Identification of clinical phenotypes in Behçet's syndrome using latent class analysis: a step toward precision medicine

S. Chadli[1], M. Maamar[1], R. Abouqal[2], W. Ammouri[1], Z. Tazi Mezalek[1,3], H. Harmouche[1]

[1]Internal Medicine and Clinical Immunology, Ibn Sina University Hospital, Mohammed V University in Rabat; [2]Laboratory of Biostatistics and Clinical Research, Faculty of Medicine and Pharmacy of Rabat, Mohammed V University in Rabat; [3]Clinical Haematology, Ibn Sina University Hospital, Mohammed V University in Rabat, Morocco.

Abstract

Objective

Behçet's syndrome (BS) is characterised by extreme clinical heterogeneity, underscoring the need for precise patient classification to enable personalised management. While traditional distance-based cluster analysis (CA) has provided new insights, its deterministic approach may not fully capture the complexity of BS. The primary objective of this study was to define BS clinical phenotypes using latent class analysis (LCA), a probabilistic, model-based clustering method that identifies hidden classes based on unobserved patterns. We also aimed to examine sex-related differences in clinical manifestations and treatment requirements across the identified classes.

Methods

We conducted a retrospective, observational, single-centre study including all adult BS patients followed in our department between 2012 and 2022, targeting a sample of 500 patients. LCA was performed using clinically relevant indicators (sex, oral and genital ulcers, skin lesions, articular involvement and major organ involvement). Models were compared based on fit indices, class number, separation, assignment and size. The final model was selected based on both clinical relevance and statistical performance.

Results

A total of 553 patients (409 males, 144 females) were enrolled, with a mean age of 32±7 years. Five latent classes (C1-C5) with distinct phenotypes were identified. C1 (n=215; 39%), 'vascular type': all patients had vascular lesions, with the highest prevalence of cardiac involvement (12%). C2 (n=171; 31%), 'ocular type': characterised by 100% uveitis and frequent mucocutaneous lesions. C3 (n=40; 7%), 'neurological type': all patients exhibited parenchymal neurological involvement, and 40% had concomitant uveitis. C4 (n=98; 18%), 'skin-mucosa and articular type': marked by 100% oral and genital ulcers, with the highest prevalence of papulopustular lesions (54%) and articular involvement (48%). C5 (n=29; 5%), 'uncertain BS': with 60% uveitis, 48% vascular lesions, and the lowest mucocutaneous involvement. Sex-related clinical differences were observed, with significant male predominance across all major organ classes (C1, C2, C3, and C5), whereas a near-equal sex distribution was noted in the skin-mucosa and articular class ($p<0.001$). Treatment patterns varied considerably, with higher corticosteroid doses and conventional immunosuppressant use in major organ classes, while biologics were mostly prescribed in the 'ocular class' (C2) and 'uncertain BS' (C5) ($p< 0.001$).

Conclusion

This study is the first to apply LCA for BS clinical phenotyping, providing a probabilistic classification that uncovers complex patient subgroups. Five latent classes were identified, with distinct clinical profiles, significant sex disparities, and varying therapeutic needs. These findings are crucial for advancing precision medicine in BS and ultimately improving patient outcomes.

Key words

Behçet's syndrome, latent class analysis, cluster analysis, phenotype, precision medicine

Sarra Chadli, MD
Mouna Maamar, MD
Redouane Abouqal, MD
Wafaa Ammouri, MD
Zoubida Tazi Mezalek, MD
Hicham Harmouche, MD

Please address correspondence to:
Sarra Chadli
Internal Medicine and Clinical Immunology,
Ibn Sina University Hospital,
Mohammed V University,
10100 Rabat, Morocco.
E-mail: sarrachadli@gmail.com
ORCID iD: 0000-0003-3681-1406

Received on July 13, 2025; accepted in revised form on October 7, 2025.

Competing interests: none declared.

Introduction

Behçet's syndrome (BS) is a complex multisystem inflammatory disorder of unknown aetiology. First described in the 1930s, successively by Benedict Adamantiades and Hulusi Behçet, it was initially defined as a combination of aphthous oral ulcers, genital ulcers, and uveitis (1, 2). Later, it was suggested by Behçet himself that the disease likely extends beyond this classic triad (3). Since then, additional major organ involvements have been reported, including the vascular, neurological, cardiac, and gastrointestinal systems (4).

Although BS can occur globally, it is much more prevalent along the ancient 'Silk Road', encompassing the Mediterranean region, the Middle East, and East Asia (5). The type and severity of clinical presentation vary between regions and within the same population (6). Despite this diversity, various associations between manifestations have been described, shaping the concept of BS phenotypes (7, 8).

As patients with BS follow a complex course with varying morbidity and mortality outcomes, the 2018 update of the EULAR recommendations emphasised the need for individualised management strategies (9). One of the primary challenges facing precision medicine in BS is the heterogeneity of patients (10). Previous studies have attempted to define BS subgroups, often relying on factor analysis (11-13). Yet, these statistical techniques, which aim to reduce variables into smaller sets of factors, have yielded inconsistent results.

In contrast, clinical clustering in heterogeneous diseases has shown promise in better identifying patient subsets that may predict disease patterns (14). Cluster analysis (CA), which groups patients based on similarities in their observed variables, was first applied to BS phenotyping in 1984 (15). Nevertheless, it quickly fell out of favour, likely due to limited results. As factor analysis and other dimension-reduction methods have been insufficient in identifying BS subsets, CA has recently regained interest as a tool for phenotyping (16-19). Yet, these studies used distance-based clustering (*e.g.* hierarchical, k-means, two-step…), which, despite offering valuable insights, relies on deterministic approaches that may oversimplify the extreme complexity and heterogeneity of BS.

Recent developments in latent class analysis (LCA), a model-based clustering method, provide a probabilistic and more precise alternative to traditional CA (20). With unsupervised learning techniques, LCA uncovers hidden patterns within the data, enabling the identification of unobserved or 'latent' classes within a population (21). Although LCA has delivered impactful results in other medical conditions such as diabetes, systemic lupus erythematosus, osteoarthritis, and sepsis, it has not yet been applied in BS (22-25).

Hence, the primary objective of our work was to identify clinical phenotypes in BS using LCA. A secondary aim was to explore sex-related differences in clinical manifestations and assess therapeutic needs across the identified classes. Defining these clinical subgroups is fundamental for improving our understanding of BS heterogeneity and providing more accurate patient classification, thereby advancing precision medicine in this population.

Material and methods

Study design

We conducted a retrospective, single-centre, observational, descriptive, and analytical study in the Internal Medicine and Clinical Immunology Department at Ibn Sina University Hospital, Rabat, Morocco. Data were collected from medical records and hospitalisation documentation between 2012 and 2022.

We included all adult patients (age ≥18 years) who fulfilled at least one of the following classification criteria for BS: revised International Criteria for Behçet Disease (ICBD) or revised International Study Group criteria (ISG) for Behçet Disease. Files with substantial missing information, particularly on clinical manifestations, were excluded.

The research was conducted in accordance with the Declaration of Helsinki. Informed consent was not applicable due to the retrospective observational nature of the study.

Data collection

We collected patients' detailed demographic and medical information, including sex, age at BS onset and enrolment, past medical history, smoking status, clinical symptoms, physical examination findings, laboratory work-up, imaging, and endoscopy reports.

Clinical evaluation assessed mucocutaneous involvement (oral ulcers, genital ulcers, papulopustular lesions, erythema nodosum-like lesions, and pathergy reaction) and articular involvement (arthralgias and arthritis).

Ocular involvement was documented with detailed findings on the affected segments, type of lesions, and laterality. Neurological involvement included central nervous system (CNS) parenchymal involvement**,** diagnosed through lumbar puncture, cerebral CTA/MRA, cerebrospinal MRA, and peripheral nervous system involvement, confirmed by EMG.

Vascular involvement was evaluated by Doppler ultrasound and/or CTA, showing venous (superficial and deep venous thrombosis), and/or arterial (aneurysm, thrombosis, stenosis) lesions.

Cardiac involvement was assessed based on clinical findings, cardiac biomarkers, ECG, cardiac TTE/MRI, and coronary angiography. Gastrointestinal involvement was established through clinical manifestations supported by biological, radiologic, endoscopic, and histopathologic findings.

Therapeutic management was documented, including corticosteroid dosage, conventional immunosuppressant, and biological agent use. We also reported colchicine, anticoagulants, and antiplatelet prescriptions**.** Surgical and interventional procedures were noted. The mortality rate was recorded.

Statistical analysis

Statistical analysis was conducted using R (v. 4.4) and Stata (v. 14.3). Continuous variables were reported as means and standard deviations for normally distributed data, and as medians and interquartile range (IQR) for skewed distributions. Categorical variables were presented as percentages within each category. Univariate analysis was conducted using Pearson's chi-squared test for categorical variables and Student t- or non-parametric Mann-Whitney test for continuous variables. An alpha of 0.05 was used as the cut-off for significance.

A minimum sample size of 500 patients was estimated to perform LCA (21). We selected ten clinically relevant indicators for model building: sex, oral ulcers, genital ulcers, papulopustular lesions, erythema nodosum-like lesions, articular involvement, and major organ involvement (ocular, neurological, vascular, cardiac, and gastrointestinal). The clustering algorithm was run with 100 random initialisations, testing solutions with 2 to 6 classes.

Models were compared using several criteria, including class number, fit indices, class separation, individual probabilities for class membership, and class size. The primary approach was to select the model with the fewest classes that best suited the data. As adding parameters improves a model's fit but reduces its generalisability, fit indices were used to balance accuracy and avoid overfitting. The Bayesian information criterion (BIC) was the primary metric, complemented by the Akaike information criterion (AIC), log-likelihood, and bootstrapped p-values. Entropy, a class separation measure, was another key factor, with a value of 1 indicating perfect class separation and values >0.8 considered strong. Posterior individual probabilities for class membership were examined, with a cut-off of >0.5 for class assignment. Lastly, class size was evaluated to ensure that the smallest class represents a genuine subset rather than statistical anomalies, with a threshold of 5% applied.

The final model was selected according to both clinical relevance and statistical performance.

Results

Descriptive characteristics

We enrolled a total of 553 patients diagnosed with BS, all of Moroccan origin. There were 409 males and 144 females, resulting in a sex ratio of 2.8:1. The mean age at BS onset was 30±11 years (7-66), with the mean age at enrolment being 42±13 years (15-79). Smoking was reported in 22% of cases.

Table I. Descriptive characteristics of BS patients, Ibn Sina University Hospital, Rabat, Morocco (2012-2022).

	n=553
Male sex*	409 (74)
Age at BS onset**	30 ± 11
Oral ulcers*	524 (95)
Genital ulcers *	464 (84)
Skin lesions*	265 (48)
Papulopustular lesions*	220 (40)
Erythema nodosum-like lesions*	55 (10)
Articular involvement*	164 (30)
Ocular involvement*	266 (48)
Vascular involvement*	229 (41)
Neurological involvement*	70 (13)
Cardiac involvement*	37 (7)
Gastrointestinal involvement*	22 (4)
Corticosteroids*	475 (86)
Conventional Immunosuppressants*	354 (64)
Biological agents*	46 (8)
Mortality	12 (2)

*n (%); **Mean ± SD.

Past medical history comprised diabetes mellitus (4%), dyslipidaemia (4%), and arterial hypertension (3%).

Oral aphthosis was the most prevalent manifestation (95%), followed by genital aphthosis (85%). Skin lesions were frequently reported (48%), predominantly as papulopustular lesions (40%) and erythema nodosum-like lesions (8%). Pathergy reaction was observed in 14% of the patients. Articular involvement was noted in 30% of the cases, categorised into arthralgias (28%) and arthritis (6%).

Uveitis represented the most common major organ involvement, affecting 48% of the patients. It involved the posterior (82%) and anterior (55%) segments, with panuveitis observed in 39% of cases. The vascular system was the second most frequently affected major organ (41%), categorised into venous (80%) and arterial (36%) involvements. Venous involvement mainly consisted of DVT (92%), primarily located in the limbs (65%), vena cava (29%), and cerebral veins (18%). Arterial involvement included aneurysms (70%), thrombosis (41%), and stenosis (11%). The other major organ involvements were neurological (13%), cardiac (7%) and gastrointestinal (4%).

Most patients were treated with corticosteroids (86%), with a median dosage of 10 mg/day [5; 30]. Conventional immunosuppressants were commonly

prescribed (64%), comprising azathioprine (70%), cyclophosphamide (48%), methotrexate (7%), and mycophenolate mofetil (1%). Biological agents were administered to 46 patients (8%), primarily consisting of TNF-α inhibitors (n=45), with one patient receiving an anti-IL-6 agent. Most patients were on colchicine (98%). Anticoagulants and antiplatelet agents were used in 33% and 12% of cases, respectively. Surgical (5%) and interventional (2%) procedures were uncommon. Mortality was recorded in 12 patients (2%).
Patients' characteristics are summarised in Table I.

LCA model selection
We selected the model with five classes, given its clinical relevance, lower fit indices, high entropy, and acceptable smallest class size. For most patients, individual probabilities for class membership were close to 1.0 for one class and close to 0 for the others, further corroborating the good fit of the model. The main statistical features for model selection are presented in Supplementary Table S1.

Latent Classes
Five distinct classes were identified, each characterised by specific clinical features (Fig. 1).

Class 1 (n=215; 39%), 'Vascular type'
This was the largest class, featuring the highest male predominance (81%), with a male-to-female ratio of 4.3:1. The mean age at BS onset was 29±10 years. All patients presented with vascular involvement, consisting of 80% venous and 36% arterial lesions. The highest rate of cardiac involvement was observed in this class (12%). Mucocutaneous lesions were common, with 100% of patients reporting oral ulcers, 84% genital ulcers, 42% papulopustular lesions, and 12% erythema nodosum-like lesions. Articular involvement was noted in 25% of cases (Fig. 2).

Class 2 (n=171; 31%), 'Ocular type'
This class exhibited the second-highest male predominance (80%), with a male-to-female ratio of 4:1. The mean age at BS onset was 30±11 years. All patients had uveitis, associated with frequent mucocutaneous lesions, mainly oral ulcers (98%), genital ulcers (88%), papulopustular lesions (41%), and erythema nodosum-like lesions (9%). Articular involvement was reported in 28% of the patients (Fig. 3).

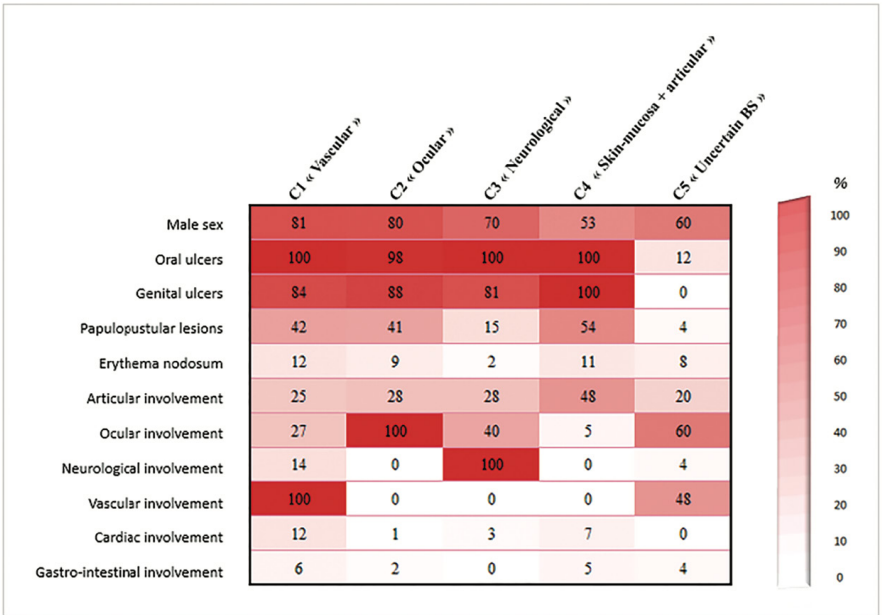

Fig. 1. Heatmap of the clinical characteristics across latent classes in BS patients, Ibn Sina University Hospital, Rabat, Morocco (2012-2022).

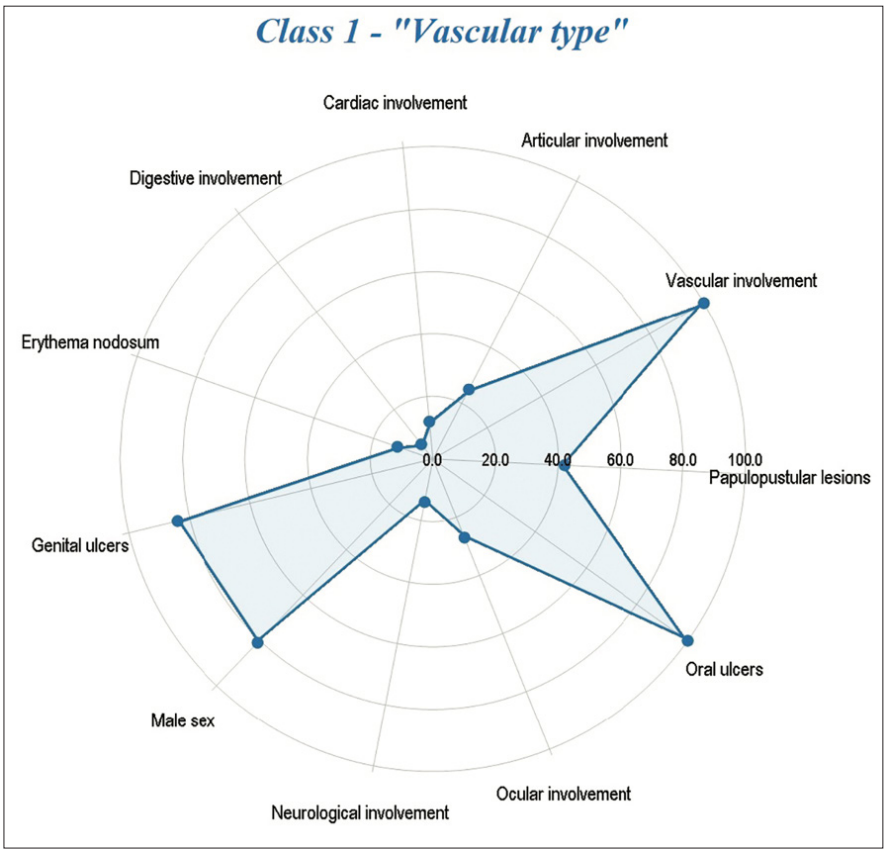

Fig. 2. Radar plot of Class 1 ("vascular type") clinical phenotype in BS patients.

Class 3 (n=40; 7%), 'Neurological type'
Significant male predominance was also noticed in this class (70%), with a male-to-female ratio of 2.3:1. The mean age at BS onset was 30±10 years. Neu-

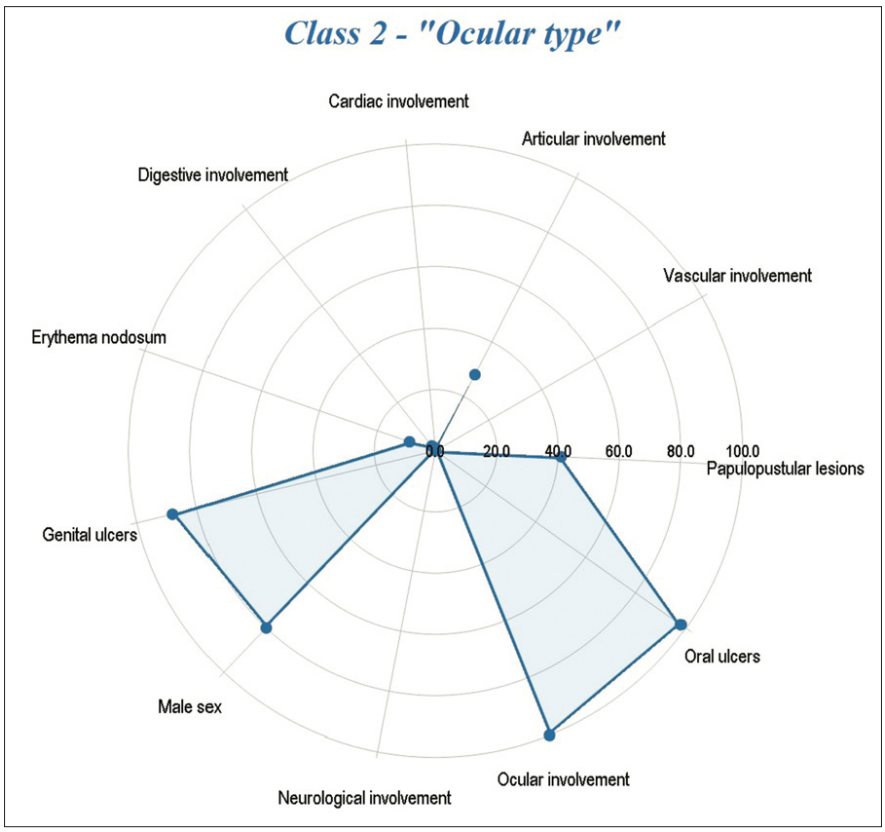

Fig. 3. Radar plot of Class 2 ("ocular type") clinical phenotype in BS patients.

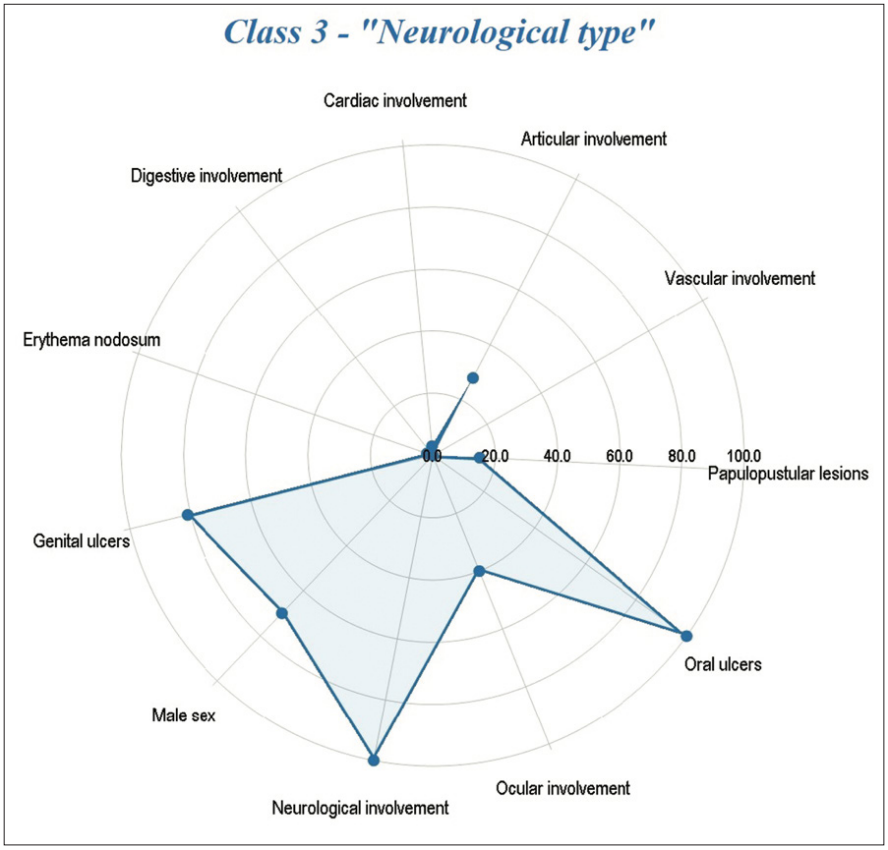

Fig. 4. Radar plot of Class 3 ("neurological type") clinical phenotype in BS patients.

rological parenchymal involvement was present in all cases, with 40% concomitant ocular involvement, mostly affecting the posterior segment (83%). All patients exhibited oral ulcers, with 81% genital ulcers, and less common skin lesions (15% papulopustular lesions and 2% erythema nodosum-like lesions). Articular involvement was noted in 28% of cases (Fig. 4).

Class 4 (n=98; 18%), 'Skin-mucosa and articular type'

This class displayed the highest female predominance, with males representing 53% of the patients, resulting in a male-to-female ratio of 1.1:1. The mean age at BS onset was 31±12 years. All patients reported oral ulcers and genital ulcers (100%). This class was characterised by the highest prevalence of papulopustular lesions (54%) and articular involvement (48%). Erythema nodosum-like lesions were observed in 11% of cases (Fig. 5).

Class 5 (n=29; 5%), 'Uncertain BS'

This was the smallest class, marked by a less pronounced male predominance (60%), with a male-to-female ratio of 1.5:1. A later onset was observed, with a mean age of 38±14 years at BS initial symptoms. Uveitis was present in 60% of patients, and nearly half exhibited vascular lesions (48%). This class was notable for having the fewest oral ulcers (12%) and no genital ulcers. Skin lesions were rare, with only 4% papulopustular lesions and 8% erythema nodosum-like lesions. The rate of articular involvement was 20% (Fig. 6).

Sex-phenotype analysis

Univariable analysis showed a significant association between male sex and vascular involvement (OR=1.75 [1.17–2.62], p=0.006), whereas no such link was observed for other major organ involvements, including ocular, neurological, cardiac, and gastrointestinal systems. Female sex was associated with erythema nodosum (OR=0.56 [0.31–1.02], p=0.05) and articular involvement (OR=0.38 [0.25–0.57], p<0.001). Conversely, LCA revealed a significant male predominance across all major organ classes (p<0.001), with the highest

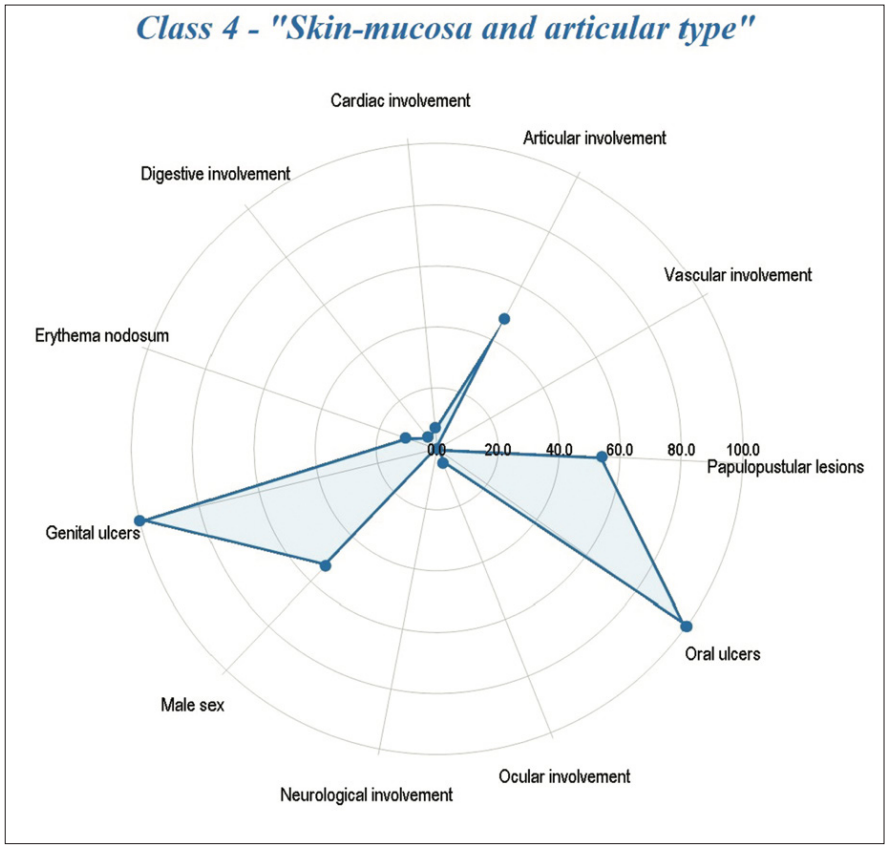

Fig. 5. Radar plot of Class 4 ("skin-mucosa and articular type") clinical phenotype in BS patients.

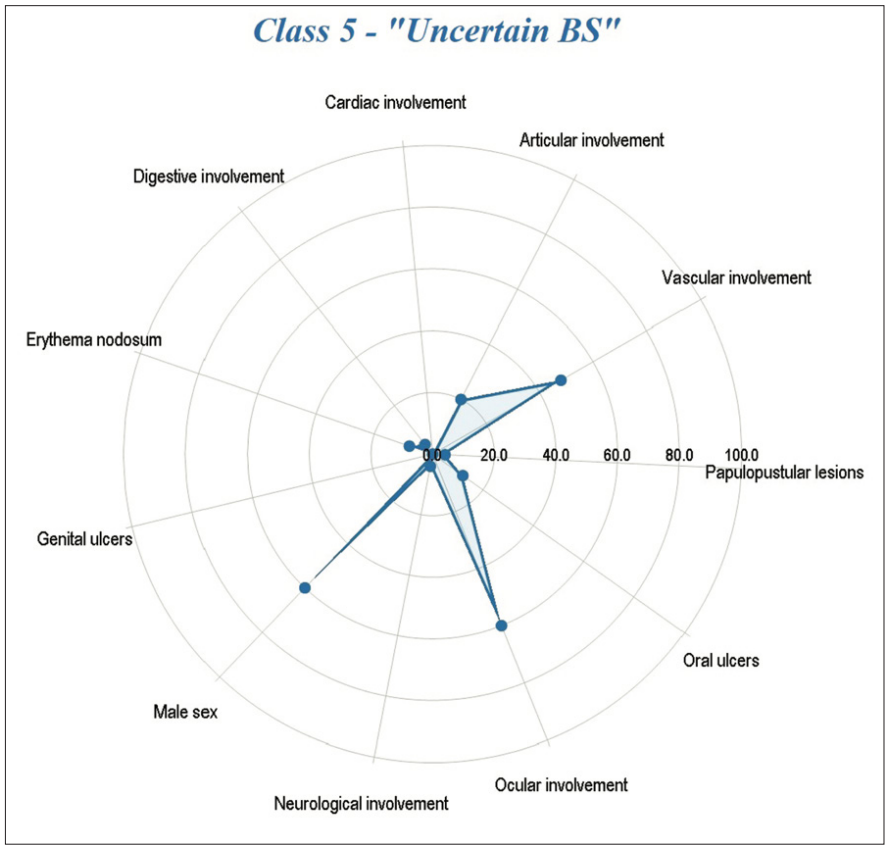

Fig. 6. Radar plot of Class 5 ("uncertain BS") clinical phenotype in BS patients.

rates in the 'vascular type' (81%) and 'ocular type' (80%), followed by the 'neurological type' (70%) and 'uncertain BS' (66%). In contrast, the 'skin-mucosa and articular type' displayed a near-equal sex distribution ($p<0.001$). The main sex-related clinical differences identified using LCA are illustrated in Figure 7.

Therapeutic management

Treatment requirements varied considerably between classes. Higher doses of corticosteroids were prescribed in the 'neurological type', with a median dosage of 30 mg/day. Lower dosage was used in the 'ocular type' (20 mg/day) and 'uncertain BS' (14 mg/day), followed by the 'vascular type' (10 mg/day). The 'skin-mucosa and articular type' had the lowest corticosteroid exposure, with a mean dosage of 5 mg/day ($p=0.004$).

Conventional immunosuppressants were frequently used across all major organ classes, with the highest rates in the 'neurological type' (80%), 'vascular type' (76%), and 'ocular type' (75%), followed by the 'uncertain BS' (62%). In contrast, only 13% of patients from the 'skin-mucosa and articular type' received this therapy ($p<0.001$). Cyclophosphamide was the most frequently prescribed immunosuppressant, particularly in the 'neurological type' (79%). It was used in 52% of patients in the 'vascular type' and 41% in the 'ocular type', compared with 21% in the 'uncertain BS' and 18% in the 'skin-mucosa and articular type' ($p<0.001$).

Biological agents, mostly consisting of TNF-α inhibitors, were primarily used in the 'ocular type' (17%) and the 'uncertain BS' (10%), followed by the 'vascular type' (6%), and 'skin-mucosa and articular type' (1%) ($p<0.001$).

The main differences in treatment requirements across classes are detailed in Table II.

Discussion

This is the first clustering study on BS in Morocco and, importantly, the first worldwide to apply LCA as a tool for phenotyping in BS. In this large retrospective cohort of 553 BS patients, LCA identified five distinct clinical

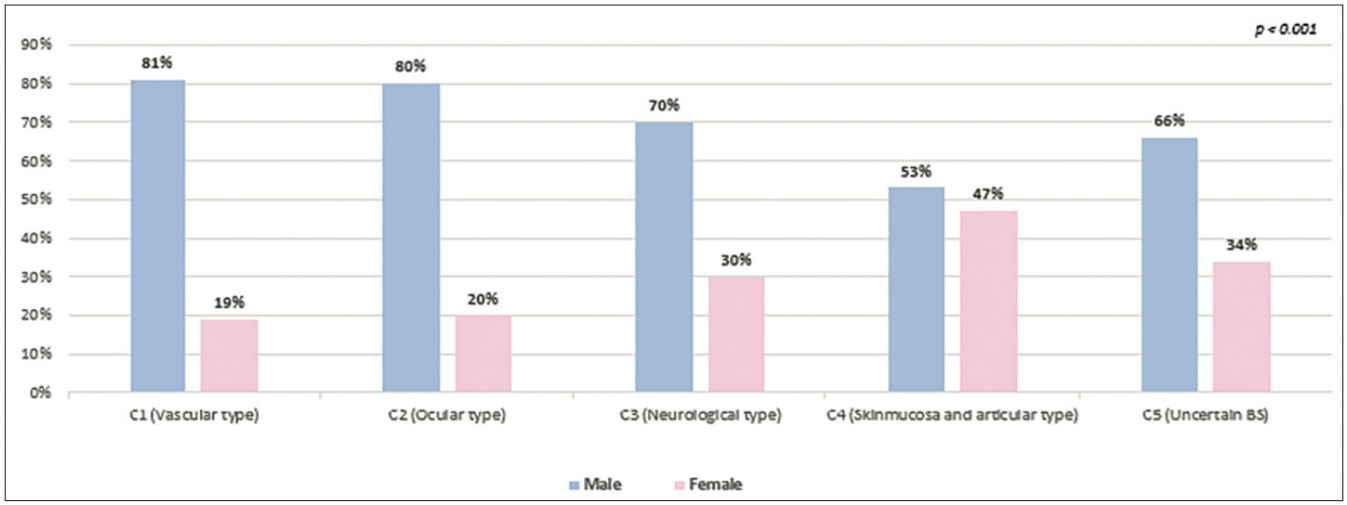

Fig. 7. Sex distribution across latent classes in BS patients, Ibn Sina University Hospital, Rabat, Morocco (2012-2022).

Table II. Comparative treatment requirements across latent classes in BS patients, Ibn Sina University Hospital, Rabat, Morocco (2012-2022).

	C1	C2	C3	C4	C5	*p*
Corticosteroids* (mg/d)	10 [5; 20]	20 [6; 60]	30 [5; 60]	5 [5; 10]	14 [7; 36]	0.004 [1]
cDMARDs**	163 (76)	128 (75)	32 (80)	13 (13)	18 (62)	<0.001 [2]
Cyclophosphamide**	62 (52)	43 (41)	22 (79)	2 (18)	3 (21)	<0.0011 [2]
Azathioprine**	79 (66)	72 (69)	21 (75)	9 (82)	11.0 (79)	0.681 [2]
Methotrexate**	5 (4)	10 (10)	1 (4)	3 (27)	0 (0)	0.021 [2]
Mycophenolate mofetil**	1 (1)	0 (0)	0 (0)	0 (0)	1 (7)	0.051 [2]
bDMARDs**	13 (6)	29 (17)	0 (0)	1 (1)	3 (10)	<0.0011 [2]

csDMARDs: conventional disease-modifying anti-rheumatic drugs; bDMARDs: biologic disease-modifying anti-rheumatic drugs.
*Median [IQR]; **n (%); [1] Kruskall-Wallis test; [2] Pearson's Chi-squared test.

classes, namely the 'vascular type' (C1), 'ocular type' (C2), 'neurological type' (C3), 'skin-mucosa and articular type' (C4), and 'uncertain BS' (C5). Significant sex-related disparities were found in clinical manifestations and major organ involvement, with varying therapeutic needs across classes.

We used LCA to identify clinically relevant BS phenotypes due to its multiple advantages over traditional CA. First, as a probabilistic model-based clustering method, LCA provides individual probabilities for class membership instead of fixed assignments, allowing for uncertainty estimation and resulting in more flexible and precise classifications. Additionally, LCA accounts for unobserved (latent) data within the observed variables, which may not be apparent through standard methods. Moreover, LCA captures complex relationships between variables, enabling the detection of overlapping patterns, whereas traditional CA assumes distinct group separation, potentially overlooking subtle or intricate patterns. LCA also integrates clinical relevance alongside statistical criteria, unlike traditional CA, which relies strictly on distance metrics (Suppl. Table S2) (20, 21, 26). Notably, comparative studies have demonstrated LCA's superiority with a fourfold reduction in the risk of misclassification compared to other clustering methods (27, 28). Therefore, LCA is likely better equipped to address the complexity and heterogeneity of BS, justifying its application in this study.

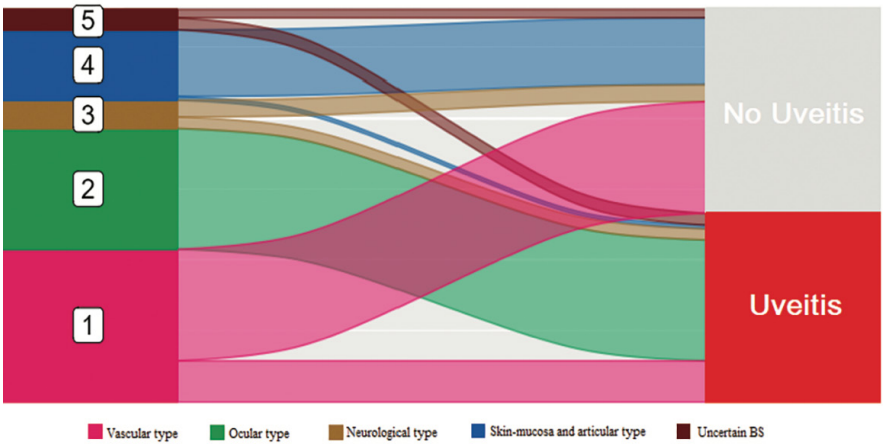

Fig. 8. Alluvial diagram of uveitis across latent classes in BS patients, Ibn Sina University Hospital, Rabat, Morocco (2012-2022).

It is important to note that, although the latent classes in our cohort may superficially resemble previously proposed clinical phenotypes, they are funda-

mentally distinct and not directly comparable to results from earlier phenotype studies using dimension-reduction methods. For instance, in the 'ocular type' (n=171), all patients presented uveitis. However, this class accounted for only two-thirds of all patients with ocular involvement (n=264), as uveitis was also observed in the 'uncertain BS' (60%), 'neurological type' (40%), 'vascular type' (27%), and 'skin-mucosa and articular type' (5%) (Fig. 8). This challenges the previously described ocular phenotype and highlights the complexity of BS subgroups, underscoring the importance of advanced analytical tools such as LCA for optimal patient classification.

Interestingly, while most classes in our cohort yielded generally expected results, the fifth class stood out as unusual. This smallest group, comprising merely 29 patients, was characterised by frequent ocular (60%) and vascular (48%) lesions, which contradicts the negative association typically observed with these manifestations (8). Additionally, patients in this group exhibited very few oral ulcers, no genital ulcers, and less frequent skin lesions. One possible explanation is that this class could represent a rare phenotype of BS. Alternatively, despite meeting the ISBD/ISG criteria at enrolment, these patients could be classified as having 'uncertain BS' given their atypical clinical features. A similar cluster of 'suspicious BS' was described in the Japanese cohort, also characterised by the lowest frequency of oral ulcers and predominant ocular involvement (17). Identifying these 'uncertain BS' subgroups is essential, as they warrant careful follow-up for the potential emergence of new symptoms that could point to BS mimics, ultimately guiding different management.

Compared with previous clustering studies from other countries, the clinical phenotypes identified in our cohort present both similarities and differences. For example, the 'vascular type' (C1), which is the largest group in our cohort (39%), was significantly more prevalent than in Turkey (17%) and China (15%) (16, 29). In Japan, the vascular cluster was absent (17). This finding aligns with epidemiological studies, highlighting a higher prevalence of the vascular phenotype in the Mediterranean region compared to Middle Eastern and Far Eastern countries (30).

Conversely, the 'skin-mucosa and articular type' (C4) accounted for only 18% of patients in our cohort, with 48% of them exhibiting articular involvement. This differs from China and Turkey, where the skin-mucosa clusters were the largest, comprising respectively 36% and 35% of patients, with distinct articular clusters identified in 14% and 22% of cases (16, 29). In Japan, two separate clusters were identified: 'mucocutaneous with arthritis' (21%) and 'mucocutaneous without arthritis' (25%), the latter being the largest group of the cohort (17).

Notable differences also include the absence of the gastrointestinal class in our cohort, similar to clustering studies from Turkey (19, 29). This contrasts with the gastrointestinal cluster described in East Asian countries, such as China and Japan (16, 17). Previous research has demonstrated a higher frequency of gastrointestinal involvement in Far East Asian countries compared to Mediterranean and Middle Eastern regions (31, 32). However, it is noteworthy that the preferential use of Japanese diagnostic criteria in these countries, which include gastrointestinal symptoms, could play a role in the generation of this cluster (33).

While geographical heterogeneity is characteristic of BS, the exact causes of these phenotypic distributions remain unclear. Several theories have been proposed, especially regarding different genetic backgrounds, as evidenced by various gene associations with specific phenotypes (*e.g.* HLA-A*26 and uveitis, HLA-B*46 and gastrointestinal involvement, etc.) (34, 35). Environmental factors, including microbiome changes, may also influence disease expression (36, 37). However, it is essential not to underestimate the potential bias introduced by artificial heterogeneity, which may arise not only during the analytical phases but also in pre-analytical ones (*e.g.* diagnostic criteria, definition of disease manifestations, etc.) (38). International clustering studies using consistent methodologies would be valuable for enabling cohort comparisons and elucidating ethnic and geographic variations.

This study also applied LCA to explore sex disparities in clinical manifestations, identifying distinct sex-related clinical profiles, with males being significantly more represented in all major organ classes, whereas females were more likely to belong to the 'skin-mucosa and articular type'. This distribution may be partly explained by genetic factors, as recent research suggests males carry a higher genetic risk, particularly involving the HLA class I region (39). Additionally, various hypotheses have been proposed regarding the influence of hormones, as well as environmental factors such as exposure to infectious agents and intestinal dysbiosis, which may contribute to these sex-related clinical differences (29, 40, 41).

Furthermore, our analysis showed distinct variations in treatment requirements across classes. Higher doses of corticosteroids and increased use of conventional immunosuppressants, especially cyclophosphamide, were observed in the 'neurological type', 'ocular type', and 'vascular type', closely followed by the 'uncertain BS'. Conversely, as anticipated, the 'skin-mucosa and articular type' had the lowest use of both corticosteroids and conventional immunosuppressants. Notably, biological agents were most frequently prescribed in the 'ocular type' (17%) and the 'uncertain BS' (10%), where ocular involvement was prevalent, likely reflecting the critical urge to preserve visual function.

We acknowledge certain limitations in this study. First, the retrospective design may have introduced information bias and did not allow for inclusion of genetic data, such as HLA genotyping, performed only in a few cases of diagnostic uncertainty. Second, being a single-centre study conducted at a tertiary hospital with exclusively Moroccan patients, it may limit the generalisability of our findings. In addition, the complexity of classes may not be fully captured by the chosen labels, and since LCA provides probabilities for

class membership, the reported class sizes are approximate. Finally, while we demonstrated varied therapeutic requirements across classes, the study design did not allow longitudinal assessment of patient outcomes.

Conclusion

This study is the first to assess clinical phenotypes in BS using LCA. Five latent classes were identified in our cohort, namely the 'vascular type', 'ocular type', 'neurological type', 'skin-mucosa and articular type', and 'uncertain BS'. Distinct sex-related clinical profiles and varying treatment requirements were observed across classes.

These findings provide critical guidance for more accurate patient classification, paving the way for precision medicine in BS and improved patient outcomes. Further validation in prospective, independent cohorts incorporating both clinical and genetic data would be valuable to enhance our understanding of BS heterogeneity.

References

1. ADAMANTIADES B: Sur un cas d'iritis a hypopyon recidivante. 1931. https://www.sid.ir/paper/541154/fa
2. BEHÇET H: Uber rezidiverende aphthose durch ein virus verursachte Geschwure am Mund, am Auge und an den Genitalien. 1937. https://www.sid.ir/paper/540679/fa
3. BEHÇET H: Some observations on the clinical picture of the so-called triple symptom complex. *Dermatology* 1940; 81(2): 73-83. https://doi.org/10.1159/000253787
4. FILALI-ANSARY N, TAZI-MEZALEK Z, MOHATTANE A *et al*.: [Behçet disease. 162 cases]. *Ann Med Interne* (Paris) 1999; 150(3): 178-88.
5. KEINO H, OKADA AA: Behçet's disease: global epidemiology of an Old Silk Road disease. *Br J Ophthalmol* 2007; 91(12): 1573-74. https://doi.org./10.1136/bjo.2007.124875
6. DAVATCHI F, SHAHRAM F, CHAMS-DAVATCHI C *et al*.: Behçet's disease: from east to west. *Clin Rheumatol* 2010; 29(8): 823-33. https://doi.org./10.1007/s10067-010-1430-6
7. SEYAHI E: Phenotypes in Behçet's syndrome. *Intern Emerg Med* 2019; 14(5): 677-89. https://doi.org/10.1007/s11739-019-02046-y
8. BETTIOL A, PRISCO D, EMMI G: Behçet: the syndrome. *Rheumatology* (Oxford) 2020; 59(3): 101-7. https://doi.org./10.1093/rheumatology/kez626
9. HATEMI G, CHRISTENSEN R, BANG D *et al*.: 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 2018; 77(6): 808-18. https://doi.org./10.1136/annrheumdis-2018-213225
10. YAZICI H, SEYAHI E, HATEMI G, YAZICI Y: Behçet syndrome: a contemporary view. *Nat Rev Rheumatol* 2018; 14(2): 107-19. https://doi.org/10.1038/nrrheum.2017.208.
11. KRAUSE I, LEIBOVICI L, GUEDJ D, MOLAD E, UZIEL Y, WEINBERGER A: Disease patterns of patients with Behçet's disease demonstrated by factor analysis. *Clin Exp Rheumatol* 1999; 17(3): 347-50.
12. TUNC R, KEYMAN E, MELIKOGLU M, FRESKO I, YAZICI H: Target organ associations in Turkish patients with Behçet's disease: a cross sectional study by exploratory factor analysis. *J Rheumatol* 2002; 29(11): 2393-96.
13. SOTA J, RIGANTE D, EMMI G *et al*.: Behçet's syndrome in Italy: a detailed retrospective analysis of 396 cases seen in 3 tertiary referral clinics. *Intern Emerg Med* 2020; 15(6): 1031-39. https://doi.org./10.1007/s11739-019-02248-4
14. İLGEN U: Clusters in Behçet's syndrome. *Arthritis Res Ther* 2022; 24(1): 242. https://doi.org./10.1186/s13075-022-02937-0
15. DAVIES PG, FORDHAM JN, KIRWAN JR, BARNES CG, DINNING WJ: The pathergy test and Behçet's syndrome in Britain. *Ann Rheum Dis* 1984; 43(1): 70-73. https://doi.org./10.1136/ard.43.1.70
16. ZOU J, LUO JF, SHEN Y, CAI JF, GUAN JL: Cluster analysis of phenotypes of patients with Behçet's syndrome: a large cohort study from a referral center in China. *Arthritis Res Ther* 2021; 23(1): 45. https://doi.org./10.1186/s13075-021-02429-7
17. SOEJIMA Y, KIRINO Y, TAKENO M *et al*.: Changes in the proportion of clinical clusters contribute to the phenotypic evolution of Behçet's disease in Japan. *Arthritis Res Ther* 2021; 23(1): 49. https://doi.org./10.1186/s13075-020-02406-6
18. CHUNG KB, CHOI S, BANG D, KIM DY: Skin manifestation as an explaining factor of heterogeneity in Behçet's disease: A focused analysis in full-blown conditions. *J Dermatol* 2022; 49(3): 349-58. https://doi.org./10.1111/1346-8138.16250
19. OGUZ E, BEKTAŞ M: Characteristics of patients with Behçet disease from the Van Province, Eastern Turkey: definition of disease clusters in a tertiary referral center. *J Clin Rheumatol* 2023; 29(6): 285. https://doi.org./10.1097/rhu.0000000000001996
20. VERMUNT JK, MAGIDSON J: Latent Class Cluster Analysis. *In*: HAGENAARS J, MCCUTCHEON A (Eds.): Applied latent class analysis. 2002, 89-106.
21. SINHA P, CALFEE CS, DELUCCHI KL: Practitioner's guide to latent class analysis: methodological considerations and common pitfalls. *Crit Care Med* 2021; 49(1): e63. https://doi.org./10.1097/ccm.0000000000004710
22. RAZAGHIZAD A, NI J, MARQUES P *et al*.: Cardiovascular phenotypes in type 2 diabetes: Latent class analysis of the CANVAS Program and CREDENCE trial. *Diabetes Obes Metab* 2024; 26(11): 5025-35. https://doi.org./10.1111/dom.15768
23. ARNAUD L, MERTZ P, AMOURA Z *et al*.: Patterns of fatigue and association with disease activity and clinical manifestations in systemic lupus erythematosus. *Rheumatology* (Oxford) 2021; 60(6): 2672-77. https://doi.org./10.1093/rheumatology/keaa671
24. FRENCH HP, CUNNINGHAM J, BENNETT K *et al*.: Patterns of pain medication usage and self-reported pain in older Irish adults with osteoarthritis: a latent class analysis of data from the Irish Longitudinal Study on Ageing. *BMC Musculoskelet Disord* 2024; 25(1): 773. https://doi.org./10.1186/s12891-024-07854-8
25. SOUSSI S, SHARMA D, JÜNI P *et al*.: Identifying clinical subtypes in sepsis-survivors with different one-year outcomes: a secondary latent class analysis of the FROG-ICU cohort. *Crit Care* 2022; 26(1): 114. https://doi.org./10.1186/s13054-022-03972-8
26. WELLER BE, BOWEN NK, FAUBERT SJ: Latent class analysis: a guide to best practice. *J Black Psychol* 2020; 46(4): 287-311. https://doi.org./10.1177/0095798420930932
27. MAGIDSON J, VERMUNT JK: Latent class models for clustering: a comparison with K-means. *CJMR* 2002; 20(1): 36-43.
28. SCHREIBER JB, PEKARIK AJ: Technical note: using latent class analysis versus K-means or hierarchical clustering to understand museum visitors. *Curator: The Museum J* 2014; 57(1): 45-59. https://doi.org./10.1111/cura.12050
29. KILIÇ G, KÖRÜKLÜ KF, KUMCU MG, ÇAKIR E, KARKUCAK M, KILIÇ E: Gender disparities in Behçet's syndrome: identifying distinct phenotypes through cluster analysis. *Immunol Res* 2024; 72(5): 975-81. https://doi.org./10.1007/s12026-024-09498-1
30. TAZI MEZALEK Z, KHIBRI H, CHADLI S *et al*.: Vascular complications of Behçet disease. *Minerva Med* 2021; 112(6): 767-78. https://doi.org./10.23736/s0026-4806.21.07490-5
31. IDEGUCHI H, SUDA A, TAKENO M *et al*.: Gastrointestinal manifestations of Behçet's disease in Japan: a study of 43 patients. *Rheumatol Int* 2014; 34(6): 851-56. https://doi.org./10.1007/s00296-013-2838-5
32. KIM DY, CHOI MJ, CHO S, KIM DW, BANG D: Changing clinical expression of Behçet disease in Korea during three decades (1983-2012): chronological analysis of 3674 hospital-based patients. *Br J Dermatol* 2014; 170(2): 458-61. https://doi.org./10.1111/bjd.12661
33. MIZUSHIMA Y: [Revised diagnostic criteria for Behçet's disease in 1987]. *Ryumachi* 1988; 28(1): 66-70.
34. KATO H, TAKEUCHI M, HORITA N *et al*.: HLA-A26 is a risk factor for Behçet's disease ocular lesions. *Mod Rheumatol* 2021; 31(1): 214-18. https:/doi.org./10.1080/14397595.2019.1705538
35. JUNG ES, ELLINGHAUS D, DEGENHARDT F *et al*.: Genome-wide association analysis reveals the associations of *NPHP4, TYW1-AUTS2* and *SEMA6D* for Behçet's disease and *HLA-B*46:01* for its intestinal involvement. *Dig Liver Dis* 2024; 56(6): 994-1001. https://doi.org./10.1016/j.dld.2023.10.021
36. BILGE NY, BROCAL VP, KASIFOGLU T *et al*.: Intestinal microbiota composition of patients with Behçet's disease: differences between eye, mucocutaneous and vascular involvement. The Rheuma-BIOTA study. *Clin Exp Rheumatol* 2020; 38(Suppl. 127): S60-S68.
37. LECCESE P, ALPSOY E: Behçet's disease: an overview of etiopathogenesis. *Front Immu-*

nol 2019; 10: 1067. https://doi.org./10.3389/fimmu.2019.01067
38. ILGEN U: Cluster analysis as a clinical and research tool in Behçet's syndrome. *Curr Opin Rheumatol* 2024; 36(1): 3-8. https://doi.org./10.1097/bor.0000000000000980
39. JO YG, ORTIZ-FERNANDEZ L, COIT P *et al*.: Sex-specific analysis in Behçet's disease reveals higher genetic risk in male patients. *J Autoimmun* 2022; 132: 102882. https://doi.org./10.1016/j.jaut.2022.102882
40. BONITSIS NG, LUONG NGUYEN LB, LAVALLEY MP *et al*.: Gender-specific differences in Adamantiades-Behçet's disease manifestations: an analysis of the German registry and meta-analysis of data from the literature. *Rheumatology* (Oxford) 2015; 54(1): 121-33. https://doi.org./10.1093/rheumatology/keu247
41. YAVUZ S, OZILHAN G, ELBIR Y, TOLUNAY A, EKSIOGLU-DEMIRALP E, DIRESKENELI H: Activation of neutrophils by testosterone in Behçet's disease. *Clin Exp Rheumatol* 2007; 25(Suppl. 45): S46-51.