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Risk factors of cardiovascular involvement in patients with Behcet's disease

Yuqian Wang, Sheng Li, Shunli Tang, Xiaoxuan Cai, Juan Bai, Qingmiao Sun, Jianjun Qiao **, Hong Fang *

Department of Dermatology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, People's Republic of China

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ABSTRACT

Objectives: Behcet's disease (BD) is a multi-systemic inflammatory vasculitis which may be life-threatening if combined with cardiovascular problems. The aim of the study was to identify potential risk factors associated with cardiovascular involvement in BD.

Methods: We reviewed the medical databases of a single center. All BD patients identified as fulfilling the 1990 International Study Group criteria or the International Criteria for Behcet's Disease criteria. Cardiovascular involvement, clinical manifestations, laboratory features, and treatments were recorded. The relationship between parameters and cardiovascular involvement was analyzed.

Results: 111 BD patients were included: 21 (18.9%) had documented cardiovascular involvement (CV BD group) and 99 (81.1%) had no cardiovascular involvement (non-CV BD group). Compared with non-CV BD, the proportion of males and smokers were significantly increased in CV BD ($p = 0.024$ and $p < 0.001$, respectively). Levels of activated partial thromboplastin time (APTT), cardiac troponin I and C-reactive protein were significantly higher ($p = 0.001$, $p = 0.031$, and $p = 0.034$, respectively) in the CV BD group. Cardiovascular involvement was associated with smoking state, the presence of papulopustular lesions, and higher APTT in multivariate analyzed ($p = 0.029$, $p = 0.021$, and $p = 0.006$, respectively). The ROC curve showed that APTT predicts the risk of cardiovascular involvement ($p < 0.01$) at a cut-off value of 33.15 s with a sensitivity of 57.1% and specificity of 82.2%.

Conclusion: Cardiovascular involvement in BD patients was associated with gender, smoking state, the presence of papulopustular lesions, and higher APTT. All patients newly diagnosed with BD should be systematically screened for cardiovascular involvement.

1. Introduction

Behcet's disease (BD) is a chronic, multisystem inflammatory disease characterized by mucocutaneous, ocular, gastrointestinal, and central neurological involvement [1,2]. Two sets of classification criteria based on these manifestations have been proposed for BD: the 1990 International Study Group criteria [3] or the International Criteria for Behcet's Disease (ICBD) criteria [4].

Cardiovascular involvement in BD is usually recognized as a systemic vasculitis which can potentially involve both veins and arteries of all sizes [5]. The vascular involvement emerged in approximately 5–40% of BD patients [6,7]. Vascular involvement of BD is characterized by arterial occlusions, aneurysm and pseudoaneurysm formation, Budd–Chiari syndrome, and venous thrombotic occlusion [8–10]. Cardiac involvement is rare in BD, which is presented as intracardiac thrombosis, sinus of Valsalva aneurysms, myocarditis, valvular insufficiency, pericarditis, and coronary arteritis [11–13]. Despite its rarity, cardiovascular involvement is significantly associated with morbidity and mortality in patients with BD [14].

Early detection of cardiovascular involvement and appropriate management can improve patient prognosis. Therefore, it is critical to early identify the risk factors potentially associated with cardiovascular involvement. Herein, we provide a retrospective study summarizing the clinical features and further explored the potential risk factors for cardiovascular involvement in BD.

* Corresponding author. Department of Dermatology, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou, 310000, People's Republic of China.

** Corresponding author. Department of Dermatology, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou, 310000, People's Republic of China.

E-mail addresses: qiaojianjun@zju.edu.cn (J. Qiao), fanghongzy@zju.edu.cn (H. Fang).

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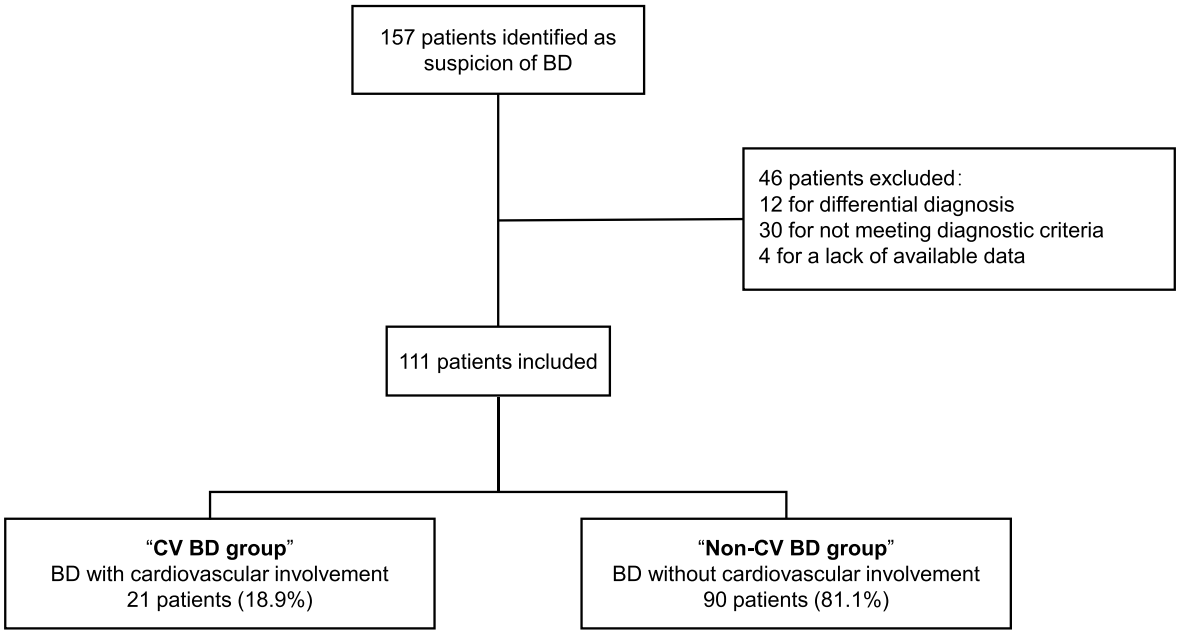

Fig. 1. Patient flow chart.

2. Materials and methods

2.1. Patients and controls

This retrospective study was conducted in the First Affiliated Hospital, Zhejiang University School of Medicine. Clinical data of all inpatients with BD suspicion between January 2011 and December 2021 were collected from the hospital databases. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University (IIT20220300B) and performed in accordance with the Declaration of Helsinki.

All BD patients fulfilled the 1990 International Study Group (ISG) criteria [3] or the International Criteria for Behcet's Disease (ICBD) criteria [4].

Cardiovascular involvements of BD were confirmed with clinical assessments and imaging techniques, including transthoracic echocardiography, transesophageal echocardiography, computed tomography (CT) angiography, magnetic resonance imaging (MRI) angiography, and Doppler ultrasonography. Arterial involvement was defined as aneurysm, false aneurysm formation, stenosis, and occlusion [15]. Venous involvement was defined as deep venous thrombosis (DVT), superficial thrombophlebitis (ST) and Budd–Chiari syndrome [16,17]. Cardiac involvement was defined as intracardiac thrombosis, pericarditis, myocarditis, endocarditis with valvular regurgitation, valvular insufficiency, coronary arteritis, and sinus of Valsalva aneurysms [12,13].

The whole study group was divided into two groups: the CV BD group, which contained BD patients with cardiovascular involvement, and the non-CV BD group of BD patients without cardiovascular involvement.

2.2. Data collection

Medical records were collected on a standardized form: sex, age at diagnosis, smoking and drinking state; clinical manifestations (oral ulcers, genital ulcers, erythema nodosum, papulopustular lesions, ocular lesions, and gastrointestinal involvement); the occurrence and type of cardiovascular involvement; the clinical manifestations and examination of cardiovascular involvement; laboratory tests (levels of leukocytes (WBC), polymorphonuclear cells (PMNs), lymphocyte (LYM), Neutrophile-to-lymphocyte ratio (NLR), platelet (PLT), platelet-to-lymphocyte ratio (PLR), fibrinogen (FIB), activated partial thromboplastin time (APTT), thrombin time (TT), D-Dimer (D-D), erythrocyte sedimentation rate (ESR), cardiac troponin I (cTnI), lactate dehydrogenase (LDH), creatine kinase-myocardial subfraction (CKMB), and C-reactive protein (CRP)); treatments administered for BD or cardiovascular conditions.

2.3. Statistical analysis

Normal data distribution was assessed by the Shapiro-Wilk test. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared between groups with Student's *t*-test. Continuous variables with skewed distribution were expressed as medians and interquartile range (1st quartile Q1, 3rd quartile Q3) and compared between groups with the Mann–Whitney test. Categorical variables were described as frequencies and percentages (%), and were compared between groups with chi-squared or Fisher's exact tests. Binary logistic regression was used to analyze factors associated with cardiovascular involvement. Variables with $p < 0.1$ in univariate analysis were incorporated into multivariable analysis. The results are described as odds ratio (OR) with 95% confidence interval (CI). The difference was considered statistically significant when p-value of <0.05. The receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive value of cardiovascular involvement in BD patients. The cut-off value, sensitivity and specificity were determined based on the ROC curve. All statistical analysis was performed using IBM SPSS 26.0 and GraphPad Prism 9 software.

3. Results

3.1. Study population

The patient flow chart is shown in Fig. 1. The clinical data of 157 patients with suspected BD were collected, 113 of whom met the established inclusion criteria. Of these, 21 (18.9%) were considered to have BD with cardiovascular involvement and were included in the "BD + CV group". The remaining 90 (81.1%) patients were considered to have BD without cardiovascular involvement and were included in the "control group".

Table 1
Characteristics of cardiovascular events in the CV BD group.

	CV BD (n = 21)
Type of cardiac involvement: n (%)	
Arterial involvement	7 (33.3)
Venous involvement	8 (38.1)
Cardiac involvement	12 (57.1)
Multiple vascular involvement	6 (28.6)
Time of appearance of cardiovascular involvement: n (%)	
Before or at diagnosis of BD	7 (33.3)
During first year	5 (23.8)
After first year	9 (42.9)
Clinical manifestations: n (%)	
Dyspnea	9 (42.9)
Chest pain	10 (47.6)
Abdominal pain	4 (19)
Headache	2 (9.5)
Limb pain	6 (28.6)

BD: Behcet's disease; CV BD: BD with cardiovascular involvement.
Values are expressed as number (%).

Table 2
Comparison of clinical features in BD patients with and without cardiovascular involvement.

	non-CV BD (n = 90)	CV BD (n = 21)	p-value
Male, n (%)	44 (48.9%)	16 (76.2%)	**0.024**
Age at diagnosis (years)	40.54 ± 13.93	38.76 ± 12.00	0.590
Smoking, n (%)	15 (16.7%)	12 (57.1%)	**< 0.001**
Drinking, n (%)	5 (5.6%)	2 (9.5%)	0.615
Oral ulcers, n (%)	85 (94.4%)	19 (90.5%)	0.615
Genital ulcers, n (%)	79 (87.8%)	17 (81.0%)	0.478
Papulopustular lesions, n (%)	14 (15.6%)	12 (57.1%)	**< 0.001**
Erythema nodosum, n (%)	30 (33.3%)	6 (28.6%)	0.675
Ocular lesions, n (%)	14 (15.6%)	2 (9.5%)	0.732
Parenchymal neurologic involvement, n (%)	6 (6.7%)	1 (4.8%)	0.295
Gastrointestinal involvement, n (%)	14 (15.6%)	5 (23.8%)	0.366
WBC (G/L)	7.0 (5.34,8.83)	7.6 (7.10,9.03)	0.171
PMNs (G/L)	64.04 ± 14.77	68.43 ± 11.58	0.205
LYM (G/L)	25.77 ± 11.76	22.64 ± 9.78	0.261
NLR	2.25 (1.66,4.17)	2.74 (2.15,4.97)	0.183
PLT (G/L)	243.5 (175.3,309.3)	240.0 (192.5,313.5)	0.743
PLR	8.76 (5.83,16.22)	11.68 (8.41,16.91)	0.201
FIB (G/L)	3.82 (2.94,4.91)	4.39 (2.70,5.31)	0.635
APTT(s)	27.95 (25.08,31.5)	34.4 (28.0,40.3)	**0.001**
TT(s)	17.1 (16.38,17.93)	16.5 (15.65,17.45)	0.096
D-D (mg/L)	322.0 (170.0,816.5)	525.0 (201,2009.5)	0.114
ESR (mm/h)	27.0 (12.0,51.0)	38.0 (6.5,60.0)	0.646
cTnI (pg/mL)	0.001 (0.001,0.003)	0.003 (0.001,0.053)	**0.031**
LDH (ng/mL)	166.0 (147.0,194.0)	165.0 (155.5,283.8)	0.376
CKMB (ng/mL)	12.0 (10.0,17.0)	10.0 (8.25,13.75)	0.223
CRP (mg/L)	13.23 (4.78,46.8)	36.19 (13.17,63.7)	**0.034**

Bold values indicate statistical significance between non-CV BD and CV BD.
BD: Behcet's disease; non-CV BD: BD without cardiovascular involvement; CV BD: BD with cardiovascular involvement.; WBC: White blood cell; PMNs: Polymorphonuclear; LYM: Lymphocyte; NLR: Neutrophile-to-lymphocyte ratio; PLT: Platelet; PLR: Platelet-to-lymphocyte ratio; FIB: Fibrinogen; APTT: Activated partial thromboplastin time; TT: Thrombin time; D-D: D-Dimer; ESR: Erythrocyte sedimentation rate; cTnI: Cardiac troponin I; LDH: Lactate dehydrogenase; CKMB: Creatine kinase-myocardial subfraction; CRP = C-reactive protein.

3.2. Features of cardiovascular involvement

Among 21 BD patients with cardiovascular involvement, 7 (33.3%) had arterial involvement, 8 (38.1%) had venous involvement, 12 (57.1%) had cardiac involvement and 6 (28.6%) had multiple vascular involvement (Table 1). There were no specific treatments before or during the diagnostic stage in 7 cases (33.3%). The suggestive symptoms were dyspnea in 9 patients (42.9%), chest pain in 10 patients (47.6%), abdominal pain in 4 patients (19%), headache in 2 patients (9.5%) and limb pain in 6 patients (28.6%).

Fourteen patients were treated with surgery and twelve patients have received non-steroidal anti-inflammatory drugs (NSAIDs). Anticoagulant therapy was administered to sixteen patients.

3.3. Demographic and clinical features of the BD population

The comparison of clinical features in BD patients with and without cardiovascular involvement was summarized in Table 2. There were no significant differences in age and history of alcohol intake among the two subgroups (all $p > 0.05$). Compared with non-CV BD, the proportion of males and smokers were increased in CV BD ($p = 0.024$ and $p < 0.001$, respectively). The clinical manifestations were similar in the two groups, except for papulopustular lesions, which was more common in the CV BD group ($p < 0.001$).

Regarding the laboratory indicators, APTT, cTnI, and CRP demonstrated significant differences among groups ($p < 0.05$). The levels of these laboratory biomarkers were significantly higher in the CV BD group ($p = 0.001$, $p = 0.031$ and $p = 0.034$, respectively). Remarkably, all patients with BD had high median levels of NLR and PLR which may be potential indexes to evaluate the disease activity of BD [18,19]. Compared with non-CV BD, CV BD group had a higher NLR and PLR, with no clinically relevant difference.

3.4. Results of univariate and multivariate analysis

We performed univariate and multivariate logistic regression analyses to determine predictive factors of cardiovascular involvement at diagnosis (Table 3). Univariate logistic regression analyses revealed that smoking ($p < 0.001$), papulopustular lesions ($p < 0.001$), APTT ($p = 0.001$), and D-Dimer ($p = 0.067$) were significantly associated with cardiovascular involvement during the course of the disease. Age and other laboratory parameters were not associated with cardiovascular involvement in this analyzed. Particularly, sex was not included in the analysis because smoking rate of males is much higher than that of females in China [20].

In multivariate logistic regression analysis, CV BD group was associated with smoking (OR = 3.938, 95% CI = 1.152–13.469, $p = 0.029$), the presence of papulopustular lesions (OR = 4.279, 95% CI = 1.243–14.729, $p = 0.021$) and high APTT (OR = 1.119, 95% CI = 1.033–1.213, $p = 0.006$). However, D-Dimer was no longer considered an independent predictor of cardiovascular involvement ($p = 0.424$). ROC curve analysis showed that the best cut-off value of APTT was 33.15 s, with a sensitivity of 57.1% and specificity of 82.2% (The area under the curve (AUC): 0.7389, 95% CI: 0.6217–0.8561, $p = 0.0007$) (shown in Fig. 2b).

3.5. Treatment

The main treatments prescribed for BD were corticosteroids for 89 patients (80%), immunosuppressives agents (DMARD) (azathioprine, methotrexate, ciclosporin A and Tripterygium wilfordii) for 27 patients (24%), NSAIDs for 27 patients (24%), colchicine for 16 patients (14%), thalidomide for 58 patients (52%), anti-Tumor necrosis factor alpha (TNFα) for 8 patients (7%) and HCQ for 7 patients (6%) during diagnostic assessment (Table 4). Corticosteroid, immunosuppressives, NSAIDs and anti-TNFα treatment were more frequently used in the BD +

Table 3
Univariable and multivariable logistic regression analyses for relevant factors associated with cardiovascular involvement in BD patients.

	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Demographic factors						
Age at diagnosis (years)	0.99	0.955–1.026	0.586			
Smoking, n (%)	6.667	2.388–18.614	**< 0.001**	3.938	1.152–13.469	**0.029**
Drinking, n (%)	1.789	0.322–9.930	0.506			
Oral ulcers, n (%)	0.559	0.101–3.101	0.506			
Genital ulcers, n (%)	0.592	0.168–2.083	0.414			
Papulopustular lesions, n (%)	7.238	2.570–20 . 383	< 0.001	4.279	1.243–14.729	**0.021**
Erythema nodosum, n (%)	0.8	0.282–2.271	0.675			
Ocular lesions, n (%)	0.571	0.120–2.732	0.483			
Parenchymal neurologic involvement, n (%)	0.7	0.080–6.146	0.748			
Gastrointestinal involvement, n (%)	1.696	0.535–5.383	0.370			
Laboratory features						
WBC (G/L)	1.108	0.945–1.300	0.206			
PMNs (G/L)	1.023	0.988–1.508	0.204			
LYM (G/L)	0.976	0.935–1.018	0.259			
NLR	1.012	0.945–1.107	0.576			
PLT (G/L)	1.001	0.996–1.005	0.824			
PLR	1.001	0.974–1.030	0.925			
FIB (G/L)	1.104	0.805–1.514	0.538			
APTT(s)	1.142	1.059–1.231	**0.001**	1.119	1.033–1.213	**0.006**
TT(s)	1.029	0.977–1.084	0.273			
D-D (mg/L)	1.000	1.000–1.001	**0.067**	1.000	1.000–1.001	0.424
ESR (mm/h)	1.001	0.988–1.013	0.907			
LDH (ng/mL)	1.003	0.999–1.007	0.102			
CKMB (ng/mL)	0.947	0.852–1.053	0.319			
CRP (mg/L)	1.007	0.996–1.018	0.208			

P values less than 0.05 are bolded.
BD: Behcet's disease; WBC: White blood cell; PMNs: Polymorphonuclear; LYM: Lymphocyte; NLR: Neutrophile-to-lymphocyte ratio; PLT: Platelet; PLR: Platelet-to-lymphocyte ratio; FIB: Fibrinogen; APTT: Activated partial thromboplastin time; TT: Thrombin time; D-D: D-Dimer; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; CKMB: Creatine kinase-myocardial subfraction; CRP = C-reactive protein.

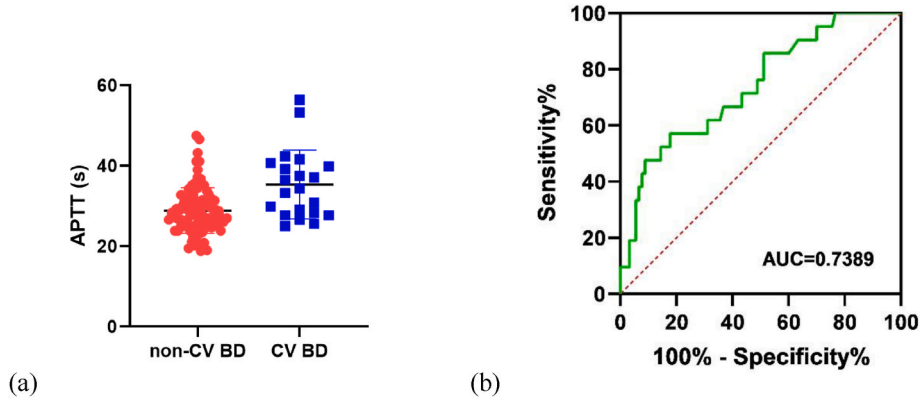

Fig. 2. Receiver operating characteristic (ROC) curve of APTT. (a) Comparison of APTT between non-CV BD and CV BD. (b) The area under the curve (AUC) of APTT for predicting the prognosis of cardiovascular involvement was 0.7389, and the best cut-off value was 33.15 s. The sensitivity and specificity of APTT to predict cardiovascular involvement in BD patients were 57.1% and 82.2%, respectively.

CV group than in the control group.

4. Discussion

BD is a systemic vasculitis that involves multiple organs, including the oral mucosa, eyes, skin, vascular, gastrointestinal, and neurologic system [21]. Patients with cardiovascular BD may experience serious mortality and poor quality of life than patients with other subtype of BD, which necessitates the development of appropriate risk factors. This study highlights the clinical features and relevant factors of cardiovascular involvement in BD.

In BD patients with cardiovascular involvement, arteries and veins of various sizes can be affected. True aneurysms and pseudoaneurysms are the major causes of death in patients with BD [22]. In the previous nationwide survey of China, 3.8% of Chinese BD patients had venous involvement, 2.5% had arterial involvement, and 4% had cardiac involvement. We found that the overall prevalence of cardiovascular involvement in our population of BD patients was 18.9% [23]. However, the higher prevalence of venous involvement in our cohort was 7.2%, the prevalence of arterial involvement was 6.3%, and the prevalence of cardiac involvement was 10.8%. The causes of this discrepancy might be that all our patients were inpatients, while patients from Zhang's study were inpatients and outpatients.

It is well known that cardiovascular involvement is seen mainly among men [16]. Same as recent reports, 76.2% of the BD patients with cardiovascular complication in our cohort were male. In addition, smoking, one of traditional cardiovascular risk factors, is potentially contributed to cardiovascular involvement in BD patients [24]. We showed that the smoking state was significantly associated with a higher risk of cardiovascular involvement in univariate analysis which was

Table 4
Comparison of treatment in BD patients with and without vascular involvement.

	Non-CV BD (n = 90)	CV BD (n = 21)	P value
Corticosteroid treatment: n (%)	69 (77%)	20 (95%)	0.069
DMARD: n (%)	15 (17%)	12 (57%)	**< 0.001**
NSAIDs: n (%)	17 (19%)	10 (48%)	**0.006**
Colchicine: n (%)	14 (16%)	2 (10%)	0.479
Thalidomide: n (%)	48 (53%)	10 (48%)	0.637
Anti-TNFα: n (%)	5 (6%)	3 (14%)	0.164
HCQ: n (%)	6 (7%)	1 (5%)	1

P values less than 0.05 are bolded.
BD: Behcet's disease; Non-CV BD: BD without cardiovascular involvement; CV BD: BD with cardiovascular involvement; DMARD: immunosuppressive agent; NSAIDs: nonsteroidal anti-inflammatory drugs, Anti-TNFα: tumor necrosis factor-alpha inhibitors; HCQ: Hydroxychloroquine.
Values are expressed as number (%).

confirmed in multivariable analysis. We have also noted a significant association of cardiovascular involvement with papulopustular lesions. Papulopustular lesions is an important early diagnostic symptom when the intensity of inflammation is high. Univariate and multivariable analysis demonstrated that papulopustular lesions was one of risk factors against cardiovascular involvement.

BD is an autoinflammatory diseases characterized increased neutrophilic activity and overexpression of inflammatory cytokines [25]. Therefore, in this study, 15 laboratory parameters were investigated in our cohort to assess their clinical association with cardiovascular involvement. We found that the levels of biological markers of inflammation, including neutrophil count, white blood cell count, NLR, ESR, D-Dimer and CRP, were significantly increased in patients with cardiovascular involvement. Our results are consistent with the result of Hammad et al. [26]. Although previous reports [27,28] stated a close interaction between neutrophils, NLR and thrombosis, which amplifies the inflammatory response, we didn't find any correlation between neutrophil count and cardiovascular involvement.

However, multivariate analysis confirmed that APTT was an independent risk factor for cardiovascular involvement in BD patients. In our study, ROC analysis demonstrated that the cut-off value of 33.15s was obtained at optimal AUC of 0.7389 for identifying cardiovascular involvement in BD, with a sensitivity of 57.1% and a specificity of 82.2%. To our knowledge, this is the first report on the association of APTT with cardiovascular involvement. Furthermore, some biomarkers, such as Interleukin 37 (IL-37) [29], Ischemia-modified albumin (IMA) [30], and lectin-like oxidised LDL receptor-1 (LOX-1) [31] may act as valuable biomarkers for cardiovascular involvement.

Currently, there is no definitive therapeutic modality for cardiovascular involvement of BD. Immunosuppressive therapy is essential and several retrospective studies have shown that it can reduce the recurrence rate [32,33]. Cyclophosphamide and glucocorticoid pulses are used to treat life-threatening conditions such as PAI, Budd–Chiari syndrome, and peripheral arterial aneurysms/occlusions. Besides, azathioprine with short-term glucocorticoids is used to treat other types of venous thrombosis [34]. Patient refractory to immunosuppressive agents can be treated by surgery. In BD most evidence is available for tumor necrosis factor (TNF)-blocking agents such as Infliximab and Adalimumab [35]. In our series, corticosteroid, immunosuppressive agents, NSAIDs and anti-TNFα treatment were more frequently used in patients with cardiovascular involvement.

The key limitations of the study include its retrospective nature, small sample size and selection bias among patients.

5. Conclusion

In conclusion, about 18.9% of BD patients in our study had cardiovascular involvement. This complication was associated with gender, smoking state, the presence of papulopustular lesions, and higher APTT. Combination therapy of corticosteroid, immunosuppressants, anticoagulant or surgery are effective and prognosis remains good. All patients newly diagnosed with BD should be systematically screened for cardiovascular involvement. Further studies are required to assess potential predictive factors associated with cardiovascular involvement in BD.

Consent for publication

All authors have reviewed the final version and agree with its submission and publication.

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Credit author statement

Yuqian Wang: conceptualization, formal analysis, writing – original draft, writing – review & editing. Sheng Li: conceptualization, formal analysis, supervision. Shunli Tang: conceptualization, validation, methodology. Xiaoxuan Cai: conceptualization, methodology. Juan Bai: conceptualization, methodology. Qingmiao Sun: conceptualization, methodology. Jianjun Qiao: supervision, writing – review & editing. Hong Fang: supervision, writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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