Regional distinction for the clinical severity of Behçet's disease in Korea: four university-based medical centre studies

J.-Y. Choe[1,2], W.-T. Chung[3], S.-W. Lee[3], S.-S. Lee[4], C.-B. Choi[5], S.-H. Park[1,2], S.-K. Kim[1,2]

[1]Department of Internal Medicine and [2]Arthrits and Autoimmunity Research Centre, Catholic University of Daegu, Daegu, South Korea; [3]Department of Internal Medicine, Dong-A University, Pusan, South Korea; [4]Department of Internal Medicine, Chonnam National University Medical School, Gwangju, South Korea; [5]Department of Rheumatology, Hospital for Rheumatic Diseases, Hanyang University, Seoul, South Korea.

Jung-Yoon Choe, MD, PhD
Won-Tae Chung, MD, PhD
Sung-Won Lee, MD, PhD
Shin-Seok Lee, MD, PhD
Chan-Bum Choi, MD, PhD
Sung-Hoon Park, MD
Seong-Kyu Kim, MD, PhD

Please address correspondence and reprint requests to: Seong-Kyu Kim, MD, PhD, Dept. of Internal Medicine, Catholic University of Daegu School of Medicine, 3056-6 Daemyung 4-Dong, Namgu, Daegu 705-718, South Korea. E-mail: kimsk714@cu.ac.kr

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ABSTRACT

Objective. *To analyse the clinical manifestations and severity of Behçet's disease (BD) in Korea according to geographic region of residence, and to identify risk factors associated with clinical severity.*

Methods. *We enrolled 246 BD patients (88 males) who fulfilled the criteria of the International Study Group for BD. These patients were assigned into two groups: a Western group comprising 127 residents in west regions and an Eastern group comprising 119 residents of the SoBaek Mountains situated in the center of Korea. Clinical severity was assessed using a severity scoring index of BD.*

Results. *BD patients from the Western group had a greater prevalence of typical skin lesions, deep vein thrombosis, gastrointestinal bleeding, posterior/panuveitis, and retinal vasculitis than did the Eastern group ($p<0.001$, $p=0.009$, $p=0.032$, and $p=0.007$, respectively). The Western group also had higher severity scores than did the Eastern group (5.88±2.5 for the Western group vs. 4.94±2.6 for the Eastern group, $p=0.004$). Male BD patients had higher severity scores than did female patients (6.14±2.8 vs. 5.03±2.4, $p=0.001$). The disease duration of BD in the Western group showed a significant association with total severity scores ($r=0231$, $p=0.009$), but this was not observed for the Eastern group.*

Conclusions. *We found distinct differences in the clinical manifestations as well as severity of BD according to geographic region in Korean BD patients. Males, particularly those from the Western region of Korea, had significantly higher severity scores than did females.*

Introduction

Behçet's disease (BD) is a multisystemic inflammatory disease characterised by recurrent aphthous oral ulcerations, genital ulcers, skin lesions, and ocular inflammations (1, 2). Articular, gastrointestinal, renal, pulmonary, vascular, and central nerve system (CNS) involvement is also frequently observed. Although BD has a worldwide distribution, it is highly prevalent in Eastern Mediterranean, Central Asian, and Far East Asian countries along the ancient Silk Road (2, 3). However, the prevalence of BD in Europe and the United States is low (between 0.12 to 0.64 per 100,000 population) (3, 4). Interestingly, it was demonstrated in Japan that the prevalence of BD within a single ethnic group can differ according to geographic region (5, 6).

The diagnosis of BD is based primarily on the clinical criteria defined by the International Study Group (ISG) of BD (7), even though specific diagnostic criteria or tests for BD have not been developed. The clinical courses of BD are presented with wax and wane. The clinical spectrum of BD is extremely diverse, and can include recurrent aphthous oral ulcerations, eye diseases including anterior uveitis with hypopyon, posterior uveitis, retinal vasculitis, skin diseases, nondestructive arthritis, venous involvements from superficial thrombophlebitis to deep vein thrombosis, and CNS involvements (1-4). Some of these clinical features, including severe ocular inflammations, CNS involvements, and major vascular diseases, may be closely associated with poorer prognosis and higher morbidity (8-11). Therefore, BD severity assessment is clinically significant. However, a clinical index to assess the severity of BD has not yet been established, although a scoring system for all clinical features of BD was reported by Krause *et al*., based on clinical studies (12-14). Despite some publications for epidemiological and clinical data for Korean BD patients (15-17), detailed assessment of the clinical severity of the disease in Korean patients has not been

performed. Significant geographic distribution of BD was demonstrated through a nationwide survey in which twenty hospitals in Korea participated, showing highest prevalence in Seoul (16). In addition, Chang *et al*. illustrated that BD patients resided in northeast regions presented more prevalence of vascular lesions and epididymitis than data from other Korean studies (18). Until now, the differences of BD manifestations and severity according to geographic region of residence have not been investigated. Life style and dialect between western and eastern regions were significantly different on the border of the SoBaek Mountains (19). Therefore, our hypothesis is that there are some differences for BD clinical features and their severity according to geographic distribution in Korea, even within a single ethnic group. In this study, we compared the clinical features and severity of BD between patients living in Eastern and Western regions of Korea and identified risk factors associated with severity in BD.

Patients and methods

Subjects

We consecutively enrolled a total of 246 BD patients from four university-based medical centres who met the criteria of the ISG for BD (7). All subjects recruited in this study were unrelated Koreans. The patients were formally assessed by physicians employed at the time of enrolment by the rheumatology clinics of Daegu Catholic University Medical Centre, Dong-A University Medical Centre, Chonnam National University Medical Centre, and Dankook University Medical Centre. The grouping of enrolled patients was performed according to whether patients resided west or east of the SoBaek Mountains, which are in the geographic centre of Korea.

We recorded gender, mean age at enrolment, mean disease duration, and mean age at disease onset. We also investigated clinical features including oral ulcerations, genital ulcerations, skin lesions, articular lesions, vascular lesions, gastrointestinal lesions, ocular inflammations, CNS lesions, epididymitis, pathergy response, HLA-B51 positivity, and mean severity score (Table I). Additional clinical information and laboratory findings were obtained based on detailed patient interviews and review of medical records. The research protocol was approved by the Institutional Review Boards of all of the medical centres listed above. All of the enrolled subjects provided written informed consent.

Assessment of severity

We used the clinical severity index described by Krause *et al*. in their previous studies (12-14). A clinical severity score was calculated based on the clinical features expressed in each enrolled patient. The severity of BD was described as mild, moderate, or severe. Oral ulcers, genital ulcers, typical skin lesions, arthralgia, recurrent headaches, epididymitis, mild gastrointestinal discomfort, pleuritic pain, and superficial vein thrombosis were classified as mild severity symptoms. Arthritis, deep vein thrombosis, anterior uveitis, and GI bleeding were classified as moderate severity symptoms, while posterior/panuveitis, retinal vasculitis, arterial thrombosis or aneurysm, major vein thrombosis, neuro-Behçet, and bowel perforation were considered severe symptoms. The total severity score was estimated by assigning one point to each mild feature, two points to each moderate feature, and three points to each severe feature and then summing the symptom scores (14).

Statistical analysis

Data are presented as mean ± standard deviation or numbers (% of each parameter). The Chi-square test was performed to compare the frequency of non-parametric variables between the two groups. If any cell in the frequency assessment had an expected sample size less than five, Fisher's exact test was used. Student's *t*-test was performed to compare quantitative variables between the two groups. Risk factors contributing to total severity scores were confirmed using multivariate linear regression analysis. Correlations between severity scores and quantitative clinical values including age and disease duration were estimated by Pearson's correlation analysis. A value of $p<0.05$ was considered statistically significant. The statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA).

Results

1. *General characteristics of the Korean BD patients*

A total of 246 BD patients enrolled from four university-based medical

Table I. General demographics and clinical manifestations of enrolled patients in this study.

Clinical parameters	Number (%)
Male/Female	88/158 (35.8/64.2)
Mean age at enrolment (years)	41.5 ± 10.5
Mean disease duration (years)	7.1 ± 6.2
Mean age at disease onset (years)	34.4 ± 9.9
Clinical manifestations	
Oral ulceration	246 (100)
Genital ulceration	196 (79.7)
Skin lesions	193 (78.5)
Articular lesions	100 (40.7)
Vascular lesions	34 (13.8)
Gastrointestinal lesions	45 (18.3)
Ocular lesions	78 (31.7)
Central nerve system lesions	41 (16.7)
Epididymitis	11 (4.5)
Pathergy response	68 (27.6)
HLA-B51 positivity	100 (40.7)
Total severity score*	5.43 ± 2.6

HLA-B51: human leukocyte antigen-B51.

*Total severity score means summation of mild, moderate, and severe severity scores and severity index is cited from references 12, 13, 14.

centres were assessed in this study. The mean age at the time of enrolment was 41.5±10.5 years, the mean disease duration was 7.1±6.2 years, and 88 patients were male (35.8%) (Table I). The frequencies of clinical manifestations are presented in Table I. The proportion of HLA-B51 positive patients was 40.7% (n=100). The mean total severity score was 5.43±2.6.

2. *Comparison of clinical manifestations and severity between the Eastern and Western populations of Korea*

We classified the 246 BD patients into two groups: a Western group and an Eastern group (Fig. 1), and then compared clinical features between the two groups (Table II). No differences in the male to female ratio or disease duration were noted between the groups (p=0.080, p=0.898, respectively), whereas a greater proportion of younger patients were enrolled from Western regions than from Eastern regions (average age 39.4±9.5 years in the Western group *vs*. 43.7±11.1 years in the Eastern group, p<0.001). When clinical features were compared, we found that the frequencies of typical skin lesions, deep vein thrombosis, GI bleeding, and posterior/panuveitis, retinal vasculitis were significantly higher in the Western group than in the Eastern group (p<0.001, p=0.009, p=0.032, and p=0.007, respectively). The frequency of HLA-B51 positivity was not different between the two groups (p=0.381).

We calculated severity scores for each patient using the severity scoring system described by Krause *et al*. and compared the severity scores between the Western and Eastern groups (Fig. 2). The mild severity score was not different between the two regions (3.27±0.9 for the Western group *vs*. 3.24±1.3 for the Eastern group, p=0.822), nor was the moderate severity score (1.15±1.3 for the Western group *vs*. 0.92±1.2 for the Eastern group, p=0.162). However, severe severity scores were significantly different between the two regions (1.46±1.8 for the Western group *vs*. 78±1.4 for the Eastern group, p=0.001). In terms of the total severity scores, patients residing in the Western region of Korea had much higher scores than the patients residing in Eastern regions of Korea (5.88±2.5 for the Western group *vs*. 4.94±2.6 for the Eastern group, p=0.004). This finding suggests that patients residing in Western regions of Korea have more severe clinical manifestations of BD than do Eastern patients.

Fig. 1. Geographic distribution of four university-based medical centers in Korea. (■ Western region of Cheonan and Gwangju cities, ● Eastern region of Daegu and Pusan cities).

Table II. Comparison of clinical manifestations in patients of two geographic regions.

Clinical parameters	Western *vs*. Eastern region		p-value
	Western (n=127)	Eastern (n=119)	
Male/Female	52/75 (40.9/59.1)	36/83 (30.3/69.7)	0.080
Mean age at enrolment (years)	39.4 ± 9.5	43.7 ± 11.1	0.001
Mean disease duration (years)	7.2 ± 5.8	7.1 ± 6.6	0.898
Mean age at disease onset (years)	32.2 ± 8.7	36.7 ± 10.6	<0.001
Oral aphthous ulcer	127 (100)	119 (100)	NA
Genital ulcer	97 (76.4)	99 (83.2)	0.184
Typical skin lesions	122 (96.1)	71 (59.7)	<0.001
Arthralgia	39 (30.7)	49 (41.2)	0.087
Recurrent headaches	9 (7.1)	15 (12.6)	0.145
Epididymitis	6 (4.7)	5 (4.2)	0.843
Mild GI symptoms	10 (7.9)	15 (12.6)	0.220
Pleuritic pain	1 (0.8)	5 (4.2)	0.110*
Superficial vein thrombosis	4 (3.1)	7 (5.9)	0.300
Arthritis	31 (24.4)	38 (31.9)	0.189
Deep vein thrombosis	14 (11.0)	3 (2.5)	0.009
Anterior uveitis	10 (7.9)	7 (5.9)	0.538
Gastrointestinal bleeding	18 (14.2)	7 (5.9)	0.032
Posterior/panuveitis, retinal vasculitis	44 (34.6)	23 (19.3)	0.007
Arterial thrombosis or aneurysm	6 (4.7)	1 (0.8)	0.121*
Major vein thrombosis	0 (0.0)	0 (0.0)	NA
Neuro-Behçet	12 (9.4)	7 (5.9)	0.295
Bowel perforation	0 (0.0)	0 (0.0)	NA
HLA-B51 positivity	55 (43.3)	45 (37.8)	0.381

Western region in Korea means a group consisting of patients residing at Cheonan and Gwangju. Eastern region in Korea means a group consisting of patients residing at Daegu and Pusan.
NA: not statistically assessed.
*p-value: Fisher's exact test was performed. HLA-B51: human leukocyte antigen-B51.

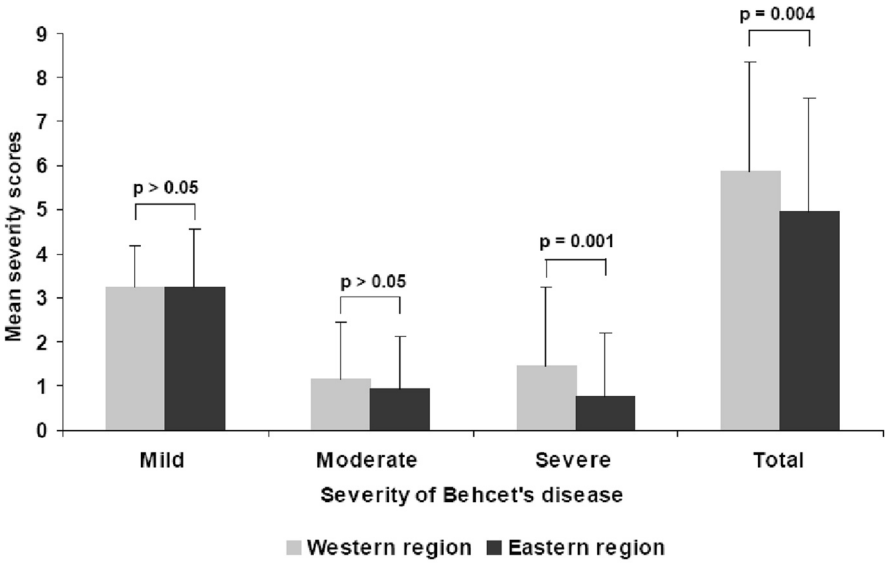

Fig. 2. Comparison of mean severity scores according to clinical severity of BD between two regions.

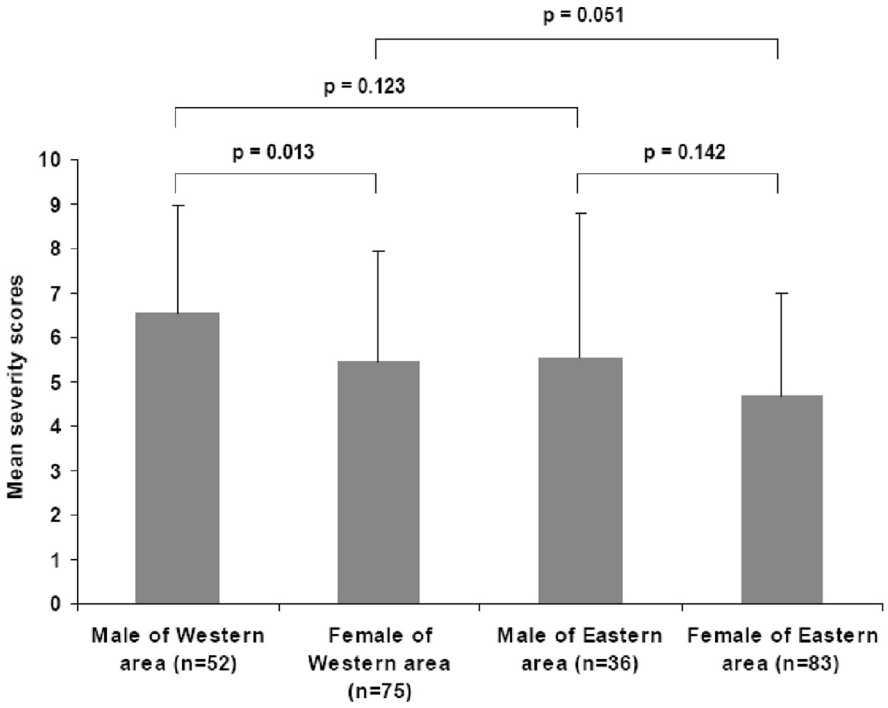

Fig. 3. Comparison of mean severity scores based on both gender and geographic distribution.

3. *Differences in clinical severity according to gender and region of residence*

We investigated the differences in clinical severity according to gender in our patient cohort of 246 BD patients. No significant differences in the frequency of mild and moderate BD symptoms were found between males and females (p=0.736 for mild severity symptoms, and p=0.062 for moderate severity symptoms), whereas male BD patients showed more severe symptoms than did female patients (p=0.002). We also found that male BD patients had higher severity scores than female patients (6.14±2.8 *vs*. 5.03±2.4, respectively, p=0.001).

In addition, the influence of gender on the clinical severity of BD according to geographic regions was also assessed in this study. Significantly more male patients from the Western group had more severe symptoms than did female Western patients (6.54±2.4 for Western males *vs*. 5.43±2.5 for Western females, p=0.013), whereas the clinical severity of BD was similar for males and females from the Eastern regions of Korea (5.56±3.2 for Eastern males *vs*. 4.67±2.3 for Eastern females, p=0.142) (Fig. 3). Regional differences in the total clinical severity scores were not found for either male or female patients (p=0.123 between Western and Eastern males, and p=0.051 between Western and Eastern females), although moderate symptom scores in males and severe symptom scores in female were significantly different according to region of residence (p=0.016 for moderate symptoms between Western and Eastern males, and p=0.016 for severe symptoms between Western and Eastern females).

4. *Identification of risk factors associated with clinical severity scores*

Correlations between severity scores and quantitative variables including mean age at enrolment, mean disease duration, and mean age at disease onset were estimated. The results showed that only disease duration and the severity scores of severe symptoms were significantly correlated (r=0.186, p=0.004), whereas mean age at enrolment, mean disease duration, and mean age at disease onset were not associated with severity score. The disease duration of BD in Western BD patients was significantly associated with the severity score for severe symptoms and total severity scores (r=0.274, p=0.002 and r=0231, p=0.009, respectively). However, no associations between any other quantitative variables and severity scores were found. These results indicate that longer disease duration is associated with increased risk for severe symptoms.

We analysed the associations between total severity scores and clinical features including skin lesions, deep vein thrombosis, GI bleeding, and ocular inflammation using multivariate regression analysis, and found that these were significantly different between patients from the two geographic regions (Table III). Thus typical skin lesions, deep vein thrombosis, GI bleeding, poste-

rior/panuveitis, and retinal vasculitis were closely associated with the clinical severity of BD in this study.

Table III. Multivariate linear regression analysis of clinical parameters as risk factors for total severity score in Behçet's diseases.

Clinical parameters	B	*p*-value	95% Confidence interval for B
Typical skin lesions	1.452	<0.001	0.890 – 2.014
Deep vein thrombosis	1.844	<0.001	0.909 – 2.780
Gastrointestinal bleeding	1.530	<0.001	0.751 – 2.308
Posterior/panuveitis, retinal vasculitis	3.312	<0.001	2.792 – 3.831

B: unstandardised coefficients.

Discussion

The prevalence of BD is world-widely distributed, although the geographic prevalence of BD is greater in countries that formed part of the ancient Silk Road from the Eastern Mediterranean to Far East Asia (2, 3) than in Western countries such as the United States and the United Kingdom (3, 4). In addition to the prevalence of BD, the clinical characteristics of BD, including disease duration and the types of organs involved, vary according to the study population. However, few investigations of the clinical severity of BD have been performed.

Krause *et al*. demonstrated large differences in the clinical severities of BD when they compared Jewish and Arab BD patients living in Israel; the Jewish BD patients had higher severity BD than did the Arab patients (14). In addition, there were also significant differences in clinical severity between Jewish patients from various regions including Iran/Iraq, Turkey, and North African countries. These authors therefore proposed that the clinical severity of BD may be influenced by ethnic or geographic origin. In the current study, we investigated differences in the clinical severity of BD in Korean BD patients, a single ethnic group. Patients in this study were classified into one of two groups based on whether they resided west or east region of the SoBaek Mountains. We assessed clinical severity using the BD severity scoring index suggested by Krause *et al*. (12-14). We found large differences in the clinical severities of BD between patients from these two regions; significantly higher severity scores were found in patients from Western regions than in those from Eastern regions. The significant differences in severity were significantly associated with severe clinical manifestations of BD rather than mild or moderate BD symptoms. These findings demonstrate that there are differences in the clinical severity of BD within a single ethnic group, namely Koreans.

Despite indices to assess the clinical activity of BD (20-22), reliable definitions or classifications of the clinical severity of BD have not been established. Assessment of the severity of BD is important, because severe clinical features are associated with increased mortality/morbidity and a poorer prognosis. A recent 20-year outcome study of 387 Turkish patients illustrated that poor prognosis and high morbidity/mortality were significantly associated with ocular, vascular, and CNS lesions (10). Akman-Demir *et al*. also revealed increased mortality in patients with neurological problems in their seven-year follow-up study (20). A ten-year mortality survey of 152 Turkish BD patients also found that vascular complications such as pulmonary arterial aneurysms and major venous involvements were the major causes of deaths (11). Previous studies implicated ocular, major vascular, CNS involvement may be classified into severe clinical manifestations in BD with poor prognosis. Kim *et al*. (23) and Park *et al*. (24) classified patients as having severe manifestations if the patient had more than one of the following clinical features of BD: posterior uveitis, retinal vasculitis, gastrointestinal ulcers with bleeding or perforation, and major organ or major vessel involvement. However, it seems that their classification for severity in BD is lack of values of objective and quantitative assessments. One study proposed that interleukin (IL)-8 level can be a reliable tool in discrimination of the disease severity, compared to clinical and laboratory findings (25). However, this finding needs to be confirmed through longitudinal studies, due to a rapid change of IL-8 level according to diverse clinical situations. Krause *et al*. reported a severity assessment tool based on the summation of points for each clinical feature (12-14). They classified ocular inflammations such as posterior/panuveitis and retinal vasculitis, vascular lesions including arterial thrombosis and major venous thrombosis or aneurysms, CNS involvement, and bowel perforation, as severe clinical features. We consider Krause's severity index a reasonable method to assess the severity of BD, although further validation studies are required.

The clinical phenotypes of BD are known to vary according to geographic location. For instance, a higher risk of neurological and vascular involvement has been demonstrated for patients from Jordan, Saudi Arabia, Tunisia, and Egypt compared to patients from Far East Asian countries (3, 26, 27), whereas patients in Japan and Taiwan have a higher prevalence of gastrointestinal involvement (3, 28). These epidemiologic data suggest that patients residing in countries in the Eastern Mediterranean and Central Asia may suffer from more severe clinical features than patients in East Asian countries. We found that the average severity score of our 246 BD patients was 5.43±2.6, which is much lower than that of the 100 Israel BD patients (6.62±2.58 in Jewish patients and 6.38±2.51 in Arab patients) (14). This finding is consistent with the observed differences in clinical severity between ethnic groups (3, 26-28).

The epidemiologic and clinical characteristics of Korean BD patients have been investigated previously (15-18). However, the clinical severity of BD was not assessed in these studies. In our study, we found significant differences in the clinical severities of BD according to geographic region. Furthermore, the prevalence of typical skin lesions,

deep vein thrombosis, gastrointestinal bleeding, and severe ocular inflammations such as posterior/panuveitis and retinal vasculitis was greater in BD patients from Western regions of Korea than in those from Eastern regions of Korea. Why these differences are observed in not clear, although environmental factors or genetic susceptibility may be contributing factors. No significant differences in disease duration or HLA-B51 prevalence were noted in this study, although age at enrolment was significantly different between the two geographic groups. No association between HLA-B51 status and clinical features were observed in a previous study of 108 Korean BD patients (24). Together with our non-significant HLA-B51 results, this suggests that HLA-B51 does not have an influence on the clinical severity of BD in Korean patients. We found that disease duration was significantly associated with severity scores in BD patients, especially in patients from the Western regions of Korea. Given the similar disease duration in the two groups, it appears that regional factors may influence BD severity with the exception of disease duration.

The clinical course of BD is known to be influenced by gender; male BD patients demonstrate a more severe clinical course than do female patients (10, 11, 17, 20, 27, 29). Houman *et al*. demonstrated more frequent development of deep vein thrombosis in males than in females, although no gender differences in vascular and CNS involvements were identified (27). A ten-year mortality survey in a Turkish population suggested that young male BD patients show increased mortality (11). Furthermore, the clinical manifestations of BD have been shown to be less severe in female patients based on a 20-year clinical outcome survey of 387 BD patients (10). In addition, severe complications such as ocular and vascular involvement have been reported to be more frequent in male than in female Korean BD patients (17). In this study, we found that severity scores in males were significantly higher than those in females, consistent with previous studies. Furthermore, we found significant differences in severity scores between the two genders living in Western regions of Korea, but not the two genders living in Eastern regions of Korea. These findings suggest that gender influences the clinical severity of BD and that this occurs to a greater extent in Western regions of Korea.

In conclusion, this study was designed to identify differences in the clinical severity of BD between Korean BD patients from two different geographical regions in Korea. The second major aim was to determine risk factors associated with BD severity. BD patients resident in Western regions of Korea showed higher severity scores than did those from Eastern regions, and males had more severe symptoms than females, with this effect more pronounced in patients from Western regions of Korea. Furthermore, the disease duration of BD was closely associated with the severity of BD, especially in patients residing in Western regions of Korea. Together, these results suggest that in Korean BD patients, differences in clinical severity are associated with geographic distribution and gender.

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