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Increased risk of atrial fibrillation in patients with Behçet's disease: A nationwide population-based study

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ABSTRACT

Background: Chronic inflammation plays a role in the pathophysiology of atrial fibrillation (AF). However, there is a paucity of information about whether Behçet's disease (BD) is associated with an increased risk of AF. This population-based study aimed to determine the risk of AF in patients with BD.

Methods: A total of 6636 newly diagnosed BD patients without a history of AF were included from the Korean National Health Insurance Service database between 2010 and 2014. Newly diagnosed non-valvular AF was identified using the claims data. An age- and sex-matched non-BD subjects were extracted at a ratio of 1:5 (n = 31,040). The incidence and risk of AF were compared between groups.

Results: During a mean follow-up of 3.6 ± 1.5 years, AF was newly diagnosed in 173 patients (51 in the BD group, 122 in the control group). The incidence was 2.3 and 1.1 per 1000 person-years, respectively. After adjustment, the BD group showed a 1.8-fold higher risk of AF compared to the control group. Patients with BD aged ≤40 years had a higher risk of AF, while patients aged ≥65 years showed a similar risk. Men with BD had a 2.5-fold increased risk of AF, whereas women with BD did not. Severe BD had a higher risk for AF compared to non-severe BD and controls.

Conclusions: BD was associated with an increased risk of AF, particularly in men and young patients. Active surveillance and treatment are needed in BD patients and those with arrhythmic symptoms.

1. Introduction

Behçet's disease (BD) is a rare inflammatory disease that is characterized by recurrent oral aphthous ulcers and genital ulcers [1]. As it is more common in Turkey, the Middle East, and Eastern Asia than other regions, it is also called "Silk Route disease" [2]. BD is known to involve blood vessels of all sizes on the arterial and venous sides of the circulation [3]. The systemic involvement of BD occurs in two-thirds of patients [4]. The spectrum of cardiac involvement is wide in that pericarditis, cardiomyopathy, endocarditis, endomyocardial fibrosis, intracavitary thrombosis, and coronary artery disease can occur [5]. Meanwhile, arrhythmic complications are relatively uncommon. Conduction abnormalities are combined with aortic root involvement [6], while tachyarrhythmias have been reported in only a small number of studies [7,8]. Atrial fibrillation (AF), the most common arrhythmia in clinical practice, increases in frequency in the aging population [9,10]. Previous studies reported associations between chronic inflammatory diseases and AF. In a Danish nationwide cohort study, patients with rheumatoid arthritis had a 1.4-fold increased incidence of AF compared to the general population [11]. Also, patients with psoriasis or ankylosing spondylitis reportedly have an increased risk of AF compared to age- and the sex-matched general population [12,13]. Patients with BD have impaired left atrial (LA) function measured by echocardiography, which is correlated with C-reactive protein and erythrocyte sedimentation rate, compared with healthy subjects [14]. P-wave dispersion, a known predictor of the development of AF, is prolonged in patients with BD compared to controls [15]. Those evidences suggest the possibility of a positive association between BD and AF, but there is a paucity of data regarding the

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relationship between BD and AF. Therefore, here we aimed to evaluate the risk of AF in patients with BD using a Korean nationwide population database.

2. Methods

2.1. Database

The National Health Insurance Service (NHIS) is the obligatory universal health insurance program that covers almost all residents in Korea (nearly 50 million people). The agency established a nationwide claims database and provided a data-sharing service for policy-making and research purposes. The database includes all beneficiaries' demographic, socioeconomic, prescription, procedural, and diagnosis data according to the 10th revised International Classification of Diseases (ICD-10). The database can be used by any researcher under the authorization of the agency's official review committee. Furthermore, a registration program for Rare Intractable Diseases (RID), a part of the NHIS, has provided medical expense support to patients with rare and intractable diseases since 2006. We used diagnostic codes of the ICD-10 and RID to verify the patients with BD. This study was approved by the review committee of the NHIS (NHIS-2017-1-200) and exempted from the Seoul National University Hospital Institutional Review Board (E-1707-006-864), which waived the requirement for informed consent because the provided database was completely anonymized.

2.2. Study population

Patients with BD was defined as ≥1 hospitalization or ≥2 outpatient clinic visits with a diagnosis of BD (M35.2 in ICD-10 codes) and a RID code (V139) between 2010 and 2014. The diagnostic criteria of BD were a recurrent oral ulcer and any 2 of the following: 1) recurrent genital ulcer, 2) eye involvement, 3) skin involvement, and 4) positive pathergy test. A certified physician assigned the ICD-10 diagnostic code and RID code to a patient. Previous studies defined the severity of BD on clinical features such as symptoms, systemic involvement, and inflammatory markers [16,17]. However, these data were not available in the claims database, so, we defined "severe" patients as having a history of prescription of immunosuppressants and tumor necrosis factor-alpha (TNF-α) inhibitors. The patients who were ≫20 years old at enrollment were included the study cohort; those who were diagnosed with AF prior to or within a month after the BD diagnosis were excluded. An age- and sex-matched control group was extracted at a ratio of 1:5. All study populations were followed up until the end of 2015 or disqualification of insurance by death or emigration.

2.3. Comorbidities and endpoint

Congestive heart failure (CHF), dyslipidemia, prior history of stroke, myocardial infarction (MI), and peripheral arterial disease (PAD) were defined as at least 1 discharge or outpatient diagnosis based on their relevant ICD-10 codes. Hypertension (HTN) and diabetes mellitus (DM) were more prevalent than other comorbidities; thus, those had stricter definitions. Each component of the CHA_2DS_2-VASc score (CHF, HTN, age ≫ 75 years, DM, stroke/transient ischemic attack [TIA]/thromboembolism [TE], vascular disease, age 65–74 years, and sex category) used the same definition of comorbidities except TIA, TE, and vascular disease. The primary endpoint was newly diagnosed non-valvular AF during the follow-up period. AF was defined as at least 1 discharge diagnosis of AF (ICD-10 codes: I48.0–I48.4, I48.9) or ≫2 outpatient diagnoses. To exclude patients with valvular AF, patients diagnosed with mitral stenosis (I050, I052, and I059), or those with mechanical heart valves (Z952–Z954) were excluded from the analysis. Detailed definitions are described in Supplementary Table 1 and were validated in previous studies [18,19].

2.4. Statistical analysis

Categorical variables are expressed as numbers and percentages and were compared using the Chi-square test. Continuous variables are expressed as mean and standard deviation and were compared using Student's *t*-test. The endpoint was the incidence of 1000 person-years. The risk of AF was calculated by Cox proportional hazard regression models and adjusted for age, sex, income level, living place, CHF, HTN, DM, ischemic stroke, MI, PAD, dyslipidemia, and use of antihypertensives, anti-diabetics and anti-inflammatory drugs including non-steroidal anti-inflammatory drugs (NSAIDs), systemic steroid, and TNF-α inhibitors. Hazard ratio (HR) and 95% confidence intervals (CI) were suggested. The cumulative risk of AF was estimated using the Kaplan-Meier method. A log-rank test was used to check the differences in risk of AF between patients with BD and controls. Two-sided *p*-values were used, and those ≪0.05 were considered statistically significant. All data management and statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline characteristics of the study population

Among the 6636 patients with BD identified between 2010 and 2014, 102 with known AF and 326 patients ≪20 years of age were excluded. Finally, a total of 6208 patients with BD and 31,040 age- and sex-matched non-BD controls were analyzed. Table 1 summarizes the baseline characteristics of the study population. Mean age was 44.5 ± 12.5 years; two-thirds of the patients were women (67.2%). Patients with BD had more cardiovascular (CV) comorbidities including dyslipidemia, PAD, history of ischemic stroke, and CHF than the control group. The mean CHA_2DS_2-VASc score of the patients with BD was higher than that of the control group (1.2 ± 1.1 vs. 1.0 ± 0.94, $p \ll 0.001$). Prescription history of systemic steroid, immunosuppressant, and TNF-α inhibitor was significantly higher in the BD patients group.

3.2. Incidence and risk of development of AF in patients with BD and controls

During a mean follow-up of 3.6 ± 1.5 years, 51 patients (30 men, 21 women) with incident AF were identified among 6208 patients with BD, whereas 123 patients with AF (47 men, 75 women) were identified in the 31,040 individuals in the control group. The crude incidence of each group was 2.3 and 1.1 per 1000 person-years, respectively (Table 2). The crude HR in patients with BD was 2.1 (95% CI, 1.52–2.89). After the adjustment for CV comorbidities such as heart failure, HTN, DM, prior ischemic stroke/TIA/TE, prior MI, PAD, dyslipidemia, income level, living place and use of medications, patients with BD showed a higher risk of AF development (HR, 1.8; 95% CI, 1.21–2.81) (Table 2). The incidence of AF was higher in men with BD than in those without BD (4.2 vs. 1.3 per 1000 person-years), whereas there was no significant difference in the incidence of AF between women with or without BD (1.4 vs. 1.0 per 1000 person-years). After the adjustment for age, sex, income level, living place, CHF, HTN, ischemic stroke, MI, PAD, dyslipidemia, and use of advanced anti-inflammatory drugs, men still had an increased risk of AF compared to the control group (adjusted HR, 2.5; 95% CI, 1.36–4.64), whereas women did not (adjusted HR, 1.5; 95% CI, 0.81–2.62) (Fig. 1). Severe patients showed a higher incidence of AF compared to non-severe patients and controls (2.81 vs. 2.09 vs. 1.10 per 1000 person-years, respectively, Supplementary Table 2). Risk of developing AF in severe patients (HR 2.85, 95% CI, 1.68–4.83) was also higher than non-severe patients (HR 2.03, 95% CI, 1.34, 3.09) compared

Table 1
Baseline characteristics of the study cohort.

	Patients with BD (*N* = 6208)	Control (N = 31,040)	*p*-Value
Age[a]	44.5 ± 12.5	44.5 ± 12.5	1
20–39	2255 (36.3)	11,275 (36.3)	
40–64	3575 (57.6)	17,875 (57.6)	
≥65-	378 (6.1)	1890 (6.1)	
Men	2038 (32.8)	10,190 (32.8)	1
Living place, Urban	2895 (47.1)	14,371 (46.5)	0.3576
Low income level[b]	1524 (24.6)	7282 (23.5)	0.0653
Congestive heart failure	84 (1.4)	168 (0.5)	≪0.0001
Hypertension	885 (14.3)	3947 (12.7)	0.001
Diabetes mellitus	322 (5.2)	1509 (4.9)	0.279
Ischemic stroke	204 (3.3)	305 (1.0)	≪0.0001
Myocardial infarction	53 (0.9)	93 (0.3)	≪0.0001
Peripheral arterial disease	537 (8.7)	921 (3.0)	≪0.0001
Dyslipidemia	796 (12.8)	2678 (8.6)	≪0.0001
CHA_2DS_2-VASc score[a]	1.22 ± 1.1	1.01 ± 0.94	≪0.0001
Score ≥2	1557 (25.1)	4911 (15.8)	≪0.0001
Aspirin	742 (12.0)	2634 (8.5)	≪0.0001
Oral anticoagulant	143 (2.3)	113 (0.4)	≪0.0001
NSAID	4569 (73.6)	15,590 (50.2)	≪0.0001
Systemic steroid	5.944 (95.8)	20,648 (66.5)	≪0.0001
Immunosuppressant	1851 (29.8)	83 (0.3)	≪0.0001
TNF-α inhibitor	89 (1.43)	19 (0.1)	≪0.0001
Newly diagnosed AF	51 (0.8)	122 (0.4)	
Duration of AF, year[a]	3.56 ± 1.45	3.57 ± 1.44	

AF, atrial fibrillation; BD, Behcet's disease; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; TNF, tumor necrosis factor.

[a] Data are represented as mean ± standard deviation. Other data are presented as number and percentage.

[b] Low income level was defined as below 10 percentiles.

Table 2
Incidence rate and hazard ratio of atrial fibrillation in patients with Behçet's disease and control group.

	Number	AF	Follow-up duration (person-years)	Incidence rate (1000 person-year)	Adjusted hazard ratio (95% confidence interval)
Control	31,040	122	110,733.2	1.10	1 (reference)
Behçet's disease	6,208	51	22,073.4	2.31	1.84 (1.21–2.81)[a]

[a] Adjusted hazard ratio was calculated by Cox proportional hazards regression models, including age, sex, income level, living place, congestive heart failure, hypertension, diabetes mellitus, prior stroke, prior myocardial infarction, peripheral arterial disease, dyslipidemia, NSAIDs, systemic steroid, immunosuppressant, and TNF-α inhibitor.

to non-BD subjects (Supplementary Fig. 1). Cox regression analysis showed that age (adjusted HR, 1.05; 95% CI, 1.04–1.06), male (adjusted HR, 1.90; 95% CI, 1.38–2.62), history of congestive heart failure (adjusted HR, 4.98; 95% CI, 2.81–8.82), history of ischemic stroke (adjusted HR, 2.02; 95% CI, 1.17–3.50), CHA2DS2-VASc score ≥2 points (adjusted HR, 2.24; 95% CI, 1.36–3.69) and numbers of admission due to BD (adjusted HR, 1.96; 95% CI, 1.42–2.70) are associated with increased risk of AF (Supplementary Table 3).

3.3. Subgroup analysis

The subgroup analysis in patients with BD showed a consistently increased risk of AF. There was a significant interaction in the subgroups of sex, age, CHF, and CHA_2DS_2-VASc score. The incidence of AF was higher in men with BD than in women with BD (4.2 vs. 1.4 per 1000 person-years). Men with BD had a 2.5-fold higher risk of AF than the control group (HR, 2.5; 95% CI, 1.36–4.64), whereas women with BD showed a similar risk of AF to that of the control group (HR, 1.5; 95% CI, 0.81–2.62) (Fig. 2). For age, the incidence of AF was the lowest in young patients (1.5 per 1000 person-years) and the highest in older patients (6.2 per 1000 person-years). However, the risk of developing AF in patients with BD under 65 years was higher than their matched control. Furthermore, patients with BD under 40 years of age showed a 10.4-fold increased risk of incident AF compared to controls (age 20–39 years: HR, 10.4; 95% CI, 2.49–43.08; age 40–64 years: HR, 1.9; 95% CI, 1.09–3.24). However, patients older than 65 years showed a similar risk of AF to that of the control group (HR, 1.1; 95% CI, 0.45–2.47) (Fig. 2). The incidence of AF was higher in subjects with CV comorbidities than in those without CV comorbidities. However, the effect of BD on AF development was relatively weaker in those with CV comorbidities than in those without.

4. Discussion

In this Korean nationwide population database, the main findings we found are as follows: (1) patients with BD were at an increased risk of AF compared to those without BD. (2) Severe patients had a higher risk of AF than non-severe patients and controls. (3) The risk of AF was higher in young patients with BD, but not older patients with BD; and (4) men with BD were at higher risk of AF, whereas women with BD had a similar risk of AF to that of the controls. (5) Age, male sex, history of congestive heart failure and ischemic stroke, CHA_2DS_2-VASc ≥2, and numbers of admission due to BD are independent risk factors of AF in patients with BD. It is well known that the range of cardiac involvement of BD is diverse, but there is a paucity of evidence regarding the relationship between BD and arrhythmias. To the best of our knowledge, this is the first study to report that BD is an independent risk factor of AF.

4.1. Association between inflammation and AF

Although the mechanism of AF development in patients with BD is unclear, there are several possible mechanisms to explain the association between BD and AF. First, inflammation is a well-known risk factor for AF. In healthy subjects, levels of inflammatory biomarkers like high-sensitivity C-reactive protein and cytokines such as interleukin-6 are increased in patients with AF compared to normal subjects [20]. Inflammation of atrial tissues, including the infiltration of white blood cells, atrial myocyte necrosis, and fibrosis was observed in lone AF patients but not in patients with sinus rhythm [21]. As a result, inflammatory processes lead to electrical and structural remodeling of the atria that would be potential substrates of AF [22]. Second, patients with BD showed evidence of structural atrial remodeling. Karabag et al. reported that atrial electromechanical conduction times were increased in patients with BD compared to controls [15]. Aktürk et al. analyzed the left atrial volume and function of patients with BD assessed by real-time three-dimensional echocardiography and reported that those were impaired in the patients with BD [14]. Various inflammatory diseases were correlated with the development of AF. Rheumatoid arthritis is a well-known risk factor of AF [11]. Systemic lupus erythematosus, systemic sclerosis, celiac disease, psoriasis, and herpes zoster were

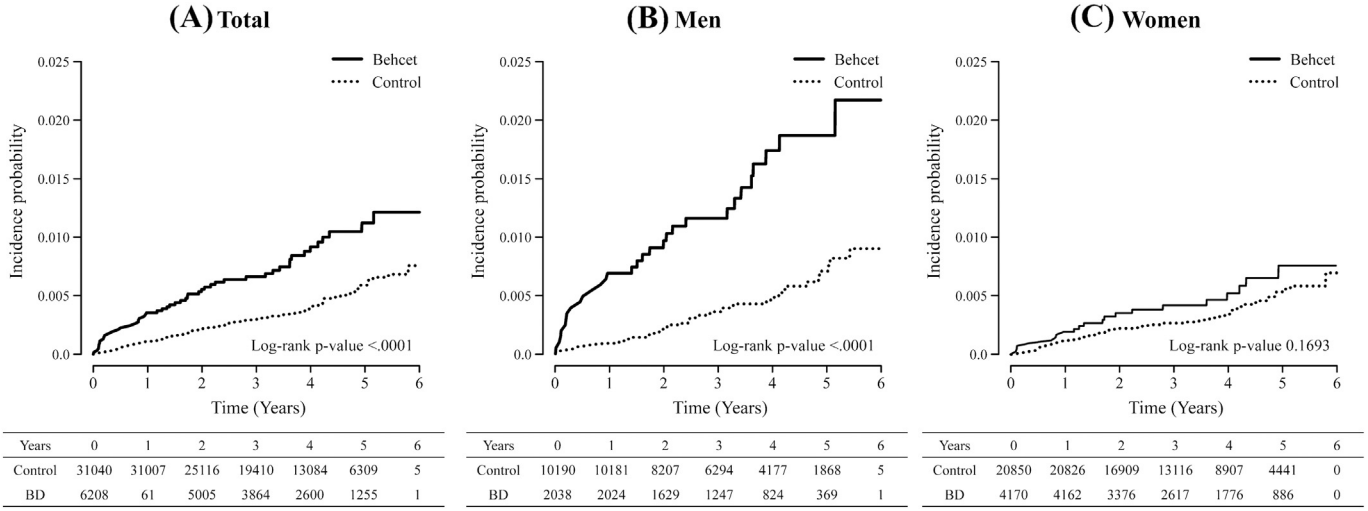

Fig. 1. Cumulative incidence of atrial fibrillation in patients with and without Behçet's disease. Cumulative incidence of AF was plotted by Kaplan-Meier curves in (A) total study population, in (B) men, and in (C) women. Overall cumulative incidence of AF were increased in patients with BD, mostly due to increased incidence in men. There is no difference in women.

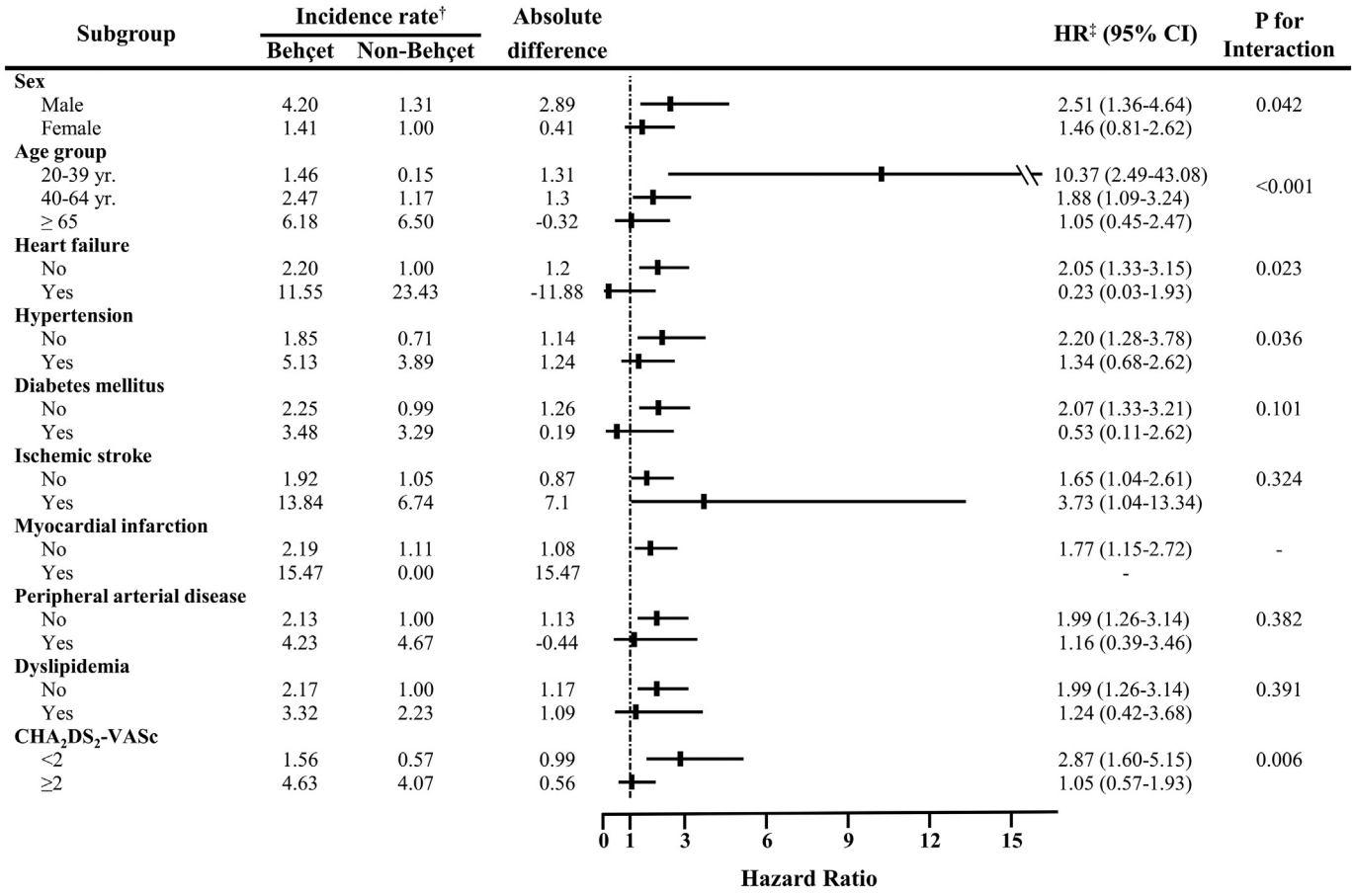

Fig. 2. Subgroup analysis for risk of AF in patients with BD. †Per 1000 person-years. ‡Adjusted for age, sex, income level, living place, heart failure, hypertension, diabetes mellitus, prior ischemic stroke/transient ischemic attack/systemic thromboembolism, peripheral arterial disease, dyslipidemia, aspirin medication.

also related to an increased risk of AF [13,23–25]. Also, inflammation and its severity were associated with an increased risk of AF. Patients with inflammatory bowel disease showed an increased risk of AF, particularly in a flare or persistent state [26]. In rheumatoid arthritis, increased erythrocyte sedimentation rates and severe extra-articular rheumatoid arthritis were risk factors for the development of AF [27]. Severe, but not mild, psoriasis significantly increased AF and TE risk [13]. Patients with severe herpes zoster infection requiring hospitalization showed an increased risk of AF, whereas those with mild herpes zoster infection did not [25]. In this study, we found that severe BD patients who used immunosuppressants and TNF-α inhibitors had a higher risk of AF. Also, the number of admission due to BD was also associated with an increased risk of AF. Therefore, our results were consistent with the previous studies that BD itself and its severity had an association with a higher risk of AF development. Use of immunosuppressants and TNF-α inhibitors and number of admission due to BD could be surrogate markers for disease activity of BD and risk factors for AF, but further studies would be needed to confirm our observation.

4.2. Differences in risk of AF according to age and sex

We found that the risk of AF was increased in young patients with BD (age ≪ 40 years) compared to the age-matched control group, but the same was not true in older patients with BD. Previous studies showed that the clinical manifestations of BD were associated with the patient's age. Kural-Seyahi et al. reported that young male patients had much higher mortality rates than the general population. Also, symptoms were usually active in the early phase of the disease and decreased gradually with age [28]. Kaklamani et al. found that symptoms of BD and the frequency of recurrence decreased over time [29]. In line with previous reports, our findings suggested that young patients with BD should be screened for AF. Interestingly, men with BD had a higher risk of AF than women with BD. However, women with BD were not at increased risk of AF compared with controls. The same pattern is observed for the cumulative risk of AF occurrence. Although the mechanism of the sex-based effect in BD is unclear, it is well known that the clinical manifestations of patients with BD differ between the sexes. For instance, male patients with BD present more severe forms of clinical manifestations; thus, their prognosis was worse than that of women [28]. A retrospective study reported that male patients with BD had a worse mean clinical severity score than female patients with BD, so sex was a significant risk factor for severity [30]. In 1901 Korean patients with BD, men had more ocular and vascular symptoms that were related to severe complications or mortality than women [31]. Also, a review of Japanese nationwide registration data revealed that men had more ocular lesions, and women had more genital ulcers [32]. In the general population, the incidence of AF in men is higher than that in women [9], and the same appears true in patients with BD. In line with previous studies, we found that the risk of AF was elevated only in male patients with BD as the sex-based differences seem to be unique features of BD itself. Several studies reported that hormones might affect the symptoms of BD [33–35]. In women, the onset of uveitis peaked during the late stage of the menstrual cycle, when the anti-inflammatory effect of sex hormones became weak [33]. Serum prolactin level and bioavailable testosterone possibly affect the clinical manifestations of BD [34,35]. Unfortunately, the mechanism of

sex-based differences could not be explained in our study because laboratory information was not available in our database. Further studies are needed to identify the mechanisms of sex-based differences.

4.3. Risks of AF and CV comorbidities

The risk of AF in patients with BD who did not have each CV disease was about 1.7–2.5 times higher than that of the control group. In contrast, the risk of AF in BD patients with each CV disease was similar to that of the control group. Furthermore, the same trend was observed in patients with BD who had multiple comorbidities, represented by a CHA_2DS_2-VASc score of 2 or more. Those findings suggested that the effect of BD for AF was weaker than that of the traditional CV comorbidities. CV comorbidities are known risk factors for AF, and their effects were significant in patients with BD and controls. Since controls with CV diseases also had a higher incidence of AF, the risk of developing AF in patients with BD seemed insignificant. Although the HR appeared numerically low, the crude incidence rates were higher in BD patients with CV comorbidities than in those without them. Therefore, the influence of CV comorbidities on AF should not be underestimated. In Cox regression analysis, age (per 1 year), male sex, history of congestive heart failure and ischemic stroke, CHA_2DS_2-VASc score ≥2 and the number of admission due to BD are independent risk factors of AF in the patients with BD. Except for the number of admission, others are well-known risk factors in the general population [36].

4.4. Limitations

There are several limitations to this study. First, this was an observational cohort study of nationwide claims data that has limited information for patient-level clinical manifestations and laboratory information such as inflammatory biomarkers. Although systemic involvements of BD, especially in the cardiovascular system, would have an impact on the risk of AF, the operational definition using the ICD-10 codes and prescription showed limited power to evaluate cardiac involvement of BD in this study. Thus, we could not elucidate the correlations between the disease activity and inflammatory state of BD and AF. Second, the definitions of BD, comorbidities, and outcomes were based on the combinations of diagnostic codes and claim records; thus, misclassification was possible. The definition of BD used in this study has not been fully proven in previous studies. Extra efforts were made to minimize BD misclassifications by adding Korean rare disease registration data. Also, our definitions of CV terms were validated in previous studies [37–39]. Third, BD showed ethnic and regional differences in disease expression. However, our findings were derived from a cohort that consisted of homogenous ethnicity. Therefore, the application of our results in the clinical setting must be done cautiously in other regions or populations, and further studies are needed. Fourth, we did not observe CV outcomes like heart failure or ischemic stroke in patients with BD and AF. Nevertheless, this is the first large population-based study to describe the relationship between BD and the development of AF.

5. Conclusion

This is the first nationwide population-based study to elucidate the association between BD and AF. The patients with BD had a 2-fold increased risk of AF compared to the control group. The risk of AF was increased, particularly in young and male patients with BD, but was not in older patients and female patients with BD. Age, male, history of heart failure, and stroke are independent risk factors of AF, and anti-inflammatory treatment may reduce the risk. The physicians should consider the possibility of AF in patients with BD, especially young and male patients, and provide active treatment to all patients with BD.

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Conflict of interest statement

All authors declare that there is no conflict of interest relevant to the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.045.

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