ORIGINAL ARTICLE

INTESTINAL RESEARCH

Old Age at Diagnosis Is Associated With Favorable Outcomes in Korean Patients With Inflammatory Bowel Disease

Jae Hyuk Choi[1], Eun Soo Kim[1], Kwang Bum Cho[1], Kyung Sik Park[1], Yoo Jin Lee[1], Sang Min Lee[1], Yu Jin Kang[1], Byung Ik Jang[2], Kyeong Ok Kim[2]; Daegu-Gyeongbuk Gastrointestinal Study Group (DGSG)

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keimyung University School of Medicine[1], Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeungnam University College of Medicine[2], Daegu, Korea

Background/Aims: Despite the rising incidence and prevalence of inflammatory bowel disease (IBD) in Asian populations, data regarding clinical characteristics of patients in Asia based on age at diagnosis are relatively sparse. The aim of this study was to compare clinical characteristics based on the age at diagnosis according to the Montreal Classification in Korean IBD patients. **Methods:** We recruited consecutive patients with IBD at two tertiary hospitals and retrospectively reviewed their medical information. Patients were divided into three groups according to their age at diagnosis: youth (<17 years), young adult (17–40 years), and middle-old (>40 years). The main clinical characteristics for comparison were the achievement of a remission state at the last follow-up visit, cumulative rate of surgery, and cumulative use of immunomodulators and tumor necrosis factor-α (TNFα) blockers during the follow-up period. **Results:** In total, 346 IBD patients were included (Crohn's disease [CD] 146 and ulcerative colitis 200; 36 youth, 202 young adult, and 113 middle-old). The middle-old group with CD was characterized by a predominance of uncomplicated behavior (*P*=0.013) and a lower frequency of perianal disease (*P*=0.009). The middle-old group was associated more with a less aggressive disease course than the younger group, as shown by more frequent remission (*P*=0.004), being less likely to undergo surgery (*P*<0.001), and lower cumulative use of immunomodulators and TNFα blockers (*P*<0.001). **Conclusions:** Age at diagnosis according to the Montreal Classification is an important prognostic factor for Korean IBD patients. **(Intest Res 2015;13:60-67)**

Key Words: Inflammatory bowel diseases; Age of onset; Prognosis; Crohn disease; Colitis, ulcerative

INTRODUCTION

Patients are most often diagnosed with IBD in the second or third decades of life; however, epidemiological studies of IBD have revealed a bimodal distribution of disease onset, with an initial peak in the third decade, "early-onset IBD," and a smaller, second peak between the ages of 40 and 70, "late-onset IBD."[1-4] IBD flares do not exhibit any monthly or seasonal associations.[5] Approximately 10% of patients at the first flare of IBD are 60 years or older, with similar distributions between UC and CD; 50% of them are diagnosed between 60 and 70 years of age.[6,7] As the number of elderly people in the total population continues to increase, the proportion of late-onset IBD also appears to be increasing globally.[7-9]

Previous studies have suggested that late-onset IBD differs from early-onset IBD. Several studies have identified lower requirements for steroids, immunomodulators, and surgery, and fewer admissions for flares in late-onset IBD, suggesting a milder disease course.[10,11] Several other studies have em-

phasized that middle-old age IBD patients have an increased rate of postoperative complications, along with an increased length of admission and increased operation durations.[1,12] It is important to understand the differences between early and late-onset IBD as a first step in improving the quality of care delivered to late-onset IBD patients.

To address aspects of clinical definitions and classification within IBDs and the current status of genetic and serological studies, the World Congress of Gastroenterology introduced the Montreal Classification system. Using the Montreal Classification system, IBD is classified based on age at diagnosis, disease extent, and severity.[13] Previous studies that compared clinical characteristics between early and late-onset IBD yielded conflicting results.[9,11,14-16] One of the reasons for these mixed results may be that the prior studies did not consistently classify IBD according to a unified classification system.[10-12] Thus, in our study, the Montreal Classification system was used to classify the clinical spectrum of IBD. There is little information available on the clinical characteristics of IBD based on the age at diagnosis in Asian populations according to the Montreal Classification system. Therefore, the aim of this study was to compare the clinical characteristics of IBD based on age at diagnosis in Korean patients according to the Montreal Classification system.

METHODS

1. Subjects

To assess whether the age at which patients had been diagnosed was associated with the clinical characteristics of IBD, the age at diagnosis was divided using the Montreal Classification system into youth (<17 years), young adult (17–40 years), and middle-old (>40 years) groups.[13] The main clinical characteristics compared were the achievement of a remission state at the last follow-up visit, cumulative rate of surgery, and cumulative use of immunomodulators and tumor necrosis factor-α (TNFα) blockers during the follow-up period.

2. Design and Setting

This was a retrospective study conducted at Keimyung University Dongsan Hospital and Yeungnam University Hospital in Daegu Gyeongbuk province, in South-East Korea. The diagnosis of IBD was confirmed by standard clinical, radiological, endoscopic, and pathological features.[13,17,18] Complete medical records for at least one year after diagno-

sis were required for inclusion in this study. All records were reviewed for accuracy and completeness, and validated by the responsible investigator (ESK). Patients with indeterminate colitis, segmental colitis associated with diverticulosis, ischemic colitis, and primary neoplasms were excluded. The study protocol was approved by the Institutional Review Boards of both hospitals.

3. Variable Definitions

According to the Montreal Classification system, the maximum extent and severity of clinical characteristics of IBD at any time point from the time of diagnosis to the most recent clinical evaluation was used for the clinical characteristics of IBD.[13]

CD location was classified as L1 (ileal), L2 (colonic), L3 (ileocolonic), or L4 (isolated upper disease). Behavior was classified as B1 (non-stricturing, non-penetrating), B2 (stricturing), B3 (penetrating), or perianal disease. B2 (stricturing) and B3 (penetrating) were combined and defined as "complicated behavior." Perianal disease included abscesses and/or fistulas. Extent of UC was classified as E1 (ulcerative proctitis), E2 (left-sided UC), or E3 (extensive UC).

Clinical remission was defined as an absence of corticosteroid treatment and complete relief of symptoms for one year, based on the physician's global assessment and patient report. Regarding surgery, our study included procedures involving incision, excision, and anastomosis in small bowel surgery, other large bowel surgery, rectal and perirectal surgery, and other abdominal surgery.[19] Use of immunomodulators (azathioprine) or TNFα blockers (infliximab) was included if prescribed at least once during follow-up. TNFα blockers were supplied via 5 mg/kg infusions at weeks 0, two, and six, followed by every eight weeks. Follow-up duration was measured in months from the time of diagnosis to the time of the last patient visit.

4. Data Analysis

Statistical analyses were performed using SPSS (version 17.0; IBM Inc., Chicago, IL, USA). We compared the unadjusted association between the categorical outcome variables using the chi-squared test and Fisher's exact test. Differences between the mean scores on continuous variables were assessed using one-way ANOVA. Surgery and cumulative use of immunomodulators or TNFα blockers during follow-up, based on the age at diagnosis, were estimated by Kaplan-Meier survival analysis. The log-rank test was used

to measure significant differences according to the Montreal Classification system. *P*-values <0.05 were considered to be statistically significant.

RESULTS

1. Patient Demographics

In total, 146 patients with CD and 200 patients with UC were enrolled. The median age at diagnosis was 32 years (range, 12–81 years). The age distribution of UC at diagnosis showed a bimodal distribution with two peaks corresponding to the characterizations of early and late-onset UC. The two peak ages were in the third and sixth decades of life. In the subgroup analysis of CD, however, we did not find a second peak. The distribution of age at diagnosis is shown in Fig. 1.

The youth, young adult, and middle-old groups contained 31 (9.0%), 202 (58.4%), and 113 (32.7%) patients, respec-
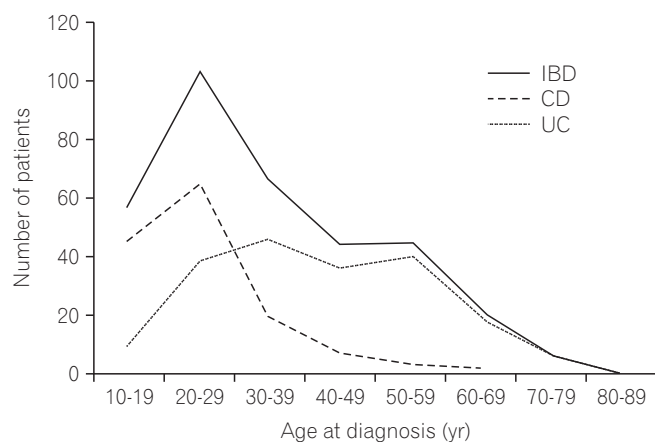
Fig. 1. The age distribution of IBD at diagnosis. Showing a bimodal distribution with the two peaks corresponding to the characterizations of early-onset and late-onset UC. The two peak ages were in the third and sixth decade of life. In CD, however, we did not find a second peak.

tively. The median follow-up duration in patients with IBD was 52 months (range, 27–86 months). There was no significant difference in the follow-up duration in the youth, young adult, and middle-old groups (median, 64, 50, and 51 months; *P*=0.604).

The most common manifestations at diagnosis in patients with IBD were hematochezia (39.9%), followed by abdominal pain (32.7%), and diarrhea (23.4%). The younger group had more abdominal pain as a presenting manifestation compared to the other groups (youth, 41.9%; young adult, 33.2%; middle-old, 29.2%), while the older group had more hematochezia (youth, 29.0%; young adult, 33.7%; middle-old, 54.0%; *P*<0.001; Table 1). However, no such difference was observed when subjects were divided into CD and UC groups (data not shown).

2. Locations and Behaviors of CD According to Age at Diagnosis

The median age of the patients with CD at diagnosis was 23 years (range, 12–66 years). The young adult group (72.6%) had the largest proportion of CD patients, followed by the youth group (18.5%) and the middle-old group (8.9%). Overall, CD patients were predominantly male (68.5%). When compared by age at diagnosis, the younger groups (youth and young adult) had more male patients compared with the middle-old group (70.4, 72.6, and 30.8%, respectively; *P*=0.013). In all groups, L1 (ileal) was the most frequent location of CD, and there was no significant difference in locations of CD among the age groups (*P*=0.933).

Behaviors of CD were as follows: 72 (49.3%) in B1 (non-stricturing, non-penetrating), 33 (22.6%) in B2 (stricturing), and 41 (28.1%) in B3 (penetrating). When compared based on the age of diagnosis, there was a significant difference (*P*=0.030). B3 (penetrating) was the most common type in the youth group (51.9%), while B1 (non-stricturing, non-penetrating) was the most common type in the young adult

Table 1. The Most Common Manifestations at Diagnosis in Patients With IBD

Variables	Youth group (n=31)	Young adult group (n=202)	Middle–old group (n=113)	*P*–value*
Hematochezia	9 (29.0)	68 (33.7)	61 (54.0)	<0.001
Abdominal pain	13 (41.9)	67 (33.2)	33 (29.2)	
Diarrhea	6 (19.4)	58 (28.7)	17 (15.0)	
Anal pain	3 (9.7)	9 (4.5)	0	
Tenesmus	0	0	2 (1.8)	

Values are presented as n (%).
*Chi-squared, Fisher's exact test.

Table 2. Clinical Characteristics According to Age of Diagnosis in Patients With CD

Variables	Youth group (n=27)	Young adult group (n=106)	Middle-old group (n=13)	*P*-value*
Male gender	19 (70.4)	77 (72.6)	4 (30.8)	0.013
Location				NS
L1	14 (51.9)	53 (50.0)	5 (38.5)	
L2	7 (25.9)	26 (24.5)	4 (30.8)	
L3	6 (22.2)	27 (25.5)	4 (30.8)	
Behavior				0.030
B1	11 (40.7)	55 (51.9)	6 (46.2)	
B2	2 (7.4)	27 (25.5)	4 (30.8)	
B3	14 (51.9)	24 (22.6)	3 (23.1)	
Perianal disease	16 (59.3)	47 (44.3)	1 (7.7)	0.009
Follow-up duration, month (median)	55 (18–76)	54 (33–87)	47 (35–79)	NS[†]

Values are presented as n (%).
Location and behavior in CD based on the Montreal classification.
L1, ileal; L2, colonic; L3, ileocolonic; B1, non-stricturing, non-penetrating; B2, stricturing; B3, penetrating.
*Chi-squared, Fisher's exact test.
[†]ANOVA test.

Table 3. Clinical Characteristics According to Age of Diagnosis in Patients With UC

Variables	Youth group (n=4)	Young adult group (n=96)	Middle-old group (n=100)	*P*-value*
Male/Female	3/1	55/41	60/40	NS
Extent, n (%)				NS
E1	1 (25)	42 (43.8)	44 (44.0)	
E2	0	31 (32.3)	32 (32.0)	
E3	3 (75.0)	23 (24.0)	24 (24.0)	
Follow-up duration, mo (median)	84 (79–163)	50 (26–93)	51 (21–79)	NS[†]

Location in UC based on the Montreal classification.
E1, ulcerative proctitis; E2, left sided UC; E3, extensive UC.
*Chi-squared, Fisher's exact test.
[†]ANOVA test.

(51.9%) and middle-old groups (46.2%).

Additionally, perianal disease, which is known to be related to a poor prognosis in CD, was more frequently observed in the youth group than the young adult and middle-old groups (59.3, 44.3, and 7.7%; *P*=0.009). The phenotypic presentation of CD is shown in Table 2.

**3. Extent of UC According to Age at Diagnosis**

The median age of the patients with UC at diagnosis was 41 years (range, 15–81 years). The middle-old group (50.0%) had the highest proportion, followed by the young adult group (48.0%), and the youth group (2.0%). Males were predominant (59.0%) in UC patients and there were no

significant differences among the groups in terms of gender (*P*=0.804), unlike CD.

The extents of UC were as follows: 87 (43.5%) in E1 (ulcerative proctitis), 63 (31.5%) in E2 (left sided UC), and 50 (25.0%) in E3 (extensive UC). There were no significant differences in extent of UC according to age at diagnosis (*P*=0.349). The phenotypic presentation of UC is shown in Table 3.

4. Main Clinical Outcomes According to Age at Diagnosis

We compared disease courses of IBD, including achieving a remission state at last follow-up, cumulative rate of surgery,
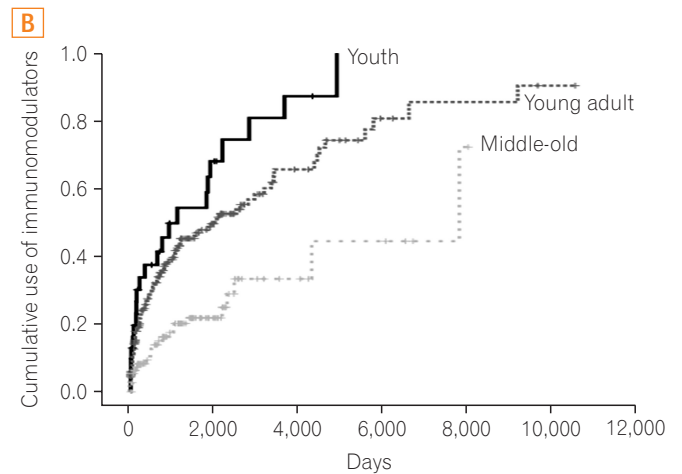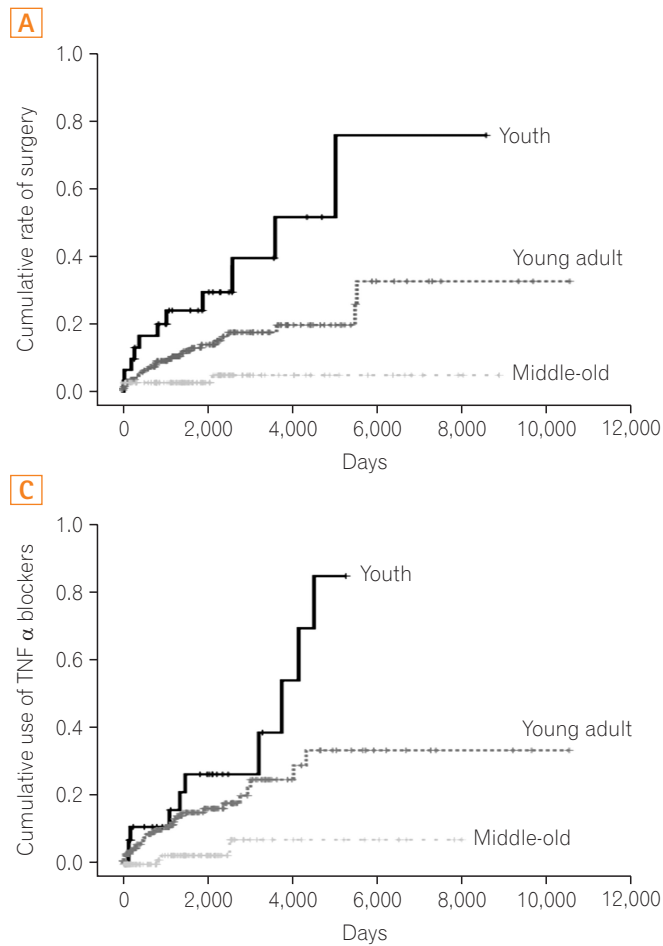
Fig. 2. Comparison of duration from diagnosis to disease outcomes between different age groups. (A) Younger group patients were more likely to require surgery earlier than those in the middle-old group (150.4±31.7, 288.8±18.6, and 303.5±7.1 months, mean±SD; *P*<0.001). (B) Younger group patients were more likely to require earlier use of immunomodulators than those in the middle-old group (58.0±12.3, 116.0±13.6, and 187.5±19.6 months, mean±SD; *P*<0.001). (C) Younger group patients were more likely to require earlier use of tumor necrosis factor-*α* blockers than those in the middle-old group (118.7±13.8, 275.9±18.9, and 270.4±9.9 months, mean±SD; *P*<0.001).

and cumulative use of immunomodulators and TNF*α* blockers during follow-up.

A remission state at last follow-up occurred in 67.7, 81.7, and 91.2% of the youth, young adult, and middle-old groups, respectively. Overall, the achievement of remission state was more common in the older group than the younger group (*P*=0.004).

Of the 346 patients with IBD, 44 (12.7%) underwent surgery. Surgery was more common in the younger group than in the older group (35.5, 14.4, and 3.5%, respectively; *P*<0.001).

Patterns of IBD medication use were analyzed, focusing specifically on immunomodulators and TNF*α* blockers during follow-up. The younger group was associated with a greater use of immunomodulators and TNF*α* blockers than the older group during follow-up (*P*<0.001).

When comparing the three groups by duration from diagnosis to surgery by means of a Kaplan-Meier analysis, patients in the younger group were more likely to require surgery earlier than those in the older group (150.4±31.7,

288.8±18.6, and 303.5±7.1 months, mean±SD; *P*<0.001; Fig. 2A). With respect to IBD medications, patients in the younger group were more likely to require earlier use of immunomodulators (58.0±12.3, 116.0±13.6, and 187.5±19.6 months, mean±SD; *P*<0.001; Fig. 2B) and TNF*α* blockers (118.7±13.8, 275.9±18.9, and 270.4±9.9 months, mean±SD; *P*<0.001; Fig. 2C) than those in the older group.

DISCUSSION

The results of this study demonstrated that age at diagnosis according to the Montreal Classification is an important prognostic factor in Korean IBD patients. Middle-old age at diagnosis (>40 years) was related to favorable outcomes, reflected by a higher chance of remission, lower requirement for surgery, and less use of immunomodulators and TNF*α* blockers during the follow-up period.

It has been reported that the site of disease involvement differs between early and late-onset CD patients, supporting the notion that anatomical involvement at the time of diag-

nosis is predictive of the clinical course.[16,20] For example, a younger age of onset is associated with small bowel disease, resulting in a higher association with stricturing disease and a greater need for surgery. In contrast, increasing age at diagnosis is more likely to be associated with isolated colonic disease, which shows a non-complicated disease course.

However, we did not find a difference in the site of disease involvement in patients with CD, but did note that the small bowel was the most common site in all age groups (Table 2). Interestingly, small bowel involvement may be a unique feature of Korean IBD patients. Ye et al. reported that two-thirds of Korean CD patients had small bowel disease, whereas only 10% had isolated colonic disease.[21] This result is consistent with those from Japanese studies, suggesting that the location of CD in East Asian countries may differ from that in European countries, in which isolated colonic disease was found to be the most common type of CD.[22,23] Thus, this might explain the discrepancy in the results regarding the CD disease site between previous Western studies and ours.

Nonetheless, we found that the youth group had more complicating-type disease, such as penetrating, while the young adult and middle-old age groups were more likely to have non-complicating disease than the youth age group (Table 2). Furthermore, perianal disease, which is associated with prognosis in CD, was less common in the middle-old age group, also supporting the notion that a late-onset of disease is associated with better clinical behavior in CD. These results are consistent with those of Western studies demonstrating that late-onset CD was less likely to exhibit complicated behavior and perianal disease.[16,20]

The male predominance observed in Asian CD patients, including in Korea, Japan, and Hong Kong,[24-26] also differs from findings in Western studies that have reported a slight female predominance.[27,28] Males (68.5%) were also dominant among our CD patients. Intriguingly, this male dominance was greater in the younger age groups (youth and young adult) compared with the middle-old age group (70.3 and 72.6% vs. 30.8%, P=0.013). Although the cause of the gender difference among age groups remains unclear, this result suggests that different genetic and environmental influences affect younger- and older-onset individuals. Further study is required to confirm and explain this gender difference among age groups in Asian CD patients.

In our patients with UC, there were no differences in disease extent among age groups. This is comparable to the recent report by Ha et al., which also used the Montreal Classification system to categorize disease extent according to age at diagnosis.[14] A retrospective Greek study also reported no difference in UC disease extent according to age at diagnosis.[15] In contrast, several studies have demonstrated that a later age of diagnosis is associated with less extensive disease. We suggest that differing designs and study populations may explain these seemingly contradictory results.

A notable finding of our study was that middle-old age at diagnosis of IBD was significantly associated with a high rate of remission, a lower rate of surgery, and less use of immunomodulators and TNFα blockers during the follow-up period compared with early- onset disease. The benign clinical course of the middle-old age group was also confirmed by Kaplan-Meyer analysis, which showed a significantly lower cumulative rate of surgery and less cumulative use of immunomodulators and TNFα blockers in the middle-old age group. Previous studies[14,29,30] also reported more occurrences of steroid-free remission and decreased risks of surgery with increasing age of diagnosis, again suggesting favorable prognosis in the late-onset group of IBD patients.

There are several plausible explanations for the superior clinical outcome in late-onset IBD patients. First, it has been reported that older patients better adhere to their treatment regimens than younger age groups. Younger patients tend to have lower compliance with medication than older patients because they put more importance on personal and social goals and usually spend more time outside.[31,32] Non-adherence is a critical issue in IBD care because non-adherent patients are more likely to have chronically active disease or experience relapse.[33] Second, the relatively immunodeficient state due to age-related changes in the middle-old group may weaken the aberrant immune response that would characterize continuous disease flares and perhaps expedite better responses to medical therapy, leading to an improved disease course. There are diminished CD4- and CD8-mediated responses, incomplete T-cell differentiation, and overall decreased cell-mediated immunity in the aging immune system.[34,35] Furthermore, the production of new lymphocytes declines because of thymic atrophy in older age.

We found a bimodal distribution of the age at diagnosis of IBD, with peaks in the third and sixth decades consistent with previous reports.[7,8,36] As the number of aged persons is increasing worldwide, substantial attention should be paid to this population. Middle-old-age colitis is not an infrequent disease, and should be considered in the evaluation of elderly patients with clinical features suggestive of IBD.[6] Awareness of the possibility of late-onset IBD could contribute to accurate diagnosis and timely treatment.[37] Furthermore, better knowledge of the clinical characteristics of IBD based on the age at diagnosis in Asian populations may represent

the first step in preventing complications and improving the quality of care delivered to elderly Asian patients.

Our study had several strengths. First, this was a retrospective study of a relatively large number of Korean IBD patients with a lengthy follow-up duration. Additionally, despite the dynamic progression of IBD, follow-up durations did not differ according to age at diagnosis. Second, we used the Montreal Classification system to classify the clinical spectrum of IBD. Otherwise, our study was limited by the fact that the youth group comprised a smaller proportion of the total number of patients than the young adult and middle-old groups. In our study, the majority of the youth group was composed of patients with CD. In contrast, the majority of the middle-old group was composed of patients with UC. It is possible that the youth and middle-old group in our study represent the general characteristics of patients with CD and UC. Our patients were from a tertiary referral program and were therefore likely to have more severe clinical characteristics.

In conclusion, older age (>40) at diagnosis, according to the Montreal Classification, is an important prognostic factor associated with favorable clinical characteristics, including prescribing patterns and disease course, in Korean IBD patients.

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