Behçet's disease beyond the criteria: insights from a tertiary centre in Turkey

B. Firlatan Yazgan[1], E.A. Sahin Mavi[2], G.S. Kart Bayram[1], B. Bulat[1], M. Ekici[1], E. Unaldi[1], G. Sandal Uzun[1], G. Ayan[1], Z. Ozsoy[1], S.A. Germe[1], B. Farisogulları[1], E. Duran[1], G.K. Yardimci[1], E.C. Bolek[1], E. Bilgin[1], B. Armagan[1], A. Sari[1], A. Erden[1], L. Kilic[1], B. Kisacik[1], Y. Maras[1], I. Dogan[1], O. Karadag[1], A. Akdogan[1], S. Apras Bilgen[1], S. Kiraz[1], A.I. Ertenli[1], U. Kalyoncu[1]

[1]Division of Rheumatology, Department of Internal Medicine, Hacettepe University School of Medicine, Hacettepe University Vasculitis Research Centre, Ankara;
[2]Department of Internal Medicine, Hacettepe University School of Medicine, Ankara, Turkey.

Abstract

Objective

There are no pathognomonic findings for diagnosing Behçet's disease (BD), the diagnosis relying primarily on clinical evaluation. We aimed to assess patients with BD based on two classification criteria the International Study Group (ISG) criteria and the International Criteria for Behçet's Disease (ICBD), both at diagnosis and throughout the disease, and to explore the characteristics of patients who do not meet the criteria but are clinically diagnosed with BD.

Methods

Patients with BD were identified from the Hacettepe University Vasculitis Research Centre database. Paediatric cases and those with incomplete clinical data were not included. Demographics, clinical characteristics, and treatments were assessed. The physician's clinical judgment determined the gold standard for diagnosis. The patients' fulfilment of the ISG and ICBD criteria was evaluated at diagnosis and during the follow-up.

Results

The study included 804 patients with BD (49.8% males). The mean age at diagnosis was 28.9±10.4 years. At diagnosis, 52.6% of patients fulfilled the ISG criteria, and 81.0% met the ICBD criteria. During follow-up, these rates increased to 59.0% and 84.7%, respectively. Significant organ involvement (ocular, vascular, or neurological) was present in 47.9% of patients not meeting ISG criteria and 30.9% of those not meeting ICBD criteria. The use of at least one immunosuppressive agent was 48.5% and 38.2% in these groups, respectively.

Conclusion

According to various classification criteria, 15-40% of patients with BD do not meet established classification criteria at any point during follow-up, yet significant organ involvement remains prevalent. These findings highlight the limitations of strict criteria-based diagnosis and underscore the importance of clinical expertise in recognising and managing BD.

Key words

Behçet's disease, International Study Group (ISG), International Criteria for Behçet's Disease (ICBD), classification criteria

Busra Firlatan Yazgan, MD
Ezgi Aysu Sahin Mavi, MD
Gozde Sevgi Kart Bayram, MD
Bugu Bulat, MD
Mustafa Ekici, MD
Erdinc Unaldi, MD
Gul Sandal Uzun, MD
Gizem Ayan, MD
Zehra Ozsoy, MD
Serife Asya Germe, MD
Bayram Farisogulları, MD
Emine Duran, MD
Gozde Kubra Yardimci, MD
Ertugrul Cagrı Bolek, MD
Emre Bilgin, MD
Berkan Armagan, MD
Alper Sari, MD
Abdulsamet Erden, MD
Levent Kilic, MD
Bunyamin Kisacik, MD
Yuksel Maras, MD
Ismail Dogan, MD
Omer Karadag, MD
Ali Akdogan, MD
Sule Apras Bilgen, MD
Sedat Kiraz, MD
Ali Ihsan Ertenli, MD
Umut Kalyoncu, MD

Please address correspondence to:
Busra Firlatan Yazgan
Division of Rheumatology,
Department of Internal Medicine,
Hacettepe University School of Medicine,
Sihhiye, 06100 Ankara, Turkey.
E-mail: busra.firlatan@gmail.com,
busrafirlatan@hacettepe.edu.tr

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ORCiD
B. Firlatan Yazgan: 0000-0002-9072-5683
U. Kalyoncu: 0000-0001-7129-2109

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Introduction

Behçet's disease (BD) is a chronic inflammatory disorder with a broad spectrum of clinical manifestations, including mucocutaneous, ocular, vascular, cardiac, neurological, gastrointestinal and articular involvement. BD is more prevalent in countries along the Silk Road, with both its prevalence and clinical manifestations varying across different geographic regions. As there are no specific biomarkers, histological or imaging features for its diagnosis, it is primarily based on physicians' experience in evaluating clinical signs and symptoms (1, 2).

There are more than ten sets of diagnostic and classification criteria for BD, each demonstrating varying sensitivity and specificity across different patient populations. Of these, the International Study Group (ISG) criteria and the International Criteria for Behçet's Disease (ICBD) criteria are internationally accepted and commonly used in studies (3-5). The ICBD criteria exhibited higher sensitivity, but lower specificity compared to the ISG criteria. When a threshold of ≥5 points was used for diagnosing BD, the highest diagnostic consistency between the ISG and ICBD criteria was observed (6).

While distinct sets of diagnosis/classification criteria have been developed for BD, some patients, particularly those at referral centres, may not meet these criteria but are nonetheless clinically diagnosed with BD. This study aims to assess patients diagnosed with BD based on two classification criteria, both at the time of diagnosis and throughout the disease, and to explore the characteristics of patients who do not meet the criteria but are still clinically recognised as having BD.

Methods

Study design and patients

This study included patients diagnosed with Behçet's disease from the Hacettepe University Vasculitis Research Center (HUVAC) database, a longitudinal registry established in 2014. Currently encompassing 1058 patients, paediatric cases and those with incomplete clinical data were excluded from the analysis. A total of 804 patients with a clinician-confirmed BD diagnosis, who had undergone at least one evaluation and had fully accessible clinical records, except for pathergy test and HLA-B51 results, were included. The medical records of these patients were retrospectively analysed from January 1, 2000, to December 31, 2023.

Patient data were evaluated at the time of diagnosis and throughout the follow-up. Demographic characteristics, symptoms, diagnosis and last visit dates, family history of BD, smoking status, HLA-B51 results, disease involvement at diagnosis and throughout the disease course, and treatments received were documented. The clinical features including oral aphthosis (OA), genital ulcers (GU) (either physician-observed or patient-reported), erythema nodosum (EN) (assessed clinically and/or pathologically), papulopustular lesions (PPL), ophthalmologic findings indicative of BD, vascular involvement (venous, arterial, combined venous+arterial involvement and their locations, and thrombophlebitis), cardiac involvement (intracardiac thrombus), neurological involvement (both parenchymal and non-parenchymal), gastrointestinal involvement (based on colonoscopic and pathological evaluations), musculoskeletal involvement (including acute and chronic arthritis, and presence of spondyloarthropathy), and pathergy test results were recorded.

Diagnosis and classification criteria

There is no pathognomonic test that definitively identifies BD; diagnosis relies primarily on clinical signs and symptoms. Therefore, in this study, the clinical judgment of the physician managing the patient determined the gold standard for diagnosis. And the patients' fulfilment of the ISG (3) and the ICBD criteria (4) was evaluated at the time of diagnosis and during the follow-up period.

The ISG criteria, established in 1990, require the presence of oral aphthous lesions occurring at least three times within 12 months, along with any two of the following: genital ulcerations, characteristic eye lesions, characteristic skin lesions, or a positive pathergy

Table I. Demographic and clinical characteristics of patients with Behçet's disease according to fulfilling ISG and ICBD criteria at the time of diagnosis.

		At the time of diagnosis					
	Total Cohort (n: 804)	**ISG (+) (n: 423)**	**ISG (-) (n: 381)**	***p***	**ICBD (+) (n:651)**	**ICBD (-) (n:153)**	***p***
Sex (female/male)	404/400	198/225	206/175	**0.040**	333/318	82/71	0.291
Age at onset (years)	28.9 ± 10.4	28.5 ± 9.9	29.4 ± 10.9	0.199	28.7 ± 10	29.9 ± 12.2	0.267
Oral aphthosis (n, %)	762 (94.8)	423 (100)	339 (89)	**<0.001**	646 (99.2)	116 (75.8)	**<0.001**
Genital ulcer (n, %)	504 (62.7)	342 (80.9)	162 (42.5)	**<0.001**	500 (76.8)	4 (2.6)	**<0.001**
Cutaneous involvement (n, %)	409 (50.9)	316 (74.7)	93 (24.4)	**<0.001**	341 (52.4)	68 (44.4)	0.077
Papulopustular lesion	189 (23.5)	148 (35)	41 (10.8)		165 (25.3)	24 (15.7)	
Erythema nodosum	179 (22.3)	136 (32.2)	43 (11.3)		143 (22)	36 (23.5)	
PPL + EN	41 (5.1)	32 (7.6)	9 (2.4)		33 (5.1)	8 (5.2)	
Ocular involvement (n, %)	280 (34.8)	214 (50.6)	66 (17.3)	**<0.001**	261 (40.1)	19 (12.4)	**<0.001**
Vascular involvement (n, %)	110 (13.7)	42 (9.9)	68 (17.8)	**0.001**	92 (14.1)	18 (11.8)	0.443
Only venous	66 (8.2)	29 (6.9)	37 (9.7)		59 (9.1)	7 (4.6)	
Only arterial	23 (2.9)	4 (0.9)	19 (5)		17 (2.6)	6 (3.9)	
Venous + arterial	7 (0.9)	2 (0.5)	5 (1.3)		4 (0.6)	3 (2)	
Thrombophlebitis	14 (1.7)	7 (1.7)	7 (1.8)		12 (1.8)	2 (1.3)	
Cardiac involvement (n, %)	5 (0.6)	2 (0.5)	3 (0.8)	0.672	4 (0.6)	1 (0.7)	1
Neurological involvement (n, %)	46 (5.7)	12 (2.8)	34 (8.9)	**<0.001**	31 (4.8)	15 (9.8)	**0.016**
Parenchymal	25 (3.1)	6 (1.4)	19 (5)		14 (2.2)	11 (7.2)	
Cerebral venous sinus thrombosis	21 (2.6)	6 (1.4)	15 (3.9)		17 (2.6)	4 (2.6)	
Gastrointestinal involvement (n, %)	12 (1.5)	3 (0.7)	9 (2.4)	0.054	8 (1.2)	4 (2.6)	0.257
Musculoskeletal involvement (n, %)							
Arthritis	110 (13.7)	57 (13.5)	53 (13.9)	0.858	85 (13.1)	25 (16.3)	0.288
Spondyloarthropathy	13 (1.6)	6 (1.4)	7 (1.8)	0.638	9 (1.4)	4 (2.6)	0.285
Pathergy test positivity (n, %)*	127 (40.2)	113 (62.4)	14 (10.4)	**<0.001**	116 (47.4)	11 (15.5)	**<0.001**
Treatment (n, %)							
Colchicine	707 (87.9)	386 (91.3)	321 (84.3)	**0.001**	590 (90.6)	117 (76.5)	**<0.001**
Penicillin	111 (13.8)	60 (14.2)	51 (13.4)	0.724	89 (13.7)	22 (14.4)	0.841
Steroid	213 (26.5)	112 (26.5)	101 (26.5)	0.996	169 (26)	44 (28.8)	0.478
Azathioprine	205 (25.5)	126 (29.8)	79 (20.7)	**0.003**	175 (26.9)	30 (19.6)	0.058
Cyclosporine	26 (3.2)	24 (5.7)	2 (0.5)	**<0.001**	26 (4)	0 (0)	**0.008**
Interferon	74 (9.2)	44 (10.4)	30 (7.9)	0.208	60 (9.2)	14 (9.2)	0.962
Cyclophosphamide	32 (3.9)	12 (2.8)	20 (5.3)	0.083	23 (3.5)	9 (5.9)	0.186
Anti-tumour necrosis factor alpha inhibitors	43 (5.3)	23 (5.4)	20 (5.3)	0.894	37 (5.7)	6 (3.9)	0.375
Fulfilled ISG criteria (n, %)	423 (52.6)	423 (100)	N/A		423 (65)	0 (0)	
Fulfilled ICBD criteria (n, %)	651 (81)	423 (100)	228 (59.8)		651 (100)	N/A	

n=804, unless otherwise specified.
* At diagnosis (n=316); ever (n=336).

test for the diagnosis of BD (3). The ICBD criteria, developed in 2014, assign two points each to oral aphthosis, genital aphthosis, and ocular lesions, while cutaneous, neurological, and vascular manifestations receive one point. The pathergy test, if performed, is also scored one point. Scoring greater than or equal to four points is classified as having BD (4).

Statistical analysis

Categorical variables are presented as frequencies and percentages, while continuous variables are expressed as mean ± standard deviation or median (IQR). The normality of the data was assessed using the Kolmogorov-Smirnov test. For comparisons, the chi-square test was used for categorical variables, and either the Student's t-test or Mann-Whitney U test was applied for continuous variables. A *p*-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the IBM SPSS version 25.0 (Statistical Package for Social Sciences).

Ethical considerations

The study was approved by the ethics committee of Hacettepe University (SBA 24/687) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Results

Demographic and clinical characteristics

The study included 804 patients with BD, comprising 49.8% males. The mean age at diagnosis was 28.9±10.4 years, with a median (IQR) follow-up duration of 11 (4-19) years. The distribution of disease manifestations at the time of diagnosis in the overall study population was as follows: oral aphthae 94.8%, genital ulcers 62.7%, cutaneous involvement 50.9%, ocular involvement 34.8%, musculoskeletal involvement 15.3%, vascular involvement 13.7%, neurological involvement 5.7%, gastrointestinal involvement 1.5%, cardiac involvement 0.6%, and

Table II. Demographic and clinical characteristics of patients with Behçet's disease according to fulfilling ISG and ICBD criteria during the follow-up (ever).

		During the follow-up (ever)					
	Total Cohort (n: 804)	**ISG (+) (n:474)**	**ISG (-) (n:330)**	***p***	**ICBD (+) (n:681)**	**ICBD (-) (n:123)**	***p***
Sex (female/male)	404/400	202/254	184/146	**0.009**	342/339	62/61	0.970
Age at onset (years)	28.9 ± 10.4	28 ± 9.8	30.2 ± 11.1	**0.005**	28.5 ± 10	31 ± 12.5	**0.041**
Oral aphthosis (n, %)	768 (95.5)	474 (100)	294 (89.1)	**<0.001**	675 (99.1)	93 (75.6)	**<0.001**
Genital ulcer (n, %)	514 (63.9)	386 (81.4)	128 (38.8)	**<0.001**	511 (75)	3 (2.4)	**<0.001**
Cutaneous involvement (n, %)	463 (57.6)	370 (78.1)	93 (28.2)	**<0.001**	405 (59.5)	58 (47.2)	**0.011**
Papulopustular lesion	205 (25.5)	158 (33.3)	47 (14.2)		182 (26.7)	23 (18.7)	
Erythema nodosum	210 (26.1)	173 (36.5)	37 (11.2)		181 (26.6)	29 (23.6)	
PPL + EN	48 (6)	39 (8.2)	9 (2.7)		42 (6.2)	6 (4.9)	
Ocular involvement (n, %)	327 (40.7)	265 (55.9)	62 (18.8)	**<0.001**	314 (46.1)	13 (10.6)	**<0.001**
Vascular involvement (n, %)	177 (22)	93 (19.6)	84 (25.5)	0.050	161 (23.6)	16 (13)	**0.009**
Only venous	103 (12.8)	66 (13.9)	37 (11.2)		99 (14.5)	4 (3.3)	
Only arterial	36 (4.5)	9 (1.9)	27 (8.2)		31 (4.6)	5 (4.1)	
Venous + arterial	19 (2.4)	9 (1.9)	10 (3)		14 (2.1)	5 (4.1)	
Thrombophlebitis	19 (2.4)	9 (1.9)	10 (3)		17 (2.5)	2 (1.6)	
Cardiac involvement (n, %)	8 (1)	3 (0.6)	5 (1.5)	0.284	8 (1.2)	0 (0)	0.616
Neurological involvement (n, %)	95 (11.8)	51 (10.8)	44 (13.3)	0.266	82 (12)	13 (10.6)	0.642
Parenchymal	62 (7.7)	37 (7.8)	25 (7.6)		51 (7.5)	11 (8.9)	
Cerebral venous sinus thrombosis	33 (4.1)	14 (3)	19 (5.8)		31 (4.6)	2 (1.6)	
Gastrointestinal involvement (n, %)	21 (2.6)	13 (2.7)	8 (2.4)	0.781	17 (2.5)	4 (3.3)	0.547
Musculoskeletal involvement (n, %)							
Arthritis	126 (15.7)	77 (16.2)	49 (14.8)	0.592	104 (15.3)	22 (17.9)	0.463
Spondyloarthropathy	29 (3.6)	17 (3.6)	12 (3.6)	0.970	27 (4)	2 (1.6)	0.293
Pathergy test positivity (n, %)*	131 (39)	117 (57.4)	14 (10.6)	**<0.001**	123 (44.2)	8 (13.8)	**<0.001**
HLAB51 positivity, ever (n, %)**	223 (66)	115 (66.9)	108 (65.1)	0.727	172 (64.9)	51 (69.9)	0.429
Treatment (n, %)							
Colchicine	739 (91.9)	449 (94.7)	290 (87.9)	**<0.001**	638 (93.7)	101 (76.5)	**<0.001**
Penicillin	157 (19.5)	103 (21.7)	54 (16.4)	0.060	131 (19.2)	26 (21.1)	0.635
Steroid	338 (42)	207 (43.7)	131 (39.7)	0.244	294 (43.2)	44 (35.8)	0.114
Azathioprine	352 (43.8)	235 (49.6)	117 (35.5)	**<0.001**	321 (47.1)	31 (25.2)	**<0.001**
Cyclosporine	46 (5.7)	41 (8.7)	5 (1.5)	**<0.001**	46 (6.8)	0 (0)	**0.003**
Interferon	177 (22)	125 (26.4)	52 (15.8)	**<0.001**	159 (23.3)	18 (13.6)	**0.031**
Cyclophosphamide	63 (7.8)	34 (7.2)	29 (8.8)	0.400	54 (7.9)	9 (7.3)	0.809
Anti-tumour necrosis factor alpha inhibitors	145 (18)	93 (19.6)	52 (15.8)	0.163	132 (19.4)	13 (10.6)	**0.019**
At least one immunosuppressive treatment	458 (57)	298 (62.9)	160 (48.5)	**<0.001**	411 (60.4)	47 (38.2)	**<0.001**
Fulfilled ISG criteria (n, %)	474 (59)	474 (100)	N/A		474 (69.6)	0 (0)	
Fulfilled ICBD criteria (n, %)	681 (84.7)	474 (100)	207 (62.7)		681 (100)	N/A	

n=804, unless otherwise specified.
*At diagnosis (n=316); ever (n=336).
**Ever (n=338).

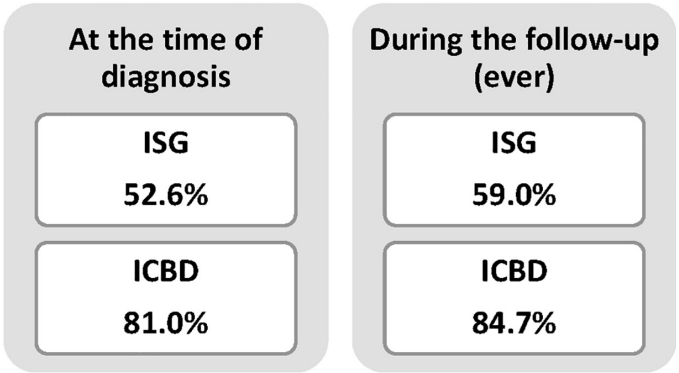

Fig. 1. Proportions of patients fulfilling ISG and ICBD criteria at diagnosis and during the follow-up.

pathergy test positivity (n=316) 40.2% (Table I).

A slight increase in the prevalence of all disease manifestations, except for pathergy test positivity, was observed over the follow-up period. The cumulative prevalence of BD manifestations was as follows: oral aphthae 95.5%, genital ulcers 63.9%, cutaneous involvement 57.6%, ocular involvement 40.7%, vascular involvement 22.0%, musculoskeletal involvement 19.3%, neurological involvement 11.8%, gastrointestinal involvement 2.6%, cardiac involvement 1%, pathergy positivity (n=336) 39.0%, and HLA-B51 positivity (n=338) 66.0% (Table II).

Colchicine was the most commonly administered drug in the study cohort (91.9%). At the time of diagnosis, 38% of patients had received at least one immunosuppressive therapy,

Table III. Comparison of patients with ocular, vascular, neurological and gastrointestinal involvement based on ISG criteria fulfilment (ever).

	Ocular involvement (n: 327)			Vascular involvement (n: 177)			Neurological involvement (n: 95)		
	ISG (+) (n: 265)	**ISG (-) (n:62)**	***p***	**ISG (+) (n: 93)**	**ISG (-) (n:84)**	***p***	**ISG (+) (n: 51)**	**ISG (-) (n:44)**	***p***
Sex (female/male)	104/161	30/32	0.188	19/74	23/61	0.278	24/27	21/23	0.948
Age at onset (years)	27.7 ± 9.5	30.3 ± 11.4	**0.047**	25.7 ± 8.1	29.6 ± 9.4	**0.002**	25.3 ± 9.4	29.7 ± 11.2	**0.048**
Oral aphthosis (n, %)	265 (100)	46 (74.2)	**<0.001**	93 (100)	76 (90.5)	**0.002**	51 (100)	35 (79.5)	**0.001**
Genital ulcer (n, %)	197 (74.3)	5 (8.1)	**<0.001**	76 (81.7)	29 (34.5)	**<0.001**	46 (90.2)	11 (25)	**<0.001**
Cutaneous involvement (n, %)	190 (71.7)	5 (8.1)	**<0.001**	75 (80.6)	26 (31)	**<0.001**	36 (70.6)	10 (22.7)	**<0.001**
Papulopustular lesion	72 (27.2)	2 (3.2)		29 (31.2)	19 (22.6)		13 (25.5)	6 (13.6)	
Erythema nodosum	95 (35.8)	3 (4.8)		35 (37.6)	5 (6.0)		18 (35.3)	3 (6.8)	
PPL + EN	23 (8.7)	0 (0)		11 (11.8)	2 (2.4)		5 (9.8)	1 (2.3)	
Ocular involvement (n, %)	265 (100)	62 (100)	N/A	55 (59.1)	12 (14.3)	**<0.001**	35 (68.6)	10 (22.7)	**<0.001**
Vascular involvement (n, %)	55 (20.8)	12 (19.4)		93 (100)	84 (100)		8 (15.7)	12 (27.3)	
Only venous	39 (14.7)	4 (6.5)	**0.021**	66 (71)	37 (44)	**<0.001**	5 (9.8)	4 (9.1)	0.362
Only arterial	7 (2.6)	6 (9.7)	**0.008**	9 (9.7)	27 (32.1)	**<0.001**	0 (0)	6 (13.6)	**0.042**
Venous + arterial	3 (1.1)	1 (1.6)	0.555	9 (9.7)	10 (11.9)	0.633	1 (2)	1 (2.3)	1
Thrombophlebitis	6 (2.3)	1 (1.6)	1	9 (9.7)	10 (11.9)	0.633	2 (3.9)	1 (2.3)	0.537
Cardiac involvement (n, %)	1 (0.4)	0 (0)	1	2 (2.2)	5 (6.0)	0.259	2 (3.9)	1 (2.3)	1
Neurological involvement (n, %)	35 (13.2)	10 (16.1)	0.548	8 (8.6)	12 (14.3)	0.233	51 (100)	44 (100)	N/A
Parenchymal	28 (10.6)	8 (12.9)		4 (4.3)	5 (6.0)		37 (72.5)	25 (56.8)	
Cerebral venous sinus thrombosis	7 (2.6)	2 (3.2)		4 (4.3)	7 (8.3)		14 (27.5)	19 (43.2)	
Gastrointestinal involvement (n, %)	8 (3)	2 (3.2)	1	4 (4.3)	2 (2.4)	0.685	0 (0)	1 (2.3)	0.463
Musculoskeletal involvement (n, %)	52 (19.6)	9 (14.5)		10 (10.8)	12 (14.3)		12 (23.6)	2 (4.5)	
Arthritis	44 (16.6)	6 (9.7)	0.173	8 (8.6)	10 (11.9)	0.468	11 (21.6)	2 (4.5)	**0.016**
Spondyloarthropathy	8 (3)	3 (4.8)	0.443	2 (2.2)	2 (2.4)	1	1 (2)	0 (0)	1
Pathergy test positivity* (positive/n)	43/89	1/17	**0.001**	28/41	4/36	**<0.001**	11/17	1/17	**<0.001**
HLAB51 positivity** (positive/n)	59/88	17/27	0.695	21/32	26/39	0.926	14/18	13/23	0.154

* Ever (n=336).
**Ever (n=338).

a proportion that increased to 57% throughout follow-up. Overall, the most frequently preferred immunosuppressive agents were azathioprine (43.8%), interferon (22%), and anti-TNF therapies (18%), respectively. Steroid therapy was received by 42% of patients (Table II).

The potential influence of smoking habits on the development of OA was evaluated in our cohort. Of the 804 patients, 296 (36.8%) had never smoked, 160 (19.9%) were current smokers, 51 (6.3%) were ex-smokers, and 297 (36.9%) had an unknown smoking status. The oral aphthae prevalence was high across all groups: 96.3% in never smokers, 95.0% in current smokers, 98.0% in ex-smokers, and 94.9% in those with unknown smoking status. No significant difference in the prevalence of OA was detected among the different smoking status groups. However, due to the retrospective nature of our study, we were unable to precisely assess the temporal relationship between smoking status and the development of OA.

Fulfilling ISG criteria and ICBD criteria

At diagnosis, 52.6% of patients fulfilled the ISG criteria, and 81.0% met the ICBD criteria. During follow-up, these rates increased to 59.0% and 84.7%, respectively (Fig. 1). Fifty-one patients who did not meet the ISG criteria at diagnosis and 30 patients who did not meet the ICBD criteria subsequently fulfilled them. Throughout the observation period, at least one ocular, vascular, or neurological manifestation developed in 46 of 381 patients (12.1%) who did not meet the ISG criteria at diagnosis, and in 12 of 153 patients (7.8%) who did not meet the ICBD criteria at diagnosis.

During the follow-up period, patients who met the ISG criteria were more commonly male (53.6% *vs*. 44.2%, *p*=0.009) and were younger at disease onset (28±9.8 years *vs*. 30.2±11.1 years, *p*=0.005).This group also exhibited significantly higher rates of OA (100% *vs*. 89.1%), GU (81.4% *vs*. 38.8%), cutaneous involvement (78.1% *vs*. 28.2%), ocular involvement (55.9% *vs*. 18.8%), and pathergy test positivity (57.4% *vs*. 10.6%, n=336). In contrast, the prevalence of vascular, cardiac, neurological, gastrointestinal, and musculoskeletal involvement did not differ significantly between patients who met and did not meet the ISG criteria.

Similarly, patients meeting the ICBD criteria had significantly higher rates of OA (99.1% *vs*. 75.6%), GU (75% *vs*. 2.4%), cutaneous involvement (59.5% *vs*. 47.2%), ocular involvement (46.1% *vs*. 10.6%), vascular involvement (23.6% *vs*. 13%), and pathergy positivity (44.2% *vs*. 13.8%). The rates of cardiac, neurological, and gastrointestinal involvement, as well as arthritis and spondyloarthropathy, were comparable between the groups.

Among patients who did not meet the ISG criteria, 47.9% exhibited significant organ involvement, including ocular, vascular, or neurological manifestations, compared to 30.9% of those not meeting the ICBD criteria. Specifically, ocular involvement was observed in 18.8% of patients not fulfilling ISG

criteria and 10.6% of patients not fulfilling ICBD criteria, vascular involvement in 25.5% and 13%, and neurological involvement in 13.3% and 10.6%, respectively.

Patients meeting the ISG and ICBD criteria had significantly higher rates of colchicine, azathioprine, cyclosporine, and interferon use ($p<0.05$ for all). Additionally, TNF inhibitor therapy was more frequently prescribed in the ICBD-positive group than in those who did not meet the criteria (19.4% *vs.* 10.6%, $p=0.019$). In contrast, the use of penicillin, corticosteroids, and cyclophosphamide was comparable between the groups (Table II). Throughout the follow-up period, 48.5% of patients in the ISG (-) group and 38.2% in the ICBD (-) group received at least one immunosuppressive treatment.

Patients with severe manifestations, including ocular, vascular, and neurological were compared based on whether they fulfilled the ISG criteria (Table III). It was observed that patients with ocular, vascular, or neurological involvement who did not meet the ISG criteria had a later onset of disease. Additionally, these patients exhibited a lower frequency of oral aphthae, genital ulcers, and cutaneous involvement ($p<0.05$ for all). Although overall vascular involvement was comparable between the ISG-positive and ISG-negative groups, a notable difference was observed: venous involvement was more prevalent in patients meeting the ISG criteria, whereas arterial involvement was more frequently observed in those not meeting the criteria.

Discussion

In this study, we assessed the fulfilment of ISG and ICBD criteria among 804 patients diagnosed with BD based on expert clinical judgment. At the time of diagnosis, 52.6% of patients met the ISG criteria, while 81.0% fulfilled the ICBD criteria. These rates increased during follow-up to 59.0% and 84.7%, respectively, as additional clinical manifestations emerged over time. Despite the increased fulfilment of classification criteria during follow-up, a notable proportion of patients (15-40%) did not meet any established criteria at any point. However, of the patients who did not fulfil the ISG criteria, 47.9% exhibited significant organ involvement, including ocular, vascular, or neurological manifestations, while this proportion was 30.9% among those who did not meet the ICBD criteria.

Compared to the ISG criteria, it is well established that the ICBD criteria offer greater sensitivity especially in early disease but at the expense of lower specificity (4). This lower specificity may lead to the misclassification of patients with other conditions that closely mimic Behçet's disease, particularly in terms of mucocutaneous findings, thereby raising the potential for overdiagnosis. The limitations of the ICBD criteria are particularly relevant in populations where Behçet's disease is less prevalent. In a study from a specialised Behçet's service in the UK reported that the specificity of both criteria was lower than expected, particularly for the ICBD criteria, which was as low as 19.05% (11.30-29.08). This was mainly due to many patients with only oro-genital ulcers later being diagnosed with other conditions, resulting in more false positives (7). A similar problem may arise in ophthalmology settings, where all uveitis patients receive two points for ocular lesions; if they also have non-specific oral aphthae, they may be classified as BD even without other typical features (6). On the other hand, the ISG criteria demonstrate higher specificity; however, a key limitation is that they do not include vascular, neurological, or gastrointestinal involvement as part of the criteria, which may lead to underdiagnosis in patients who primarily present with these major organ manifestations (8). Considering the variable performance of classification criteria across different settings, careful clinical assessment and follow-up are essential in managing a heterogeneous disease like BD.

Yazici *et al*. argued that the distinction between diagnostic and classification criteria is artificial, as both exist on a continuum and rely on similar cognitive processes. They also noted that developing universal criteria is particularly challenging for rare diseases like BD, where variations in prevalence, clinical presentation, and subspecialty practices affect diagnostic accuracy. Moreover, the concept of universal classification criteria in research is also debated, as patient selection should align with specific study hypotheses, with different questions requiring distinct populations. Therefore, they suggested that adapting criteria to specific clinical settings or specialties can improve sensitivity and specificity by reflecting variations in disease presentation and prevalence (9-11). In our study, patients were assessed using two distinct criteria sets, and it was observed that 15-40% of those being followed with a diagnosis of BD did not meet the established criteria. Consistent with our findings, a multicentre study conducted across three centres in Japan and the United States between 2003 and 2010 by Kobayashi *et al*., which evaluated 769 patients, reported that 61.5% of those from the United States and 63.7% of those from Japan met the ISG criteria. Similarly, female predominance was observed, while the frequencies of oral aphthae, ocular and vascular involvement, and pathergy positivity were lower. In contrast to our cohort, this study identified higher rates of genital ulcers (particularly among patients from the United States), skin involvement, gastrointestinal involvement, and arthritis (12). In 2019, Davatchi *et al*. published a large cohort data of 7641 patients with BD from Iran. Regarding the fulfilment of classification criteria, the sensitivities of the criteria were found to be 96.6% for ICBD and 76.2% for ISG, both of which were higher than those observed in our cohort (13). However, in this research, cataracts and conjunctivitis were considered part of ocular involvement, gastroduodenitis and peptic ulcer as gastrointestinal involvement, and arthralgia as musculoskeletal involvement. Variations in the definition of manifestations and geographical differences may have contributed to these findings.

In our cohort, although the proportion of patients meeting the criteria increased throughout follow-up, the values remained relatively close (52.6% at

diagnosis and 59% ever for ISG; 81% at diagnosis and 84.7% ever for ICBD). Ideguchi *et al*. chronologically analysed the onset of BD symptoms and found that oral aphthae appeared during the pre-diagnostic stage in most patients. Although other symptoms also emerged before diagnosis, the incidence of genital ulcers, skin symptoms, and ocular involvement increased rapidly closer to the time of diagnosis. In contrast, although CNS, gastrointestinal, and vascular involvements appeared as initial symptoms in some patients, they were found to develop later in the majority of cases. The cumulative incidence of the symptoms assessed in this study increased up to the time of diagnosis, with a plateau observed during the 20-30 years of follow-up (14). Kobayashi *et al*. categorized BD patients into three groups according to the duration since the onset of BD symptoms (≤3 months, 3-24 months, >24 months). Although the proportion of patients meeting the ISG criteria increased with time, no statistically significant differences were found. They concluded that the time elapsed since the diagnosis of BD had no significant impact on the likelihood of fulfilling the criteria (12). However, it should be noted that the patients' treatment following diagnosis may have hindered the emergence of new findings during follow-up, potentially influencing their failure to meet the criteria.

Yazici *et al*. conceptualised BD as a construct, emphasizing that it comprises both strong and weak elements. In this framework, oral and genital ulcers, ocular involvement, major vascular manifestations, and parenchymal neurological disease were identified as the strong elements. Additionally they suggested that the diagnostic specificity of these manifestations may be more pathognomonic (15). Aligning with this perspective, our study at a tertiary referral centre in Turkey, a country with a high prevalence of BD, revealed that significant organ involvement strongly suggestive of BD (ocular, vascular, or neurological) was present in 47.9% of patients not meeting ISG criteria and 30.9% of those not meeting ICBD criteria. This finding is particularly critical for treatment decisions, as these patients should not be excluded from recommended therapies solely due to their failure to fulfil diagnostic/classification criteria. In our cohort, 48.5% of patients in the ISG-negative group and 38.2% in the ICBD-negative group received at least one immunosuppressive treatment. These results underscore the limitations of strict criteria-based diagnostic approaches, which may delay timely recognition and treatment, ultimately impacting patient outcomes.

Our study has several limitations. First, the data were collected retrospectively. Clinical findings were determined solely from patient histories for patients diagnosed with BD before evaluation at our department. The absence of pathergy test results for all patients may have led to an underestimation of those meeting the criteria. However, pathergy test results were available for 43% of patients meeting the ISG criteria and 40% of those who did not. Among the 468 patients with unknown pathergy test results, 270 (57.7%) fulfilled the ISG criteria, while 403 (86.1%) met the ICBD criteria. When a best-case scenario is applied, assuming all patients with missing pathergy test results are positive, the proportion of patients fulfilling the ISG and ICBD criteria at diagnosis was calculated as 76.4% and 86.6%, respectively. During follow-up, these proportions were estimated to be 78.3% for ISG and 89.3% for ICBD. However, considering the rate of pathergy test positivity observed in the Turkish population (approximately 60%) (16), these values would likely be lower. Additionally, variations in the experience levels of the evaluating physicians represent a limitation. Nevertheless, all patients were recruited from a centre with expertise in vasculitis. Finally, in some cases, the follow-up period may have been insufficient for clinical findings to manifest, or patients may have been lost to follow-up before such findings could develop.

In conclusion, according to various classification criteria, 15-40% of patients diagnosed with BD by clinicians do not meet the criteria at any point during follow-up. Nevertheless, significant organ involvement, including ocular, vascular, and neurologic, remains prevalent in these cases. These findings underscore the essential role of experienced rheumatologists in diagnosing and managing BD. Moreover, further research is needed to tailor diagnostic/classification criteria to specific clinical settings or specialties, considering variations in disease presentation and prevalence.

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