

Clinical characteristics and predictors for cardiovascular system involvement in patients with Behçet's disease

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Abstract

Objective

The purpose of this study is to analyse the clinical characteristics of Behçet's disease (BD) patients in China with or without cardiovascular system involvement, and to develop a risk model to identify factors related to cardiovascular involvement in BD.

Methods

This retrospective cohort study, using the information on BD in Shenzhen People's Hospital from January 2000 to December 2021, included 95 patients: BD patients without cardiovascular system involvement (n=63) and with cardiovascular system involvement (n=32).

Results

Patients with BD who were males and had a combination of hypertension and a longer duration of disease were more likely to have cardiovascular involvement ($p < 0.05$). Compared to patients without cardiovascular involvement, manifestations of genital ulcers are rarely observed in those with cardiovascular involvement (60.32% vs. 37.50%, $p=0.035$).

The binary logistic regression analysis found that ascending aortic widening and a history of hypertension were independent risk factors for BD with cardiovascular system involvement (OR=1.277, 95% CI 1.09, 1.495, $p=0.002$; OR=11.578, 95% CI 1.308, 102.639, $p=0.028$). The established prediction model indicated that can help to predict the likelihood of cardiovascular involvement in a patient with BD.

Conclusion

Cardiovascular involvement in BD is not at all rare, however, it is often underreported due to a lack of specificity. BD patients who are male, have a history of combined hypertension, and have a long duration of disease should be focused on the presence of combined cardiovascular system involvement, with particular attention to the patient's ascending aortic internal diameter.

Key words

Behçet's disease, cardiac involvement, cardiovascular system involvement, clinical characteristics, risk factors

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Introduction

Behçet's disease (BD) is a chronic autoimmune disorder, characterised by recurrent oral and genital ulcerations, uveitis, skin lesions, and multiple system involvement (1). Cardiac involvement is called cardiac Behçet's disease (CBD), including valvular disease, aneurysms of the coronary arteries, sinus of Valsalva, myocardial infarction, conduction system disturbances, pericarditis, myocarditis, endocarditis, and intracardiac thrombus (2). The incidence and risk factors of cardiovascular system involvement in BD are not yet understood in China, which is one of the leading causes of death (3). In the early stage of CBD, most of them are asymptomatic, which is difficult to detect, being discovered until symptoms such as heart failure appear. In addition, there are few treatment options for CBD, such as surgical treatment is preferred for those with valvular lesions, but there is a high rate of postoperative complications (4). Based on the above background, this study aims to provide a basis for risk stratification of patients with CBD, especially asymptomatic patients, by analysing the clinical characteristics of patients with or without cardiovascular system involvement and the correlation factors of the disease to heart damage, so as to achieve the purpose of early diagnosis and early treatment.

Methods

Patients

A systematic search was conducted using the research information platform of Shenzhen People's Hospital from 2000-2021 for patients who were admitted with a diagnosis of BD or suspected BD. The total number of patients was 272. The International Study Group for Behçet Disease (ISGBD) (5) was selected for inclusion. Patients with clear secondary cardiovascular structural involvement such as hypertension, severe hepatic and renal insufficiency, congenital heart disease, coronary artery disease, cardiomyopathy, valvular disease were systematically excluded. In addition, rheumatic heart disease, infective endocarditis, Marfan syndrome and tumour patients (except for MDS(6)) should also be excluded. Using the above crite-

ria, 79 duplicate cases, 74 cases with insufficient data, and 31 cases that did not meet the inclusion criteria were excluded. Figure 1 shows the specific inclusion process. Demographic, clinical manifestations and echocardiographic data were collected for all enrolled patients. Patients with cardiovascular system involvement were defined as concomitant valvular disease and/or coronary aneurysm and/or myocardial infarction and/or conduction system disorders and/or pericarditis and/or myocarditis and/or endocarditis and/or cardiac thrombosis and/or arteriovenous disease (e.g. aneurysm or stenosis, venous thrombosis or occlusion).

Statistical analysis

A *p*-value less than 0.05 was considered statistically significant. SPSS26.0 software was used for data statistical analysis. Continuous variables were represented as means and standard deviation or medians (P25, P75), and categorical variables as proportions. Baseline characteristics of BD who involved the cardiovascular system were compared with those who did not. Binary logistic regression was used to analyse the risk factors for cardiovascular system involvement in BD, with ROC curves plotted to assess the diagnostic efficacy and value of the regression equation for it. Normally distributed measures were compared using the t-test, non-normally distributed or variance-dependent variables were compared applying the non-parametric test, and categorical variables were compared via the chi-square test. *p*<0.05 was considered to be statistically significant.

Results

Characteristics of BD

with cardiac involvement

Thirty-two patients with cardiovascular involvement out of a total of 95 BD cases (33.68%) were included in this study. The main clinical characteristics of cardiovascular involvement are shown in Table I.

12 cases showed dilated ascending aorta or sinus of aorta, 10 cases showed aortic sinus aneurysm of which 4 cases exhibited aortic sinus aneurysm rupture. Valve regurgitation occurred in

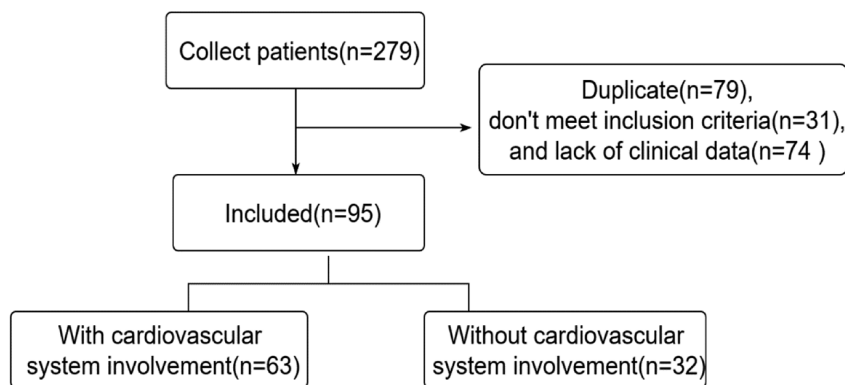


Fig. 1. The process of selection of included patients.

Table I. Specific manifestations of cardiac involvement in 32 BD patients.

Parameters	The number of cases (n, %)
Conduction system involvement	5 (15.63%)
Aortic regurgitation	5 (15.63%)
Mitral regurgitation	6 (18.75%)
Tricuspid regurgitation	9 (28.13%)
Aortic valve prolapse	3 (9.38%)
Mitral valve prolapse	2 (6.25%)
Tricuspid valve prolapse	1 (3.13%)
Dilated ascending aorta or sinus of aorta	12 (37.50%)
Sinus aneurysm of aorta	6 (18.75%)
Coronary artery disease	5 (15.63%)
Pulmonary hypertension	4 (12.50%)
Patent foramen oval	3 (9.38%)
Interventricular septum dissection	1 (3.13%)
Aortic dissection	1 (3.13%)
Right coronary sinus thrombosis	1 (3.13%)
Septal tumour	1 (3.13%)
Artery stenosis or aneurysm	13 (40.63%)
Venous thrombosis	9 (28.13%)

18 cases, including 14 cases of aortic valve regurgitation, 6 cases of mitral valve regurgitation and 9 cases of tricuspid valve regurgitation. 5 cases of valve prolapse were recorded, 3 cases of aortic prolapse, 2 cases of mitral valve prolapse; 1 case of tricuspid valve prolapse. There were 5 cases with conduction system involvement. Coronary artery disease affected 5 patients. Artery stenosis or aneurysm occurred in 13 patients. Venous thrombosis was reported in 9 patients.

Clinical differences between BD patients with and without cardiac involvement

The male percentage of the BD patients with cardiovascular involvement was significantly higher than who did not (65.63% vs. 34.92%, $p=0.004$). Patients with BD who had a combination of hypertension and a longer duration

of disease were more likely to have cardiovascular involvement ($p<0.05$). The time from first symptoms to diagnosis, age at first symptom, age at diagnosis and age at hospitalisation and heart rate at admission, cardiovascular risk factors (such as history of smoking, hyperlipidaemia, and diabetes), and common clinical manifestations of BD (such as oral ulcers, ocular lesions, skin lesions, arthritis, and pathergy positivity) were similar between the groups, without statistically significant differences. However, compared to patients without cardiovascular involvement, manifestations of genital ulcers are rarely observed in those with cardiovascular involvement (60.32% vs. 37.50%, $p=0.035$). In addition, other system involvement (e.g. digestive system, renal system, haematologic system, ear, nervous system) also did not significantly differ between the two groups (Table II).

Relevant echocardiographic data (e.g. AOD, LVIDd, EDV, SV, A) were significantly different between the two groups ($p<0.05$) (Table III). The median inner diameter of the ascending aorta in patients with cardiovascular involvement was within the normal range, but wider than that in patients without cardiovascular involvement.

Risk factors for BD with cardiac involvement

Variables with significant differences between with and without cardiovascular involvement groups including sex, duration of illness, SBP, hypertension, genital ulcers and relevant echocardiographic data were statistically analysed using a multiple logistic regression model to anticipate independent risk factors for BD with heart involvement. It was demonstrated that hypertension and ascending aortic internal diameter were independent risk factors for BD with cardiovascular system involvement (OR=11.587, 95% CI 1.308, 1.02.639, $p=0.028$; OR=1.277, 95% CI 1.090, 1.495, $p=0.002$) (Table IV). The incidence of cardiovascular involvement was 111.587 times higher in BD patients with hypertension than in those who did not. The risk of getting cardiovascular involvement in patients of BD with wider internal diameter of the ascending aorta was 1.277 times higher than those with smaller internal diameter of the ascending aorta.

ROC curve for predicting cardiovascular involvement in BD

ROC curve analysis showed that the Youden index of the regression equation to predict cardiovascular system involvement in BD was 0.451, with a sensitivity of 59.4% and a specificity of 85.7%. The AUC was 0.798, between 0.7 and 0.9, with a moderate diagnostic value and a standard error of 0.049, with a 95% confidence interval of (0.703, 0.893), $p<0.001$, indicating the high predictive efficacy of the established equation, as shown in Figure 2.

Discussion

The main findings of this study were: (a) BD patients with cardiovascular in-

Table II. Characteristics of BD patients with or without cardiac involvement.

Parameters	All (n=95)	Without CBD (63)	With CBD (n=32)	Z/t/X ²	p-value
Males, n (%)	43 (45.26%)	22 (34.92%)	21 (65.63%)	8.075	0.004*
Age at hospitalisation	38 (29~47)	36 (28~44)	39 (32.25~49)	-1.292	0.196
Age at first symptom	31.49 ± 12.41	31.21 ± 12.72	32.06 ± 11.95	-0.316	0.752
Age at diagnosis	36 (28~4)	34 (28~43)	38.5 (31.5~48.25)	-1.359	0.174
Time from symptom to diagnosis	4 (1~10)	3 (0.5~10)	5 (2~10)	-1.564	0.118
Duration of illness	5 (1~10)	4 (1~10)	6.5 (3.25~10.75)	-1.99	0.047*
SBP	116.20 ± 14.52	113.86 ± 13.40	120.81 ± 15.72	-2.254	0.027*
DBP	76.35 ± 10.26	75.73 ± 9.33	77.56 ± 11.94	-0.822	0.413
MAP	89.63 ± 10.25	88.44 ± 10.01	91.98 ± 10.46	-1.604	0.112
HR	84.06 ± 12.79	83.02 ± 12.63	86.13 ± 13.06	-1.121	0.265
Fertility situation	69 (72.63%)	44 (69.84%)	25 (78.13%)	0.733	0.392
Smoking history	7 (7.37%)	4 (6.35%)	3 (9.38%)	0.014	0.906
Hypertension	9 (9.47%)	2 (3.17%)	7 (21.88%)	6.61	0.01*
Hyperlipidaemia	1 (1.05%)	1 (1.59%)	0 (0.00%)	0	1
Diabetes	4 (4.21%)	3 (4.76%)	1 (3.13%)	0	1
Family history	16 (16.84%)	11 (17.46%)	5 (15.63%)	0.051	0.821
Oral ulcers	94 (98.95%)	62 (98.41%)	32 (100.00%)	0	1
Genital ulcers	50 (52.63%)	38 (60.32%)	12 (37.50%)	4.432	0.035*
Ocular lesions	19 (20.00%)	12 (19.05%)	7 (21.88%)	0.106	0.745
Skin lesions	53 (55.79%)	33 (52.38%)	20 (62.50%)	0.881	0.348
Arthritis	42 (44.21%)	28 (44.44%)	14 (43.75%)	0.004	0.949
Pathergy positivity	7 (7.37%)	3 (4.76%)	4 (12.50%)	0.901	0.343
Gastrointestinal involvement	21 (22.11%)	17 (26.98%)	4 (12.50%)	2.856	0.108
Kidney involvement	2 (2.11%)	1 (1.59%)	1 (3.13%)	0	1
Haematologic involvement	1 (1.05%)	1 (1.59%)	0 (0.00%)	0	0.474
Ear involvement	2 (2.11%)	1 (1.59%)	1 (3.13%)	0	1
Nervous system involvement	7 (7.37%)	3 (4.76%)	4 (12.50%)	0.901	0.343

SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate.

* $p < 0.05$, statistically significant difference.

Table III. Comparison of echocardiographic data of BD with or without cardiovascular system involvement.

Parameters	Without CBD (n=64)	With CBD (n=32)	Z/t value	p-value
EF (%)	66 (63~70)	67.2 (60.85~71)	-0.327	0.744
AOD (mm)	27 (24~30)	30 (28~36.25)	-3.848	0.000*
LA (mm)	30 (28~33)	30 (26.25~32.5)	-0.629	0.529
IVSd (cm)	0.86 ± 0.15	0.88 ± 0.14	-0.623	0.535
LVIDd	4.5 (4.18~4.8)	4.69 (4.35~5.31)	-2.367	0.018*
LVPWd (cm)	0.8 (0.72~0.89)	0.85 (0.74~0.97)	-1.360	0.174
EDV (ml)	92 (78.6~108)	107 (86.5~136)	-2.717	0.007*
ESV (ml)	31 (26.5~35.6)	33 (27.975~50.25)	-2.079	0.038
SV (ml)	65.5 (53.3~70)	68.08 (61.5~86.0)	-2.260	0.024*
E (cm/s)	84.9 (70.1~93)	86 (69~100)	-0.685	0.493
A (cm/s)	56.3 (49~64)	65.1 (49.75~84.5)	-2.013	0.044*
E/A	1.5 ± 0.46	1.4 ± 0.41	1.833	0.07

EF: ejection fraction; AOD: aortic diameter; LA: left atrium; IVSd: interventricular septum end diastolic; LVIDd: left ventricular end diastolic dimension; LVPWd: left ventricular posterior wall end diastolic; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; E: peak E of mitral valve flow; A: peak A of mitral valve flow.

* $p < 0.05$, statistically significant difference.

involvement had a longer duration of disease, higher blood pressure and more common in male: (b) AOD, LVIDd, EDV, and SV were larger in BD patients combined with cardiovascular involvement than without cardiovascular involvement; (c) combined hy-

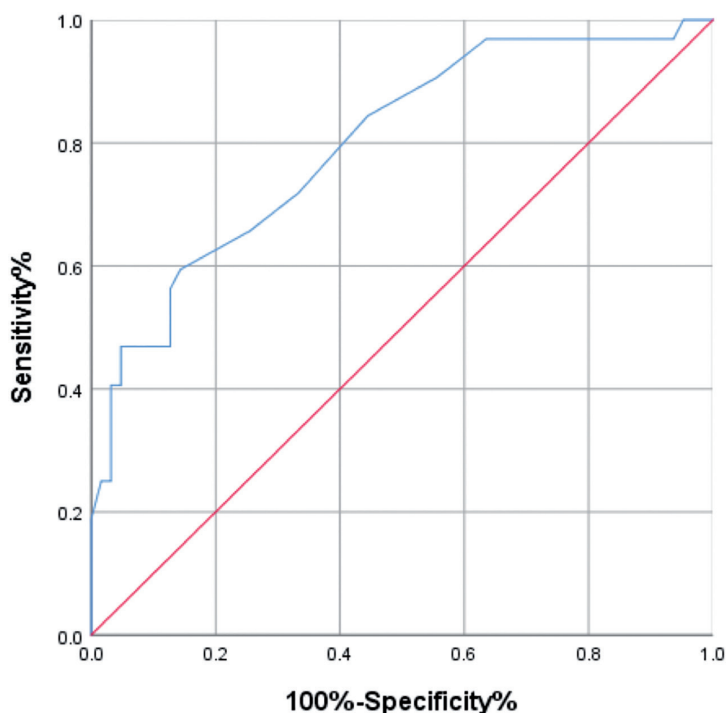
per-tension and ascending aortic internal diameter width were predictors of the cardiovascular involvement in BD patients; (d) the established regression equation had a high diagnostic value in predicting cardiovascular involvement in BD patients.

Because of the differences in the geographic populations selected and study methodology, the odds of cardiovascular involvement in BD reported in previous studies had varied widely, fluctuating from 7% to 46% (7). Cardiovascular system involvement was comparatively common in this study, being observed in 33.68% of patients. In this study, males were more likely to have cardiovascular system involvement, consistent with previous studies (3, 8-11). This may be related to the fact that oestrogen downregulates inflammatory genes to reduce cellular infiltration, as well as its ability to inhibit the inflammatory function of vascular endothelial cells and neutrophils, preventing the progression of the disease (12). Furthermore, oestrogen may guard against endothelial and myocardial dysfunction caused by transient ischemia/reperfusion through antioxidant effects, which explains the lower incidence of cardiovascular events in premenopausal females (13). Previous studies have demonstrated

Table IV. Multivariable logistic regression analysis to predict risk factors for patients of BD with cardiac involvement.

Parameters	B-value	B.E.	Wald	OR (95%CI)	p-value
Constant	3.195	3.923	0.663		0.415
Males, n (%)	-0.114	0.673	0.029	0.892 (0.238,3.337)	0.865
Duration of illness	0.011	0.05	0.052	1.011 (0.918,1.115)	0.819
SBP	-0.02	0.025	0.59	0.98 (0.932,1.031)	0.443
Hypertension	2.45	1.113	4.846	11.587 (1.308,102.639)	0.028*
Genital ulcers	-0.898	0.617	2.117	0.407 (0.122,1.366)	0.146
AOD	0.244	0.081	9.183	1.277 (1.090,1.495)	0.002*
LVIDd	-1.164	0.764	2.321	0.312 (0.07,1.396)	0.128
EDV	0.066	0.056	1.389	1.069 (0.957,1.193)	0.239
ESV	0.024	0.07	0.118	1.024 (0.894,1.174)	0.731
SV	-0.066	0.054	1.484	0.936 (0.842,1.041)	0.223
A	0	0.017	0	1 (0.967,1.034)	0.987

* $p < 0.05$, statistically significant difference.

**Fig. 2.** ROC analysis set to identify BD with cardiovascular involvement.

that cardiovascular disease is the major cause of death in patients with autoimmune diseases and that traditional risk factors play a relevant role in this increased risk (14). Hypertension is one of these traditional risk factors contributing to the progression of atherosclerosis (15). In the present study, patients suffering from hypertension were more likely to develop cardiovascular disease, consistent with previous studies (16). However, hypertension is often underdiagnosed in patients with autoimmune diseases (17, 18). Consequently, clinical emphasis should be placed

on screening for hypertensive disorders in patients with BD.

Dilation of the aortic root is an early sign of BD invasion of the aorta, followed by progressive aneurysm formation (19). Based on the inflammation and fibrosis of the vessel wall, the expansion and dilatation can lead to the formation of true aneurysm or, if tearing occurs, pseudoaneurysm (20). Aneurysms are the leading cause of death owing to the risk of rupture (21). In this study, there were 12 patients with dilated ascending aorta or aortic sinus, 6 patients with aneurysm of the aortic

sinus, of which one patient had rupture of the aortic sinus into the ventricular septum to form ventricular septal dissection. Its mechanism is as well due to inflammation, which leads to structural destruction of the aortic sinus wall causing tearing of the intima under the impact of high-pressure blood flow, and the interventricular septal dissection is developed (22). Ventricular septal entrapment is extremely hazardous to be taken seriously. In addition, the present study demonstrates that the ascending aorta is wider in patients with BD who develop cardiovascular system involvement, which is a predictor of suffering cardiovascular involvement in patients with BD. Therefore, echocardiography should be routinely performed in patients with BD, with a focus on the ascending aorta, especially in patients without cardiovascular involvement.

To date, no studies have examined the predictive value of cardiovascular risk score in BD patients. The ROC curve calculated according to the independent risk factors of cardiovascular system involvement in this study has a good predictive value for the occurrence of BD cardiovascular system involvement. In clinical work, for BD patients, in addition to paying attention to the general clinical manifestations, attention should also be paid to the presence or absence of traditional cardiovascular risk factors such as hypertension and routine echocardiography to minimise the occurrence of missed diagnosis.

Conclusion

BD involvement of the cardiovascular system is not rare at all, however, it is often overlooked due to lack of specificity. For patients with unexplained valvular disease, large artery disease, conduction block or young coronary artery disease without common risk factors, attention should be paid to the exclusion of BD. Echocardiography can be performed to determine whether the cardiovascular system is involved in patients with confirmed BD, especially in those who are male, have a history of combined hypertension, and have a long duration of disease. The predictive value of the ROC curve analysis regression model was superior for BD

combined with cardiovascular system involvement.

This study was conducted in a single centre with relatively small sample size, with the possibility of selection bias. Additionally, the analysis of patient prognosis and its associated factors was not addressed. Future large-sample, multicentre prospective studies are needed to analyse the prognosis of patients with cardiovascular system involvement in BD so as to provide a guiding clinical recommendation.

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