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Original article

Influence of gender on Behçet's disease phenotype and irreversible organ damage: Data from the International AIDA Network Behçet's Disease Registry☆

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ABSTRACT

Objectives. – Gender impact on phenotypical expression of Behçet's disease (BD) has been specifically investigated only in a few large-scale studies. The main goal of the study was to examine gender differences in a large cohort of patients affected by BD.

Methods. – Data were retrieved from the International AIDA Network Registry for BD. We assessed differences between males and females in terms of Behçet's syndrome Overall Damage Index (BODI), differences in the disease manifestations at onset and in the cumulative manifestations throughout disease course, as well as differences in the cardiovascular risk. Finally, predictive factors leading to major organ involvement were investigated.

Results. – In total, 1024 BD patients (567 males, 457 females) were enrolled in the study, with a male-to-female ratio of 1.24/1. Males displayed a significantly higher mean ± SD BODI (1.92 ± 2.09) at the last follow-up, compared to female patients (1.25 ± 1.87) ($P < 0.0001$). Uveitis ($P < 0.0001$) and vascular involvement ($P = 0.0076$) were significantly more frequent among males whereas female patients were significantly over-represented in arthralgia ($P < 0.0001$), arthritis ($P = 0.00025$), isolated headache ($P < 0.0001$), central nervous system (CNS) involvement ($P = 0.040$), and gastrointestinal involvement ($P = 0.00046$). Regarding cardiovascular risk, no differences between the two groups emerged ($P = 0.617$). Four variables were associated with the development of major organ involvement: male gender (OR = 2.104, $P = 0.001$), current treatment with biologic agents (OR = 2.257, $P = 0.0003$), origin from endemic countries (OR = 2.661, $P = 0.0009$), and disease duration (OR = 1.002, $P = 0.024$).

Conclusion. – BD displays a more severe course among males. This subgroup develops more irreversible damage and presents more frequently ocular and vascular involvement during disease course. On the other hand, female patients are prone to experience articular involvement, headache, CNS and gastrointestinal involvement. These data suggest the existence of a gender-driven disease expression.

1. Introduction

Behçet's disease (BD) represents a multisystemic immune-mediated inflammatory disorder of uncertain etiology [1,2]. The complex and largely unknown pathogenesis is reflected in a highly heterogeneous clinical picture that may vary in each patient. Indeed, despite being originally described as the triple symptom complex comprising oral aphthous, genital ulcers and uveitis, virtually any organ could be involved [3–5]. The factors driving the heterogeneous phenotypical expression could lie on genetic background as testified by the marked geographical variability across countries. BD is particularly prevalent among the ancient "Silk Route" populations with a very high prevalence reported in Turkey (42 cases per 10,000 inhabitants) [6]. On the contrary, a lower prevalence has been detected in Western countries [7]. Regarding clinical features, the highest frequency of gastrointestinal involvement has been reported in Japan [8]. Similarly, pathergy test has shown a higher diagnostic accuracy in Middle East populations and considerably lower in other countries [9,10]. Gender and its effects on disease expression could be responsible for an additional influence on the already complex and protean clinical picture. Indeed, young males have been found to display a significantly higher mortality rate due to vascular and neurological involvement, as well as a higher morbidity in terms of visual prognosis [11–13].

The impact of gender in disease expression has been specifically investigated only in few large-scale studies [11,14–20]. We herein provide our multicentre experience on the influence of gender in BD from a large cohort of patients enrolled in the international Autoinflammatory Disease Alliance (AIDA) registry for BD with a particular focus on potential differences in long-standing damage accrual and disease phenotype.

2. Methods

2.1. Study population and participants

Data for the present study were retrieved from medical records of patients diagnosed with BD and enrolled in the international AIDA Network for BD registry until January 9th, 2024. The registry is a clinical physician-driven and electronic-based instrument implemented for the retrospective and prospective collection of real-life data about demographics, clinical, therapeutic, laboratory, instrumental, and socioeconomic information from BD patients [21], and currently upholds data on more than 1076 patients (April 24th, 2024).

2.2. Data collection

The following demographic and clinical data were collected: gender, ethnicity, family history, age at onset, age at diagnosis, human leukocyte antigen (HLA)-B*51 typing, disease manifestations at disease onset, cumulative manifestations throughout disease course, clinical duration, Behçet's syndrome overall damage Index (BODI) recorded at last follow-up visit and cardiovascular risk data. Detailed treatment data for each follow-up visit were not retrieved for the purposes of this study. BODI consists of 34 items and 12 subitems, categorized into nine organ/system domains designed to assess the extent and type of organ damage accrual [22]. Age at disease onset was established as the age of the first disease-related clinical manifestation. The diagnostic delay was considered as the duration from the first disease-related manifestation to definite BD diagnosis, according to the International Study Group (ISG) criteria and/or International Criteria for Behçet's Disease (ICBD) [23,24]. BD-related uveitis was classified according to the Standardization of Uveitis Nomenclature criteria [25]. Vascular involvement included venous manifestations (thrombosis, superficial phlebitis) and arterial manifestations (aneurysm, stenosis, occlusion). Neuro-BD, both parenchymal and non-parenchymal, was detected by the rheumatologist and the dedicated neurologist according to the International Consensus on Neuro-BD of 2014, contemplating recognized neurological features, characteristic magnetic resonance imaging findings and/or cerebrospinal fluid findings [26], while unexplained isolated headache was analyzed separately. Similarly, abdominal pain without endoscopic evidence did not count as gastrointestinal involvement for inferential statistical analysis. Major organ involvement was defined

as the involvement of any one of the following systems: ocular, neurological, vascular, or gastrointestinal.

Patients with unspecified gender and/or insufficient registry data were excluded from the study. All patients were systematically followed up every 3-to-6 months or in case of necessity (disease flare and/or safety issues).

2.3. Aims and endpoints

The primary aim of the study was to estimate potential gender differences in the development of long-term irreversible organ damage. Secondary aims were to: (i) evaluate gender differences in the disease manifestations at onset and, cumulatively (from onset to the last follow-up visit), (ii) investigate potential gender differences in the cardiovascular risk, (iii) find predictive factor of major organ involvement and (iv) impact of gender in BD phenotypes divided in 5 clusters (mucocutaneous, articular, predominantly ocular, predominantly vascular, predominantly neurologic).

The primary endpoint was analyzed by potential statistical differences between male and female patients regarding the accrual of long-term damage measured with the BODI. Secondary endpoints were examined by any statistical differences between male and female patients in disease manifestations at onset and throughout the disease course, as well as in the cardiovascular risk. Cardiovascular risk was defined by the presence of any of the following: hypercholesterolemia, diabetes mellitus, excessive alcohol consumption, history of smoking, presence of arterial hypertension, cardiovascular events and body mass index higher than 30 kg/m^2. Predictive factors of major organ involvement and the influence of gender in disease clusters were identified via binary regression analysis.

2.4. Protocol approval

The present study was conducted according to the tenets of the Declaration of Helsinki and received approval from the local Ethics Committee of the University of Siena (Reference No. 14951). All patients or their legal guardians gave written informed consent.

2.5. Statistical analysis

Data were analyzed using IBMSPSS Statistics for Windows, version 28 (IBM Corp., Armonk, NY, US). Normality distribution of continuous variables was assessed with the Shapiro–Wilk test. Descriptive statistics was employed to calculate mean and standard deviation (SD) or median and interquartile range (IQR) as required. Cross-tables were analyzed by Pearson's Chi^2 test and post hoc test with adjusted residuals in case of contingency tables with dimensions greater than 2×2, while continuous variable were tested with the Mann–Whitney U test. Potential predictors of major organ involvement and the influence of gender in disease clustering were identified by binary logistic regression with the backward stepwise method and multinomial regression analysis, respectively. All tests were 2-sided and the threshold of statistical significance was set at 0.05.

3. Results

In total, 1024 patients with BD (567 males and 457 females) were enrolled in the study, with a male-to-female ratio of 1.24/1. The ethnic origin was composed mainly of Caucasian ($n = 640$) and Arab ($n = 286$) patients, followed by African ($n = 22$), Hispanic ($n = 21$) and Asian ($n = 14$) patients, other ($n = 3$), unspecified ($n = 38$). Fig. 1 displays the cohort selection process and patients excluded from the study for insufficient data. The mean ± SD age at the onset of the entire cohort was 27.72 ± 12.44 years. Mean ± SD

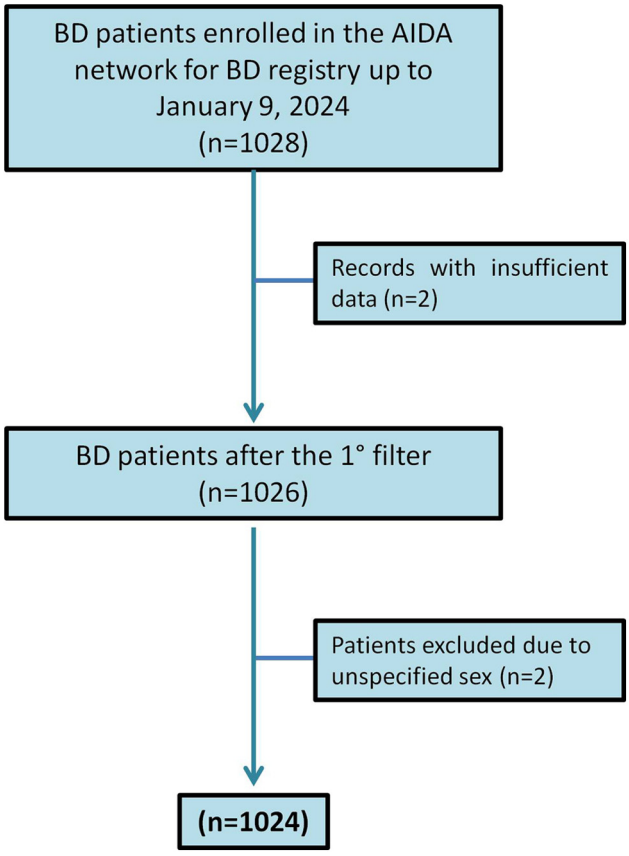

Fig. 1. Chart showing the selection process for the cohort enrolled. AIDA: Autoinflammatory Disease Alliance; BD: Behçet's disease.

age at onset for males and females was 27.13 ± 14.80 years and 28.49 ± 20.20 years, respectively, without any statistically significant difference ($P = 0.092$). The age distribution at onset according to pre-established age groups is illustrated in Fig. 2.

Oral aphthosis was the most frequent disease manifestation at onset (1004/1024, 98.05%), followed by genital ulcers (570/1024, 55.66%), skin lesions (529/1024, 51.66%) and intraocular inflammation (477/1024, 46.58%). Table 1 lists demographic and clinical features at disease onset and all the manifestations experienced throughout the disease course for the entire cohort. Table 2 details the same data separated by gender and their respective statistical significance. Female patients displayed a significantly older age at diagnosis ($P < 0.001$), diagnostic delay ($P < 0.01$) and disease duration ($P < 0.01$). Additionally, HLA-B*51 positivity was significantly more frequent among female patients ($P < 0.001$).

Male patients displayed a significantly higher BODI at the last follow-up than female patients ($P < 0.0001$). Specifically, the mean ± SD [median (IQR)] BODI was 1.92 ± 2.09 [1.0 (3.0)] and 1.25 ± 1.87 [1.0 (2.0)] in males and females, respectively.

Regarding the influence of gender on disease manifestations experienced throughout the disease course, uveitis ($P < 0.001$) and vascular involvement ($P < 0.01$) were significantly more frequent among male patients whereas female patients were significantly over-represented in arthralgia ($P < 0.001$), arthritis ($P < 0.001$), isolated headache ($P < 0.001$), and gastrointestinal involvement ($P < 0.001$), central nervous system (CNS) involvement ($P < 0.05$). The CNS involvement was subsequently separated into parenchymal and non-parenchymal form, revealing a statistically significant difference in the former ($P < 0.05$), whereas no disparities were observed in non-parenchymal CNS involvement ($P = 0.543$). Female patients were also inclined to display more frequently recur-

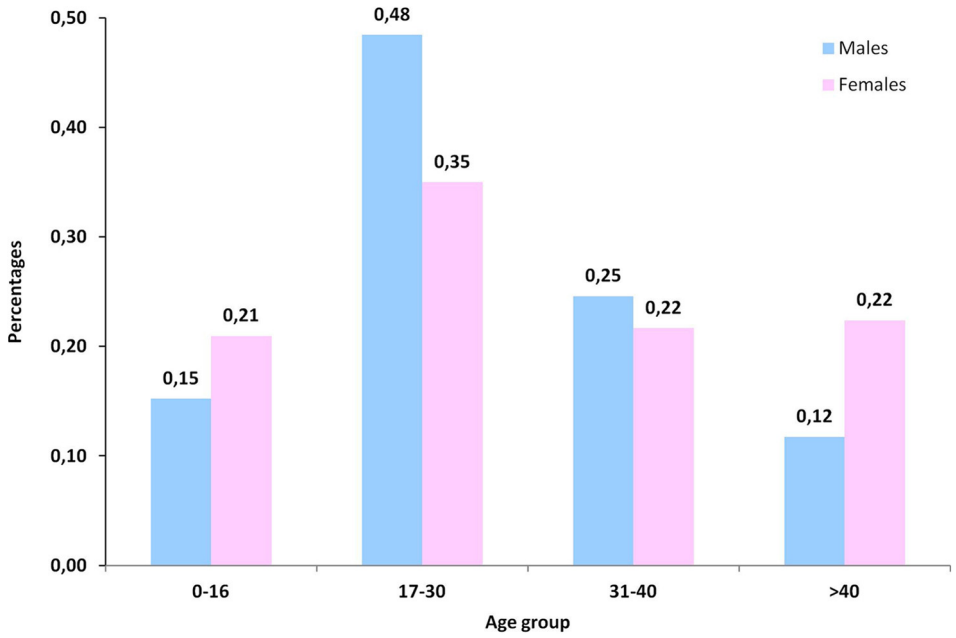

Fig. 2. Distribution of age at onset (expressed in years) separated by gender for Behçet's disease patients according to different age groups.

Table 1
Demographic data and clinical features at disease onset and during disease course of our cohort of BD patients.

Demographic features	
Male/female (*n*)	567/457
Mean age at onset ± SD (years)	27.72 ± 12.44
Mean age at diagnosis ± SD (years)	32.82 ± 12.50
Median (IQR) diagnostic delay (years)	4.72 (7.22)
Mean disease duration ± SD (years)	14.21 ± 10.45
HLA-B*51	411/795 (51.70%)
Clinical features at onset	***n*** **(%)**
Oral aphthosis	938 (96.0)
Genital ulcers	570 (55.7)
Skin manifestations	529 (51.7)
Uveitis	477 (46.6)
Arthralgia	390 (38.1)
Arthritis	258 (25.2)
Vascular involvement	183 (17.9)
CNS	143 (14.0)
Abdominal pain	142 (13.9)
Cardiac involvement	21 (2.1)
Psychiatric manifestations	17 (1.7)
Clinical features throughout disease course	***n*** **(%)**
Oral aphthosis	1004 (98.0)
Genital ulcers	589 (57.5)
Skin manifestations	584 (57.0)
Uveitis	528 (51.6)
Arthralgia	589 (57.5)
Arthritis	314 (30.7)
Vascular involvement	211 (20.6)
CNS	172 (16.8)
Isolated headache	300 (29.3)
Fever	213 (20.8)
Gastrointestinal involvement	233 (22.8), 75 (7.3%) if only endoscopic lesions were considered
Cardiac involvement	42 (4.1)
Psychiatric manifestations	62 (6.1)

BD: Behçet's disease; CNS: central nervous system; HLA: human leukocyte antigen; IQR: interquartile range; SD: standard deviation.

Table 2
Frequency of clinical manifestations of BD patients occurring during disease course, stratified by gender.

	Male patients	Female patients
Mean age at onset ± SD (years)	27.13 ± 11.58	28.50 ± 13.46
Mean age at diagnosis ± SD (years)***	31.07 ± 11.47	35.04 ± 13.37
Median (IQR) diagnostic delay (years)**	1.40 (4.60)	2.00 (8.20)
Mean disease duration ± SD (years)**	10.92 ± 11.79	12.83 ± 15.31
HLA-B*51 positivity *n* (%)***	184 (43.60)	227 (60.85)
Clinical features at onset *n* (%)		
Oral aphthosis	544 (95.94)	439 (96.06)
Genital ulcers	303 (53.44)	267 (58.42)
Skin manifestations	297 (52.38)	232 (50.77)
Uveitis***	313 (55.20)	164 (35.89)
Arthralgia**	122 (21.52)	136 (29.76)
Arthritis***	175 (30.86)	215 (47.05)
Vascular involvement**	120 (21.16)	63 (13.79)
CNS (isolated headache included)*	67 (11.82)	76 (16.63)
Abdominal pain***	49 (8.64)	93 (20.35)
Cardiac involvement	12 (2.11)	9 (1.97)
Psychiatric manifestations	9 (1.59)	8 (1.75)
Clinical features throughout disease course *n* (%)		
Oral aphthosis	555 (97.88)	449 (98.25)
Genital ulcers	316 (55.73)	282 (61.71)
Skin manifestations	324 (57.14)	260 (56.89)
Uveitis***	334 (58.90)	194 (42.45)
Arthralgia***	274 (48.32)	315 (68.93)
Arthritis***	147 (25.92)	167 (36.54)
Vascular involvement**	134 (23.63)	77 (16.85)
CNS*	83 (14.63)	89 (19.47)
Isolated headache***	126 (22.22)	174 (38.07)
Fever**	100 (17.64)	113 (24.73)
Gastrointestinal involvement***	27 (4.76)	48 (10.50)
Cardiac involvement	19 (3.35)	23 (5.03)
Cardiovascular risk	367 (64.72)	280 (61.27)
Psychiatric manifestations	27 (4.76)	35 (7.66)

BD: Behçet's disease; CNS: central nervous system; HLA: human leukocyte antigen; IQR: interquartile range; SD: standard deviation

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

Table 3
Result from regression analysis for each variable included in the model alongside their respective *P*-values, odds ratios and confidence intervals.

Variable	*P*-value	Odds ratio	95% confidence interval
Gender	< 0.001	2.104	1.353–3.273
Disease duration (years)	< 0.05	1.002	1.0003–1.004
Ethnic origin	< 0.001	2.661	1.494–4.738
Current treatment with biologic agents	< 0.001	2.257	1.459–3.493

rent genital ulcers and psychiatric comorbidities with borderline statistically significant differences ($P = 0.054$, $P = 0.053$). A similar trend was also observed for clinical features at disease onset, with male patients reporting a significantly higher frequency of uveitis ($P < 0.001$) and vascular involvement ($P < 0.01$), whereas female patients were significantly more likely to present with arthralgia ($P < 0.01$), arthritis ($P < 0.001$), CNS involvement ($P < 0.05$), abdominal pain ($P < 0.001$). With reference to cardiovascular risk, 367 (64.73%) male patients and 280 (61.27%) female patients were considered at increased risk of cardiovascular events, without any statistically significant gender differences ($P = 0.617$).

Four variables were associated with the development of major organ involvement during the disease course: male gender (OR = 2.104, CI: 1.353–3.273, $P < 0.01$), current treatment with biologic agents (OR = 2.257, CI: 1.459–3.493, $P < 0.001$), origin from endemic countries (OR = 2.661, CI: 1.494–4.738, $P < 0.001$) and disease duration (OR = 1.002, CI: 1.0003–1.004, $P < 0.05$). The findings regarding regression analysis are summarized in Table 3.

Male gender was significantly associated with the ocular and the vascular cluster ($P < 0.001$, OR = 2.853, CI: 1.615–5.039 and $P < 0.05$, OR = 2.293, CI: 1.050–5.007, respectively) while a longer disease duration (expressed in years), the absence of HLA-B*51 and a shorter diagnostic delay were significantly associated with the ocular cluster ($P < 0.01$, OR = 1.007, CI: 1.003–1.011, $P < 0.05$, OR = 0.517, CI: 0.329–0.990, $P < 0.01$, OR = 0.919, CI: 0.872–0.970, respectively).

Concerning treatment approach, conventional disease-modifying anti-rheumatic drugs were the most frequent prescribed therapy (49.23%), followed by colchicine (48.16%) and biologics (42.94%) variably combined between each other. The most frequent biologic employed were anti-tumor necrosis factor agents (92.86%).

4. Discussion

In the present international registry-based study, we have analyzed the demographic and clinical characteristics of a large cohort of BD patients focusing on potential gender differences. Our cohort was characterized by a heterogeneous ethnic origin and exhibited a slight male prevalence, with a male-to-female ratio of 1.24 to 1. Indeed, in studies with large sample sizes, gender distribution tends to equalize, approaching ratios reported in nationwide surveys [27,28]. The mean age at onset was 27.72 years, which is consistent with previous reports [29–31], indicating that disease usually outbreaks in the second or third decade of life. Similarly, the overall clinical picture of the present cohort of patients aligns with preceding studies [6,15,29,32], with mucocutaneous lesions as the most common features at disease onset, followed by uveitis, articular and vascular involvement.

Our data revealed several gender differences. Firstly, male patients displayed a significantly higher BODI assessed at the last follow-up visit. This finding becomes even more meaningful when considering a significantly shorter disease duration and a lower diagnostic delay in male patients enrolled in the AIDA registry. Therefore, it is plausible to assume that male patients carry a higher propensity of accumulating irreversible damage over time, despite a shorter disease duration and early diagnosis. Our findings are consistent with a couple of studies exploring gender differences in relation to BODI, with one study revealing a higher BODI in males in univariate analysis [33], and the other one reporting male gender as associated with higher BODI values in multivariate analysis [34]. This aspect further supports the notion of a more severe course and poorer prognosis among males.

Regarding clinical manifestations, uveitis, and vascular involvement were significantly over-represented in male patients, both at disease onset and throughout disease course, while female patients exhibited more frequent articular involvement, CNS involvement and abdominal pain at disease onset. These data are consistent with previous large-scale studies reporting more frequent ocular and vascular involvement in male patients [12,15,35–37]. On the other hand, Davatchi et al., in a very large series of patients, while revealing statistically significant differences, found no strong association between the male gender and major organ involvement, except for vascular lesions. In fact, a strong association with an odds ratio > 2 was reported only for venous and arterial involvement [38].

Interestingly, the higher occurrence of gastrointestinal involvement during disease course persisted among females despite excluding abdominal pain and considering only lesions detected on endoscopic examination. The diagnostic delay and the consequent longer time-to-treatment, among females could be a contributing factor in the female predominance CNS and gastrointestinal involvement. Furthermore, gastrointestinal and CNS involvement are relatively late manifestations in BD. Finally, the sheer volume of data regarding endoscopically documented gastrointestinal involvement was low (27 males and 48 females). In this context, it is likely that a greater amount of data might nullify or even overturn this difference.

Female patients were also more likely to experience isolated headaches and fever during the whole disease course. Non-structural headaches, particularly tension-type headaches, have been reported with a significantly higher frequency in female patients affected by BD [39]. Also, a borderline significant tendency was observed toward genital ulcers and psychiatric manifestations throughout the disease course in female patients. It has been reported that patients presenting with mucocutaneous manifestations are less likely developing major organ involvement [37]. Therefore, a higher occurrence of genital lesions in females is potentially associated with the lower females' BODI score.

Taken together, these data indicate that several disease aspects appear to be gender-related and the gender-driven influence on disease phenotype is prominent. Male predominance in ocular and vascular involvement and female predominance of genital ulcer is a consistent finding in most of the available literature [11,12,15–20,35–37,40–46]. Similar results have been recently published by Kılıç et al. reporting a higher likelihood of ocular involvement and papulopustular lesions among male patients while a female predominance was shown in the occurrence of genital ulcers. The implementation of cluster analysis also in the context of gender-specific studies may potentially identify disease phenotypes, optimize treatment and ultimately lead to a personalized care [47]. In fact, our multinomial regression analysis found male gender significantly more prevalent in the ocular and vascular cluster, further supporting the male predominance in these disease phenotypes. The shorter diagnostic delay among male patients could also explain the association of a shorter diagnostic delay with the ocular cluster. Additionally, the relatively low prevalence of HLA-B*51 in the ocular cluster could be explained by the improvement in the diagnostic techniques and the improved knowledge in BD ocular manifestations that helps refer patients to the rheumatologist even in the absence of HLA-B*51.

Regarding gender differences in neurological and gastrointestinal involvement, data are more inconclusive and somewhat controversial [17,19,46–49]. Differences in design, in specific-organ

assessments and in therapeutic approach may account for the disparities encountered across studies.

Concerning potential predictors in the development of major organ involvement throughout the disease course, regression analysis identified the male gender among other variables, as independently and positively associated with the development of major organ involvement. This further supports the concept of a more severe course in male patients. Current treatment with biologic agents was another factor associated with major organ involvement. This is to be expected, since cases with a severe course have been treated more aggressively in order to minimize the detrimental long-term sequelae that would otherwise develop as disease progresses.

The underlying mechanisms in such notable gender differences in clinical phenotype, disease severity and prognosis may have a hormonal background. In this context, testosterone might play a pivotal role in disturbing neutrophil apoptosis in BD patients [50]. It appears to have a strong influence on neutrophil activation associated with significantly elevated levels of IL-2 and IL-12 in Th1 type immune response and marked downregulation of *IL-10* gene expression. Testosterone has also been associated with altered expression of Toll-like receptor 4, ERAP 1 and C-C motif of chemokine receptor 1 leading to Th1 polarization [51]. In addition to hormonal differences, the increased occurrence of vascular involvement in male patients could also be attributed to significantly higher homocysteine levels in this subgroup [52].

Despite providing robust real-life registry-based data, some limitations should be mentioned. First, The inherent nature of registry-based studies introduces several shortcomings including differences in patient management practices across centers, and the lack of standardized follow-up protocols. Secondly, we did not retrieve detailed descriptions of each manifestation as it was beyond the scope of the present study. In addition, the non-prospective collection for some of the variables precludes any assessment of causality or temporal relationship between them. For the same reason, therapeutic data and outcome measures related to treatment response were not retrieved. As a consequence, the impact of each therapeutic agent and its influence as a confounding factor were not assessed. Thirdly, while the heterogeneous cohort composed of different ethnic backgrounds allows to generalize our findings on one hand, makes it challenging to accurately establish gender-based differences in a firmly manner. Lastly, data for this study derive mainly from reference tertiary referral centers, which in turn collect patients with more severe disease thus generating a potential referral bias and missing a considerable portion of milder cases.

Whether gender is a major determinant in shaping the disease phenotype remains to be corroborated in future *ad-hoc* studies specifically designed to investigate each organ's involvement separately.

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Disclosure of interest

The authors declare that they have no competing interest.

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