의학박사 학위논문

베체트 병 환자에서 심혈관계 질환의 위험성: 전국민 기반 표본 코호트의 후향적 분석

Risk of cardiovascular disease in patients with Behçet disease: Retrospective analysis of the nationwide population-based cohort

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이 논문을 의학박사 학위 논문으로 제출함

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Abstract

Few studies have investigated the correlation between Behçet disease (BD) and cardiovascular diseases (CVD). We investigated the risk of CVD in patients with BD. Between 2003 and 2015, we performed a retrospective cohort study involving patients with BD selected from the National Health Insurance Service-National Sample Cohort database and age- and sex-matched controls. Logistic regression analysis was performed to examine the association between BD and comorbidities. Cox proportional hazards regression analysis was performed to compare the hazard ratio (HR) of diseases that showed significance using logistic regression analysis. Among the 998 patients with BD and the 4,990 controls studied, patients with BD showed a significantly higher risk for angina pectoris (adjusted HR 1.522, 95% confidence interval [CI] 1.020–2.273) and peripheral arterial disease (adjusted HR 2.939, 95% CI 1.296–6.664) than controls. The cumulative incidence rates of these diseases in patients with BD were also significantly higher than those in controls (log-rank p=0.005 and 0.007 for angina pectoris and peripheral arterial disease, respectively). This study

demonstrated that patients with BD showed an independent risk for angina pectoris and peripheral arterial disease.

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Introduction

Behçet disease (BD) shows a global distribution; however, it is particularly prevalent in the Middle East and the Far East along the Silk Road.[1] This could be attributed to genetic factors, such as the association of BD with HLA-51.[2] BD is considered a systemic vasculitis presenting with diverse clinical symptoms involving the skin and the mucous membranes, as well as ocular, arthritic, and vascular signs.[3, 4] However, vascular involvement observed in patients with BD is nonspecific, unlike other symptoms. The association of HLA-51 with vascular manifestations is not linked,[5] and vascular manifestations were included in the diagnostic criteria for BD only after 2014.[6] However, vascular involvement is known to occur and its incidence varies from 7%–50%.[7, 8] A few studies have investigated the relationship between cardiac lesions and BD in relation to vascular involvement.[9, 10] However, no study has established to quantitatively analyze the risk for cardiovascular diseases (CVD) in BD. We performed a Korean population-based cohort study using the

National Health Insurance Service–National Sample Cohort (NHIS-NSC) database to investigate the risk of CVD in patients with BD.

Materials and methods

Study design and database

This was a retrospective cohort study that investigated records of 1,108,369 representative patients obtained from the NHIS-NSC database. Of note, 100% of the Korean population is covered by the NHIS, and this population is classified into 3 categories: The NHI program for employees, for the self-employed groups, and the medical aid system. In 2013, 97.2% (n=49,989,620) of the population was covered by the NHI and the remaining 2.8% (n=1,458,871) by the medical aid system.[11] Owing to the large volume of the database and the lack of confidentiality in regards to personal information available with the National Health Information Database (NHID), the NHIS-NSC was modeled as a representative sample database, which contains a substantial volume of representative information that does

not require privacy regulations.[12] We obtained information from the NHIS-NSC database between January 2002 and December 2015 for our study. Patients who had been treated for any type of BD or comorbidities during the screening period (2002) were excluded. Age, sex, residential location, income, and diagnostic codes based on the International Classification of Diseases, Tenth Revision (ICD-10) were recorded. This study was approved by the Ethics Committee of Korea University Anam Hospital (2018AN0009) and was performed according to the principles of the Declaration of Helsinki. The flow chart of the study is summarized in **Figure 1.**

Definition of clinical outcomes

Patients with ICD-10 codes M352 (BD) were identified from the NHIS-NSC. BD is diagnosed by the national registry of rare intractable disease program in NHIS-NSC. To be diagnosed in the rare intractable disease registration, the diagnosis must be suitable for specific diagnostic criteria defined by the Korean health ministry. Patients with comorbidities were defined as those with hypertension (ICD-10 codes I10-13 and I15), diabetes mellitus (ICD-10 codes E11-14), dyslipidemia (ICD-10 codes E78), angina pectoris

(ICD-10 codes I20), myocardial infarction (ICD-10 codes I21 and I22), cerebral infarction (ICD-10 codes I63), cerebral hemorrhage (ICD-10 codes I60), or peripheral arterial disease (PAD) (ICD-10 codes I70, I70.0, I70.2-70.3, I70.8-70.9, I74.2-74.5). To improve the accuracy of the analysis, we only included patients with at least 2 principal diagnostic codes

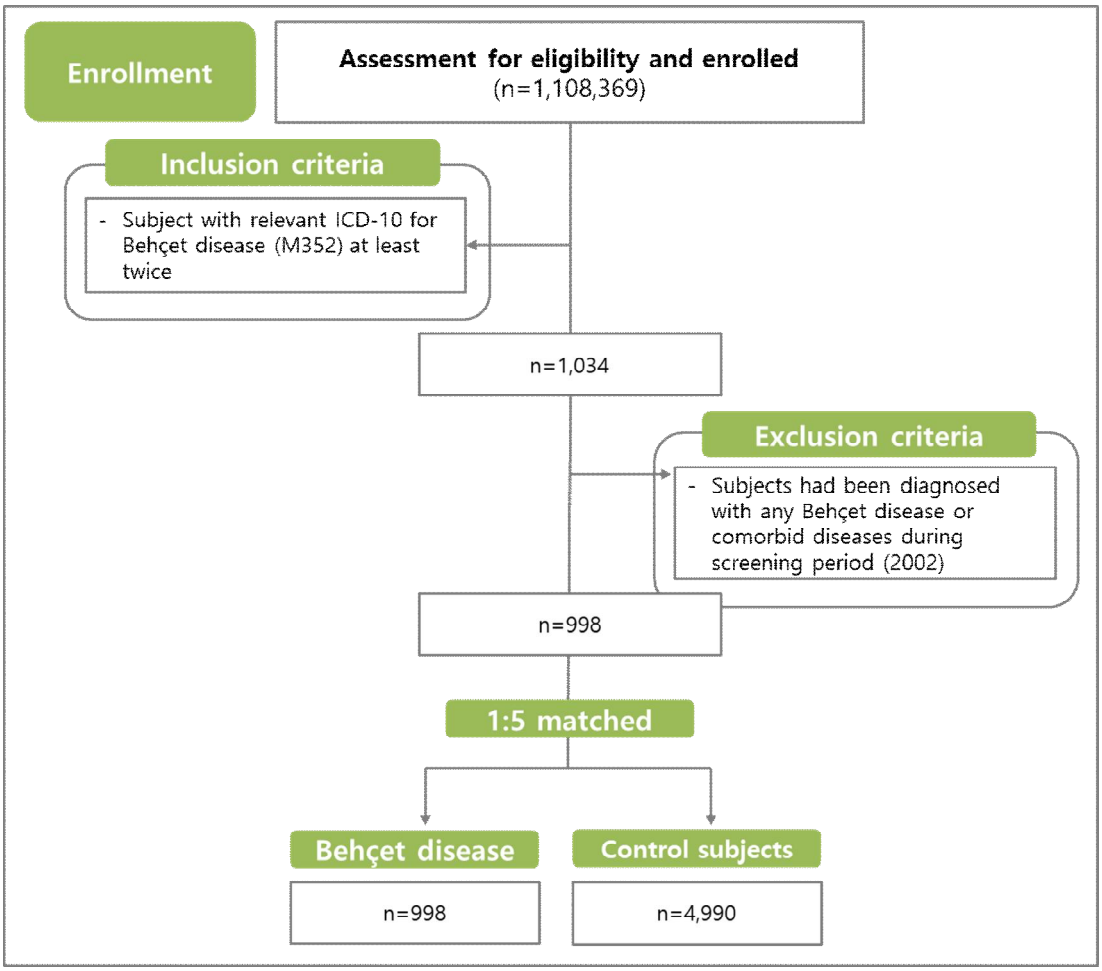

Figure 1. Flowchart of the study

for each disease. The date of diagnosis of the diseases was used as the entry date for patients with the disease. Age- and sex-matched controls were selected randomly from the NHIS-

NSC database at a frequency of 1:5.

Statistical analysis

The Pearson's chi-squared test or the Fisher exact test was used to assess significant differences between nominal variables. Logistic regression analysis was performed to examine the association between BD and comorbidities including hypertension, diabetes mellitus, dyslipidemia, angina pectoris, myocardial infarction, cerebral infarction, cerebral hemorrhage, or PAD. Variables showing a p value <0.10 using the univariate model were subjected to analysis using a multivariate model, followed by backward elimination to retain the final significant predictors in the model. Incidence rates were calculated by dividing the number of events by person-years at risk. Both, univariate and multivariate Cox proportional hazards regression analyses were performed using α=0.05 as the significance level to calculate the crude hazard ratio (HR) and the mutually adjusted HRs with their 95% confidence intervals (CI) after adjusting for residential location, income, and comorbidities. Survival curves of angina pectoris and PAD in patients with BD and in controls were plotted using the Kaplan–Meier method, and statistical significance was examined using the log-

rank test. A p value <0.05 was considered statistically significant. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline and clinical characteristics of patients with Behçet disease and controls

Between January 2003 and December 2015, we identified 998 patients with BD and 4,990 matched controls without BD (ratio 1:5). The sex ratio among patients with BD was female:male=63.43:36.57. The highest prevalence of sleep disorders was observed among patients aged 30–39 years (27.15%), followed by those aged 40–49 years (26.05%). In both groups, the most prevalent comorbidity was hypertension, followed by diabetes mellitus. Demographic and clinical characteristics of the study population are summarized in **Table 1**.

Association between Behçet disease and comorbidities

We performed univariate and multivariate logistic analyses to evaluate the association between BD and comorbidities (**Table 2**). Univariate analysis showed a positive trend between BD and PAD (odds ratio [OR] 1.886, 95% CI 0.968–3.674, p=0.058), and this trend

became significant after adjusting for variables (p=0.024). However, univariate analysis showed a significant association between BD and angina pectoris (OR 1.535, 95% CI 1.130–2.087, p=0.006), although the significance disappeared after adjusting for variables (p=0.058). The association between BD and comorbidities other than angina pectoris and PAD was not statistically significant compared to controls.

Table 1. Demographic and clinical characteristics of the study population

Characteristics	Patients with Behçet disease (n=998)	Controls (n=4,990)	*p* value
Age, n (years)			1.000
0–19	105 (10.52)	525 (10.52)	
20–29	180 (18.04)	900 (18.04)	
30–39	271 (27.15)	1,355 (27.15)	
40–49	260 (26.05)	1,300 (26.05)	
50–59	119 (11.92)	595 (11.92)	
≥60	63 (6.31)	315 (6.31)	
Sex, n (%)			1.000
Male	365 (36.57)	1,825 (36.57)	
Female	633 (63.43)	3,165 (63.43)	
Residential location, n (%)			0.569
Urban	266 (26.65)	1,374 (27.54)	

Rural	732 (73.35)	3,616 (72.46)	
Income, n (%)			0.005
0–20	111 (11.62)	674 (13.90)	
20–40	132 (13.82)	785 (16.19)	
40–60	223 (23.35)	1,124 (23.18)	
60–80	245 (25.65)	1,119 (23.07)	
80–100	244 (25.55)	1,148 (23.67)	
Comorbidities			
Hypertension	213 (21.34)	1,117 (22.38)	0.470
Diabetes mellitus	103 (10.32)	481 (9.64)	0.508
Dyslipidemia	100 (10.07)	477 (9.56)	0.652
Angina pectoris	56 (5.61)	186 (3.73)	0.006
Myocardial infarction	5 (0.50)	27 (0.54)	0.874
Cerebral infarction	28 (2.81)	119 (2.38)	0.433
Cerebral hemorrhage	2 (0.20)	13 (0.26)	0.729
Peripheral arterial disease	12 (1.20)	32 (0.64)	0.058

Table 2. Logistic regression analysis for comorbidities in patients with Behçet disease compared to controls

Comorbidities	Univariate analysis		Multivariate analysis*	
	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Hypertension	0.941 (0.797–1.110)	0.470	-	
Diabetes mellitus	1.079 (0.862–1.350)	0.508	-	
Dyslipidemia	1.054 (0.840–1.322)	0.652	-	
Angina pectoris	1.535 (1.130–2.087)	0.006	1.366 (0.989–1.886)	0.058
Myocardial infarction	0.927 (0.356–2.412)	0.874	-	
Cerebral infarction	1.182 (0.778–1.794)	0.433	-	
Cerebral hemorrhage	0.769 (0.173–3.412)	0.729	-	
Peripheral arterial disease	1.886 (0.968–3.674)	0.058	2.192 (1.110–4.325)	0.024

CI: confidence interval, OR: odds ratio

*Adjusted for residential location, income, and variables showing a *p* value <0.10 using univariate analysis

Incidence of cardiovascular diseases in patients with Behçet disease

Based on the results of logistic analyses, we chose angina pectoris and PAD as the comorbidities that could be affected by BD. In patients with BD and controls, the incidence of angina pectoris was 4.28 and 2.87, and the incidence of PAD was 1.00 and 0.49 per 1000 person-years, respectively. Cox proportional hazards regression analysis showed that the risk for angina pectoris (crude HR 1.693, 95% CI 1.163–2.465) and PAD (crude HR 2.868, 95% CI 1.294–6.357) was significantly higher in patients with BD than in controls. This significance was maintained even after adjusting for residential location, income, and comorbidities (adjusted HR 1.522, 95% CI 1.020–2.273 for angina pectoris and adjusted HR 2.939, 95% CI 1.296–6.664 for PAD) (**Table 3**).

The Kaplan–Meier curves for angina pectoris and PAD between patients with BD and controls are plotted in **Figure 2**. The cumulative incidence of angina pectoris (log-rank p=0.005) and PAD (log-rank p=0.007) was significantly higher in patients with BD than in controls.

Table 3. Incidence rates of angina pectoris and peripheral arterial disease per 1000 person-years in patients with Behçet disease compared to controls

	Event	Person-years of follow-up	Incidence rate per 1000 person-years	Adjusted HR* (95% CI)	*p* value
Angina pectoris					
Controls	186	64,781.5	2.87	Reference	
Patients with Behçet disease	33	7,711.4	4.28	1.522 (1.020–2.273)	0.040
Peripheral arterial disease					
Controls	32	65,662.4	0.49	Reference	
Patients with Behçet disease	8	7,983.8	1.00	2.939 (1.296–6.664)	0.010

CI: confidence interval, HR: hazard ratio

*Adjusted for residential location, income, and comorbidities

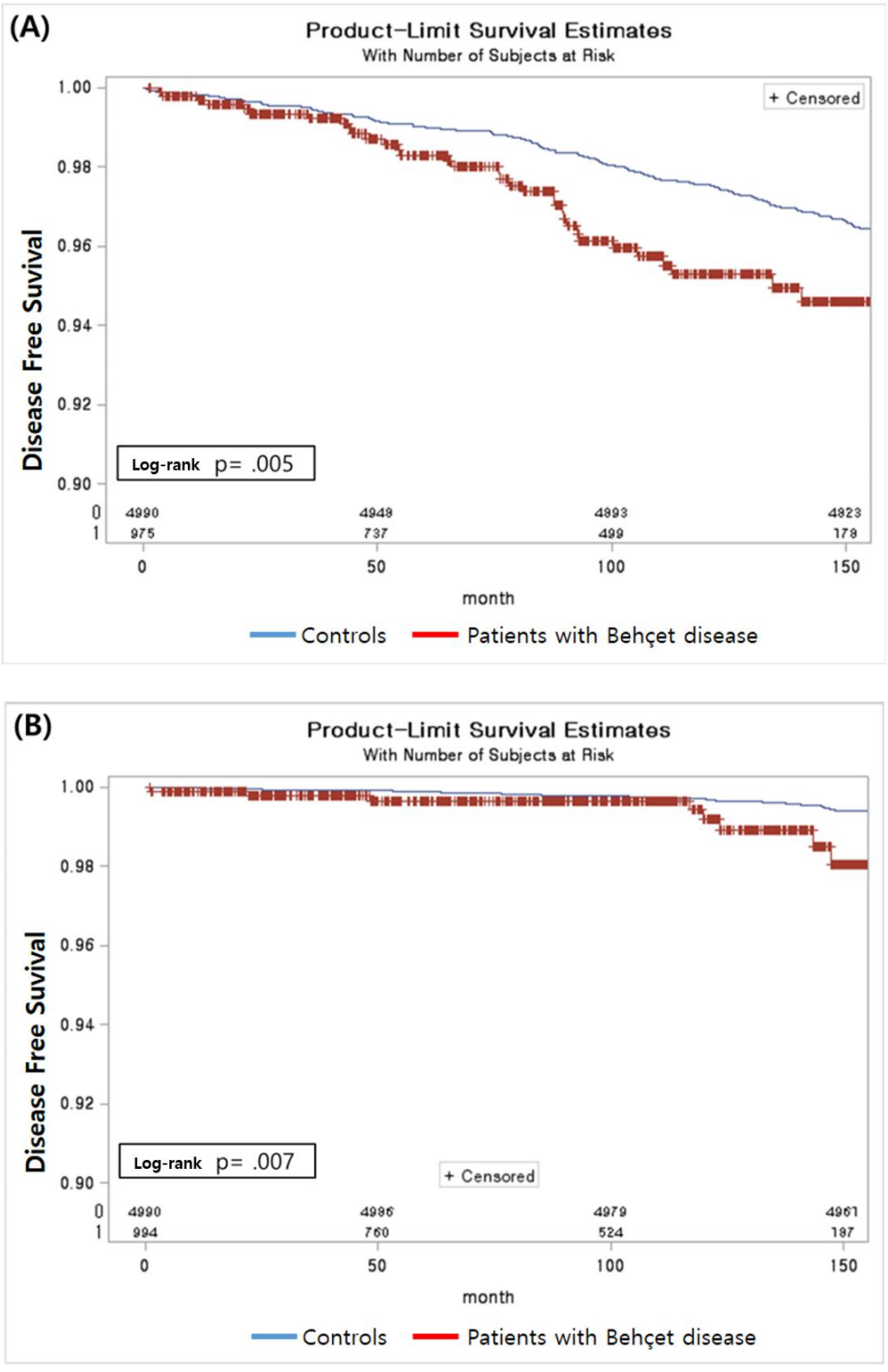

Figure 2. Kaplan-Meier estimate plotted to show the survival probabilities of angina pectoris (A) and peripheral arterial disease (B) in patients with Behçet disease and controls between 2003 and 2015.

Discussion

We performed a retrospective cohort study between 2003 and 2015 in 998 patients with BD and 4,990 controls to investigate the risk of CVD in patients with BD. This study highlighted important findings. Among various comorbidities, patients with BD showed a significantly higher risk for angina pectoris and PAD than controls. The cumulative incidence of these diseases in patients with BD was also significantly higher than that in controls. This result was observed after adjusting for age, sex, risk factors of CVD, income, and residential location with the control group.

A complex interplay between endothelial dysfunction, coagulopathy, inflammatory, and immunological reactions leads to arterial atherosclerosis, which is the cause of CVD, [13] and these factors work synergistically to induce atherosclerosis. These same factors contribute to atherosclerosis in patients with BD. High levels of selectins, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and matrix metalloproteinases observed in patients with BD are known to trigger endothelial activation.[14] Although the exact cause of a hypercoagulable state in patients with BD remains unclear, thrombotic occlusion of vessels

is attributed to platelet dysfunction and excessively high levels of plasma coagulation factors. This procoagulant tendency also explains the vascular involvement observed in patients with BD. [8] Based on the aforementioned observations and facts, it is theoretically reasonable to conclude that BD is a risk factor for PAD and angina.

In a study assessing the risk factors of CVD, Kayatas et al. reported that patients with BD show lower serum levels of low density lipoprotein than controls.[15] Our study did not show an intergroup difference in prevalence rates of dyslipidemia.

Arterial lesions were reported in 1.0–7.0% of patients with BD.[16, 17] A previous retrospective cohort study involving 412 patients with BD reported that 26 patients showed large-vessel involvement.[18] Another cross-sectional study reported by Ugurlu et al. showed that intermittent claudication was significantly more common in patients with BD. [19] In this study, patients with BD showed a significantly higher risk for PAD than controls. Vascular involvement is a potentially life-threatening condition because arterial lesions observed in patients with BD include aneurysms of large vessels and peripheral arterial occlusion. [16]

Although vascular involvement is known to occur in patients with BD, the association between BD and coronary heart disease including angina pectoris and myocardial infarction remains unclear. Our analysis showed that patients with BD demonstrated a significantly higher risk of angina pectoris than that in controls over 13-year follow-up. However, the previous study reported by Ugurlu et al. showed that the prevalence of angina pectoris, myocardial infarction, and other forms of coronary heart disease did not significantly differ between patients with BD and non-BD controls.[19] This discrepancy in results is attributable to differences in study design. Another interesting result is that income levels in patients with BD were higher than those in controls. Other studies have shown similar results in that socioeconomic status was higher in the BD than in the control group.[10] This result is attributable to the fact that patients belonging to the higher socioeconomic strata of society are more likely to visit a hospital more frequently and receive more frequent medical care.

Limitations of our study: 1) Smoking is a well-known risk factor for CVD; however, this factor was not analyzed in our study. Smoking is a typical risk factor and should ideally be included in the multivariate analysis. 2) It is difficult to confirm the diagnosis of the disease

because these conditions were diagnosed based on the NHIS claims database without reviewing the detailed clinical charts. However, in Korea, the benefit extension policy is applied to all patients with BD; thus, it is reasonable to assume a high accuracy in the diagnosis of BD using the database. This is the first study to report the association between BD and CVD using the population-based NHIS-NSC database.

Conclusion

This retrospective cohort study demonstrated that patients with BD show a significantly higher risk of angina pectoris and PAD than controls. The strength of this study was its longitudinal design with a 13-year follow-up period.

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국문 요약

베체트 병은 혈관의 병적인 변화로 발생하는 질환으로 알려져 있으나, 아직 베체트 병에서 심혈관 질환의 위험도가 어느정도 인지 구체적으로 조사한 연구는 없다. 우리는 전국민 건강 보험 서비스 데이터 베이스에서 추출한 표본 집단 데이터를 사용하여 이를 확인하고자 하였다. 연구는 데이터 베이스에서 확인한 베체트 병 환자와, 연령 및 성별, 지역, 소득 수준 등을 맞춰서 선정한 대조군을 후향적으로 비교 분석하는 방식으로 진행되었다. 베체트 병 환자와 심혈관 질환들 사이의 연관성을 조사하기 위해 로지스틱 회귀 분석이 수행되었다. 분석 결과 유의성을 나타내는 심혈관 질환들은 위험비를 비교하기 위해 Cox 비례 위험 회귀 분석을 실시 하였다. 위의 분석 결과, 베체트 병을 가진 998 명의 환자와 선정된 4,990 명의 대조군에서 협심증 (보정된 위험비 1.522, 95% 신뢰 구간 1.020-2.273) 및 말초 동맥 질환 (보정된 위험비 2.939, 95% 신뢰 구간 1.296-6.664)이 베체트 병 환자에서 발생 위험이 높은 것으로 나타났다. 누적 발병율

역시 대조군에 비해 유의하게 높았다 (협심증 및 말초 동맥 질환에 대한 log-rank p = 0.005 및 0.007). 결론적으로 이 연구를 통해서 베체트 병이 협심증 및 말초 동맥 질환의 독립적인 위험 인자임을 확인하였다.