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HLA-B27 Frequency and Clinical Correlates in Turkish Patients with Various Subtypes of Spondyloarthritis: A Single-Center Cohort Study

Türk Hastalarda Spondiloartritin Farklı Alt Tiplerinde HLA-B27 Sıklığı ve Klinik Korelasyonları: Tek Merkezli Bir Kohort Çalışması

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ABSTRACT

Aim: This study aimed to evaluate the frequency of human leukocyte antigen (HLA)-B27 positivity and its clinical correlations in Turkish patients with ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-associated arthritis, peripheral spondyloarthritis (pSpA), and non-radiographic axial SpA (nr-axSpA).

Materials and Methods: In this retrospective single-center cohort study, data from 524 AS, 380 PsA, 28 IBD-associated SpA, 45 pSpA, and 236 nr-axSpA patients were analyzed. Clinical features, HLA-B27 status, inflammatory markers, and imaging results were collected. Statistical analyses included the Chi-square tests, the Mann-Whitney U tests, Spearman's rank correlations, and logistic regression.

Results: HLA-B27 positivity was detected in 58.2% AS, 31.1% PsA, 25.0% IBD-SpA, 40.0% pSpA, and 35.2% nr-axSpA patients. In AS, HLA-B27 positivity correlated with higher C-reactive protein levels (p=0.001), elevated bath AS disease activity index (BASDAI) (p=0.0234), and bath ankylosing spondylitis functional index (BASFI) (p=0.0207) scores, male sex (p=0.0017), and younger age at onset (p=0.034). In PsA, higher PsA disease activity score were significantly associated with HLA-B27 positivity (p<0.0001). For IBD-SpA, HLA-B27 positivity correlated with younger age at disease onset (p=0.016), increased BASDAI (p=0.0003), and BASFI (p=0.0004). In nr-axSpA, male sex (p=0.00015), elevated BASDAI (p<0.0001), BASFI (p<0.0001), and increased biologic usage (p=0.0277) were significantly associated with HLA-B27 positivity, while non-steroidal anti-inflammatory drug responsiveness was higher in negatives (p=0.0058). Magnetic resonance imaging sacroiliitis negatively correlated with HLA-B27 positivity in AS (rho=-0.140, p=0.002).

Conclusion: HLA-B27 positivity varies across SpA subtypes, significantly correlating with male sex, disease activity, and functional impairment scores in axial SpA groups, with the highest prevalence in AS. While certain associations with disease activity and treatment patterns were observed, the overall clinical impact of HLA-B27 was limited. These findings highlight the complex and heterogeneous nature of HLA-B27's role in SpA and emphasize the need for further prospective studies to clarify its prognostic significance.

Keywords: HLA-B27, spondyloarthritis, seronegative spondyloarthritis

ÖZ

Amaç: Ankilozan spondilit (AS), psöriatik artrit (PsA), enflamatuvar bağırsak hastalığı (İBH)-ilişkili artrit, periferik spondiloartrit (pSpA) ve non-radiographic axial SpA (nr-axSpA) tanılı Türk hastalarda insan lökosit antijeni (HLA)-B27 pozitifliği sıklığını ve bunun klinik korelasyonlarını değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif, tek merkezli kohort çalışmasında 524 AS, 380 PsA, 28 İBH-ilişkili SpA, 45 pSpA ve 236 nr-axSpA hastasına ait veriler analiz edildi. Klinik özellikler, HLA-B27 durumu, enflamatuvar belirteçler ve görüntüleme sonuçları toplandı. İstatistiksel analizlerde ki-kare testi, Mann-Whitney U testi, Spearman korelasyonları ve lojistik regresyon kullanıldı.

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Bulgular: HLA-B27 pozitifliği AS hastalarının %58,2'sinde, PsA hastalarının %31,1'inde, İBH-ilişkili SpA hastalarının %25,0'ında, pSpA hastalarının %40,0'ında ve nr-axSpA hastalarının %35,2'sinde pozitif saptandı. AS grubunda HLA-B27 pozitifliği, yüksek C-reaktif protein düzeyleri (p=0,001), artmış bath AS hastalık aktivite indeksi (BASDAİ) (p=0,0234) ve bath ankilozan spondilit fonksiyonel indeksi (BASFİ) (p=0,0207) skorları, erkek cinsiyet (p=0,0017) ve daha genç başlangıç yaşı (p=0,034) ile ilişkiliydi. PsA grubunda, daha yüksek PsA hastalık skorları HLA-B27 pozitifliği ile anlamlı şekilde ilişkiliydi (p<0,0001). İBH-ilişkili SpA hastalarında, HLA-B27 pozitifliği daha genç başlangıç yaşı (p=0,016), artmış BASDAİ (p=0,0003) ve BASFİ (p=0,0004) ile koreleydi. nr-axSpA grubunda, erkek cinsiyet (p=0,00015), artmış BASDAİ (p<0,0001), BASFİ (p<0,0001) ve biyolojik tedavi kullanımı (p=0,0277) HLA-B27 pozitifliği ile anlamlı ilişkiliydi; buna karşılık steroid olmayan anti-enflamatuvar ilaç yanıtı negatiflerde daha yüksekti (p=0,0058). AS hastalarında manyetik rezonans görüntüleme ile saptanan sakroileit HLA-B27 pozitifliği ile negatif korelasyon gösterdi (rho=-0,140, p=0,002).

Sonuç: HLA-B27 pozitifliği SpA alt tipleri arasında farklılık göstermekte olup, aksiyal SpA gruplarında erkek cinsiyet, hastalık aktivitesi ve fonksiyonel bozulma skorları ile anlamlı ilişkiler göstermekte ve en yüksek sıklık AS grubunda gözlenmektedir. Hastalık aktivitesi ve tedavi paternleri ile bazı ilişkiler saptansa da HLA-B27'nin genel klinik etkisi sınırlıdır. Bulgular, HLA-B27'nin SpA'daki karmaşık ve heterojen rolünü vurgulamakta ve prognostik önemini netleştirmek için ileriye dönük çalışmalara ihtiyaç olduğunu göstermektedir.

Anahtar Kelimeler: HLA-B27, spondiloartrit, seronegatif spondiloartrit

INTRODUCTION

Spondyloarthropathies (SpA) comprise a set of conditions that predominantly involve the spine and peripheral joints. SpA is typically subclassified into conditions such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), reactive arthritis, and undifferentiated variants[1]. In recent years, these diseases have been further classified into additional subgroups: peripheral SpA (pSpA) and non-radiographic axial SpA (nr-axSpA)[2]. One of the key genetic predispositions associated with SpA is the presence of human leukocyte antigen (HLA)-B27. It has been linked to the onset of axial SpA (axSpA), with or without peripheral arthritis, and is also linked to enthesitis, acute anterior uveitis, more pronounced radiological progression, and gastrointestinal inflammation[3].

AxSpA involves spinal column and sacroiliac joints (SIJ). It is further subdivided into two categories: radiographic axSpA (r-axSpA, formerly known as AS) and nr-axSpA, the latter defined by the absence of radiographic SIJ changes[4]. A well-established relationship exists between the frequency of HLA-B27 and occurrence of SpA within various samples. The strongest link has been identified with AS, with some countries reporting HLA-B27 positivity rates of up to 90% among individuals with AS, although the literature presents varying results[5]. While HLA-B27 is highly prevalent in AS, its frequency in nr-axSpA is comparatively lower, averaging about 50%[6]. In individuals with psoriasis, PsA can develop as a chronic inflammatory disease. Estimates of axial skeleton involvement in PsA cases differ substantially, varying between 25% and 70%[7]. While HLA-B27 appears in a notable portion of axial PsA patients (14-40%) and less frequently in peripheral cases (~10%), its link to PsA is not as substantial as in AS[8,9].

The occurrence of arthralgia among individuals with IBD has been documented to vary between 6% and 46%. Arthritis associated with IBD, affects approximately 5% to 20% of individuals with IBD[10]. The frequency of HLA-B27 in individuals with arthritis related to IBD-associated arthritis is relatively low, approximately 40% in those with axial SpA and around 10% in those with pSpA. However, it is significantly higher in those with spondylitis or sacroiliitis associated with IBD, reaching approximately 60%[11]. pSpA refers to various SpA subsets, with enthesitis, arthritis, and dactylitis being the predominant clinical manifestations. HLA-B27 positivity has also been linked to the axial involvement in pSpA as well[12,13].

Considering the differences in HLA-B27 frequency in SpA observed in the literature and the inter-racial variations, this work explores the proportion of HLA-B27 among a Turkish cohort diagnosed with axSpA, nr-axSpA, pSpA, enteropathic arthritis, and PsA, and to examine the association between its presence and clinical features.

MATERIALS AND METHODS

The retrospective cross-sectional study was carried out with approval from the local ethics committee, adhering to the principles of the Helsinki Declaration, between 2020-2025, at the department of rheumatology of a university hospital utilizing data from electronic databases and hospital medical records Approval was obtained from the Non-Interventional and Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (decision no: 2024.324.12.08, date: 31.12.2024). The study population comprised 380 PsA cases, 45 pSpA, 236 nr-axSpA, 28 IBD-associated SpA, and 524 AS cases. Classification of PsA was based on the CASPAR criteria[14], AS was diagnosed based on the modified New York criteria, while nr-axSpA was classified using the ASAS classification criteria[15,16]. pSpA was defined using the ASAS classification criteria for pSpA[17], while IBD-associated SpA was defined using the Amor and European Spondyloarthropathy Study Group criteria[18,19]. Each participant met at least one of the aforementioned classification criteria. In cases where patients exhibited overlapping clinical features, classification was determined according to the predominant

clinical phenotype and the criteria most strongly met. Each patient was assigned to a single SpA subtype to ensure mutually exclusive groupings and to facilitate clearer subgroup analyses. Information on demographics (age and sex), disease duration, diagnostic year, time to diagnosis, family history, biologic treatment, and non-steroidal anti-inflammatory drug (NSAID) response was collected. The presence of clinical features such as (inflammatory low back pain), peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis and IBD were evaluated.

Initial inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), obtained from patients' outpatient visits, were recorded. Initial composite index scores, including the bath AS disease activity index (BASDAI) and the bath AS functional index (BASFI), PsA disease activity score (PASDAS)[20] were utilized for the assessment of disease severity and physical function.

The association between these recorded measures and HLA-B27 positivity was statistically analyzed. Individuals under aged 18 years; those with incomplete laboratory or medical data; lacking radiological imaging; with uncertain diagnoses; active infections; malignancies; advanced organ failure; or who had undergone major treatment changes, defined as the initiation or switching of biologic or conventional disease-modifying anti-rheumatic drugs therapy within the three months prior to the recorded evaluation, were excluded to minimize potential acute effects of therapy on disease activity and inflammatory markers.

HLA-B27 allele detection and genotyping were carried out using the Genvinset® HLA-B27v5 kit (Blackhills Diagnostic Resources, Spain) as per the manufacturer's instructions. The QIAamp DNA Blood Mini Kit was employed to isolate genomic DNA from whole blood and QIAcube automated system (Qiagen, Germany), providing consistent yields and reducing contamination risk[21]. DNA extraction, amplification, and fluorescence-based detection were performed as described by the kit instructions.

All patients underwent imaging of the SIJ using pelvic radiographs and magnetic resonance imaging (MRI). Sacroiliitis on X-rays was evaluated in accordance with modified New York criteria[16]. MRI evaluations focused on detecting bone marrow edema, following the ASAS guidelines[15].

Statistical Analysis

All statistical procedures were carried out using SPSS Statistics 27.0. Categorical variables were compared using the chi-square test or the Fisher's exact test, depending on data suitability. The distribution of continuous variables was assessed with the Shapiro-Wilk test. For non-normally distributed data, the Mann-Whitney U test was employed. Associations between continuous variables and HLA-B27 status were explored using Spearman's rank correlation. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 524 individuals diagnosed with AS were enrolled, of whom 58.2% tested positive for HLA-B27. A significantly older age at disease onset (p=0.034) was observed among HLA-B27 negative individuals, whereas male predominance was greater in the HLA-B27 positive group (p=0.002). Dactylitis was significantly associated with HLA-B27 negativity (p=0.022). No meaningful relationship was observed between HLA-B27 and peripheral arthritis, psoriasis, enthesitis, uveitis, IBD, or family history. Mean CRP level was 14.6±21.0 mg/L [interquartile range (IQR): 14.23] and mean ESR was 22.4±16.0 mm/h (IQR: 19.0). CRP levels were markedly increased in individuals with HLA-B27 positivity (p=0.001), in contrast, ESR levels showed no statistically significant variation (p=0.057). The baseline BASDAI and BASFI scores were notably elevated in HLA-B27 positive individuals compared to negatives (6.10±3.20 vs. 4.85±3.60 and 5.80±3.10 vs. 4.35±3.70), with p-values of 0.0234 and 0.0207) No significant differences were found regarding NSAID responsiveness or biological therapy use. Radiographic sacroiliitis was detected in all AS patients irrespective of HLA-B27 status. MRI positivity was significantly more frequent among HLA-B27 negative individuals. [p=0.002; odds ratio (OR)=0.41; Spearman's rho=-0.140].

A total of 380 PsA patients were analyzed. Of the patients, 31.1% exhibited HLA-B27 positivity. No meaningful correlation was observed between HLA-B27 status and either age at disease onset (p=0.845) or sex (p=0.836). Additionally, HLA-B27 positivity showed no significant association with NSAID response, use of biologic agents, or clinical manifestations. Average CRP and ESR levels were 11.48±22.40 mg/L (IQR: 9.0) and 26.24±22.06 mm/h (IQR: 25.0), respectively, and did not significantly differ according to HLA-B27 status. A mean PASDAS score of 6.06±0.9 was recorded, with significantly higher values among HLA-B27 positive individuals (p<0.0001). No significant correlation was found between radiographic sacroiliitis and HLA-B27 positivity (Spearman's rho=-0.086, p=0.125; OR=0.89) or between MRI positivity and HLA-B27 status (Spearman's rho=-0.055, p=0.345; OR=0.77).

Twenty-eight patients with IBD-SpA were included. One-quarter (25.0%) of the cohort tested positive for HLA-B27. Disease onset time was significantly earlier in HLA-B27 positive patients (p=0.016), while no association was found between HLA-B27 status and sex (p=1.000). Clinical features did not significantly differ according to HLA-B27 status. Average CRP and ESR levels were 19.30± 3.41 mg/L (median: 8.65 mg/L, IQR: 6.6 mg/L) and 38.07±25.63 mm/h (median: 31.0 mm/h, IQR: 41.0

mm/h), with no significant differences according to HLA-B27 status. NSAID response and biologic therapy use were similarly unrelated to HLA-B27 positivity. Elevated BASDAI and BASFI scores were significantly associated with HLA-B27 positivity (BASDAI: 7.58±0.41 vs. 5.67±0.64, p=0.0003; BASFI: 6.99±0.44 vs. 5.49±0.73, p=0.0004). All patients exhibited radiographic sacroiliitis, regardless of HLA-B27 status (p=1.0), whereas MRI-detected sacroiliitis was negatively correlated with HLA-B27 positivity (rho=-0.707, p<0.001) (see Table 1 and 2).

Among the 45 individuals with pSpA, HLA-B27 positivity was identified in 40.0%. No meaningful associations were found between HLA-B27 status and sex or disease onset time. None of the clinical features, including dactylitis, enthesitis, or uveitis, were significantly associated with HLA-B27 positivity. Mean CRP and ESR levels were 11.24±16.01 mg/L and 26.32±19.13 mm/h. CRP, ESR, NSAID response and biologic usage showed no significant differences according to HLA-B27 status. Radiographic sacroiliitis was observed in 35% of pSpA patients. MRI-confirmed sacroiliitis was present in 77.8% of HLA-B27 positive patients. Sacroiliitis findings on both X-ray and MRI showed no significant correlation with HLA-B27 status.

Among the 236 nr-axSpA patients evaluated, HLA-B27 positivity was notably higher in males compared to females (p=0.00015) while no significant variation was found in the mean age at symptom onset. No significant relationship was found between HLA-B27 positivity and clinical features, CRP (18.27±34.40 vs. 11.57±20.06 mg/L; p=0.103), or ESR levels (29.25±24.71 mm/h; p=0.914). However, HLA-B27 positive patients had significantly higher disease activity and functional limitation scores, as reflected by BASDAI (6.73±0.67 vs. 5.66±0.70, p<0.0001) and BASFI (6.49±0.64 vs. 5.29±0.68, p<0.0001). Biologic treatment was more frequently used among HLA-B27 positive patients (19.3% vs. 8.5%, p=0.0277), whereas NSAID response was significantly more common in HLA-B27 negative patients (90.2% vs. 75.9%, p=0.0058). MRI positivity showed no significant correlation with HLA-B27 status (Spearman's rho=0.037, p=0.683) (see Table 3).

Regarding medications, biologic therapy was most commonly used in patients with AS (55.3%) and PsA (40.5%), followed by enteropathic arthritis (50.0%), pSpA (15.6%), and nr-axSpA (12.3%). Across all subtypes, tumor necrosis factor (TNF) inhibitors were the predominant class. The most frequently prescribed agents included adalimumab (n=142), etanercept (n=125), infliximab (n=73), golimumab (n=39), and certolizumab pegol (n=31). IL-17 inhibitors were used in 40 AS, 22 PsA, and 2 enteropathic arthritis patients, while JAK inhibitors were prescribed to 26 AS, 13 PsA, and 1 enteropathic arthritis patient. All biologic users in the nr-axSpA and pSpA groups were treated exclusively with TNF inhibitor.

Table 1. Demographic characteristics of all patients

Variables	Ax-SpA	PsA	EA	pSpA	Nr-AxSpA
Patient number (n)	524	380	28	45	236
Age, years (mean ± SD)	45.9±11.2	49.55±11.72	45.07±14.38	44.69±11.25	48.58±11.00
Symptom duration (onset) (years, mean ± SD)	12.02±7.55	9.23±7.89	6.48±5.67	5.13±4.22	8.14±608
Diagnostic delay (years, mean ± SD)	4.18±3.26	5.72±4.02	4.85±3.79	4.18±3.24	5.33±4.45
Sex (male, %)	320 (61.1)	134 (35.3)	12 (42.9)	12 (26.7)	49 (20.8)
HLA-B27 positivity (n, %)	305 (58.2)	118 (31.1)	7 (25)	18 (40)	83 (35.2)
Arthritis (n, %)	132 (25.2)	227 (59.7)	6 (21.4)	37 (82.2)	102 (43.2)
iLBP (n, %)	347 (66.2)	57 (15)	14 (50)	15 (33.3)	172 (72.9)
Dactylitis (n, %)	28 (5.3)	130 (34.2)	4 (14.3)	8 (17.8)	32 (13.6)
Psoriasis (n, %)	33 (6.3)	379 (100)	2 (7.1)	0 (0)	10 (4.2)
Enthesitis (n, %)	152 (29)	116 (30.5)	10 (35.7)	19 (42.2)	77 (32.6)
Uveitis (n, %)	78 (14.9)	13 (3.4)	2 (7.1)	3 (6.7)	12 (5.1)
Family history positivity (n, %)	117 (22.3)	55 (14.5)	6 (21.4)	10 (22.2)	40 (16.9)
IBD (n, %)	21 (4)	5 (1.3)	28 (100)	0 (0)	3 (1.3)
NSAID responsiveness (n, %)	237 (45.2)	226 (59.5)	10 (35.7)	44 (97.8)	201 (85.2)
Biologic usage (n, %)	290 (55.3)	154 (40.5)	14 (50)	7 (15.6)	29 (12.3)

Ax-Spa: Axial spondyloarthritis (ankylosing spondylitis), PsA: Psoriatic arthritis, EA: Enteropathic arthritis (inflammatory bowel disease associated spondyloarthritis), pSpA: Peripheral spondyloarthritis, Nr-AxSpA: Non radiographic axial spondyloarthritis, SD: Standard deviation, IBD: Inflammatory bowel disease, NSAID: Non-steroidal anti inflammatory drugs, iLBP: Inflammatory low back pain

Table 2. Comparison of clinical parameters according to HLA-B27 status in ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease associated spondyloarthritis cohorts

Variable	AS HLA-B27 Positive n (%)	AS HLA-B27 Negative n (%)	p-value	PsA HLA-B27 Positive n (%)	PsA HLA-B27 Negative n (%)	p-value	EA HLA-B27 Positive n (%)	EA HLA-B27 Negative n (%)	p-value
Male sex	204 (66.9)	101 (53.0)	**0.002**	43 (36.4)	91 (34.7)	0.836	3 (42.9)	9 (42.9)	1.000
iLBP	203 (66.5)	144 (65.7)	0.922	16 (13.5)	41 (15.6)	0.709	5 (71.4)	9 (42.9)	0.383
Sacroiliitis (X-ray)	305 (100)	219 (100)	1.000	31 (26.2)	86 (32.8)	0.125	7 (100)	21 (100)	1.000
Sacroiliitis (MRI positivity)	248 (81.3)	200 (91.3)	**0.002**	31 (26.2)	83 (31.6)	0.345	3 (42.9)	21 (100)	**0.0018**
Peripheral arthritis	74 (24.2)	58 (26.4)	0.634	66 (55.9)	161 (61.5)	0.367	3 (42.9)	3 (14.3)	0.287
Psoriasis	21 (6.8)	12 (5.4)	0.638	117 (99.2)	262 (100.0)	0.682	2 (28.6)	0 (0.0)	0.056
Enthesitis	88 (28.8)	64 (29.2)	1.000	40 (33.8)	76 (29)	0.402	2 (28.6)	8 (38.1)	1.000
Dactylitis	10 (3.2)	18 (8.2)	**0.022**	36 (30.5)	94 (35.8)	0.366	2 (28.6)	2 (9.5)	0.253
Family history	75 (24.5)	42 (19.1)	0.174	17 (14.4)	38 (14.5)	1.000	0 (0.0)	6 (28.6)	0.287
Uveitis	52 (17)	26 (11.8)	0.129	4 (3.3)	9 (3.4)	1.000	0 (0.0)	2 (9.5)	1.000
IBD	12 (3.9)	9 (4.1)	1.000	1 (0.8)	4 (1.5)	0.956	7 (100)	21 (100)	1.000

Statistically significant values are marked at p<0.05

AS: Ankylosing spondylitis, PsA:Psoriatic arthritis, EA: Enteropathic arthritis, iLBP: Inflammatory low back pain, HLA-B27: Human leukocyte antigen B27, MRI: Magnetic resonance ımaging, IBD: Inflammatory bowel disease

Table 3. Comparison of clinical parameters according to HLA-B27 status in peripheral spondyloarthritis and non-radiographic axial spondyloarthritis cohorts

Variable	pSpA HLA-B27 Positive n (%)	pSpA HLA-B27 Negative n (%)	p-value	Nr-axSpA HLA-B27 Positive n (%)	Nr-axSpA HLA-B27 Negative n (%)	p-value
Male sex	6 (33.3)	6 (22.2)	0.499	29 (34.9)	20 (13.1)	**0.00015**
iLBP	7 (38.9)	8 (29.6)	0.538	64 (77.1)	108 (70.6)	0.356
Sacroiliitis (X-ray)	8 (40)	8 (29.6)	0.281	0 (0.0)	0 (0.0)	1.000
Sacroiliitis (MRI positivity)	14 (77.8)	15 (55.6)	0.227	45 (54.2)	78 (51.0)	0.683
Peripheral arthritis	13 (72.2)	24 (88.9)	0.301	32 (38.6)	70 (45.8)	0.353
Psoriasis	0 (0.0)	0 (0.0)	1.000	3 (3.6)	7 (4.6)	0.991
Enthesitis	4 (22.2)	15 (55.6)	0.056	24 (28.9)	53 (34.6)	0.453
Dactylitis	3 (16.7)	5 (18.5)	1.000	13 (15.7)	19 (12.4)	0.620
Family history	4 (22.2)	6 (22.2)	1.000	15 (18.1)	25 (16.3)	0.875
Uveitis	2 (11.1)	1 (3.7)	0.714	9 (10.8)	3 (2)	**0.0079**
IBD	0 (0.0)	0 (0.0)	1.000	1 (1.2)	2 (1.3)	1.000

Statistically significant values are marked at p<0.05

PSpA: Peripheral spondyloarthritis, Nr-AxSpA: Non radiographic axial spondyloarthritis, iLBP: Inflammatory low back pain, HLA-B27: Human leukocyte antigen B27, MRI: Magnetic resonance imaging, IBD: Inflammatory bowel disease

DISCUSSION

This study assessed HLA-B27 positivity and its clinical, laboratory, and radiological correlations in a cohort comprising AS, PsA, nr-axSpA, pSpA, and enteropathic arthritis patients from Türkiye's Thrace region. Among 524 AS patients, the HLA-B27 frequency was 58.2%; among 380 PsA patients, 31.1%; among 28 IBD-associated SpA patients, 25%; among 45 pSpA patients, 40%; and among 236 nr-axSpA patients, 35.2%. These rates were lower for AS compared to Western populations but appeared comparable to other Turkish cohorts. For PsA, the frequency was similar to data reported from North America and Brazil[22,23]. The rate observed for enteropathic arthropathy was lower than that reported for enteropathic spondylitis in the literature but higher than that reported specifically for IBD-associated arthritis[22]. The frequency observed for pSpA was similar to international studies, such as the ASAS perSpA study, which reported a prevalence of 35.8%[13]. In contrast, the rate observed in nr-axSpA was somewhat lower compared to certain other Turkish cohorts. In the overall cohort, HLA-B27 positivity showed no significant association with most clinical manifestations. Despite early studies suggesting a link between HLA-B27 positivity and increased extra-articular involvement, such an association was not observed in this study. A significant relationship was observed between HLA-B27 positivity and initial BASDAI and BASFI scores in all groups; however, no such correlation was found with CRP or ESR. Among AS and nr-axSpA patients, HLA-B27 positivity was significantly associated with male sex although the relationship with age at onset was inconsistent across groups. Moreover, HLA-B27 positivity correlated with more severe radiographic sacroiliitis in AS and IBD-associated SpA while no such association was found in the remaining subtypes.

In this cohort, an HLA-B27 positivity rate of 58.2% was identified among AS patients, which is slightly lower than the 70–91% reported in Turkish cohorts[24,25], the 69% reported in Qatar by Abdelrahman et al.[26] (including 82% among Qataris, 72% among Jordanians, and 90% among Egyptians), and the 80.5% reported in a Greek cohort[27], but remains within the broader Middle Eastern range of 26.2% (Lebanon) to 91% (Türkiye)[28]. HLA-B27 carriage rates in the general population of Arab and Middle Eastern nations (0.3-6.8%) has been noted to be considerably lower than in Western populations (6-25%)[28], potentially affecting the diagnostic utility of HLA-B27-based referral strategies in these regions. Furthermore, the considerable methodological heterogeneity across regional studies, such as variations in sample sizes, classification criteria, and HLA-B27 testing techniques, should be carefully considered when comparing prevalence estimates across populations. The differences observed in HLA-B27 prevalence across studies, even within a single country, are likely influenced by genetic and environmental diversity among subpopulations. HLA-B27 positivity was significantly associated with male sex and earlier disease onset, consistent with findings from Arévalo et al.[29], as well as the DESIR and GESPIC cohorts[30,31]. Unlike Arévalo et al.[29], who found no CRP or ESR differences, this research observed significantly higher CRP levels in HLA-B27-positive patients, though ESR was similar. With respect to disease activity, our finding of elevated BASDAI and BASFI scores in HLA-B27 positive patients differs from Arévalo et al.[29], who observed higher values in those lacking HLA-B27. Radiographically, current study paradoxically showed an inverse relationship with MRI sacroiliitis, an area not assessed in Arévalo et al.[29].

In this cohort, HLA-B27 positivity showed no significant association with uveitis, enthesitis, peripheral arthritis, or IBD; however, dactylitis was significantly more common among HLA-B27 positive individuals. These findings contrast with the study of Zhang et al.,[32] where HLA-B27 positivity was linked to higher uveitis prevalence but lower rates of dactylitis and peripheral arthritis, with no clear association for enthesitis or IBD. Similarly, another Chinese cohort reported no significant differences in uveitis, enthesitis, or peripheral arthritis between HLA-B27-positive and negative AS patients, aligning with the present findings, although no relationship with dactylitis was identified in their cohort[33]. Collectively, these findings indicate that the association between HLA-B27 and extra-articular manifestations is multifaceted and potentially population-dependent.

The HLA-B27 positivity rate among PsA patients in this study was 31.1%, aligning with international reports such as the 27.3% observed by Ruiz et al.[23] and the 22.8% in a Sri Lankan SpA cohort[34], though slightly higher than the 17.6% reported by Öğretmen et al.[35]. While some studies, such as those by Ruiz et al.[23] and Kidnapillai et al.,[34] noted a male predominance among HLA-B27-positive patients, no significant association with male sex was observed here. Although earlier research has indicated a strong connection between HLA-B27 positivity and axial manifestations, especially given the reported 60% positivity rate in PsA patients with axial involvemen, the predominance of pSpA in this cohort may explain the absence of such associations. While Bonfiglioli et al.[37] identified significant associations between HLA-B27 positivity, male sex, and axial involvement in PsA, no analyses were conducted regarding composite disease activity measures such as PASDAS. Importantly, no prior research has directly explored the link between HLA-B27 status and PASDAS in PsA, with most studies instead concentrating on axial involvement measured by BASDAI or AS disease activity score (ASAS). The significant association identified here, with higher PASDAS values among HLA-B27-positive patients, suggests a potentially meaningful link between HLA-B27 status and overall disease activity in PsA.

Within this group of patients diagnosed with IBD-associated SpA, the frequency of HLA-B27 was identified as 25%, which is comparable to the 29% documented by Turkcapar et al.[38] and falls within the broader frequency range of 30-80% reported by Peluso et al.[39]. However, this rate is lower than the 46.7% noted in the Guinea cohort[40] but exceeds the 7.9% described by Huber et al.[41]. Similarly, the Brazilian research by Toledo et al.[42] found no link between HLA-B27 and enteropathic SpA, supporting the observation that HLA-B27 negativity is common in IBD-related SpA cases. Notably, Toledo et al.[42] highlighted that radiological sacroiliitis was significantly associated with HLA-B27, even beyond AS, whereas intestinal involvement tended to occur more frequently in HLA-B27-negative individuals. Regarding disease activity, HLA-B27 showed a significant connection with BASDAI and BASFI scores, reflecting its potential impact on functional status, although earlier studies offered limited insights into these measures. Notably, no significant link was identified between HLA-B27 positivity and radiographic sacroiliitis in this cohort; however, an inverse association with MRI findings was observed, highlighting a complex interplay between genetic markers and clinical expression. Across different studies, NSAID use was generally low, likely due to gastrointestinal safety concerns in IBD, while the proportion of patients on biologic therapies varied (for instance, 39.4% reported by Huber et al.[41]).

In this cohort of pSpA, the HLA-B27 positivity rate was 40%, notably higher than the ~27% reported in ASAS-based international cohorts[43]. Özsoy et al.[44] reported a lower HLA-B27 positivity specifically among Turkish pSpA patients (9.8%) although their overall SpA cohort showed a higher rate (74.7%) largely due to axial cases. Similarly, the ASAS perSpA study found a 35.8% HLA-B27 positivity in pSpA/PsA patients, reporting associations with earlier disease onset, male sex, axial involvement, tarsitis, and uveitis, but no link with dactylitis, psoriasis, or IBD[13]. While prior research has consistently shown that pSpA displays a weaker association with HLA-B27 compared to axial SpA[43], a similar pattern was observed here, with no significant associations identified between HLA-B27 status and extra-articular manifestations, inflammatory markers, NSAID response, or MRI-detected sacroiliitis. Interestingly, Özsoy et al.[44] also found no significant differences between HLA-B27 carriers and non-carriers in terms of dactylitis, enthesitis, or IBD; however, they reported a higher prevalence of uveitis among individuals expressing HLA-B27. Moreover, Arevalo Salaet et al.[13] emphasized that despite HLA-B27's links to axial features and uveitis, no association was observed with peripheral joint damage, reinforcing that structural damage pathways may be independent of HLA-B27 status.

In the current study, the HLA-B27 positivity rate among nr-axSpA patients was 35.2%, placing it within the lower-to-mid global range and notably below the 63.3% reported in the Turkish nr-axSpA cohort[45], as well as the 41.9% observed in Malaysia[46], 54.3% in Mexico[6] and 72.2% in a large cohort from China[47]. Male sex was significantly associated with HLA-B27 positivity, consistent with previous observation in Mexican cohort. No significant associations were found between HLA-B27 status and acute-phase reactants, MRI findings, or specific clinical features such as uveitis or dactylitis, aligning with earlier reports where these associations were not prominently emphasized. While Özdemirel et al.[45] reported no relationship between HLA-B27 and disease activity in Turkish nr-axSpA patients, the present study identified significant associations between HLA-B27 positivity and higher BASDAI and BASFI scores, indicating greater subjective disease burden. This may partly explain the more frequent use of biologic therapies and the lower responsiveness to NSAIDs among HLA-B27-positive individuals.

This appears to be the first study to systematically evaluate HLA-B27 prevalence across multiple SpA subtypes, including AS, nr-axSpA, IBD-associated SpA, PsA, and pSpA, in the Thrace region of Türkiye. While the key clinical characteristics of Turkish SpA patients were consistent with previous studies, several distinct differences were observed in this cohort. One of the most striking findings of the present study was the relatively low frequency of HLA-B27 positivity across all SpA subtypes, including AS (58.2%) and nr-axSpA (38.1%). These rates are notably lower than those reported in several European cohorts, where HLA-B27 positivity exceeds 80% in AS and approximately 60-70% in nr-axSpA. In contrast, our findings are more consistent with regional data from the Middle East and Mediterranean countries, where the prevalence of HLA-B27 in SpA patients tends to be lower, possibly due to ethnic and genetic diversity. Additionally, population-based studies have shown that the general prevalence of HLA-B27 in Türkiye is considerably lower than in Northern European countries, which may contribute to the relatively low detection rates observed in our cohort. Environmental exposures, differing referral patterns, and variability in disease phenotypes could also play a role in this discrepancy. These findings underscore the importance of considering regional genetic backgrounds when interpreting HLA-B27 positivity in clinical practice and research.

Study Limitations

This study has several limitations inherent to its retrospective and single-center design. Although standardized classification criteria were used, diagnostic accuracy may have been influenced by variability in physician assessments over time. The absence of longitudinal follow-up precluded the evaluation of disease progression and long-term outcomes, particularly relevant for nr-axSpA patients who may later transition to

radiographic disease. Small sample sizes in certain subgroups may have limited the statistical power. All radiographic and MRI evaluations were performed by a single radiologist, which, while ensuring consistency, may have introduced observer bias due to the lack of inter-reader validation. Additionally, data on smoking status and comorbidities were not consistently documented and were therefore excluded, potentially limiting the depth of clinical characterization. In patients with pSpA, joint activity could not be assessed using standardized joint counts or composite activity scores due to inconsistent recording in the medical files. Lastly, genetic and environmental factors specific to the study population may limit the generalizability of these findings. Future large-scale, prospective, multicenter studies are needed to validate these results and further elucidate the clinical significance of HLA-B27 across diverse SpA subtypes.

CONCLUSION

This study provides a comprehensive overview of HLA-B27 frequency and its clinical associations across multiple SpA subtypes in a large Turkish cohort. While HLA-B27 positivity rates varied between disease groups, its overall clinical impact appeared limited, with no consistent associations identified for extra-articular manifestations or inflammatory markers. Importantly, elevated disease activity and functional limitation scores were observed in HLA-B27–positive individuals, most prominently in those with axial SpA and nr-axSpA. These findings underscore the complex and subtype-specific nature of HLA-B27's clinical relevance. Future multicenter, prospective research are needed to confirm these observations and further clarify prognostic role of HLA-B27 in diverse populations.

Ethics

Ethics Committee Approval: Approval was obtained from the Non-Interventional and Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (decision no: 2024.324.12.08, date: 31.12.2024).

Informed Consent: This is retrospective cross-sectional study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.B.G., Ö.A.S., Concept: D.B.G., H.T., R.M., Design: D.B.G., H.T., R.M., Data Collection or Processing: D.B.G., H.T., Ö.A.S., R.M., Analysis or Interpretation: D.B.G., H.T., R.M., Literature Search: D.B.G., H.T., R.M., Writing: D.B.G., R.M.

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