The prevalence of Behçet's disease in Korea: data from the Health Insurance Review and Assessment Service from 2011 to 2015

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ABSTRACT

Objective. *The aim of this study is to identify the prevalence of Behçet's disease (BD) from data in the Healthcare Bigdata Hub of the Health Insurance Review & Assessment (HIRA) Service from 2011 to 2015 in Korea.*

Methods. *This study collected information on primary and auxiliary diagnoses of BD (M352) by physicians according to the Korean Standard Classification of Diseases (KCD) codes. The prevalence of BD was assessed on the basis of age, sex, and geographical distribution. We used time series analysis, using the ARIMA model for the expected prevalence of BD from 2016 to 2025.*

Results. *The overall prevalence of BD was gradually increased, ranging from 32.8 to 35.7 per 100,000 population over the study period. The male to female ratio of BD ranged from 0.54:1 to 0.56:1, revealing a female predominance from 2011 to 2015. Among five districts in Korea, the prevalence in the Seoul Metropolitan district was the highest, with a slowly increasing trend for the study period, accounting for about 60.3% of total BD patients. The expected prevalence of BD patients was estimated to range from 36.9 (95% CI 35.0–39.0) to 44.7 (95% CI 40.2–49.6) between 2016 and 2025.*

Conclusion. *This study found that the overall prevalence of BD is estimated to be approximately 35.0 per 100,000 population, with female predominance, and predicts gradually increased prevalence of BD in Korea.*

Introduction

Behçet's disease (BD) is a chronic rheumatic disease characterised by multisystemic inflammatory manifestations such as recurrent aphthous oral ulcer, genital ulcer, inflammatory ocular lesions, and positive pathergy skin reaction (1). Although it is found worldwide, distinct geographic distribution has been noted with BD, with a much higher prevalence in countries along the Silk Road, the ancient trade route following from the eastern shores of the Mediterranean and the Middle East, than in northern Europe and North America.

There are several reports on the prevalence of BD from different parts of the world, showing the highest prevalence of BD up to 420 per 100,000 persons in Turkey (2), 110 in northern China (2), 22 in Japan (2), 80 in Iran (3), 30.2 in Korea (4), and 15.2 in Israel (5). In contrast, the countries with the lowest prevalence are the 4.9 in southern Sweden (6), 2.26 in Germany (7), and 5.2 per 100,000 persons in the United States (8). The sex distribution in BD is variable according to geographical areas. BD seems to be a predominantly male disease in Middle Eastern countries and in the Mediterranean (2, 3, 5), but it is more common in women in Eastern Asian populations, including Korea and Japan (2, 4) and in parts of some western countries (7, 8).

Although Korea lies along the Silk Road, a high prevalence area, there have been no previous reports of the prevalence of BD in Korea using data from the Healthcare Bigdata Hub of the Health Insurance Review & Assessment (HIRA) Service. The objective of this study is to identify the prevalence of BD in Korea through data from the HIRA Service from 2011 to 2015.

Subjects and methods

Study population and regional distribution

This study assesses the prevalence of BD based on the Healthcare Bigdata Hub of the HIRA Service in Korea. Based on data from the Korea National Statistical Office, the population has annually increased from 49,779,440 in 2011 to 50,617,045 in 2015. Males make up an average 50.0–50.1% of the

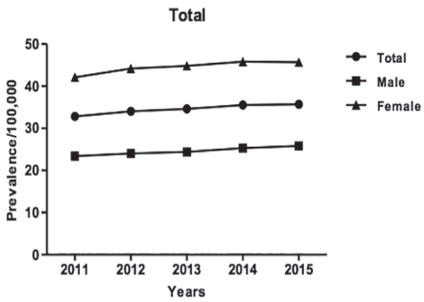

Fig. 1. The annual prevalence of Behçet's disease from 2011 to 2015 in Korea.

study population. All Koreans are covered by two forms of national health insurance such as medical insurance and medicaid in Korea. We reviewed data from the Healthcare Bigdata Hub for the number of patients who had Korean Standard Classification of Diseases (KCD) diagnostic codes consistent with BD between January 1, 2011 and December 31, 2015. We arbitrarily divided the study area into five districts. The population of the capital area, including the Seoul Metropolitan area, accounted for around 48.8–48.9% of the total population, 13.4–13.6% in Chungcheong-Kangwon, 26.4–26.5% in Gyeonsang, 10.0-10.2% in Jeolla, and 1.1–1.2% in Cheju. The study was approved by the Institutional Review Board of Daegu Catholic University Medical Centre.

Data sources

The Korea Healthcare Bigdata consists of medical institution claims data such as diagnosis, surgical treatment, and prescription medicines. Our report was based on the data containing cases with BD and information about all healthcare contacts of patients at primary care clinics and secondary clinics. The data contains information on primary and auxiliary diagnoses given by physicians according to the KCD. Since 2011, the 6th version of the KCD, reflecting the WHO recommendations for the International Classification Disease (ICD-10) update, has been used in Korea. We collected age, gender, and regional demographic data from the Korean Statistical Information Service (KOSIS). We searched the number of patients consistent with the KCD codes of BD (M352) for the period of 2011–2015.

Table I. Prevalence of Behçet's disease of both male and female in Korea according to age groups (number, prevalence/100,000).

Age groups	Male									
	2011		2012		2013		2014		2015	
0 - 9	22	0.9	20	0.8	17	0.7	12	0.5	16	0.7
10 - 19	144	4.2	110	3.3	122	3.8	130	4.2	113	3.8
20 - 29	413	11.4	402	11.2	436	12.2	465	12.9	451	12.5
30 - 39	1.117	27.0	1.096	26.7	1.074	26.5	1.013	25.4	949	24.1
40 - 49	1.972	45.4	1.975	45.5	1.927	44.4	1.948	45.1	1.949	45.5
50 - 59	1.678	47.5	1.836	49.5	1.868	48.4	2.002	50.3	2.147	52.8
60 - 69	606	30.9	694	34.4	777	37.1	860	39.0	959	40.9
70 - 79	178	15.4	189	15.6	207	16.4	252	19.5	264	20.0
≥ 80	30	9.6	29	8.5	29	7.7	34	8.3	42	9.5
Age groups	Female									
	2011		2012		2013		2014		2015	
0 - 9	17	0.8	13	0.6	21	0.9	19	0.9	15	0.7
10 - 19	229	7.4	229	7.6	219	7.5	213	7.6	182	6.7
20 - 29	811	24.6	824	25.5	800	25.0	847	26.6	755	23.7
30 - 39	1.930	48.9	1.929	49.3	1.815	47.1	1.706	45.0	1.595	42.9
40 - 49	3.438	82.1	3.498	83.4	3.441	82.0	3.447	82.2	3.357	80.3
50 - 59	3.025	85.6	3.378	91.1	3.573	92.6	3.762	94.8	3.781	93.4
60 - 69	1.135	52.4	1.299	58.8	1.433	63.0	1.605	67.4	1.808	71.7
70 - 79	369	22.8	401	23.9	468	27.2	515	29.4	542	30.6
≥ 80	46	6.2	54	6.7	55	6.3	81	8.7	83	8.3

The data are described as number of patients and prevalence/100,000 at each year.

Table II. Comparison of prevalence and gender ratio in different geographic countries.

Country of study	Prevalence/100,000	Male/female ratio
Turkey (2)	420	1.03
Northern China (2)	110	1.34
Japan (2)	22	0.98
Israel (5)	15.2	1.11
Sweden (6)	4.9	2.07
Germany (7)	2.26	0.88
United State of America [8)	5.2	0.44
Korea (4)	30.2	0.63
Iran (3)	80	1.19
Present study	32.8 - 35.7	0.54 - 0.56

Statistical analysis

Age, sex, and geographical distribution-specific prevalence rates for BD were estimated as the number of patients x 100,000/total population, if appropriate. The expected prevalence of BD from 2016 to 2025 was calculated through time series analysis using the ARIMA model. Its expected prevalence was described as prevalence rate with 95% confidence interval (95% CI). Statistical analyses were performed using IBM SPSS Statistics 19.0 software (IBM Corp., Armonk, NY, USA).

Results

Annual prevalence rate

The number of patients with BD registered by the National Health Insurance Corporation of Korea has been on the rise every year, from 16,304 (5,846 males and 10,458 females, 32.8/100,000 people) in 2011, 17,025 (6,001 males and 11,024 females, 34.0/100,000 people) in 2012, 17,370 (6,120 males and 11,250 females, 34.6/100,000 people) in 2013, 17,915 (6,377 males and 11,538 females, 35.5/100,000 people) in 2014, and 18,087 (6,525 males and

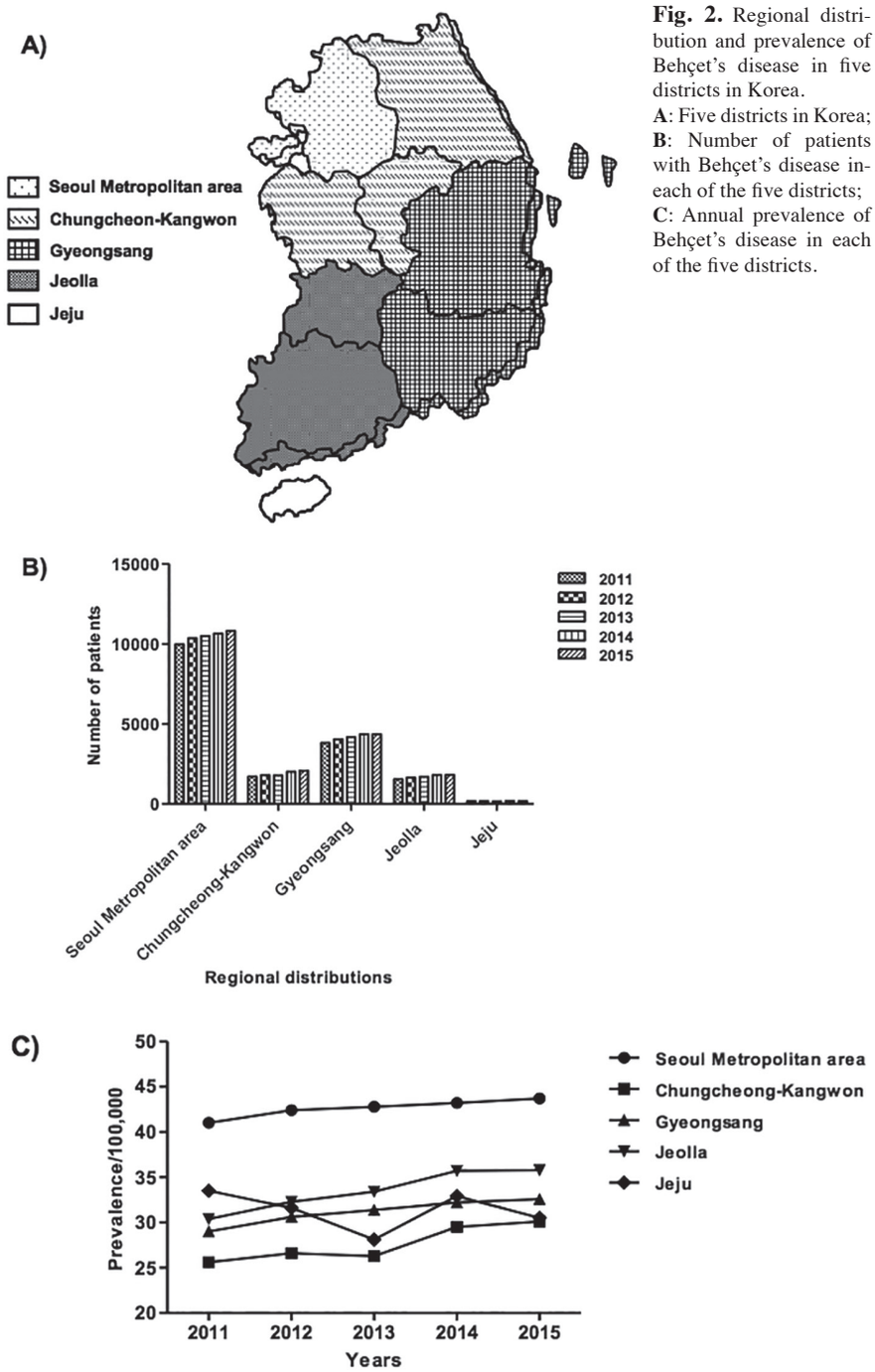

Fig. 2. Regional distribution and prevalence of Behçet's disease in five districts in Korea.
A: Five districts in Korea; **B**: Number of patients with Behçet's disease in each of the five districts; **C**: Annual prevalence of Behçet's disease in each of the five districts.

11,562 females, 35.7/100,000 people) in 2015. Our study showed that the observed prevalence rate of BD is increasing annually in the number of both male and female patients (Fig. 1). The prevalence rate was 32.8 in 2011, 34.0 in 2012, 34.6 in 2013, 35.5 in 2014, and 35.7 in 2015.

Age- and sex-specific prevalence rate

The age-specific distribution of prevalence in BD is consistently highest in the sixth decade and the second highest in the fifth decade in both genders (Table I). The prevalence for males and females was 23.4 and 42.1 in 2011, 24.0 and 44.2 in 2012, 24.4 and 44.8 in 2013, 25.3 and 45.8 in 2014, and 25.8 and 45.7 in 2015, respectively (Fig. 1). In addition, the male to female ratio of BD is estimated at 0.54:1 to 0.56:1, showing female predominance during the assessment period between 2011 to 2015 (Table II).

Regional prevalence rate and future trends

The regional distribution of Korea is divided into 5 districts (Fig. 2A). The number of BD patients was the highest in the Seoul metropolitan area, followed by Gyeongsang, Chungcheong-Kangwon, Jeolla, and the Jeju district (Fig. 2B). The observed prevalence rate of BD patients per regional population in 2015 was 43.7 in the Seoul metropolitan area, 35.8 in Jella, 32.6 in Gyeongsang, 30.5 in Jeju, and 30.1 in Chungcheong-Kangwon (Fig. 2C). In most regions, the prevalence of BD has increased annually, with some fluctuation of prevalence in Jeju. Next, we estimated the expected prevalence of BD patients from 2016 to 2025 (Fig. 3A and B), ranging from 36.9 (95% CI 35.0–39.0) to 44.7 (95% CI 40.2–49.6) in the total population, from 26.5 (95% CI 25.4–27.6) to 33.0 (95% CI 30.2 - 36.1) for males, and from 47.0 (95% CI 42.3–52.1) to 56.2 (95% CI 43.9 - 71.8) for females.

Discussion

This report is the first population-based study using data from the Korean Heathcare Bigdata in the HIRA Service from 2011 to 2015 in Korea. No other recent study has examined the prevalence and future trends of BD based on data from the HIRA Service. Based on the number of patients consistent with the BD diagnostic code (M352), we observed a prevalence of BD from 2011 to 2015 of 32.8 to 35.7 per 100,000 population with female predominance, indicating a slightly increased prevalence compared to previous data in Korea (4).

BD is a ubiquitous inflammatory disorder with a distinct geographic variation of prevalence according to country or region, with a prevalence of 15 - 420 per 100,0000 inhabitants in Asian and Middle Eastern countries such as Turkey (2), Northern China (2), Japan (2), Iran (3), and Korea (4) (Table II). In contrast, the prevalence of BD in Europe and the US is approximately 10- to 20-fold lower. Because the exact pathogenesis of BD has not yet been determined, causes for the differences in the global distribution of BD have

also not yet been established. A genetic factor such as HLA-B51 may help explain the differences in the geographic prevalence of BD. The HLA-B or HLA-B51 subtype has been found to be related to the aberrant function of neutrophils and abnormal T lymphocytes, suggesting a genetic risk factor related to the development of BD (9). In addition, the relative risk of the development of BD among subjects with the HLA-B51 allele is higher, compared to those without the gene (10). It has been recognised that geographic variation of BD might be closely related to ethnicity, due to similar genetic backgrounds. However, recent studies have demonstrated that ethnicity itself does not influence the development of BD. Fewer BD patients have been noted among Japanese subjects who emigrated to Hawaii and the mainland US, compared to cases in Japan (11). Kotter *et al*. found no significant difference in the clinical expression or severity in BD between patients of German origin and patients of Turkish origin living in Germany (12). This suggests that environmental factors also act as a potent trigger for the development of BD in genetically susceptible subjects.

In many areas, BD is more common in males than females, with 2- to 10-fold increase in Middle Eastern and other Silk Road countries such as Turkey, Iran, and China (3). In contrast, female cases are more frequently noted in East Asia and Europe, including Korea, Japan, Spain, the United Kingdom, and Germany (3). Interestingly, it has been noted that the female dominance of BD has decreased, and there has been a roughly equal male to female ratio in the last 20 years. Some epidemiologic studies in Korea showed female predominance (male: female = 0.57–0.61:1) for BD patients (13, 14). In this study, we observed a similar gender distribution, with fewer males (0.54–0.56:1). This female dominance might be related to less reluctance to establish a BD diagnosis in female patients.

BD mainly affects adults between the second and third decades of life, around 35.7 years of age in Japan, 26.2 years in Iran, 25.6 years in Turkey, 24.7 years in the UK, 33 years in Sweden, and 31 years of age in the US (3). The late second to early third decade (28–33 years) is the mean age of disease onset in Korean BD patients (13, 14, 15). Age at first visit was generally found to be one decade later than age at disease onset in the analysis of 1,527 BD patients from a multicentre-based epidemiologic study (14). At first visit, 30.2% and 41.0% of patients were in the 30–39 age group and 40-49 age group, respectively (14). Unfortunately, we could not identify the age of disease onset in our data. However, the highest prevalence rate among age groups in the present study was in the 40–49 year old age group, followed by the 50–59 age group. We found that definite diagnosis of BD occurs mainly in the fifth decade of life in this study. Although disease onset occurred much earlier, in the 20–40 age group (13, 14), it takes more time to fulfill the diagnostic criteria of BD. In real life clinical practice, clinicians are inclined to defer a definite diagnosis of BD for patients who present with one or two clinical features such as oral aphthous ulcerations or uveitis compatible with the International Study Group (ISG) criteria of BD proposed in 1990 (16). In addition, BD is generally rare in individuals younger than 10 years old and older than 80 years of age. To the best of our knowledge, data for this age group have not been presented until now. This study showed less than 1 patient per 100,000 population in both genders. Interestingly, patients 80 years or older still have a prevalence of 6–9 per 100,000 population. It could be explained by improving in therapeutic options over years and/or by a mild disease course. In addition, the mortality rate in BD has been found increased especially in young male patients with major organ involvement, such as intestinal, vascular, or neurological involvements (17).

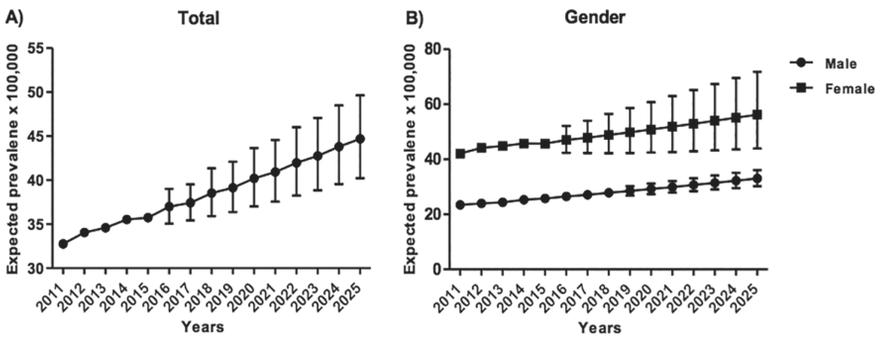

Fig. 3. Expected prevalence of Behçet's disease from 2016 to 2025 in Korea.
A: Total expected prevalence and **B**: Expected prevalence of each gender.

Another peculiar feature is that the prevalence of BD differs within ethnic populations and shows regional variation within the same country. Within Turkey, a greater than 10-fold decrease in prevalence in BD has been observed from east to west (7, 18). In addition, a 30-fold decrease in BD prevalence has been found between northern and southern Japan (11). The present study analysed the annual prevalence of 5 individual districts within Korea, revealing mean proportions of BD patients of 60.3% in the Seoul Metropolitan area, 10.8% in Chungcheong-Kangwon, 23.9% in Gyeonsang, 9.8% in Jeolla, and 1.0% in Cheju. This is a similar trend to data of a previous epidemiologic study reported in 2001 in Korea (14), where most BD patients lived in the Seoul Metropolitan area. In addition, a higher prevalence in the Gyeonsang district was noted than in western districts such as Chungcheong-Kangwon or Jeolla. The geographic deviation of BD prevalence in Korea may be proportional to population density or an influence by unknown environmental factors. Choe *et al*. demonstrated no significant differences in HLA-B51 positivity, suggesting that genetic risk factors may not explain the differential prevalence of the disease (19).

The present study has some limitations. First, HIRA data gives only limited information related to BD, including the number of patients by age group and residential area. The data does not in-

clude detailed clinical information such as age, gender, age of disease onset, diagnosis date, and clinical manifestations of BD for each patient. Therefore, we could not calculate the age- or gender-adjusted prevalence of BD. Second, the prevalence of BD may be underestimated in this study. The clinical features of BD in Korea are less severe than in Middle Eastern countries. The ISG criteria in 1990 of 92% sensitivity and 97% specificity have been commonly used for the diagnosis of BD in Korea. However, the performance analysis for ISG criteria in different countries demonstrated much lower sensitivity for BD diagnosis, showing 58% sensitivity in Korea (20). In addition, mild patients who do not need active treatment could be left off in the assessment of prevalence, because they often do not seek medical support or advice. Some patients with severe clinical manifestations such as blind or central nerve system involvement may not be able to come to hospitals or physicians. Therefore, it may be doubtful whether all patients who meet diagnostic criteria have been considered. Third, there were no data on the adequacy of the diagnostic criteria for BD within data from the Healthcare Bigdata Hub of the HIRA Service. However, recent clinical studies on Korean BD patients have applied ISG criteria of BD (21, 22). The ambiquity of the application of the diagnostic criteria seems to be somewhat resolved. A strength of the present study is that it is the first to use data from the Healthcare Bigdata Hub of the HIRA service in Korea. It has yielded useful information for a better understanding of the epidemiologic characteristics of BD in Korea.

In conclusion, this study estimated an overall prevalence of BD of about 32.8 - 35.7 per 100,000 persons in Korea, which is high relative to other countries. The prevalence by gender distribution ranged from 0.54:1 to 0.56:1, with a female predominance from 2011 to 2015 and the highest prevalence in the Seoul Metropolitan area. An increase in the annual prevalence of BD is expected to continue over the next 10 years.

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