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ORIGINAL ARTICLE

Clinical Course of Intestinal Behcet's Disease During the First Five Years

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Abstract
Background Little is known about the clinical course of patients with intestinal Behcet's disease (BD). We aimed to evaluate the clinical course of intestinal BD during the first 5 years after diagnosis, and to identify factors that could predict the 5-year clinical course.
Methods We reviewed the medical records of 130 intestinal BD patients who were regularly followed-up for at least 5 years at a single tertiary academic medical center between March 1986 and September 2011.
Results Of the five different clinical course patterns that we observed, persistent remission or mild clinical activity was the most frequent course (56.2 %). The majority of patients (74.6 %) had remission or mild clinical activity at 5 years, and only the minority (16.2 %) had multiple relapses or chronic symptoms. The clinical course of the first year after diagnosis of intestinal BD influenced the clinical course of the following years. Patients in the severe clinical course group were younger, and had a higher ESR, CRP level, and disease activity index for intestinal Behcet's disease (DAIBD), and lower albumin level at diagnosis than patients in the mild clinical course group. Initial presentation with a high DAIBD was independently associated with a severe clinical course.
Conclusions The clinical course of intestinal BD during the first 5 years was variable. A substantial proportion of patients went into remission or had a mild clinical activity, while some patients had a severe, debilitating clinical course as time progressed. High disease activity at diagnosis was a negative prognostic predictor.

Keywords Intestinal Behcet's disease · Clinical course · Prognostic factors · High disease activity

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Introduction

Behcet's disease (BD) is a chronic multisystem inflammatory disorder characterized by recurrent oral and genital ulcers, ocular and skin lesions, sometimes accompanied by vascular, neurological, or gastrointestinal involvement [1]. Intestinal BD is diagnosed if there is a typically shaped ulcer in the gastrointestinal tract and clinical findings meet the diagnostic criteria for BD [2, 3].

The exact cause of intestinal BD is unknown, but immune abnormalities, genetic factors, and environmental factors may play a significant role in its etiology and pathogenesis [4]. Similar to inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), intestinal BD is a chronic inflammatory bowel disease characterized by a heterogeneous range of clinical courses and symptoms [5]. Clinical presentation at disease onset varies, and the subsequent course may be difficult to predict, as it can range from quiescent disease to chronic refractory disease that can result in complications such as intestinal perforations, fistulas, or massive intestinal bleeding, eventually requiring surgical treatment [6]. In this regard, it would be helpful to know more about the disease course and early prognostic factors influencing the

natural history of the disease to optimize therapy and to predict prognosis.

There are many similarities between CD and intestinal BD. Both are treated with similar drugs and occasionally require surgery or repeated surgery [2, 7, 8]. Several studies have investigated CD, and as a consequence, much more is now known about this disease. Moreover, numerous studies have described the disease course and clinical outcomes in CD patients. In contrast, intestinal BD is a rare disease in Western countries, and little information is available. Therefore, our group has focused on collecting data from a large number of intestinal BD patients by investigating diagnostic criteria [3], disease activity index [9], surgical treatment [7], thiopurine therapy [10], and the influence of age and sex on prognosis [11]. However, the clinical course and natural history of intestinal BD have not been investigated in previous studies. Our purpose in the present study was to systemically investigate the various clinical courses of patients with intestinal BD for the first 5 years after diagnosis. We also sought to identify prognostic factors for subsequent outcomes based on information obtained at diagnosis.

Materials and Methods

Study Subjects and Diagnostic Criteria

We reviewed the medical records of all patients who were regularly followed-up for at least 5 years among 292 consecutive intestinal BD patients at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, between March 1986 and September 2011. Intestinal BD was diagnosed according to established criteria based on colonoscopic features and clinical manifestations [3]. Patients classified as "definite," "probable," and "suspected" were included in the study. We excluded suspected patients with any evidence of another gastrointestinal disease such as CD, intestinal tuberculosis (TB), or ischemic colitis during the follow-up period.

Clinical Evaluation and Definition of Variables

We recorded demographic factors, family history of BD, gastrointestinal symptoms at the time of diagnosis, and extra-gastrointestinal symptoms (systemic BD symptoms) during the follow-up period, as well as diagnostic subtype. We also evaluated laboratory results including leukocyte count, hemoglobin level, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and albumin level at the time of diagnosis.

We measured intestinal BD activity using the disease activity index for intestinal Behcet's disease (DAIBD) [9]. The DAIBD provides a total score drawn from eight variables (general well-being, fever, extra-intestinal manifestations, abdominal pain, abdominal mass, abdominal tenderness, intestinal complications, and number of liquid stools), and ranges in value from 0 to 325, with a higher score reflecting greater disease activity. Patients with DAIBD scores <19, 20–39, 40–74, and ≥ 75 were considered to have remission, mild, moderate, and severe disease activities, respectively. Clinical relapse was defined as a DAIBD score ≥ 40.

Some patients were first diagnosed with intestinal BD during surgery performed due to an acute or complicated presentation. All other patients underwent a colonoscopy at the time of diagnosis to identify the location, shape (oval, geographic, or volcano type), and type (typical and atypical) of intestinal ulcer. Lesions with less than five ulcers that were oval in shape, deep, had discrete borders, and were located in the ileocecal area were defined as typical ulcerations [12]. Ulcerations that did not fulfill all of these criteria were defined as atypical ulcerations.

This study was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea.

Statistical Analysis

The software program SPSS (v. 12, Chicago, IL) was used for statistical analyses. Student's t test or the Mann–Whitney U-test was used to compare numerical variables between groups. The chi-square or Fisher's exact test was used to compare categorical variables. P values <0.05 were considered statistically significant. We constructed multivariate logistic regression models to identify independent factors associated with severe clinical course. Adjusted odds ratios and 95 % confidence intervals (CIs) were calculated.

Results

Study Subjects

Of 292 patients with intestinal BD, 162 were excluded for the following reasons: a follow-up duration of less than 5 years ($n = 116$), follow-up loss ($n = 40$), and death within 5 years after diagnosis ($n = 6$). Of the six patients who died during the 5-year follow-up, five died of causes related to intestinal BD. The causes of death were as follows: panperitonitis and resultant septic shock ($n = 2$), massive intestinal bleeding ($n = 1$), and pancytopenia caused by immunosuppressant use and subsequent sepsis aggravation ($n = 2$). Finally, 130 patients who were regularly followed-up for at least 5 years for whom sufficient data were available were enrolled in this study. Of the 130

patients, 60 (46.2 %) were men and the mean age at the time of intestinal BD diagnosis was 39.5 years. The mean follow-up duration after diagnosis was 9.3 (range 5.0–30.2) years.

Medications and Surgery

During the 5-year follow-up, oral sulfasalazine or 5-aminosalicylic acid were the most commonly taken medications (124, 95.4 %). The cumulative rates of corticosteroid use after diagnosis were 26.2 and 33.9 % at 2 and 5 years, respectively, while the cumulative rates of immunosuppressant use were 12.3 and 22.3 %, respectively. Cumulative operation (intestinal resection related to intestinal BD) rates at 2 years and 5 years after diagnosis were 23.9 and 32.4 %, respectively.

Clinical Course of the Disease

Five different clinical courses were observed (Fig. 1) over the 5-year follow-up period. Of 130 patients with intestinal BD, 73 (56.2 %) experienced persistent remission or mild clinical activity during the 5-year follow-up period (curve 1), while 20 (15.4 %) experienced remission or mild clinical activity after the initial peak of activity (curve 2). Only three (2.3 %) patients experienced an increase in severity (curve 3). Chronic continuous symptoms (curve 4) and chronic intermittent symptoms (curve 5) were observed in nine (6.9 %) and 25 (19.2 %) patients, respectively.

The annual clinical courses during the first 5 years after diagnosis are shown in Fig. 2. The first year after diagnosis, 65 (50.0 %) patients experienced remission or mild clinical activity, while 36 (27.7 %), 15 (11.5 %), and 14 (10.8 %) experienced one relapse, multiple relapses, or

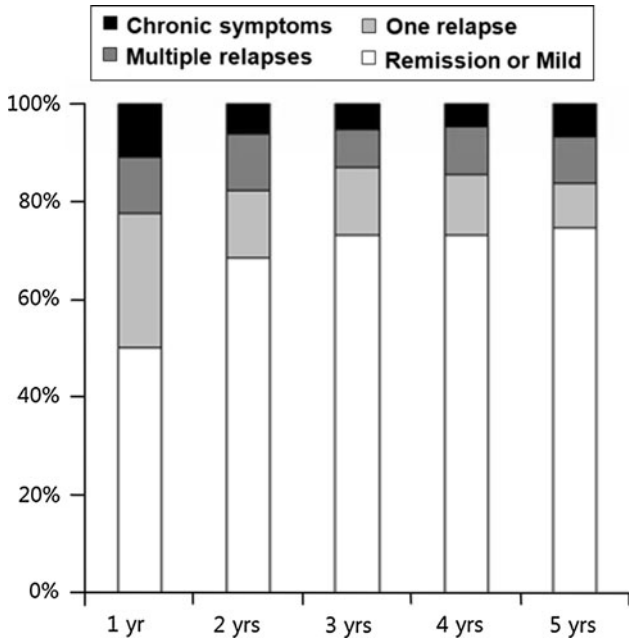

Fig. 2 Annual clinical courses during the first 5 years after diagnosis of intestinal BD

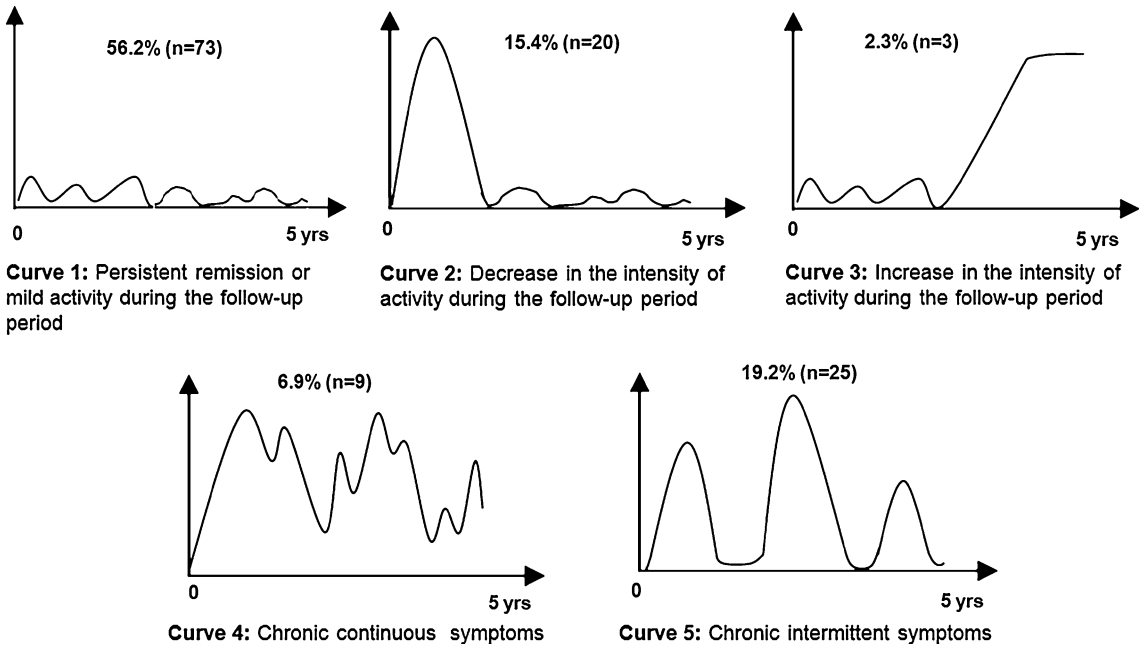

Fig. 1 Five different curves reflecting the clinical courses observed during a 5-year follow-up period

chronic symptoms, respectively (Fig. 2). The fifth year after diagnosis, three-quarters of patients (97, 74.6 %) experienced remission or mild clinical activity, while only 12 (9.2 %), 12 (9.2 %), and nine (6.9 %) patients experienced one relapse, multiple relapses, or chronic symptoms, respectively.

The clinical course of the following year according to the clinical course of the first year after diagnosis is shown in Fig. 3. Of 65 patients with remission or mild clinical activity the first year after diagnosis, 63 (96.9 %) had a similar clinical course (remission or mild clinical activity) the following year, while only two (3.1 %) experienced one relapse the following year. Of 36 patients with one relapse during the first year after diagnosis, 21 (58.3 %), 10 (27.8 %), and five (13.9 %) experienced remission/mild clinical activity, one relapse, and multiple relapses the following year, respectively. Of 15 patients with multiple relapses the first year after diagnosis, two (13.3 %), six (40.0 %), and seven (46.7 %) experienced remission/mild clinical activity, one relapse, and multiple relapses the following year, respectively. Of 14 patients with chronic symptoms the first year after diagnosis, three (21.4 %), three (21.4 %), and eight (57.1 %) experienced remission/mild clinical activity, multiple relapses, and chronic symptoms the following year, respectively.

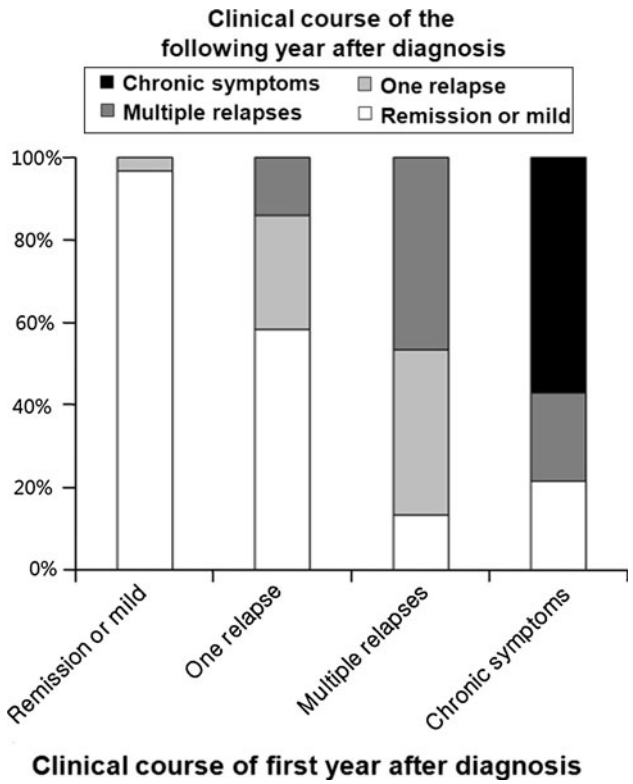

Fig. 3 Clinical courses during the years following the first year after diagnosis

Clinical Characteristics According to the Clinical Course Pattern and Risk Factors for a Severe Clinical Course

We defined curves 1 and 2 as indicating a mild clinical course, and curves 3, 4, and 5 as indicating a severe clinical course, and compared clinical characteristics between these two groups (Table 1).

The mean age at diagnosis of BD, age at onset of intestinal symptoms, and age at diagnosis of intestinal BD was significantly lower in the severe clinical course group than the mild clinical course group (32.6 vs. 38.3 years, $p = 0.007$; 34.7 vs. 40.1 years, $p = 0.012$; and 35.5 vs. 41.1 years, $p = 0.007$, respectively). ESR (38.1 vs. 26.4 mm/h, $p = 0.030$) and CRP level (4.18 vs. 1.52 mg/dL, $p = 0.009$) were significantly higher in the severe clinical course group than the mild clinical course group, whereas the albumin level (3.8 vs. 4.1 g/dL, $p = 0.023$) was significantly lower in the severe clinical course group than the mild clinical course group. The DAIBD at diagnosis was significantly higher in the severe clinical course group than in the mild clinical course group (97.7 vs. 59.8, $p < 0.001$). Volcano-shaped ulcers were more common in the severe clinical course group, while oval and geographic-shaped ulcers were more common in the mild clinical course group ($p = 0.008$).

No statistical differences in terms of sex, family history of BD, smoking status, symptoms and signs of systemic BD, intestinal involvement, type of intestinal ulcer, or diagnostic subtype were observed according to the pattern of clinical course.

In a multivariate logistic regression analysis that included significant variables from the univariate analysis, only a higher DAIBD score at diagnosis was an independent explanatory factor associated with a severe clinical course ($\geq$40 points; OR = 6.2; 95 % CI, 1.1–33.5, $p = 0.035$) (Table 2).

The severe clinical course group required more frequent corticosteroid therapy, immunosuppressant therapy, and surgical treatment than the mild clinical course group during the follow-up period (86.5 vs. 32.3 %, $p < 0.001$; 70.3 vs. 18.3 %, $p < 0.001$; and 62.2 vs. 28.0 %, $p < 0.001$, respectively) (Table 3).

Among patients in the mild clinical course group who underwent surgery (26 patients), 23 patients, two patients, and one patient underwent a single surgery, two surgeries, and four surgeries, respectively. Among patients in the severe clinical course group who underwent surgery (23 patients), 14, two, and two patients underwent a single surgery, two surgeries, or three surgeries, respectively. Five

Table 1 Comparison of baseline clinical characteristics of patients according to clinical course

Characteristic	Mild clinical course group Curves 1, 2 ($n = 93$)	Severe clinical course group Curves 3, 4, 5 ($n = 37$)	p value
Age at diagnosis of BD (years)[a]	38.3 ± 11.2	32.6 ± 9.7	0.007
Age at onset of intestinal symptoms (years)[a]	40.1 ± 11.2	34.7 ± 9.8	0.012
Age at diagnosis of intestinal BD (years)[a]	41.1 ± 10.6	35.5 ± 10.1	0.007
Sex, male (%)	40 (43.0)	20 (54.1)	0.254
Family history of BD (%)	4 (4.3)	0 (0)	0.557
Smoking status (current/ex-smoker) (%)	10 (10.8)	6 (16.2)	0.392
Symptoms and signs of BD (%)			
Oral ulcers	84 (90.3)	36 (97.3)	0.280
Genital ulcers	38 (40.9)	19 (51.4)	0.277
Ocular lesions	21 (22.6)	7 (18.9)	0.647
Skin lesions	44 (47.3)	18 (48.6)	0.890
Arthritis/Arthralgia	28 (30.1)	12 (32.4)	0.796
Vascular lesions	9 (9.7)	4 (10.8)	1.000
Neurologic lesions	2 (2.2)	1 (2.7)	1.000
Symptoms of intestinal involvement (%)			
Abdominal pain	82 (88.2)	30 (81.1)	0.291
Melena/hematochezia	21 (22.6)	8 (21.6)	0.906
Diarrhea	9 (9.7)	3 (8.1)	1.000
Abdominal mass	2 (2.2)	2 (5.4)	0.320
Weight loss	5 (5.4)	2 (5.4)	1.000
Febrile sense	5 (5.4)	3 (8.1)	0.687
Laboratory findings at diagnosis			
WBC (10^6/L)[a]	8277 ± 4523	9573 ± 5184	0.160
Hemoglobin (g/dL)[a]	12.2 ± 2.0	12.0 ± 3.0	0.616
ESR (mm/h)[a]	26.4 ± 25.8	38.1 ± 26.9	0.030
CRP (mg/dL)[a]	1.52 ± 2.54	4.18 ± 5.27	0.009
Albumin (g/dL)[a]	4.1 ± 0.7	3.8 ± 0.7	0.023
DAIBD[a] at diagnosis	59.8 ± 48.6	97.7 ± 42.6	<0.001
Location of intestinal lesions (%)			
Ileocecal area	88 (94.6)	36 (97.3)	0.674
Shape of intestinal ulcers (%)			
Oval/geographic	62 (78.5)	17 (53.1)	0.008
Volcano	17 (21.5)	15 (46.9)	
Types of intestinal ulcers (%)			
Typical type	39 (49.4)	19 (59.4)	0.339
Atypical type	40 (50.6)	13 (40.6)	
Diagnostic subtypes of intestinal BD (%)			
Definite	32 (40.5)	15 (46.9)	0.493
Probable	40 (50.6)	15 (46.9)	
Suspected	7 (8.9)	2 (6.3)	

BD Behcet's disease, *WBC* white blood cell count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAIBD* disease activity index for intestinal Behcet's disease

[a] Mean ± standard deviation

Table 2 Multivariate analysis of risk factors associated with a severe clinical course

Variable	OR	95 % CI	*P* value
Age (<40 years) at the time of diagnosis of intestinal BD	1.3	0.4–4.1	0.636
ESR (≥30 mm/h)	1.8	0.6–6.1	0.321
CRP (≥0.8 mg/dL)	1.9	0.4–8.0	0.398
Albumin (<4 g/dL)	2.4	0.7–7.8	0.153
DAIBD at diagnosis (≥40)	6.2	1.1–33.5	0.035
Shape of intestinal ulcers (volcano vs. oval/geographic)	1.1	0.4–3.2	0.866

BD Behcet's disease, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAIBD* disease activity index for intestinal Behcet's disease, *OR* odds ratio, *CI* confidence interval

Table 3 Comparison of medications and surgery according to clinical course

Medications/ Surgery	Mild clinical course group Curves 1, 2 ($n = 93$)	Severe clinical course group Curves 3, 4, 5 ($n = 37$)	*p* value
5-ASA/ sulfasalazine	89 (95.7)	35 (94.6)	1.000
Corticosteroids	30 (32.3)	32 (86.5)	<0.001
Azathiopurine/ 6-MP	17 (18.3)	26 (70.3)	<0.001
Infliximab	3 (3.2)	1 (2.7)	1.000
Surgery	26 (28.0)	23 (62.2)	<0.001

5-ASA 5-aminosalicylic acid, *6-MP* 6-mercaptopurine

Table 4 Comparison of surgery frequency according to clinical course

No. of surgeries	Mild clinical course group[a] ($N = 26$)	Severe clinical course group[a] ($N = 23$)
1	23	14
2	2	2
3		2
4	1	2
6		1
7		1
9		1

Values given as number of patients

patients underwent four or more surgeries, up to a maximum of nine operations (Table 4).

Discussion

To the best of our knowledge, no previous study has described the clinical course of intestinal BD in terms of curves as we have done. Currently, physicians attempt to determine the clinical courses or outcomes of intestinal BD using statistical indicators such as cumulative recurrence or operation rates. Moreover, disease activity indexes and quality of life questionnaires can only indicate the patient's symptoms, status, and functional level at certain points in disease course. There are few tools to evaluate disease course over time. To describe variations in the severity of symptoms and status over time, we plotted five different disease courses. This visualization of the disease courses is easy to understand and can provide useful information about the patient's symptoms and status over time.

Several studies in Norway described the clinical courses of CD and UC in terms of curves as we have done [13–16]. These were prospective, population-based follow-up studies, and the clinical course was predefined and illustrated by four different curves, which were designed to reflect clinical activity during 5- or 10-year follow-up periods. The patients who were enrolled in these studies were asked to select the curve that best described the course of their disease during the follow-up period. Therefore, these studies might have suffered from bias due to the patient's choice. For example, a recent flare-up might have led the patients to choose a more severe pattern of disease, and, conversely, adaptation to the symptoms over time might have had the opposite effect. Although our study was a retrospective study, we argue that it is more accurate and objective than previous studies because a single gastroenterologist specializing in IBD selected the curves directly. Another difference between the Norwegian studies and ours is that we added a new curve (curve 1: persistent remission or mild clinical activity). Moreover, we found that more than 50 % of our intestinal BD patients had a mild clinical course (curve 1). This result suggests that intestinal BD and IBD (CD and UC) may have different clinical courses. In other words, it is far easier to distinguish between intestinal BD patients with a mild or severe clinical course group than patients with CD. Mild and severe clinical courses of intestinal BD could be clearly differentiated based on our results that the frequency of corticosteroid use, immunosuppressant therapy, and multiple reoperations were much higher in intestinal BD patients with a severe clinical course than in those with a mild clinical course. Most intestinal BD patients with a mild clinical course never experience a disease flare-up and maintain clinical remission only with 5-aminosalicylic acid agents, or remit spontaneously. In contrast, intestinal BD patients with a severe clinical course experience frequent disease flare-ups and therefore often require corticosteroid therapy, immunosuppressant therapy, or surgical treatment. CD is rather composed of mild, moderate, and severe disease groups evenly.

We enrolled only patients who had been followed-up for at least 5 years. Therefore, a fairly large number of patients were excluded from our study because of follow-up loss. Despite the higher possibility of follow-up loss of patients with a mild course compared to those with a severe course, the prognosis for intestinal BD during the first 5 years was generally favorable. A substantial proportion of patients were in remission or had mild clinical activity as time progressed, whereas a certain portion of the patients showed chronic activity 5 years after diagnosis. Considering that three-quarters of patients ($n = 95$, 73.1 %) were diagnosed with intestinal BD after the year 2000 in our study, there is the possibility that established diagnostic methods, better access to colonoscopy, and increased awareness of intestinal BD increased the detection of mild cases. It is also possible that medical treatment may be able to alter the natural history and improve the prognosis of intestinal BD. This latter hypothesis is supported by the fact that the prognosis of IBD has changed somewhat over the last few decades as a result of progress in medical therapeutics and surgical methods [17]. A population-based study in the UK showed that risk of surgery decreased among a cohort of CD patients diagnosed more recently than those diagnosed in earlier periods, and that this reduction was associated with increased and earlier thiopurine use [18]. It would also potentially be possible to elucidate the influence of these factors by comparing our data with older data. Unfortunately, however, no older studies reporting the clinical outcomes of intestinal BD are available.

Intestinal BD should not be considered a mild disease simply on the grounds that a large proportion of patients have a mild clinical course. Intestinal BD patients with a severe clinical course required more frequent corticosteroid therapy, immunosuppressant therapy, and multiple intestinal resections than those with a mild clinical course, which suggests that patients with a severe clinical course suffer more from the disease than those with a mild clinical course. Physicians often feel that intractable intestinal BD appears to be more difficult to manage than CD. Moreover, the overall prognosis of intestinal BD was reported not better than that of CD [19].

We found that the clinical course seen during the first year after diagnosis of intestinal BD influenced the clinical course of the following year. This finding is in agreement with Danish studies that investigated disease courses in a large cohort of IBD patients. Of both CD and UC patients with active disease during the first year, 70–80 % maintained a similar status during the following year, and similarly, about 80 % of patients in remission remained in remission during the following year [20, 21]. Moreover, in CD patients, the relapse rate over the first year influenced the relapse rate in the following year, consistent with our findings [20].

Another finding of the present study is that patients in the severe clinical course group were younger, and had an elevated ESR and CRP level, lower albumin level, and higher disease activity at diagnosis than patients in the mild clinical course group. However, high disease activity at diagnosis was the only independent predictive factor of a severe clinical course. This finding in consistent with those reported for CD and UC. Munkholm et al. [20] showed that in CD, the disease activity within the initial 3 years correlated positively with the course over a 5-year period (years 3–7). Langholz et al. [21] also demonstrated that in UC, the course of disease changed between remission and relapse without significant predictors, except for disease activity in the preceding years. Furthermore, activity in the first 2 years after diagnosis was significantly correlated with an increased probability of five consecutive years of disease. In another study of UC patients who underwent corticosteroid treatment, a high initial Mayo score was strongly associated with poor outcomes [22]. Rutgeerts et al. [23] found that a high disease activity score preoperatively predicted a postoperative course with high recurrence rates. Furthermore, we demonstrated in an earlier study that a high DAIBD score at the time of diagnosis was an independent predictive factor for risk of operation [11].

Our study had several limitations. First, it was a retrospective and hospital-based study with potential bias in its design. Although IBD patients are generally managed by gastroenterology specialists in Korea, referral-center bias with inclusion of more severe cases in our cohort cannot be excluded. Nevertheless, the prognosis for intestinal BD during the first 5 years was not generally poor. Second, our study population was small and the follow-up duration was relatively short to understand the long-term clinical courses of intestinal BD. Future extended, long-term, prospective, and population-based studies are needed to elucidate the natural history of intestinal BD. Third, working capacity was not investigated in the study subjects, and thus we could not identify the extent to which the disease affects the quality of life.

In conclusion, five different clinical courses of intestinal BD were identified. Some patients had a severe clinical course and were adversely affected by the disease. However, a large proportion of patients went into remission or had mild clinical activity as time progressed. In other words, patients with intestinal BD tend to show dichotomous clinical course: mild versus severe clinical course. Therefore, the predictor of severe clinical course is very important for clinical practice, and it can be a high disease activity at diagnosis.

Conflict of interest None.

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