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Brief Communication

Clinical Characteristics of Korean Patients with Elderly-Onset Crohn's Disease: Results from the Prospective CONNECT Study

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The clinical course and prognosis of patients with elderly-onset Crohn's disease (CD) remain unclear. This study aimed to analyze the clinical characteristics and outcomes of elderly-onset CD patients from the prospective CONNECT study cohort, a nationwide, multicenter cohort study of patients with CD in Korea. Among a total of 1,175 patients in the prospective CONNECT study cohort, 94 patients (Montreal age A3) were included and divided into two groups according to their age at diagnosis: the elderly-onset group (diagnosed with CD after 60 years of age, n=26, 67.54±6.7 years) and late adult-onset group (diagnosed as CD at age 41 to 59 years, n=68, 48.06±5.1 years). The elderly-onset group was characterized by a lower Crohn's disease activity index at diagnosis (124.89±101.9 vs 189.55±128.6, p=0.023) and higher rates of previous anti-tuberculosis treatment (34.6% vs 4.4%, p<0.001) than the late adult-onset group. Compared with the late adult-onset group, the elderly-onset group showed a significantly less use of thiopurines (p=0.003), as well as anti-tumor necrosis factor-alpha agents (p=0.047). Additionally, the elderly-onset group was less likely to require bowel resection than the late adult-onset group (p=0.067), suggesting that elderly-onset CD patients in Korea appear to have more favorable clinical outcomes than late adult-onset CD patients. **(Gut Liver 2022;16:995-1000)**

Key Words: Cohort studies; Crohn disease; Elderly-onset; Prognosis

INTRODUCTION

Crohn's disease (CD) is an idiopathic, chronic, and progressive inflammatory disease of the gastrointestinal tract that requires life-long treatment.[1] Recent epidemiologic studies have shown that the incidence and prevalence of CD are increasing worldwide, including in Asia.[2-6] Typically, CD develops in young adults, that is, in teenagers and adults aged 20 to 30 years; however, it is increasingly recognized that CD can be diagnosed in the older population. Elderly-onset CD or older-onset CD is defined as CD that is newly diagnosed in patients aged over 60 years.[7] The incidence of elderly-onset CD varies among countries, ranging from 2.5 patients per 100,000 persons in a French population-based registry[8] to 12.3 patients per 100,000 persons in Olmsted County, Minnesota.[9] Elderly-onset CD patients may have disease characteristics and natural history that are distinct from those of young adults with early-onset CD and may have a less aggressive disease course.[10-14] However, there are limited data comparing the disease behavior and clinical features of elderly-onset CD patients with those of late adult-onset CD patients who are diagnosed with CD at 41 to 59 years of age.

The Crohn's Disease Clinical Network and Cohort (CONNECT) study is a nationwide, multicenter cohort study of patients with CD in Korea, which was divided into retrospective and prospective CONNECT cohorts as of 2009.[15] We investigated the clinical features and prognosis of elderly-onset CD patients and compared with those of late adult-onset CD patients who were enrolled in the prospective CONNECT cohort.

MATERIALS AND METHODS

The prospective CONNECT cohort study reported the clinical features and long-term prognosis of CD of 1,175 patients from January 2009 to September 2019.[16] Among 1,175 CD patients, 94 patients (8.0%) were classified as Montreal classification A3, and we divided these patients into two groups: elderly-onset CD patients (diagnosed with CD after 60 years of age) and late adult-onset CD patients (diagnosed with CD at 41 to 59 years of age). We evaluated and compared the clinical features at diagnosis and clinical course, including medication and bowel resection during the follow-up period, between the two groups.

This study was approved by the institutional review boards of all the participating institutions including Asan Medical Center (IRB numbers: 2008-0609, 2012-0862), and written informed consent was obtained from each patient. The CONNECT study was registered at ClinicalTrials.gov (NCT01554007). Continuous variables were expressed as mean±standard deviation, and categorical variables were expressed as numbers with percentages. The differences in the characteristics between the two groups were analyzed using the chi-square test or Fisher exact test for categorical variables and the t-test for continuous variables. The Kaplan-Meier method was used to calculate the cumulative probabilities of medication use and bowel resection. Statistical significance was set at a two-sided p-value of <0.05, and statistical analysis was performed using the SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 94 patients were included in the study: 26 patients in the elderly-onset group (age range, 62 to 85 years; 67.54±6.7) and 68 patients in the late adult-onset group (age

Table 1. Baseline Characteristics of the Patients

Variable	Elderly-onset group	Late adult-onset group	p-value
No. of patients	26	68	
Age at diagnosis, mean±SD, yr	67.54±6.7	48.06±5.1	<0.001
Male sex, No. (%)	14 (53.8)	45 (66.2)	0.269
Follow-up duration, mean±SD, mo	64.29±30.6	60.79±32.2	0.627
Symptoms to diagnosis, mean±SD, mo	24.17±52.8	33.00±63.2	0.496
Body mass index, mean±SD, kg/m^2	22.83±2.3	21.58±3.1	0.079
CDAI at diagnosis, mean±SD	124.89±101.9	189.55±128.6	0.023
Previous anti-tuberculosis treatment, No. (%)	9 (34.6)	3 (4.4)	<0.001
Smoking status at diagnosis, No. (%)			0.170
Never smoker	17 (65.4)	33 (48.5)	
Current/ex-smoker	9 (34.6)	35 (51.5)	
Disease location at diagnosis, No. (%)			0.489
Ileum (L1)	18 (69.2)	38 (55.9)	
Colon (L2)	2 (7.7)	5 (7.4)	
Ileocolon (L3)	6 (23.1)	25 (36.8)	
Perianal disease modifier at diagnosis, No. (%)	3 (11.5)	16 (23.5)	0.195
Disease behavior at diagnosis, No. (%)			0.270
Nonstricturing, nonpenetrating (B1)	20 (76.9)	44 (64.7)	
Stricturing (B2)	4 (15.4)	9 (13.2)	
Penetrating (B3)	2 (7.7)	15 (22.1)	
Laboratory findings at diagnosis, mean±SD			
Hemoglobin, g/dL	11.75±2.2	12.42±2.1	0.199
Erythrocyte sedimentation rate , mm/hr	42.48±31.7	39.03±33.1	0.677
C-reactive protein, mg/dL	2.15±3.2	4.72±10.2	0.080
Albumin, g/dL	3.77±0.7	3.63±0.6	0.401
Ever use of medication, No. (%)			
Oral 5-ASA	26 (100)	67 (98.5)	0.534
Systemic corticosteroids	12 (46.2)	29 (42.6)	0.759
Thiopurines	11 (42.3)	45 (66.2)	0.035
Anti-TNF agents	2 (7.7)	17 (25.0)	0.085

CDAI, Crohn's disease activity index; 5-ASA, 5-aminosalicylic acid; TNF, tumor necrosis factor.

range, 41 to 58 years; 48.06±5.1) (Table 1). The two groups showed no differences in sex, time from symptoms to diagnosis, duration of follow-up, and smoking status at diagnosis. The two groups also showed no differences in disease location, disease behavior, and frequency of perianal disease modifiers at diagnosis. However, the elderly-onset group tended to have a higher body mass index (p=0.079) and lower level of C-reactive protein (p=0.080) at diagnosis than the late adult-onset group. In addition, the Crohn's disease activity index at diagnosis was significantly lower in elderly-onset group (124.89±101.9) than in the late adult-onset group (189.55±128.6) (p=0.023) indicating lower clinical disease activities at the time of diagnosis. Interestingly, about one-third of the patients in the elderly-onset group (nine patients, 34.6%) had been prescribed anti-tuberculosis (TB) medication before the diagnosis of CD, which was significantly higher than that in the late-adult-onset group (p<0.001).

After the diagnosis of CD, the patients were treated with oral 5-aminosalicylic acid, systemic corticosteroids, thiopurines, and anti-tumor necrosis factor (TNF) agents. Oral 5-aminosalicylic acid was prescribed for all patients with elderly-onset CD (100%) and was prescribed to most patients with late adult-onset CD (98.5%). In addition, the cumulative probability of systemic corticosteroid use in the elderly-onset group at 1, 3, and 5 years after diagnosis were 30.8%, 39.7%, and 46.4%, respectively, and this finding was similar in the late adult-onset group (36.8%, 41.5%, and 41.5%, respectively) (p=0.678) (Fig. 1A). However, the cumulative probabilities of using thiopurines and anti-TNF agents were significantly different between the two groups. The cumulative probabilities of thiopurine use at

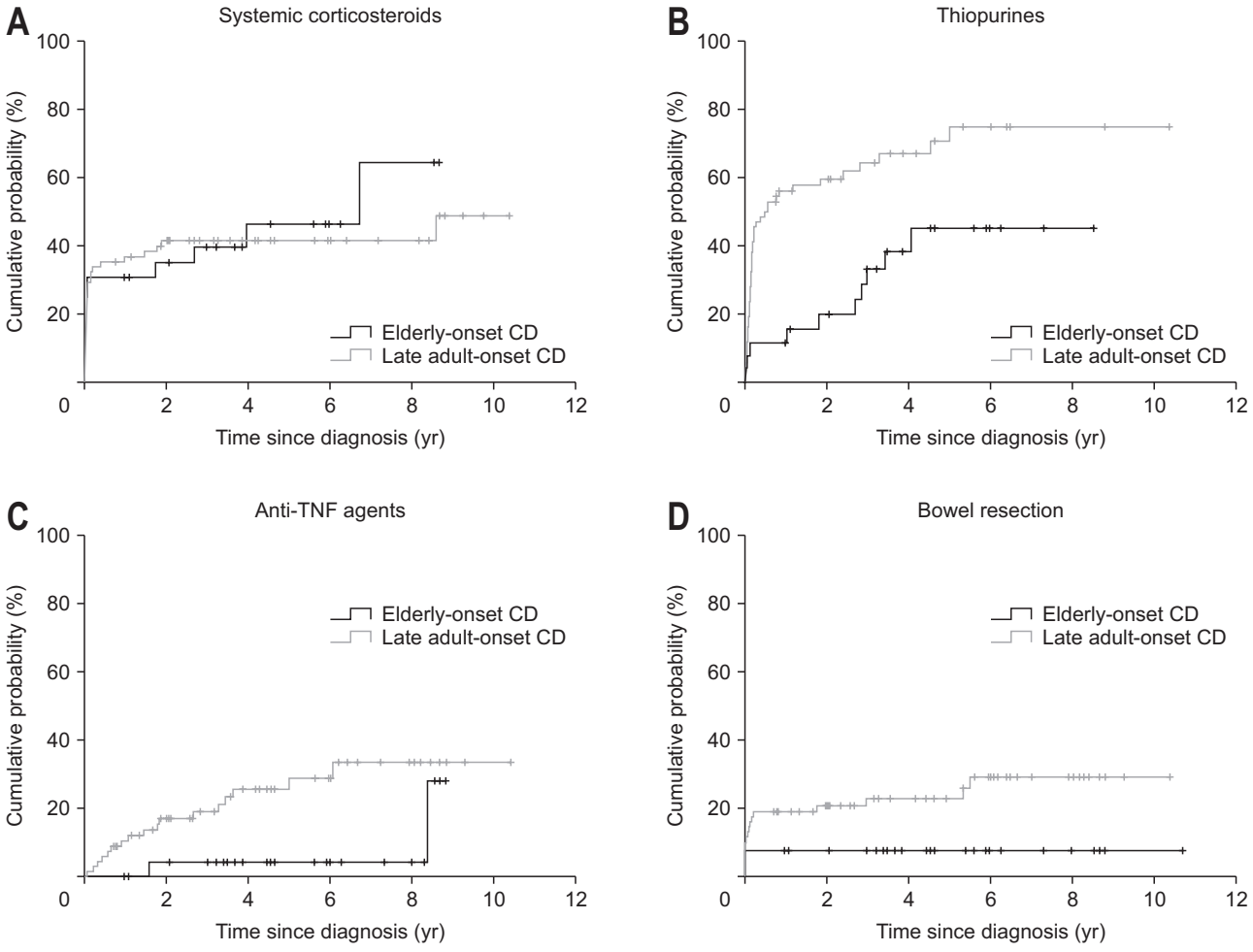

Fig. 1. Cumulative probabilities of medication use and bowel resection after diagnosis. (A) The cumulative probability of systemic corticosteroids use was similar between the two groups (p=0.678). (B) The cumulative probabilities of thiopurine use in the elderly-onset group were significantly lower than those in the late adult-onset group (p=0.003). (C) The cumulative probabilities of using anti-TNF agents in the elderly-onset group were significantly lower than those in the late adult-onset group (p=0.047). (D) The cumulative probability of bowel resection in the elderly-onset group tended to be lower than that in the late adult-onset group (p=0.067).
CD, Crohn's disease; TNF, tumor necrosis factor.

1, 3, and 5 years after diagnosis in the elderly-onset group were 15.6%, 38.3%, and 45.1%, respectively, and were significantly lower than those in the late adult-onset group (57.9%, 67.1%, and 75.0%, respectively) (p=0.003) (Fig. 1B). The cumulative probabilities of using anti-TNF agents in the elderly-onset group at 1, 3, and 5 years after diagnosis were 0.0%, 4.2%, and 4.2%, respectively, which were also significantly lower than those in the late adult-onset group (12.0%, 21.3%, and 28.9%, respectively) (p=0.047) (Fig. 1C). In addition to medication use, the cumulative probability of bowel resection in the elderly-onset group tended to be lower than that in the late adult-onset group (p=0.067) (Fig. 1D).

DISCUSSION

We found that the clinical features and long-term prognosis of elderly-onset CD patients were different from those of late adult-onset CD patients, although they were all classified as Montreal age A3. Elderly-onset CD patients had milder disease activity at diagnosis, reflected by a lower Crohn's disease activity index than late adult-onset CD patients. A higher body mass index in elderly patients with CD also reflects mild disease activity.

Regarding disease location at diagnosis, isolated terminal ileum involvement (L1) was seen in 69.2% of the patients in the elderly-onset group and 55.9% in the late adult-onset group. This is different from the findings reported from Western countries that elderly-onset CD is well-characterized by the predominance of pure colonic location (L2, 65%) at diagnosis.[12] However, this finding is similar to that of a single-center cohort study which reported a terminal ileal location at diagnosis in 63.0% of elderly-onset CD patients.[17] Additionally, it is similar to the retrospective CONNECT study results which revealed a higher frequency of L1 in late adult-onset group (38.3%) and elderly-onset group (36.7%).[18] Phenotype differences such as disease location in elderly-onset CD patients of Western and Asian countries may explain the consequent differences in the natural history of CD in these patients.[19]

The most interesting finding is that one-third of elderly-onset CD patients received anti-TB medication to rule out the diagnosis of intestinal TB (ITB) before the diagnosis of CD was made. This finding is very important because TB is still prevalent in Korea, and distinguishing ITB from CD is occasionally challenging, especially in elderly patients.[20-23] We believe that clinicians may consider the possibility of ITB rather than CD when they encounter elderly patients with ileocolonic ulcerative lesions. This may be a reasonable approach because the peak ages of onset of CD and ITB are different, and ITB usually occurs in the elderly population in Korea.[21] In addition, a probable diagnosis of ITB can be made after achieving a therapeutic response to anti-TB medication in some cases of ITB.[21,22] However, considering the toxicity of anti-TB medication and the possible delay in diagnosing CD, clinicians should be aware that CD is no longer a disease of the young, although elderly-onset CD patients (26 patients, 2.2%) constitute a very small group in the prospective CONNECT study in Korea.

In this study, elderly-onset CD patients showed better prognosis in terms of lower use of thiopurines and anti-TNF agents and lower rates of bowel resection than late adult-onset CD. The previous retrospective CONNECT study also showed that the cumulative probabilities of thiopurine and anti-TNF agent use in the late adult-onset and elderly-onset groups were significantly lower compared with those of the pediatric and early adult-onset groups (p<0.01).[18] These results are concordant with the views that different therapeutic strategies are needed for the management of CD patients according to their age at diagnosis because CD is a heterogeneous disease. Regarding use of corticosteroids, the elderly-onset CD and late adult-onset CD groups showed similar cumulative use (p=0.678), and this finding seems comparable to those of several Western reports,[11,12,24] that elderly inflammatory bowel disease patients are similarly or even more likely receive corticosteroids than younger patients. In addition, another Korean single center study[17] also showed similar results that the cumulative probabilities of corticosteroid therapy in elderly-onset CD patients at 1, 5, and 10 years were 28.0%, 42.0%, and 42.0%, respectively. They also reported the cumulative probabilities of corticosteroid therapy showed no differences among age groups. Take into account of unfavorable side effects in elderly patients caused by use of corticosteroids, use of corticosteroids should be initiated for short-term with caution and appropriate long-term maintenance therapy should be considered.

The cumulative probability of thiopurine use showed the most remarkable difference between the groups. In the prospective CONNECT study, the overall use of thiopurines was reported as 85.8%,[11] suggesting widespread administration of thiopurines to manage disease activity. However, in this study, only 11 patients (42.3%) in the elderly-onset CD group were prescribed thiopurines compared with 45 patients (66.2%) in the late adult-onset group. We believe that this result can be explained by several factors. Firstly, since the disease activity is milder in the elderly-onset group, clinicians may not consider the introduction of thiopurine for disease management. Secondly, frailty and polypharmacy are common in the

elderly. In fact, thiopurine use in the elderly patients may increase the risk of unexpected drug-drug interactions and side-effects, such as lymphoma. Therefore, clinicians may refrain from prescribing thiopurines in elderly-onset CD patients to avoid the risk of side effects and inappropriate polypharmacy.

In conclusion, elderly-onset CD patients in Korea appear to have favorable clinical outcomes compared to late adult-onset CD patients in terms of low cumulative use of thiopurines and anti-TNF agents and a lower propensity for bowel resection based on the prospective CONNECT study.

CONFLICTS OF INTEREST

Y.S.K., J.H.C., and J.P.I. 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 CONTRIBUTION

Study concept and design: Y.S.K., B.D.Y. Data acquisition: Y.S.K., M.J.N. Data analysis and interpretation: Y.S.K., M.J.N., B.D.Y., J.H.C., J.P.I., J.S.K. Drafting of the manuscript: Y.S.K., B.D.Y. Critical revision of the manuscript for important intellectual content: Y.S.K., B.D.Y., J.H.C., J.P.I., J.S.K. Statistical analysis: Y.S.K., M.J.N. Obtained funding: B.D.Y. Administrative, technical, or material support; Y.S.K, J.P.I., Study supervision: B.D.Y., J.H.C., J.S.K. Approval of final manuscript: all authors.

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