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ORIGINAL ARTICLE

Clinical phenotypes of adult-onset Behçet's syndrome: a comprehensive cross-sectional study in China

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Abstract

Behçet's syndrome (BS) is a variant vasculitis that can involve multiple organs with inflammatory manifestations. This study aimed to provide a more comprehensive analysis of the clinical phenotypes and characteristics of BS patients. We enrolled 2792 BS patients referred from China nationwide to Huadong Hospital Affiliated to Fudan University from October 2012 to December 2022. Detailed assessments of demographic information, clinical manifestations, laboratory results, gastroscopy, and medical imaging were conducted. Cluster analysis was performed based on 13 variables to determine the clinical phenotypes, and each phenotype was characterized according to the features of BS patients. A total of 1834 BS patients were included, while 958 invalid patients were excluded. The median age at onset was 31 years (IQR, 24–40 years), and the median disease duration was 10 years (IQR, 5–15 years). Eight clusters were identified, including mucocutaneous ($n=$ 655, 35.7%), gastrointestinal ($n=$ 363, 19.8%), articular ($n=$ 184, 10%), ocular ($n=$ 223, 12.2%), cardiovascular ($n=$ 119, 6.5%), neurological ($n=$ 118, 6.4%), vascular ($n=$ 114, 6.2%), and hematological phenotype ($n=$ 58, 3.2%). Ocular (RR= 1.672 (95% CI, 1.327–2.106); $P<$ 0.001), gastrointestinal (RR== 1.194 (95% CI, 1.031–1.383); $P=$ 0.018), cardiovascular (RR== 2.582 (95% CI, 1.842–3.620); $P<$ 0.001), and vascular (RR== 2.288 (95% CI, 1.600–3.272); $P<$ 0.001) involvement were more prevalent in male BS patients, while the hematological (RR= 0.528 (95% CI, 0.360–0.776); $P=$ 0.001) involvement was more common among female patients. BS presents significant heterogeneity and gender differences. The eight phenotypes of BS patients we propose hold the potential to assist clinicians in devising more personalized treatment and follow-up strategies.

Key Points

- *This cluster analysis divided adult-onset BS into eight clinical phenotypes.*
- *BS demonstrates a high level of clinical heterogeneity and gender differences.*
- *Hematologic phenotypes of BS present distinctive clinical characteristics.*

Keywords Behçet's syndrome · Clinical features · Cluster analysis · Gender · Phenotype

Abbreviations

BS	Behçet's syndrome
ISG	International Study Group
ICBD	International Criteria for Behçet's Disease
MRI	Magnetic resonance imaging
CT	Computed tomography
CVST	Cerebral venous sinus thrombosis
IQR	Interquartile range
MDS	Myelodysplastic syndrome
RR	Relative risk

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Introduction

Behçet's syndrome (BS) is a rare and heterogeneous disorder that causes inflammation of various vessels throughout the body, affecting multiple organ systems [1]. The clinical manifestations of BS are diverse, including not only common oral and genital ulcers but also manifestations in mucocutaneous, articular, ocular, vascular, neurological, and gastrointestinal, which can present as a relapsing and progressive course [2]. The pathogenesis of BS is not fully understood, but it is generally believed to result from the combined effects of susceptible genes and environmental factors [3]. Currently, the nonspecific clinical manifestations of BS and the lack of laboratory biomarkers or characteristic histopathological features pose challenges for its diagnosis and treatment. A comprehensive understanding and identification of the clinical characteristics of BS may help to improve the diagnosis and management of this disorder [4].

Recent studies have reported several BS phenotypes by cluster analysis of the pediatric and adult-onset BS together in different countries [5–10]. Despite the high degree of heterogeneity, the mucocutaneous and articular phenotypes were all conformed [6–10]. However, discrepancies arose with the ocular [6, 7], gastrointestinal [6, 8], vascular [5, 7], cardiovascular [8], and neurological phenotype [6]. Preliminary genetic, transcriptomic, and proteomic data suggest that different pathogenetic mechanisms may operate in different BS clinical phenotypes [11]. These phenotypes may reflect different underlying mechanisms and risk factors and may influence the susceptibility, severity, and prognosis of BS.

Cluster analysis has recently been employed as a phenotype research tool in BS. Studies reported different clustering patterns caused by biological variation and some degree of artificial heterogeneity [12]. In 2021, we reported what, to our knowledge, was the first cross-sectional study on clinical phenotypes of BS patients in China [13]. In this study, the aim was to advance our comprehension of BS clinical phenotypes by increasing the clinical data and updating the surveillance protocol, which contained more detailed data from 1834 BS patients from China nationwide.

Method

Patients

The Shanghai BS database registered a total of 2792 cases of BS patients who were referred nationwide from China to Huadong Hospital Affiliated to Fudan University between October 2012 and December 2022. Rigorous selection criteria were applied, encompassing patients meeting the revised International Study Group (ISG) criteria or International Criteria for Behçet's Disease (ICBD) [14, 15], with an age threshold that was set at over 16 years old due to the distinct clinical phenotypes associated with adult-onset BS [5, 16]. Exclusions comprised individuals with concurrent immune disorders, paraneoplastic pemphigus, Crohn's disease, *Helicobacter pylori*-induced gastrointestinal ulcers, and other conditions. In the updated database, we excluded 248 pediatric BS, 271 incomplete BS, and 439 patients with missing data, resulting in a final count of 1,834 patients included in the study. The flowchart for patient selection is shown in Fig. 1. This study was approved by the Ethics Committee of Huadong Hospital (No. 2018K031), and all participants gave written informed consent.

Data collection

A total of 13 disease manifestations were considered specific for cluster analysis in BS patients. The cluster analysis took into account a comprehensive compilation of symptoms observed throughout the entire duration of the disease, rather than focusing solely on symptoms that emerged within a specific timeframe. Continuous variables include the age of BS onset (first complained symptoms of BS, such as oral ulcers or genital ulcers). Categorical variables include recurrent oral ulcer, genital ulcer, skin lesion (such as erythema nodosum and pseudofolliculitis), ocular involvement (including uveitis, retinal vasculitis, and blindness) [17], gastrointestinal involvement (documented through endoscopy, encompassing esophageal and gastrointestinal ulcers) [18], cardiovascular involvement (involving aortic valve regurgitation, mitral valve regurgitation, tricuspid valve regurgitation, aortic aneurysm, pulmonary artery aneurysm, myocardial infarction) [19], vascular involvement (such as arterial dilatation, arterial stenosis, venous thrombosis) [20, 21], neurological involvement (involving intracerebral aneurysms, cerebral arterial or venous thrombosis, cerebral hemorrhage or infarction and the sequelae, white matter lesion, cerebral venous sinus thrombosis, psychotic disorder) [22], hematological involvement (including myelodysplastic syndrome, myelodysplastic disorder) [23], articular involvement (involving arthritis and arthralgia), trisomy of chromosome 8 [24], and history of Bentall surgery [25]. Bentall surgery history refers to a cardiac procedure that was specifically conducted to address aortic regurgitation, mitral regurgitation, or tricuspid regurgitation attributed to BS [26]. Each variable was recorded as a score of 1, while absence was recorded as 0. The clinical data of all patients were recorded following assessment by specialist physicians from rheumatology, gastroenterology, neurology, cardiology, ophthalmology, dermatology, and other relevant disciplines. These assessments were complemented by comprehensive examinations, such as magnetic resonance

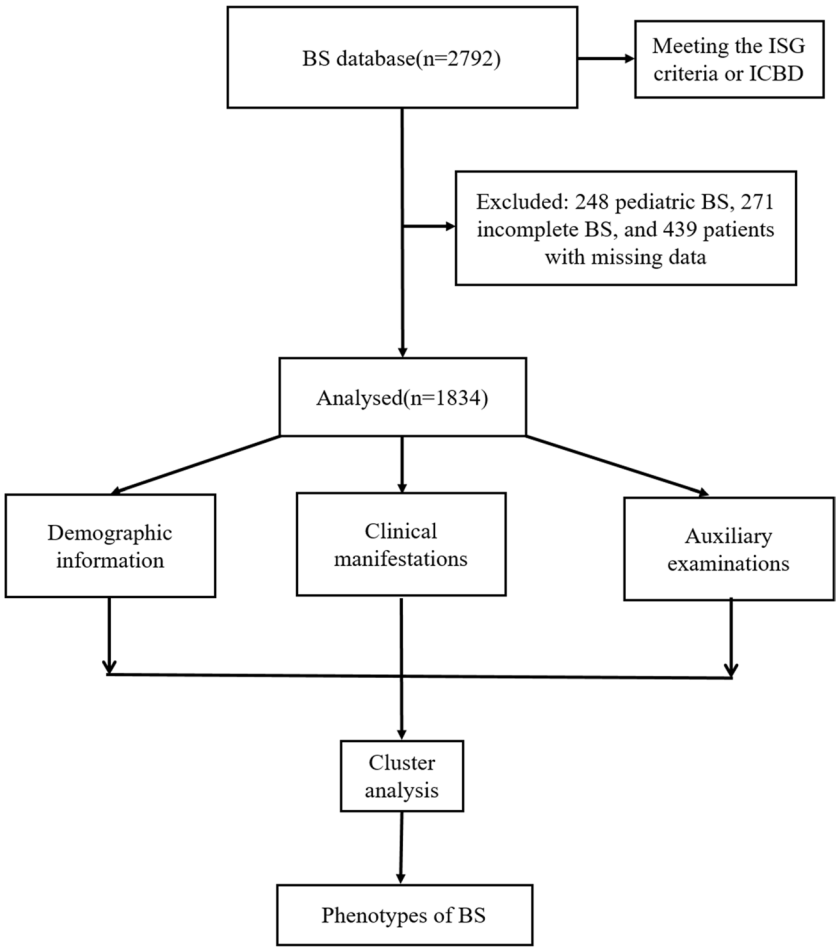

Fig. 1 The flowchart for the BS patient

imaging (MRI), computed tomography (CT), ultrasound, endoscopy, gastroscopy, etc.

Statistical analysis

Statistical analysis was performed using SPSS 24 software. Continuous variables were presented as medians with interquartile range (25–75%), while categorical variables were expressed as count (percentage). The process of two-step cluster analysis with SPSS commenced with the thirteen disease manifestations, including the age of BS onset, oral ulcer, genital ulcer, skin lesion, ocular involvement, gastrointestinal involvement, cardiovascular involvement, vascular involvement, neurological involvement, hematological involvement, articular involvement, trisomy 8, and history of Bentall surgery. Furthermore, a relative risk (RR) analysis between males and females was conducted. Continuous variables were assessed using Student's *t*-test or Mann–Whitney *U* test. Categorical variables were compared using the Chi-square test or Fisher's exact test. Kruskal–Wallis tests were employed to compare groups. A significance level of $P < 0.05$ indicated statistical differences.

Result

Cluster analysis

A total of 1834 cases of BS patients were included; 1220 cases (66.5%) met the criteria for ISG, while 1777 cases (96.9%) fulfilled the criteria for ICBD. The median age was 44 years (interquartile range (IQR), 35–53 years). The median age at onset was 31 years (IQR, 24–40 years), and the median disease duration was 10 years (IQR, 5–15 years). Recurrent oral ulceration was the most common manifestation (96.3%), followed by genital ulceration (80.2%) and skin lesions (56.3%). Cluster analysis was performed based on 13 variables to determine the clinical phenotypes for BS patients, and each phenotype was characterized according to its clinical features. We then compared the clinical features of each cluster (Table 1).

Cluster 1: Gastrointestinal involvement (363 cases, 19.8%)

In cluster 1, the median age was 42 years (IQR, 33–54 years), and the median disease course was 7 years (IQR, 3–11 years).

All patients presented gastrointestinal involvement. The male-to-female ratio was 1.6:1, including oral ulcers (338 cases, 93.1%), genital ulcers (261 cases, 71.9%), and skin lesions (176 cases, 48.5%). The most commonly involved gastrointestinal ulcer was the ileocecal region (204 cases, 56.2%), followed by upper gastrointestinal ulcers (133 cases, 36.6%), colorectal ulcers (81 cases, 22.3%), and small bowel ulcers (18 cases, 4.9%).

Cluster 2: Ocular involvement (223 cases, 12.2%)

It consisted of subjects with a median age of 41 years (IQR, 34–50 years), the median disease course was 7 years (IQR, 10–14 years), the male-to-female ratio was 1.7:1, and all had ocular involvements. Among them, uveitis accounts for 98.7% (220 cases), including anterior uveitis (25 cases, 11.2%), posterior uveitis (165 cases, 74.0%), and panuveitis (30 cases, 13.6%), as well as 3 (1.3%) cases of retinal vasculitis. Additionally, 13 (5.8%) cases experienced blindness. In this cluster, 22 cases (9.8%) and 9 cases (4.0%) overlapped with gastrointestinal and cardiovascular involvement, respectively.

Cluster 3: Vascular involvement (114 cases, 6.2%)

In this cluster, the median age was 45 years (IQR, 36–54 years), and the median disease course was 7 years (IQR, 10–15 years). The cluster demonstrated a male-predominant sex ratio of 2.3:1. Among them, 42 (36.8%) patients showed arterial involvement, including the brachiocephalic trunk (15 cases, 13.1%) and abdominal (12 cases, 10.5%) and limb arteries (18 cases, 13.1%), while 81 (71.0%) patients showed venous involvement, including venous thrombosis as well as superior and inferior vena cava thrombosis. Additionally, patients with vascular involvement also presented with articular (28 cases, 24.6%), ocular (19 cases, 16.7%), gastrointestinal (26 cases, 22.8%), cardiovascular (21 cases, 18.4%), and neurological (4 cases, 3.5%) manifestations.

Cluster 4: Hematological involvement (58 cases, 3.2%)

In cluster 4, the median age at onset was 47 years (IQR, 38–57 years), the median disease course was 10 years (IQR, 6–15 years), and all patients had hematological involvement. The male-to-female ratio was 0.5:1. Hematological involvement included trisomy of chromosome 8 (49 cases, 84.5%), while 26 cases (44.8%) coexisted with myelodysplastic syndrome (MDS). Additionally, 42 cases (72.4%) with a hematological phenotype also presented with gastrointestinal ulcers, with the ileocecal section being the primary site (30 cases, 51.7%). In this cluster, 12 cases (20.7%), 1 case (1.7%), and 1 case (1.7%) overlapped with articular, cardiovascular, and ocular involvement, respectively.

Cluster 5: Mucocutaneous involvement (655 cases, 35.7%)

In cluster 5, the median age was 44 years (IQR, 36–54 years), and the median disease course was 10 years (IQR, 5–15 years). The male-to-female ratio was 0.5:1. All patients in this cluster only had oral and genital ulcers; 464 cases (70.8%) met the criteria for ISG criteria, while 655 cases (100%) fulfilled the criteria for ICBD. Among them, 216 cases (33.0%) and 154 cases (23.5%) manifested erythema nodosum and pseudofolliculitis, respectively. The pathergy test positivity rate was 40%.

Cluster 6: Cardiovascular involvement (119 cases, 6.5%)

In this cluster, the median age was 46 years (IQR, 37–53 years), the male predominant cluster sex ratio (male to female) = 2.6:1, and the median disease course was 10 years (IQR, 5–16 years). Cardiovascular involvement consisted of aortic valve regurgitation (83 cases, 69.7%), aortic aneurysm (62 cases, 52.1%), mitral regurgitation (31 cases, 26.1%), tricuspid regurgitation (12 cases, 10.1%), pulmonary artery aneurysm (11 cases, 9.2%), and myocardial infarction (11 cases, 9.2%). It is noteworthy that in 40 cases (33.6%) of valve regurgitation after undergoing one or more conventional valve repair surgeries and still experiencing valve leakage, Bentall surgery was subsequently needed to be performed.

Cluster 7: Neurological phenotype (118 cases, 6.4%)

In cluster 7, the median age was 44 years (IQR, 36–54 years), the median disease course was 10 years (IQR, 10–15 years), and all patients had neurological involvements. The sex ratio (male to female) = 1:1. Neurological involvement consisted of a cerebral aneurysm (39 cases, 33.1%), a white matter lesion (101 cases, 85.6%), and a spinal cord injury (48 cases, 40.7%). It is noteworthy that 71 cases had coexisted with other visceral systems, accounting for 60.17%. This phenotype involved various systems, including the gastrointestinal tract (40 cases, 33.8%), articular system (38 cases, 32.2%), eyes (13 cases, 11.0%), and heart (3 cases, 2.5%).

Cluster 8: Articular involvement (184 cases, 10%)

In this cluster, the median age at onset was 47 years (IQR, 36–57 years), the median disease course was 7 years (IQR, 11–18 years), and the sex ratio (male to female) = 0.8:1. In addition to oral ulcers (176 cases, 95.6%), genital ulcers (136 cases, 73.9%), and skin lesions (136 cases, 73.9%), this cluster of patients exclusively presented arthritis or joint pain, without any concurrent visceral involvement.

Table 1 Clinical characteristics of clusters in patients with BS

Characteristic	C1 (n = 363)	C2 (n = 223)	C3 (n = 114)	C4 (n = 58)	C5 (n = 655)	C6 (n = 119)	C7 (n = 118)	C8 (n = 184)	P value
Age (years, median; IQR)	42 (33, 54)	41 (34, 50)	45 (36, 54)	47 (38, 57)	44 (36, 54)	46 (37, 53)	44 (36, 54)	47 (36, 57)	***0.009***
Age of onset (years, median; IQR)	31 (24, 41)	29 (22, 36)	31 (25, 41)	34 (28, 41)	32 (25, 41)	31 (27, 39)	32 (24, 41)	32 (25, 39)	0.167
Duration of BS (years, median; IQR)	7 (3, 11)	7 (10, 14)	7 (10, 15)	10 (6, 15)	10 (5, 15)	10 (5, 16)	10 (10, 15)	7 (11, 18)	***< 0.001***
Sex ratio (M/F)	1.6:1	1.7:1	2.3:1	0.5:1	0.5:1	2.6:1	1:1	0.8:1	***< 0.001***
Fulfilling ISG criteria (n; %)	193 (53.2)	191 (85.7)	67 (58.8)	32 (55.2)	464 (70.8)	85 (71.4)	66 (55.9)	122 (66.3)	***< 0.001***
Fulfilling ICBD criteria (n; %)	342 (94.2)	223 (100)	114 (100)	54 (93.1)	655 (100)	109 (91.6)	118 (100)	162 (88.0)	***< 0.001***
Oral ulcer (n; %)	338 (93.1)	215 (96.4)	104 (91.2)	56 (96.6)	655 (100)	113 (95.0)	109 (92.3)	176 (95.6)	***< 0.001***
1 ≥ time/month (n; %)	240 (66.1)	163 (73.1)	92 (80.7)	49 (84.5)	610 (93.1)	100 (84.0)	88 (74.6)	145 (78.8)	***< 0.001***
1 ≥ times/season (n; %)	98 (27.0)	52 (23.3)	12 (10.5)	7 (12.1)	45 (6.9)	13 (10.9)	21 (17.8)	31 (16.8)	***< 0.001***
Genital ulcer (n; %)	261 (71.9)	140 (62.8)	75 (65.8)	40 (69.0)	655 (100)	93 (78.2)	71 (60.1)	136 (73.9)	***< 0.001***
Skin lesions (n; %)	176 (48.5)	135 (60.5)	71 (62.3)	20 (34.5)	335 (51.1)	89 (74.8)	71 (60.1)	136 (73.9)	***< 0.001***
Erythema nodosum (n; %)	98 (27.0)	97 (43.5)	51 (44.7)	7 (12.1)	216 (33.0)	56 (47.1)	42 (35.6)	101 (54.9)	***< 0.001***
Pseudofolliculitis (n; %)	96 (26.4)	65 (29.1)	33 (28.9)	8 (13.8)	154 (23.5)	51 (42.8)	38 (32.2)	51 (27.7)	***0.001***
Pathergy tests (n; %)	179 (49.3)	93 (41.7)	49 (43.0)	33 (56.9)	297 (45.3)	64 (53.8)	54 (45.8)	82 (44.6)	0.096
Articular involvement (n; %)	96 (26.4)	38 (17.0)	28 (24.6)	12 (20.7)	0	29 (24.4)	38 (32.2)	184 (100)	***< 0.001***
Ocular involvement (n; %)	0	223 (100)	19 (16.7)	1 (1.7)	0	1 (0.8)	13 (11.0)	0	***< 0.001***
Uveitis (n; %)	0	220 (98.7)	18 (15.8)	1 (1.7)	0	0	3 (2.5)	0	***< 0.001***
Anterior uveitis (n; %)	0	25 (11.2)	2 (1.7)	0	0	0	3 (2.5)	0	***< 0.001***
Posterior uveitis (n; %)	0	165 (74.0)	8 (7.0)	1 (1.7)	0	0	1 (0.8)	0	***< 0.001***
Panuveitis (n; %)	0	30 (13.5)	5 (4.4)	0	0	0	2 (1.7)	0	***< 0.001***
Retinal vasculitis (n; %)	0	3 (1.3)	4 (3.5)	0	0	1 (0.8)	7 (5.9)	0	***< 0.001***
Blindness (n; %)	0	13 (5.8)	0	0	0	0	0	0	***< 0.001***
Gastrointestinal involvement (n; %)	363 (100)	22 (9.8)	26 (22.8)	42 (72.4)	0	12 (10.1)	40 (33.9)	0	***< 0.001***
Upper gastrointestinal ulcer (n; %)	133 (36.6)	10 (4.4)	11 (9.6)	2 (3.4)	0	7 (5.9)	8 (6.8)	0	***< 0.001***
Colorectal ulcers (n; %)	81 (22.3)	3 (1.3)	4 (3.5)	17 (29.3)	0	3 (2.5)	10 (8.5)	0	***< 0.001***
Small intestinal ulcer (n; %)	18 (4.9)	0	1 (0.9)	5 (8.6)	0	0	5 (4.2)	0	***< 0.001***
Ileocecal ulcer (n; %)	204 (56.2)	7 (3.1)	9 (7.9)	30 (51.7)	0	4 (3.3)	21 (17.8)	0	***< 0.001***

Table 1 (continued)

Characteristic	C1 (n= 363)	C2 (n= 223)	C3 (n= 114)	C4 (n= 58)	C5 (n= 655)	C6 (n= 119)	C7 (n= 118)	C8 (n= 184)	P value
Vascular involvement (n; %)	0	0	114 (100)	2 (3.4)	0	15 (12.6)	0	0	***< 0.001***
Brachiocephalic trunk (n; %)	0	0	15 (13.1)	0	0	5 (4.2)	0	0	***< 0.001***
Abdominal arteries (n; %)	0	0	12 (10.5)	0	0	3 (2.5)	0	0	***< 0.001***
Limb arteries (n; %)	0	0	18 (15.7)	1 (1.7)	0	2 (1.7)	0	0	***< 0.001***
Phlebothrombosis (n; %)	0	0	81 (71.1)	1 (1.7)	0	5 (4.2)	0	0	***< 0.001***
Cardiovascular involvement (n; %)	0	9 (4.0)	21 (18.4)	1 (1.7)	0	119 (100)	3 (2.5)	0	***< 0.001***
Aortic aneurysm (n; %)	0	1 (0.4)	12 (10.5)	0	0	62 (52.1)	0	0	***< 0.001***
Aortic valve regurgitation (n; %)	0	6 (2.7)	0	0	0	83 (69.7)	3 (2.5)	0	***< 0.001***
Pulmonary artery aneurysm (n; %)	0	1 (0.4)	3 (2.6)	0	0	11 (9.2)	0	0	***< 0.001***
Moderate to severe mitral regurgitation (n; %)	0	0	0	1 (1.7)	0	31 (26.1)	0	0	***< 0.001***
Moderate to severe tricuspid regurgitation (n; %)	0	0	0	1 (1.7)	0	12 (10.1)	0	0	***< 0.001***
Bentall surgery (n; %)	0	0	0	0	0	40 (33.6)	0	0	***< 0.001***
Myocardial infarction (n; %)	0	1 (0.4)	6 (5.3)	0	0	11 (9.2)	0	0	***< 0.001***
Hematological involvement (n; %)	0	0	0	58 (100)	0	0	0	0	***< 0.001***
MDS (n; %)	0	0	0	26 (44.8)	0	0	0	0	***< 0.001***
Myelodysplastic disorder (n; %)	0	0	0	4 (6.9)	0	0	0	0	***< 0.001***
Trisomy of chromosome 8 (n; %)	0	0	0	49 (84.5)	0	0	0	0	***< 0.001***
Neurological involvement (n; %)	0	0	4 (3.5)	1 (1.7)	0	21 (17.6)	118 (100)	0	***< 0.001***
Cerebral aneurysm (n; %)	0	0	4 (3.5)	0	0	4 (3.4)	39 (33.1)	0	***< 0.001***
White matter lesion (n; %)	0	0	1 (0.9)	1 (1.7)	0	10 (8.4)	101 (85.6)	0	***< 0.001***
Spinal cord injury (n; %)	0	0	1 (0.9)	0	0	6 (5.0)	48 (40.7)	0	***< 0.001***

IQR, interquartile range; *ISG*, International Study Group; *ICBD*, International Criteria for Behçet's Disease; *MDS*, myelodysplastic syndrome

In summary, this study identified eight distinct phenotypes of BS, including mucocutaneous, gastrointestinal, articular, ocular, cardiovascular, neurological, vascular, and hematological phenotypes (Fig. 2).

Gender dependences in different clusters of BS patients

Clinical characteristics and comparisons of gender in different clusters of BS patients are shown in Table 2. Female patients presented a higher incidence of genital ulcers (RR = 0.901 (95% CI, 0.860–0.945); $P < 0.001$), while male patients were more prone to skin lesions like pseudofolliculitis (RR = 1.569 (95% CI, 1.344–1.831); $P = 0.006$). Meanwhile, the proportion of BS patients with a hematological phenotype was 3.2%, with female BS patients outnumbering male BS patients (RR = 0.528 (95% CI, 0.360–0.776); $P = 0.001$).

Ocular (RR = 1.672 (95% CI, 1.327–2.106); $P < 0.001$), gastrointestinal (RR = = 1.194 (95% CI, 1.031–1.383); $P = 0.018$), cardiovascular (RR = = 2.582 (95% CI, 1.842–3.620); $P < 0.001$), and vascular phenotype (RR, 2.288 (95% CI, 1.600–3.272); $P < 0.001$) were significantly more predominant in male than female BS patients. Compared to female BS patients, males demonstrated a higher incidence of posterior uveitis (RR = 1.680 (95% CI, 1.256–2.247); $P < 0.001$), panuveitis (RR = 2.464 (95% CI, 1.225–4.956); $P = 0.009$), aortic aneurysms (RR = 4.542 (95% CI, 2.559–8.059); $P < 0.001$), aortic regurgitation (RR = 2.509 (95% CI, 1.617–3.893); $P < 0.001$), mitral regurgitation (RR = 2.293 (95% CI, 1.092–4.815); $P = 0.024$), myocardial infarction (RR = 8.339 (95% CI, 1.923–36.162); $P = 0.001$), angiopathy of limb arteries (RR = 2.606 (95% CI, 1.016–6.686); $P = 0.038$), phlebothrombosis (RR = 2.680 (95% CI, 1.456–4.935); $P = 0.001$), and small intestinal ulcers (RR = 2.397 (95% CI, 1.148–5.008); $P = 0.016$) were significantly more common in male than female BS patients. Articular and neurological phenotypes have no gender difference.

Discussion

This Shanghai BS database provided significant clinical heterogeneity in BS patients, with 65.9% of cases in this cohort involving visceral organs. This could be attributed to the referral of more severe and refractory BS patients nationwide in China to Huadong Hospital Affiliated to Fudan University. This study has identified eight distinct BS clinical phenotypes characterized by differences in gender distribution and organ involvement.

Cluster analysis for BS patients has been conducted in different countries, with the gastrointestinal tract, eyes, and joints being the most commonly affected [8–10, 27]. In a previous study, Oguz et al. classified BS into 4 categories: mucocutaneous, vascular, musculoskeletal, and ocular phenotypes [9], consistent with the Egyptian study [27]. Subsequently, Soejima et al. reported mucocutaneous, mucocutaneous arthritis, neurological, gastrointestinal, and ocular phenotypes [8]. In this study, we expanded phenotypic categorizations for BS patients. In particular, to our knowledge, our cohort is the first to propose and summarize the hematological phenotype of BS through cluster analysis.

In this cohort, the gastrointestinal phenotype was the most commonly affected internal organ. However, in the Turkish cohort, this gastrointestinal phenotype was absent, accounting for only 2.5% of gastrointestinal ulcers [9]. This discrepancy might be attributed not only to population differences but also to the potential subtlety of the disease. In our team, Ye et al. found that 61.45% of BS patients with gastrointestinal ulcers confirmed by endoscopy were asymptomatic [28]. Hence, endoscopic examination is recommended for all patients under suspicion of BS, particularly individuals with elevated CRP levels, heightened disease activity, and fever.

Patients with the hematological phenotype were predominantly female and frequently accompanied by trisomy 8, potentially linked to the increased likelihood of MDS [29, 30]. In addition, BS patients with a hematological phenotype are also most complicated with gastrointestinal ulcers, mainly in the ileocecal region [31]. Early studies have revealed that 86.7% of BS patients have concurrent MDS with trisomy 8 or with other chromosome abnormalities. In contrast, the trisomy 8 in primary MDS patients without BS is only 7–9% [32]. This necessitates vigilant oversight, with a focus on monitoring for trisomy 8 abnormalities and conducting thorough gastrointestinal endoscopy screenings. However, the association between trisomy 8, MDS, and gastrointestinal ulcers with BS remains clear [33]. We speculate that the trisomy 8 abnormality may be a genetic predisposition or a consequence of BS affecting the hematopoietic system and the intestinal mucosa. Therefore, the hematological phenotype of BS may represent a new syndrome worthy of further exploration from genetic, proteomic, and pathogenic perspectives.

This study revealed novel associations between clinical manifestations and organ damage, potentially offering new insights into the pathogenesis and etiology of BS patients [34, 35]. Previous reports by Gürgün et al. and Pu et al. highlighted cardiac involvement in BS patients, predominantly manifesting as cardiac valve abnormalities, particularly in the aortic valve [36, 37]. This has led to the recommendation of Bentall surgery under remission of primary diseases in cases of severe cardiac involvement [38].

In this cohort, we classified neurological BS as a separate phenotype. Individuals with this phenotype presented

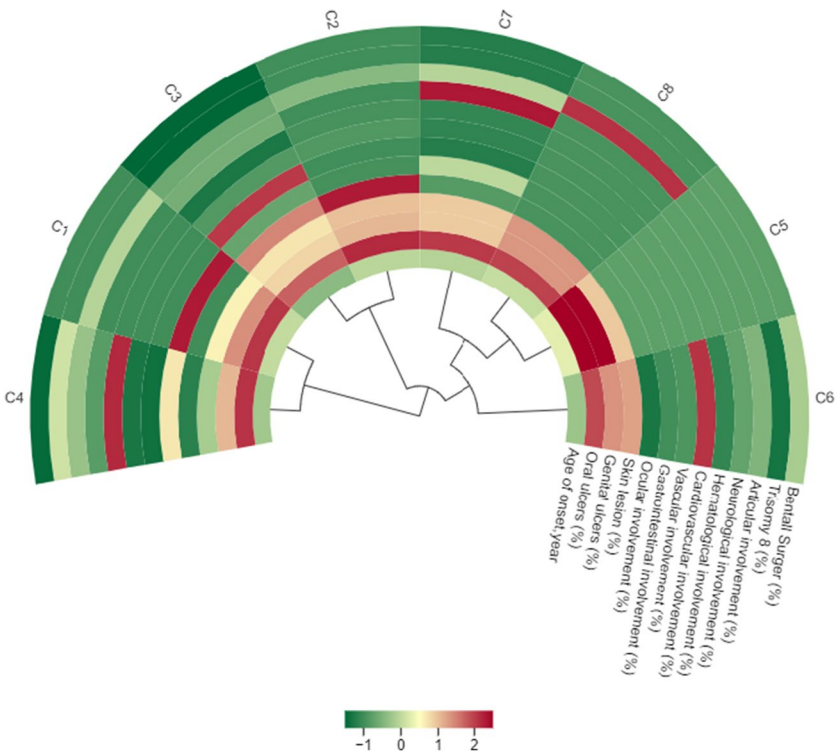

Fig. 2 The eight clusters of patients with BS. C1, gastrointestinal involvement; C2, ocular phenotype; C3, vascular phenotype; C4, hematological involvement; C5, mucocutaneous phenotype; C6, cardiovascular phenotype; C7, neurological phenotype; C8, articular phenotype

not only vascular manifestations but also experienced involvement in cerebral parenchyma and psychiatric symptoms. Intriguingly, cerebral venous sinus thrombosis (CVST), typically associated with non-parenchymal neuro-BS, manifested as an infrequent occurrence within this study, affecting only four cases of BS patients. The incidence of CVST seems to have a strong correlation with ethnicity. Previous studies indicate a notably lower incidence of CVST in Asian populations compared to countries like Turkey [39, 40]. We posit that further investigation into CVST as the primary clinical symptom of non-parenchymal NBS is necessary. Relying solely on CVST as the diagnostic cornerstone may not be deemed sufficiently reasonable [41].

Additionally, we identified five phenotypes that were more prevalent in males or females, namely ocular, gastrointestinal, cardiovascular, vascular, and hematological phenotypes. The male BS patients potentially had more visceral organ involvement and more serious conditions, which was consistent with the results reported in a review by Ilgen [11]. Specifically, males showed a higher incidence of ocular, gastrointestinal (especially small intestinal ulcer), cardiovascular, and vascular phenotypes, while females showed a higher incidence of the hematological phenotype with significantly higher rates of trisomy 8, MDS, and intestinal ulcer compared to their male counterparts. The mucocutaneous, articular, and neurological types, however, showed no gender differences. However, in some cohorts, neuro-Behcet's tend to occur more frequently in males [42, 43]. These gender-based distinctions may be indicative of different mechanisms and risk factors for BS patients.

In 2021, our team reported the clinical phenotyping of BS patients in China [13]. Compared with our previous works, this study separated the cardiovascular from the vascular phenotype, as arterial aneurysms had different features and outcomes from venous thrombosis; separated the neurological phenotype from the vascular phenotype, as neurological involvement had more concomitant organ damage and different clinical profiles than vascular involvement; and separated the hematological phenotype from the gastrointestinal phenotype, as the new phenotype of hematological involvement had a high frequency of trisomy 8 abnormality, MDS, and ileocecal ulcers. Notice that this study did not involve pediatrics because our earlier research indicated distinct clinical patterns between pediatrics and adults. Therefore, excluding pediatric data aimed to minimize the impact on adult clinical characterization [44].

The limitations of this study should be noted, as it lacks additional datasets to validate the robustness and consistency of the clustering results. Furthermore, the extended duration of this study might have led to data dynamism and variability. Lastly, the database includes referred BS patients from across China, which might not be generalizable to other populations due to differences in classifications used in various regions or countries. The primary focus of this study is on the clinical phenotype classification of BS. However, the lack of data on patients' outcomes, disease activity scores, and treatments represents a limitation of this study. These

Table 2 The comparison of clinical characteristics between the male and female BS patients

Characteristic	Total ($n=$ 1834)	Male ($n=$ 898)	Female ($n=$ 936)	$Z/t/X^2$	P value	RR (male:female)
Age (years, median; IQR)	44 (35, 53)	44 (36,53)	44 (34,54)	−0.039	0.969	NA
Age of onset (years, median; IQR)	31 (24,40)	31 (24,39)	31 (25,41)	−1.106	0.269	NA
Duration of BS, years, median (IQR)	10 (5,15)	10 (6,15)	10 (5,15)	0.071	0.071	NA
Fulfilling ISG criteria (*n*; %)	1220 (66.5)	596 (66.4)	624 (66.7)	0.014	0.907	0.994 (0.903–1.094)
Fulfilling ICBD criteria (*n*; %)	1777 (96.9)	866 (96.4)	911 (97.3)	1.546	0.214	0.836 (0.615–1.134)
Oral ulcers (*n*; %)	1766 (96.3)	863 (96.1)	903 (96.5)	0.178	0.673	0.996 (0.978–1.014)
1 ≥ time/month (*n*; %)	1487 (81.1)	712 (79.3)	775 (82.8)	3.685	0.55	0.890 (0.787–1.007)
1 ≥ times/season (*n*; %)	279 (15.2)	151 (16.8)	128 (13.7)	3.503	0.061	1.133 (0.988–1.298)
Genital ulcers (*n*; %)	1471 (80.2)	678 (75.5)	793 (84.7)	19.336	***< 0.001***	0.901 (0.860–0.945)
Skin lesions (*n*; %)	1033 (56.3)	535 (59.6)	498 (53.2)	7.564	***0.006***	1.120 (1.033–1.214)
Erythema nodosum (*n*; %)	668 (36.4)	322 (35.9)	346 (37.0)	0.243	0.622	0.970 (0.859–1.095)
Pseudofolliculitis (*n*; %)	496 (27.0)	298 (33.2)	198 (21.2)	33.622	***< 0.001***	1.569 (1.344–1.831)
Pathergy tests (*n*; %)	851 (46.4)	412 (45.9)	439 (46.9)	0.192	0.661	0.980 (0.896–1.072)
Arthritis/arthralgia (*n*; %)	425 (23.2)	208 (23.2)	217 (23.2)	0.010	0.919	0.992 (0.843–1.167)
Ocular involvement (*n*; %)	257 (14.0)	162 (18.0)	95 (10.2)	19.608	***< 0.001***	1.672 (1.327–2.106)
Uveitis (*n*; %)	242 (13.2)	151 (16.8)	91 (9.7)	20.130	***< 0.001***	1.730 (1.356–2.206)
Anterior uveitis (*n*; %)	30 (1.6)	17 (1.9)	13 (1.4)	0.724	0.395	1.363 (0.666–2.790)
Posterior uveitis (*n*; %)	175 (9.5)	108 (12.0)	67 (7.2)	12.586	***< 0.001***	1.680 (1.256–2.247)
Panuveitis (*n*; %)	37 (2.0)	26 (2.9)	11 (1.2)	6.860	***0.009***	2.464 (1.225–4.956)
Retinal vasculitis (*n*; %)	15 (0.8)	11 (1.2)	4 (0.4)	3.594	0.058	2.866 (0.916–8.969)
Blindness (*n*; %)	13 (0.7)	9 (1.0)	4 (0.4)	2.152	0.142	2.345 (0.725–7.588)
Gastrointestinal involvement (*n*; %)	505 (27.5)	265 (29.0)	240 (25.6)	5.634	***0.018***	1.194 (1.031–1.383)
Upper gastrointestinal ulcer (*n*; %)	171 (9.3)	92 (10.2)	79 (8.4)	3.781	0.052	1.319 (0.997–1.747)
Colorectal ulcers (*n*; %)	118 (6.4)	57 (6.4)	61 (6.5)	0.022	0.882	*0.974 (0.687–1.381)*
Small intestinal ulcer (*n*; %)	29 (1.6)	19 (2.1)	10 (1.1)	5.781	***0.016***	2.397 (1.148–5.0085)
Ileocecal ulcer (*n*; %)	275 (15.0)	143 (15.9)	132 (14.1)	1.826	0.177	1.161 (0.935–1.441)
Vascular involvement (*n*; %)	131 (7.1)	90 (10.0)	41 (4.4)	21.995	***< 0.001***	2.288 (1.600–3.272)
Brachiocephalic trunk (*n*; %)	20 (1.1)	10 (1.1)	10 (1.1)	0.009	0.926	1.042 (0.436–2.492)
Abdominal arteries (*n*; %)	15 (0.8)	11 (1.2)	4 (0.4)	3.594	0.058	2.866 (0.916–8.969)
Limb arteries (*n*; %)	21 (1.2)	15 (1.7)	6 (0.6)	4.290	***0.038***	2.606 (1.016–6.686)
Phlebothrombosis (*n*; %)	87 (4.7)	62 (6.9)	25 (2.7)	10.915	***0.001***	2.680 (1.456–4.935)
Cardiovascular involvement (*n*; %)	153 (8.3)	109 (12.1)	44 (4.7)	33.152	***< 0.001***	2.582 (1.842–3.620)
Aortic aneurysm (*n*; %)	75 (4.1)	61 (6.8)	14 (1.5)	32.788	***< 0.001***	4.542 (2.559–8.059)
Aortic valve regurgitation (*n*; %)	92 (5.0)	65 (7.2)	27 (2.9)	18.232	***< 0.001***	2.509 (1.617–3.893)
Pulmonary artery aneurysm (*n*; %)	15 (0.8)	9 (1.0)	6 (0.6)	0.737	0.391	1.563 (0.559–4.375)
Moderate to severe mitral regurgitation (*n*; %)	32 (1.7)	22 (2.5)	10 (1.1)	5.102	***0.024***	2.293 (1.092–4.815)
Moderate to severe tricuspid regurgitation (*n*; %)	13 (0.7)	9 (1.0)	4 (0.4)	2.152	0.142	2.345 (0.725–7.588)
Bentall surgery (*n*; %)	40 (2.2)	33 (3.7)	7 (0.8)	18.404	***< 0.001***	4.914 (2.185–11.051)
Myocardial infarction (*n*; %)	18 (1.0)	16 (1.8)	2 (0.2)	11.596	***0.001***	8.339 (1.923–36.162)
Hematological involvement (*n*; %)	58 (3.2)	26 (2.9)	32 (3.4)	11.003	***0.001***	0.528 (0.360–0.776)
MDS (*n*; %)	26 (1.4)	12 (1.3)	14 (1.5)	0.849	0.357	0.625 (0.228–1.714)
Myelodysplastic disorder (*n*; %)	4 (0.2)	2 (0.2)	2 (0.2)	0.280	0.596	0.802 (0.353–1.819)
Trisomy of chromosome 8 (*n*; %)	49 (2.7)	19 (2.1)	30 (3.2)	2.282	0.131	0.608 (0.317–1.168)
Neurological involvement (*n*; %)	144 (7.9)	70 (7.8)	74 (7.9)	0.008	0.928	0.987 (0.751–1.298)
Cerebral aneurysm (*n*; %)	47 (2.6)	27 (3.0)	20 (2.1)	1.389	0.239	1.407 (0.795–2.491)
White matter lesion (*n*; %)	113 (6.2)	63 (7.0)	50 (5.3)	2.221	0.136	1.313 (0.916–1.882)
Spinal cord injury (*n*; %)	55 (3.0)	23 (2.6)	32 (3.4)	0.904	0.342	0.773 (0.454–1.316)

IQR, interquartile range; *ISG*, International Study Group; *ICBD*, International Criteria for Behçet's Disease; *MDS*, myelodysplastic syndrome; *RR*, relative risk; *NA*, not applicable

indicators should be given more attention in subsequent research. Therefore, we anticipate broader multi-national, multi-regional, and multi-center large-sample cluster analyses for a more comprehensive understanding.

The observation of phenotypes and clustering made researchers think that different pathogenetic mechanisms may operate in different subsets of patients with BS [12]. This study's refinement of BS phenotypes may provide more comprehensive and personalized diagnostic and potential therapeutic strategies for BS based on each phenotypic characteristic. By using unsupervised clustering methods, we classified BS patients into subgroups that have similar manifestations and outcomes, which may improve the diagnostic sensitivity and specificity of BS. Moreover, an improved classification system serves as a foundation for more targeted and effective therapeutic strategies, enhancing patient care and outcomes.

Conclusion

The present study identified eight distinct phenotypes of BS in a large cohort of Chinese patients. Notably, these phenotypes encompass all previously reported variations, along with the identification of a novel hematological phenotype. The phenotypes showed differences in gender distribution and organ involvements, which may provide a novel framework for understanding and phenotypic classifying for BS diagnosis and management.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate. This work was approved by the medical ethics committee of Huadong Hospital Affiliated to Fudan University with the following reference number: 2018K031.

Conflict of interest The authors declare no conflict of interest.

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