasian patients.

A population-based cohort study is preferred for the investigation of epidemiological aspects; however, such studies are limited in the literature.[9] Two population-based cohort studies that were recently conducted in Western countries reported that the proportions of pediatric and elderly onset CD were approximately 10% to 15% and 4% to 5%, respectively.[10,20] Our study revealed that pediatric onset cases accounted for 12.7% of all CD cases and elderly onset cases accounted for 2.5%, which was similar to the results of these Western studies. The female predominance in the elderly onset group[10] and a higher frequency of perianal fistula in the pediatric onset group[20–22] are consistent with the results of previous studies.

In Western studies, elderly onset CD is well characterized by the predominance of pure colonic location, whereas the most frequent location in pediatric onset CD is ileocolonic location during follow up.[9,10,20] In our study, the most frequent location at diagnosis in pediatric onset cases was ileocolonic location, and this location remained the most frequent during follow up, which is consistent with the results of previous studies.[9,10,20,23] However, in the late adult and elderly onset cases, the frequency of the ileal location at diagnosis was higher than that of other locations, and it remained high during follow up. Several previous studies for Korean CD patients reported that the small bowel was the most common site in all age groups.[24,25] These results suggest the possibility that Western and Asian patients with CD exhibit different characteristics, especially elderly onset CD. Regarding the disease behavior at diagnosis and at follow up, the frequency of complicated behavior in the pediatric and elderly onset groups was lower than that in the other groups; however, the difference was not significant. In a French population-based study, an increased frequency of inflammatory behavior at diagnosis in pediatric and elderly onset CD was reported, which was consistent with the results of the present study.[10] The frequency of complicated behavior in the present study was higher compared to that in Western population-based studies.[10,23] This study was conducted in a retrospective manner.[12] Thus, this cohort was not representative of all possible patients with CD in Korea, and the possibility that mild cases may have been missed from the registration (selection bias) could exist. In addition, the hospitals included in this study were referral hospitals, and the population in the present study may be biased toward more severe diseases compared with that in population-based studies.

Different therapeutic strategies according to age at diagnosis have been reported.[10,20,26] In the French population-based cohort, the use of immunomodulators and anti-TNF drugs was prevalent in the patients with pediatric onset CD (61% and 24% at maximal follow up).[26] However, in the patients with elderly onset CD, the cumulative probability that immunosuppressants and anti-TNF drugs were prescribed was low (18% and 5%, respectively, at 5 years and 27% and 9%, respectively, at 10 years).[10] Similarly, in the elderly onset group in the present study, the cumulative probabilities of thiopurine and anti-TNF drug use were significantly reduced compared with the pediatric and early adult onset groups. The less frequent use of immunosuppressive and anti-TNF drugs in the elderly onset CD patients may be reflective of a favorable outcome of elderly onset CD, although it also could be explained by the under-use of immunosuppressive and anti-TNF drugs by physicians because of concerns about the side effects of these medications.

In a Hungarian population-based cohort, the risk of intestinal resection at the 5-year follow-up investigation did not differ among the pediatric, adult, and elderly onset CD patients (33.8%, 30.7%, and 28.6%, respectively).[20] However, in analyses of the risk for surgery in patients from the subgroup with non-complicated CD only, the age at diagnosis was associated with the time to bowel resection. A French population-based cohort revealed that the cumulative incidence of surgery during the 5-year follow-up period was not different between the CD patients diagnosed at age ≥ 60 years and < 60 years.[27] Similarly, in our cohort, the cumulative probability of the first intestinal resection was not significantly different among all age groups. Consistent with previous studies, an ileal location and complicated behavior at diagnosis increased the risk for intestinal resection, whereas the early use of azathioprine decreased the risk.[5,28,29] Differences in the cumulative likelihood of surgery in the elderly onset patients from our cohort were not observed despite the reduced use of thiopurine and anti-TNF drugs in these patients; possible explanations for this finding include a less aggressive disease course of elderly onset CD or the influence of the short-duration follow-up period in this cohort. Furthermore, the increased frequency of ileal involvement in elderly onset CD observed in the present study could indicate an association with stricturing disease and a greater need for surgery.

In conclusion, many differences were observed between pediatric, adult, and elderly onset CD, suggesting that the disease is heterogeneous according to the age at diagnosis. The clinical course may be mild in elderly onset CD as reflected by the reduced use of thiopurine and anti-TNF during the follow-up period. However, the cumulative probability of the first intestinal resection according to the age at diagnosis was not significantly different among the age groups. Thus, the heterogeneity of this disease should be considered when developing a tailored strategy for the treatment of CD.

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