



# Clinical features and course of ulcerative colitis diagnosed in asymptomatic subjects



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## KEYWORDS

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## Abstract

**Background and Aims:** Although some ulcerative colitis (UC) patients are diagnosed when they do not have any UC-related symptoms, clinical features and prognosis of UC diagnosed in asymptomatic patients remain unclear.

**Methods:** Data for UC patients who were asymptomatic at diagnosis were retrospectively reviewed from the IBD database of the Asan Medical Center. The clinical characteristics and prognosis of those patients were analyzed and compared with matched (1:4) symptomatic UC patients.

**Results:** Only nineteen asymptomatic UC patients (1.1%) were identified from 1665 UC patients. The proportion of males was 78.9% (n = 15), and their median age at diagnosis was 48 years (range, 34–71 years). At diagnosis, proctitis was noted in 11 patients (57.9%), left-sided colitis in 4 (21.1%), extensive colitis in 0 (0%), and atypical distribution in 4 (21.1%). The 5-year cumulative probability of symptom development was 68.5% (95% confidence interval [CI], 62.8%–74.2%). After UC diagnosis, oral 5-aminosalicylic acid (ASA) and topical 5-ASA were used in

**Abbreviations:** IBD, inflammatory bowel disease; UC, ulcerative colitis; FOBT, fecal occult blood test; PSC, primary sclerosing cholangitis; CI, confidence interval.

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14 (73.7%) and 16 (84.2%) patients, respectively. During follow-up (3.7-year median for asymptomatic patients versus 3.7-year median for symptomatic patients;  $P = 0.961$ ), the 5-year cumulative probability of corticosteroids (23.7% versus 57.1%;  $P = 0.022$ ) and azathioprine (0% versus 24.7%;  $P = 0.003$ ) use was higher in symptomatic patients than in asymptomatic patients. **Conclusions:** The frequency of asymptomatic UC patients was 1.1% in our UC patient cohort. A majority of these patients became symptomatic during follow-up. Asymptomatic UC patients at diagnosis appear to have a better prognosis than symptomatic UC patients.

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## 1. Introduction

Ulcerative colitis (UC) is a chronic, inflammatory bowel disease (IBD) that arises from an interaction between genetic and environmental factors.<sup>1</sup> The primary presenting symptom of UC is visible blood in the stools, which is reported by more than 90% of UC patients.<sup>1</sup> However, since the fecal occult blood test (FOBT) and colonoscopy have recently been used for colorectal cancer screening as part of general health screening programs, a small number of UC patients that lack UC-related symptoms are diagnosed during screening examinations.<sup>2–5</sup>

Two previous studies examined the prevalence of asymptomatic UC in the general population or in the apparently healthy subjects during a screening program for colorectal cancer using FOBT, finding rates of 33.5 per 10<sup>5</sup> in the United Kingdom<sup>3</sup> and 5.2 per 10<sup>5</sup> in Japan.<sup>4</sup> In the studies that investigated clinical features at diagnosis of UC, sixteen out of 800 patients (2%) were inactive in one Danish study,<sup>2</sup> whereas 4 out of 304 patients (1.3%) were asymptomatic at diagnosis in our previous report.<sup>5</sup> However, the clinical features and prognosis of patients with asymptomatic UC remain unclear. Hence, the aim of this study was to characterize these asymptomatic UC patients and to compare their prognosis with that of symptomatic UC patients.

## 2. Methods

### 2.1. Study subjects and data collection

Consecutive UC patients from the IBD registry of Asan Medical Center, a tertiary university hospital in Seoul, diagnosed between January 1997 and December 2011 were included in the present study. Only those patients who were followed for more than 1 year were included. During the study period, seventy-one thousand cases of screening colonoscopies were performed at our center. Of our IBD registry, UC patients who were diagnosed during screening examinations without any UC-related symptoms were identified.

UC was diagnosed in patients who showed a sigmoidoscopic or colonoscopic picture with diffusely granular, friable, or ulcerated mucosa,<sup>5,6</sup> and who also showed the characteristic histopathological signs of chronicity (crypt architecture distortion, basal plasmacytosis, Paneth cell metaplasia, and/or basally located lymphoid aggregates) and inflammatory cell infiltration, crypt abscess, and goblet cell depletion.<sup>4,7</sup> To compare the prognosis of asymptomatic UC patients with symptomatic UC patients, symptomatic controls (1 asymptomatic patient to 4 symptomatic patients) were randomly selected that were matched for gender, age at UC diagnosis ( $\pm 6$  years),

and year at UC diagnosis ( $\pm 3$  years). The Institutional Review Board of the Asan Medical Center approved the study protocol.

### 2.2. Data collection

The data obtained from the IBD registry of Asan Medical Center were analyzed retrospectively. The frequency of asymptomatic UC subjects among the entire UC patients was investigated. Baseline demographic and clinical data, including gender, age, disease extent, and Mayo score<sup>8</sup> at diagnosis, were evaluated. The disease extent was classified as proctitis, left-sided colitis, and extensive colitis according to the Montreal classification,<sup>9</sup> and atypical distribution. Atypical distribution was defined as rectal sparing or skip lesions (either patchy or segmental) that had the same characteristics as the main lesions with typical UC both endoscopically and histologically.<sup>10,11</sup> Appendiceal orifice inflammation was not considered when classifying the extent of disease. Because there were no symptoms at diagnosis in the asymptomatic patients, the Mayo score<sup>8</sup> at diagnosis represented endoscopic activity: mild (score 1), moderate (score 2), and severe (score 3).

To evaluate the natural history of asymptomatic UC patients, the proportion and cumulative probability of symptom development were investigated during follow-up. For treatment, medications including corticosteroids, azathioprine, and infliximab, and the probability of colectomy were investigated. To investigate changes in the lesions and the extent of the disease over time, follow-up colonoscopies were performed at 1- to 3-year intervals, with shorter intervals if clinically indicated. Proximal disease extension was defined as the extension, at any follow-up colonoscopy, of macroscopic inflammation beyond the initially involved segment; that is, from proctitis to left-sided or extensive colitis, or from left-sided colitis to extensive colitis. Colonoscopic biopsy specimens at the time of asymptomatic UC diagnosis were also blindly reviewed. Microscopic inflammatory activities were graded as previously described,<sup>12</sup> and were compared between patients who developed symptoms and who did not.

Baseline demographic and clinical variables, the proportion of medical and surgical treatment, and the cumulative probability of corticosteroids and azathioprine use were compared between the asymptomatic patients and the symptomatic patients.

### 2.3. Statistical methods

Continuous variables were calculated as medians with ranges. Cumulative rates of symptom development and corticosteroids use were calculated according to the Kaplan–Meier method.

To compare the asymptomatic patients with matched symptomatic patients, four asymptomatic patients were randomly matched for each symptomatic case using the greedy algorithm. In the matched data, logistic regression was performed with generalized estimating equations for categorical variables and the linear mixed model for continuous variables that accounted for the clustering of matched pairs. Cox regression with robust standard errors was used to compare the cumulative probability of corticosteroids use between asymptomatic patients and symptomatic patients. The tests were two-sided and considered significant at the  $P = 0.05$  level. All analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

### 3. Results

#### 3.1. Demographic and clinical characteristics at diagnosis

A total of 1665 patients who were diagnosed with UC between January 1997 and December 2011 and followed for more than 1 year were reviewed. Nineteen (1.1%) without symptoms were incidentally diagnosed with UC during a screening colonoscopy for cancer ( $n = 17$ , patient number 1–17 in Table 1) or colonoscopy for the evaluation of concomitant UC in patients who were already diagnosed with primary sclerosing cholangitis (PSC) ( $n = 2$ , patient number 18–19 in Table 1). The demographic and clinical characteristics at diagnosis are described in Table 1. The proportion of males was 78.9% ( $n = 15$ ), yielding a male to female ratio of 3.8:1. The median age at diagnosis was 48 years (range, 34–71 years). At diagnosis, proctitis was noted in 11 patients (57.9%), left-sided colitis in 4 (21.1%), and atypical distribution in 4 (21.1%); no patient had extensive colitis. Atypical distribution was shown as patchy or segmental involvement in the ascending, transverse, or descending colon with rectal sparing in three patients (15.8%), and two of these three patients were diagnosed with PSC before UC diagnosis. One patient (5.3%) showed rectal involvement with skip lesions in the ascending colon. The Mayo score at diagnosis was 1 in 13 patients (68.4%) and 2 in 6 (31.6%).

#### 3.2. Clinical course

The median duration of follow-up was 3.7 years (range, 1.1–13.8 years). During follow-up, twelve patients (63.2%) developed symptoms after a median time of 2 years (range, 0.3–7.5 years). At the time of symptom presentation, rectal bleeding was the most common symptom ( $n = 10$ , 83.3%), followed by diarrhea ( $n = 3$ , 25%). The 5-year and 10-year cumulative probabilities of symptom development were 68.5% (95% confidence interval [CI], 62.8%–74.2%) and 84.2% (95% CI, 78.5%–89.9%), respectively (Fig. 1).

Follow-up colonoscopic examinations were performed in 16 of the 19 patients (84.2%); Among the 10 patients with initial proctitis, two patients (20%) showed proximal extension as extensive colitis after 13 and 60 months, respectively, one patient (10%) showed left-sided colitis after 35 months, and 7 patients (70%) showed no change in extent until a median of 43 months (range, 6–165 months) after UC diagnosis. All of the 4 patients with initial left-sided colitis showed no change in

extent until a median of 37 months (range, 2–41 months) after UC diagnosis. Among the two patients with initial atypical distribution, one with initial skip lesions in the ascending colon showed extensive colitis after 36 months (patient number 16 in Table 1); the other patient who had an initial ascending colon segmental lesion with rectal sparing showed rectal inflammation after 26 months (patient number 17 in Table 1).

In 11 out of 19 patients, pathologic review of colonoscopic biopsy specimens taken at the diagnosis of asymptomatic UC was performed. Six out of 11 patients developed symptoms during follow-up. As a result, the following microscopic degrees of inflammatory activities were not related with symptom development; crypt abscesses,  $P = 0.052$ ; mucin depletion,  $P = 0.329$ ; surface epithelial integrity,  $P = 0.329$ ; chronic inflammatory cell infiltrate,  $P = 0.792$ ; and crypt architectural irregularities,  $P = 0.052$ . In addition, the patients who showed more severe acute inflammatory cell infiltrate showed more tendencies to be symptom-free during follow-up ( $P = 0.030$ ).

After UC diagnosis, oral 5-ASA was prescribed for 3 patients (15.8%), topical 5-ASA for 5 patients (26.3%), and both oral and topical 5-ASA for 11 patients (57.9%). There were no patients who were given corticosteroids, azathioprine or infliximab as an initial therapy. During follow-up, systemic corticosteroids were given to 5 patients (26.3%) at an outpatient clinic. No patient received azathioprine or infliximab, or underwent surgery. In addition, no patient was hospitalized due to flare-up.

Two patients (10.5%) were diagnosed with PSC before the diagnosis of UC. Neither underwent a liver transplantation during the 3.1 and 3.2 years of follow-up after PSC diagnosis.

No patient developed colorectal cancer or dysplasia. No patient died during the observation period.

#### 3.3. Comparison between asymptomatic UC and symptomatic UC patients

A comparison between the demographic and clinical variables of asymptomatic UC patients ( $n = 19$ ) and symptomatic UC patients ( $n = 76$ ) is shown in Table 2. Regarding the Mayo endoscopic subscore, mild disease (score 1) was more common in asymptomatic patients (68.4% versus 36.8%) and moderate or severe disease (score 2 or 3) was more common in symptomatic patients (63.2% versus 31.6%) ( $P = 0.024$ ). During follow-up, the 5-year cumulative probability of corticosteroids use was lower in asymptomatic patients (23.7%; 95% CI: 9.4%–52.4%) than symptomatic patients (57.1%; 95% CI: 44.8%–70.1%) ( $P = 0.022$ ) (Fig. 2A). In addition, the 5-year cumulative probability of azathioprine use was lower in asymptomatic patients (0%) than in symptomatic patients (24.7%; 95% CI: 15.9%–37.0%) ( $P = 0.003$ ) (Fig. 2B). Although the 5-year cumulative probability of infliximab use and surgical treatment were lower in asymptomatic patients than in symptomatic patients, the statistical significances were not observed ( $P = 0.101$  and  $P = 0.092$ , respectively).

### 4. Discussion

The major symptoms of UC are visible blood or pus in the stool and diarrhea.<sup>1</sup> In previous representative epidemiological studies, UC was diagnosed based on several criteria, which

**Table 1** Baseline patients' characteristics at the time of diagnosis of ulcerative colitis.

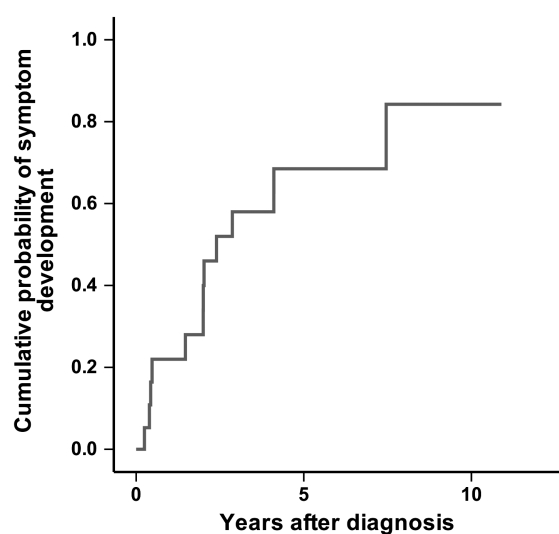
Pt	Gender/ Age	Initial extent	Mayo score	Smoking history	Family history	5-ASA therapy	Symptoms developed after diagnosis of UC	Diagnosis to symptom development, months	Final extent	Diagnosis to final endoscopy, months	Total follow-up duration, months
1	F/44	Proctitis	1	None	No	Topical	Mucoid stool	49	Proctitis	76	89
2	M/40	Proctitis	1	Past	No	Topical	Rectal bleeding	17	Proctitis	44	57
3	M/46	Proctitis	1	Past	No	Topical	Tenesmus	5	Extensive	13	96
4	M/37	Proctitis	1	Current	No	Both <sup>a</sup>	Rectal bleeding, diarrhea	89	Proctitis	165	166
5	M/48	Proctitis	1	Current	No	Both <sup>a</sup>	Rectal bleeding	24	Proctitis	41	41
6	F/48	Proctitis	2	None	No	Both <sup>a</sup>	Rectal bleeding	29	Proctitis	26	37
7	F/48	Proctitis	1	None	No	Both <sup>a</sup>	Rectal bleeding	5	Left-sided	35	41
8	M/55	Proctitis	2	Past	No	Both <sup>a</sup>	Rectal bleeding	3	Proctitis	6	30
9	M/46	Proctitis	1	Past	No	Both <sup>a</sup>	Rectal bleeding, diarrhea	24	Extensive	60	88
10	M/53	Proctitis	1	Past	No	Topical	No	N/A	Proctitis	63	69
11	M/42	Proctitis	1	Past	No	Both <sup>a</sup>	No	N/A	No follow-up	N/A	16
12	M/47	Left-sided	2	Past	No	Both <sup>a</sup>	Rectal bleeding	24	Left-sided	35	47
13	M/39	Left-sided	1	None	No	Both <sup>a</sup>	Rectal bleeding, diarrhea	6	Left-sided	40	49
14	M/52	Left-sided	2	Current	Yes <sup>b</sup>	Topical	No	N/A	Left-sided	2	13
15	M/57	Left-sided	1	Past	No	Both <sup>a</sup>	No	N/A	Left-sided	41	48
16	M/34	Atypical	1	Current	No	Oral	Rectal bleeding	34	Extensive	36	119
17	M/51	Atypical	2	Past	No	Both <sup>a</sup>	No	N/A	Atypical	26	128
18	M/71	Atypical	2	None	No	Oral	No	N/A	No follow-up	N/A	46
19	F/51	Atypical	1	None	No	Oral	No	N/A	No follow-up	N/A	37

5-ASA, 5-aminosalicylic acid; F, female; M, male; N/A, not applicable; Pt, patient number; UC, ulcerative colitis.

<sup>a</sup> Use of both oral and topical 5-ASA.

<sup>b</sup> A daughter of the patient was diagnosed as ulcerative colitis.

included a typical history of repeated episodes or more than 1 to 6 weeks of blood and/or pus in the stool.<sup>13,14</sup> However, given the recent widespread use of FOBT and colonoscopy for colorectal cancer screening as a part of general health screening programs, a small number of UC patients that do not



**Figure 1** The cumulative probability of symptom development in asymptomatic patients was 22.0% at 1 year, 68.5% at 5 years, and 84.2% at 10 years.

show UC-related symptoms are diagnosed during screening examinations.<sup>2–5</sup>

In our study, of the 1665 UC patients, nineteen patients (1.1%) without symptoms were incidentally diagnosed with UC during screening colonoscopy for cancer or for evaluating the presence of concomitant UC in patients diagnosed with PSC. These results are consistent with previous studies, which reported that 1.3%–2% of UC patients were asymptomatic at diagnosis.<sup>2,5</sup> In the case of these UC patients diagnosed with an inconsistent history and a compatible sigmoidoscopy or colonoscopy report, one previous study defined these cases as “probable UC”.<sup>13</sup> However, we diagnosed such probable UC cases as asymptomatic UC based on the hypothesis that these cases identified before the development of symptoms are macroscopically and histologically compatible with UC and that the patients would show typical symptoms compatible with UC during follow-up. To the best of our knowledge, this is the first study that not only evaluated the clinical characteristics at diagnosis and the natural history of asymptomatic UC, but also compared asymptomatic UC patients at diagnosis with symptomatic UC patients at diagnosis.

Among the 19 asymptomatic UC patients, the median age at diagnosis was 48 years, which was higher than the 40 years of age seen in our previous report.<sup>5</sup> Among 19 patients, seventeen patients were diagnosed with UC during screening colonoscopy and their median age was 47 years. Because screening colonoscopy is usually recommended for men and women over 50 years,<sup>15,16</sup> the age of asymptomatic

**Table 2** Comparison between the asymptomatic and symptomatic groups.

	Asymptomatic patients (n = 19)	Symptomatic patients (n = 76)	P-value *
Male	15 (78.9%)	60 (78.9%)	N/A
Median age at diagnosis, years (range)	48 (34–71)	47 (30–71)	N/A
Disease extent at diagnosis			0.231
Proctitis	11 (57.9%)	35 (46.1%)	
Left-sided colitis	4 (21.1%)	14 (18.4%)	
Extensive colitis	0 (0.0%)	26 (34.2%)	
Atypical distribution	4 (21.1%)	1 (1.3%)	
Mayo endoscopic subscore			0.024
1 (mild)	13 (68.4%)	28 (36.8%)	
≥ 2 (moderate or severe)	6 (31.6%)	48 (63.2%)	
Median follow-up duration, years (range)	3.7 (1.1–13.8)	3.7 (1.1–14.2)	0.961

N/A, not applicable.

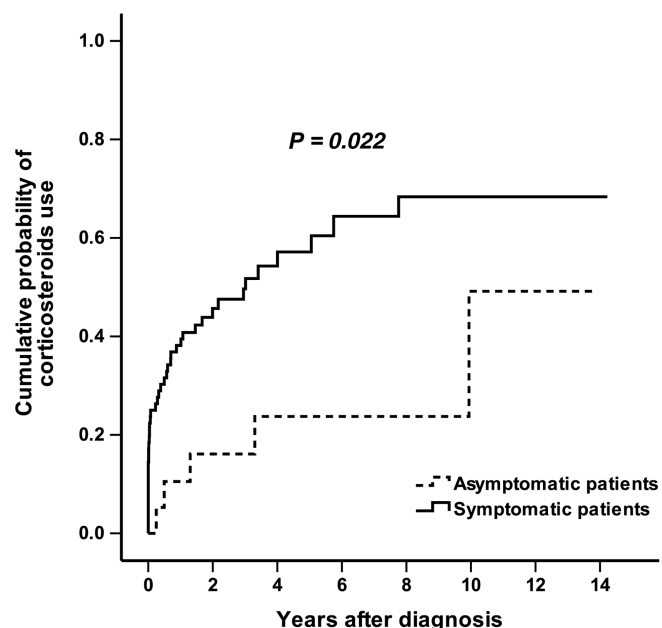
\* P-value was calculated by logistic regression with generalized estimating equations for categorical variables, and linear mixed model for continuous variables that accounted for the clustering of matched pairs.

UC patients at diagnosis would be higher than that of the symptomatic ones. Regarding gender distribution, there were 14 males (82.4%) among 17 patients. Although male predominance is in accordance with a previous report,<sup>4</sup> the reason of male predominance is not clear. In addition, age and gender distribution in our patient group might not be generalized because our study is not the population-based study.

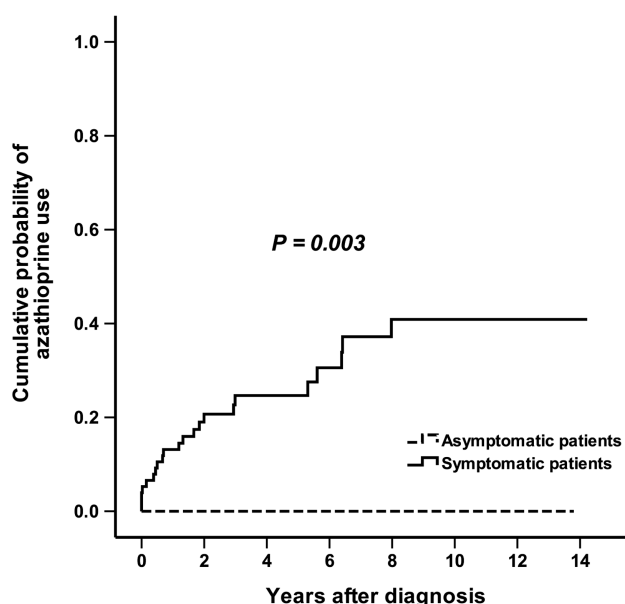
Among the 19 asymptomatic UC patients, an atypical distribution was present in four patients (21.1%). A previous study reported that 33% of asymptomatic/minimally symptomatic UC patients showed right-sided or segmental colitis,<sup>4</sup> and there are several reports that found right-sided only or skip lesions among UC patients overall.<sup>10,11,17</sup> In our previous report, two patients with segmental lesions in addition to

appendiceal orifice inflammation progressed to typical UC.<sup>18</sup> In this study, we also diagnosed the four patients with atypical distribution as UC rather than indeterminate colitis or Crohn's disease, as one of these patients progressed to show typical extensive colitis and another progressed to show rectal inflammation with diffusely granular, and friable mucosa and lymphoid aggregates in histologic examination. Another two patients who were diagnosed with PSC before UC diagnosis showed rectal sparing at initial colonoscopy and did not receive follow-up endoscopy. This phenomenon is consistent with a previous Korean study that reported that rectal sparing is more common in patients with both UC and PSC than in patients with UC only.<sup>19</sup> In addition, although we did not evaluate small bowel using small bowel follow-through or CT/MR enterography to exclude Crohn's disease in these four

### A. Corticosteroids



### B. Azathioprine



**Figure 2** The cumulative probabilities of corticosteroids use (A) and azathioprine use (B) in asymptomatic patients and symptomatic patients, respectively.

patients, no patient had terminal ileal lesions at colonoscopic examination and none of them developed complications like penetration or stricture during follow-up.

During follow-up, twelve patients (63.2%) developed symptoms; the 5-year and 10-year cumulative probabilities of symptom development were 68.5% and 84.2%, respectively. This is higher than a previous study, which reported that only 1 of 12 asymptomatic patients (8.3%) progressed to symptomatic UC.<sup>4</sup> However, that study did not report the duration of follow-up, and symptom developments would undoubtedly be more frequent with a longer follow-up. In our study, the severity of acute inflammatory cell infiltrate showed inverse association with the probability of symptom development during follow-up, which is opposite to the previous results.<sup>12</sup> However, different patients' characteristics compared with the previous study<sup>12</sup> and small number of patients ( $n = 11$ ) are making the interpretation of results difficult. Further studies are required to answer the question on the association of pathologic grading and symptom development.

An important finding of our study is that asymptomatic UC patients showed a better prognosis than symptomatic UC patients, because the 5-year cumulative probability of corticosteroids and azathioprine use was lower in asymptomatic cases. In addition, no patient received biologic therapy, underwent a colectomy, or was hospitalized. There could be a few explanations for this phenomenon. First, early diagnosis and treatment with 5-ASA might decrease the need for corticosteroids, azathioprine, or biologics. Second, milder endoscopic activity in the asymptomatic group compared with symptomatic patients might be related with better outcomes. The previous reports on the correlation between severe endoscopic lesions and poor prognosis in severe UC patients<sup>20–22</sup> appear to be compatible with our results, suggesting the relationship between index endoscopic activity and prognosis. Third, asymptomatic UC patients themselves may have better prognoses than symptomatic cases.

Our study has several limitations. First, because this study was performed at a tertiary referral center, we were unable to evaluate the population-based prevalence rate. However, to calculate the true prevalence rate of asymptomatic UC in the general population, endoscopic evaluation of the entire target population is needed; which seems to be extremely difficult to conduct. Second, as this study was performed retrospectively, follow-up intervals were not uniform and adherence to medication could not be exactly evaluated. Third, because follow-up colonoscopic examinations were not performed in three patients (15.8%), their endoscopic findings during follow-up could not be evaluated. Fourth, because the median follow-up duration was about 3 to 4 years in both groups, prognosis could change with a longer follow-up duration.

In conclusion, most of asymptomatic UC patients at diagnosis appear to progress to symptomatic cases during follow-up. These asymptomatic UC patients at diagnosis seem to show a better prognosis than symptomatic UC patients.

## Conflicts of interest

Suk-Kyun Yang has received a research grant from Janssen Korea Ltd. For the rest of the authors, there is no conflict of interest in this study.

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## Statement of authorship

SKP and BDY conceived the study; JWK and SHP collected and interpreted the data; SOK performed the statistical analysis; JK reviewed the pathologies; DHY, KWJ, KJK, JSB, SJM, and JHK cared patients and critically reviewed the manuscript; SKP drafted the manuscript; SKY and BDY critically reviewed and revised the manuscript; and BDY is the guarantor of the article and approved the final manuscript. All authors read and approved the final manuscript.

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