ORIGINAL ARTICLE
Archives of Rheumatology 2026;41(4):456-463
DOI: 10.5152/ArchRheumatol.2026.25122

Comparison of the Clinical Expression of Patients with Enthesitis/Spondylitis-Related Juvenile Idiopathic Arthritis (E/SpRJIA) from Türkiye and India

Rana İşgüder[1]
Avinash Sharma[2]
Zehra Kızıldağ[1]
Yağmur Bayındır[3]
Zeynep Balık[3]
Ümit Gül[4]
Cüneyt Karagöl[5]
Şeyma Türkmen[6]
Taner Coşkuner[6]
Sandesh Guleria[2]
Gülçin Aytaç[7]
Pratap Kumar Patra[8]
Sagar Bhattad[9]
Himanshi Chaudhary[10]
Anjani Gummadi[11]
Johnson Nameirakpam[12]
Mehmet Yıldız[4]
Elif Çelikel[5]
Betül Sözeri[6]
Güzide Aksu[7]
Seza Özen[3]
Erbil Ünsal[1]
Balahan Bora[1]

[1]Department of Pediatric Rheumatology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye
[2]Department of Pediatric Rheumatology, Dr Rajendra Prasad Government Medical College, Kangra, India
[3]Department of Pediatric Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Türkiye
[4]Department of Pediatric Rheumatology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
[5]Department of Pediatric Rheumatology, Ankara City Hospital, Ankara, Türkiye
[6]Department of Pediatric Rheumatology, University of Health Sciences, Ümraniye Training and Research Hospital, İstanbul, Türkiye
[7]Department of Pediatric Rheumatology, Ege University Faculty of Medicine, İzmir, Türkiye
[8]Department of Pediatric Rheumatology, All India Institute of Medical Sciences, Patna, India
[9]Department of Pediatric Rheumatology, Aster CMI Hospital, Bengaluru, India
[10]Department of Pediatric Rheumatology, Alpha Superspecialty Clinics, Pune, India
[11]Department of Pediatric Rheumatology, Ankura Hospitals for Women and Children, Hyderabad, India
[12]Department of Pediatric Rheumatology, Jawaharlal Nehru Institute of Medical Sciences, Manipur, India

ABSTRACT

Background/Aims: To compare the clinical characteristics of enthesitis/spondylitis-related juvenile idiopathic arthritis (E/SpRJIA), a relatively prevalent JIA subtype in Türkiye and India, and to explore potential population-specific differences in disease expression.

Materials and Methods: This multicenter, binational, retrospective cohort study included children fulfilling the provisional PRINTO classification criteria for E/SpRJIA from 12 pediatric rheumatology centers in Türkiye and India. Demographic characteristics, clinical manifestations, human leukocyte antigen B27 (HLA-B27) status, laboratory findings, disease course, and treatment-related data were collected. A multivariable logistic regression analysis was performed to identify factors independently associated with sacroiliitis at diagnosis.

Results: A total of 498 patients were included (391 Turkish and 107 Indian). At disease onset, peripheral polyarticular involvement was more common in Indian patients (40.2% vs 5.6%), whereas axial involvement was more frequent in Turkish patients (45.8% vs 18.7%). HLA-B27 positivity was higher in Indian patients than in Turkish patients (79.5% vs 56.4%). During follow-up, sacroiliitis, enthesitis, and tarsitis were more common among Turkish patients, while peripheral arthritis and dactylitis were more frequent among Indian patients. NSAIDs were used more frequently in India, whereas conventional and biologic DMARDs were more commonly used in Türkiye. In multivariable analysis, country of origin remained independently associated with sacroiliitis at diagnosis, whereas HLA-B27 positivity did not.

Conclusion: E/SpRJIA demonstrates substantial phenotypic heterogeneity between Turkish and Indian populations. Turkish patients exhibited a predominantly axial disease pattern, whereas Indian patients more commonly showed peripheral polyarticular involvement despite higher HLA-B27 positivity. These findings suggest that factors beyond HLA-B27, including broader genetic, environmental, and population-specific influences, may contribute to differences in disease expression. Further prospective and genetically informed studies are needed to clarify the determinants of this heterogeneity.

Keywords: Enthesitis/spondylitis-related juvenile idiopathic arthritis, Juvenile idiopathic arthritis, HLA-B27, India, Türkiye, Pediatric rheumatology

Copyright@Author(s) - Available online at archivesofrheumatology.com.
Content of this journal is licensed under a Creative Commons Attribution (CC BY) 4.0 International License.

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic and heterogeneous disorder in which prolonged synovial inflammation leads to structural joint damage.[1] The classification system currently in use was introduced by the International League Against Rheumatism (ILAR) in 2002. Enthesitis-related arthritis (ERA), one of the JIA categories, is characterized by inflammation of both joints and entheses, and may also involve the sacroiliac (SI) joints.[2]

The diagnosis of ERA requires the coexistence of arthritis and enthesitis, or either condition in combination with at least two minor criteria, one of which can be SI symptoms. However, some patients with isolated sacroiliitis may not fulfill the ERA classification requirements because they do not meet the required number of accompanying minor criteria.[2,3]

This group of patients may present with peripheral joint involvement and/or enthesitis, or less frequently with axial involvement alone. Currently, there are no established criteria for diagnosing isolated axial involvement in children, and applying adult standards is challenging due to the distinct clinical manifestations seen in pediatric patients.[1,2,4]

MAIN POINTS

- *E/SpRJIA demonstrated distinct clinical phenotypes in Turkish and Indian pediatric populations despite belonging to the same disease category.*
- *Indian patients more frequently exhibited peripheral polyarticular disease and higher HLA-B27 positivity, whereas Turkish patients showed more frequent axial involvement, sacroiliitis, enthesitis, and tarsitis.*
- *In multivariable analysis, country of origin remained independently associated with sacroiliitis at diagnosis, whereas HLA-B27 positivity did not.*
- *Differences in disease expression may reflect the combined influence of genetic background, environmental factors, and population-specific modifiers beyond HLA-B27 alone.*
- *Differences in treatment patterns between countries should be interpreted in the context of health care access and system-related factors.*

Corresponding author: Rana İşgüder
✉ dr.ranaisguder@yahoo.com

Received: September 11, 2025
Revision Requested: May 04, 2026
Last Revision Received: June 08, 2026
Accepted: July 30, 2026
Publication Date: September 1, 2026

Cite this article as: İşgüder R, Sharma A, Kızıldağ Z, et al. Comparison of the Clinical Expression of Patients with Enthesitis/Spondylitis-Related Juvenile Idiopathic Arthritis (E/SpRJIA) from Türkiye and India. *ArchRheumatol.* 2026;41(4):456-463.

In recent years, it has become clear that the current classification does not fully cover this group of patients because of the heterogeneous presentation. In a revision to the JIA classification criteria proposed by the Paediatric Rheumatology International Trials Organisation (PRINTO) classification committee, this group of patients was named enthesitis/spondylitis-related JIA (E/SpRJIA).[5] The PRINTO classification framework was developed to better align pediatric disease with the spectrum of juvenile and adult spondyloarthritis. Unlike the ILAR ERA category, the PRINTO criteria incorporate imaging-confirmed sacroiliitis and inflammatory back pain, thereby facilitating the classification of patients with predominantly axial disease manifestations who may otherwise remain unclassified under ILAR criteria.[6]

Recent studies have evaluated the performance of the provisional PRINTO criteria in different patient populations and demonstrated their ability to reclassify a substantial proportion of patients previously categorized as ERA or undifferentiated JIA according to ILAR criteria.[7,8] Nevertheless, ongoing investigations suggest that some children with predominantly axial disease may still not be fully captured, indicating that further refinement of the classification system remains necessary.[9] These findings highlight the continued importance of characterizing the phenotypic spectrum of E/SpRJIA across different populations.

The clinical features of E/SpRJIA may vary between patient populations, particularly because of differences in distributions of HLA and other genetic factors, as well as different environmental factors, particularly the microbiota.[10] Despite recent advances in the classification of E/SpRJIA, comparative studies evaluating the clinical expression of this disease across different ethnic and geographic populations remain scarce. There is only one study comparing the demographic and clinical variables of E/SpRJIA patients from different countries. Ghantous et al compared the 39 Israeli and 48 US patients with JSpA regarding demographic, clinical, and radiologic features at diagnosis.[11]

Our aim in this study was to compare E/SpRJIA patients in India and Türkiye in terms of demographic, clinical, serological, and radiological features and treatments, for possible effects of ethnic and geographical differences on the heterogeneous clinical characteristics of this patient group.

Materials and Methods

This study was designed as a multicenter, binational, retrospective cohort and conducted with data from six pediatric rheumatology centers in Türkiye from May 2004 to March 2023 and six pediatric rheumatology centers from India from February 2017 to January 2023.

Six centers that shared data from Türkiye were Ankara Bilkent City Hospital, Cerrahpaşa University Faculty of

Medicine, Dokuz Eylül University Faculty of Medicine, Ege University Faculty of Medicine, Hacettepe University Faculty of Medicine and University of Health Sciences Ümraniye Training and Research Hospital.

Participating centers from India were Dr Rajendra Prasad Government Medical College, Aster CMI Hospital, AIIMS Patna Hospital, Alpha Superspeciality Clinic & Ruby Hall Clinics, Ankura Hospitals for Women and Children, and Thoubal District Hospital, Jawaharlal Nehru Institute of Medical Sciences.

All patients aged 0 to 18 years who had been followed with a diagnosis of ERA or juvenile spondyloarthritis at the participating pediatric rheumatology centers in Türkiye and India until March 2023 were screened for eligibility. Medical records were retrospectively reviewed, and patients fulfilling the provisional PRINTO classification criteria for enthesitis/spondylitis-related JIA (E/SpRJIA) were identified. At the time of study design and patient selection, the provisional PRINTO classification criteria for E/SpRJIA represented the most contemporary classification framework available. Although the final PRINTO classification criteria for JIA were published subsequently, the E/SpRJIA category was retained within the updated framework. Therefore, patients were classified according to the provisional PRINTO criteria applicable during the study period.

Inclusion Criteria[5,11,12]

Enthesitis/spondylitis-related JIA

- Peripheral arthritis and enthesitis, or
- Arthritis or enthesitis, plus ≥3 months of inflammatory back pain and sacroiliitis on imaging, or
- Arthritis or enthesitis plus two of the following:
  1. SI joint tenderness;
  2. inflammatory back pain;
  3. presence of HLA-B27 antigen;
  4. acute (symptomatic) anterior uveitis; and
  5. history of an SpA in a first-degree relative.
  6. If peripheral arthritis is present, it should persist for at least 6 weeks.

Exclusion Criteria[5,11,12]

- Age at onset >16 years
- Presence of another rheumatologic disorder either at the time of E/SpRJIA diagnosis or developing thereafter (eg, reactive arthritis, inflammatory bowel disease, chronic noninfectious osteomyelitis, psoriasis).

If SI tenderness or inflammatory back pain was reported in the medical history, sacroiliitis was confirmed radiologically using either conventional radiography or magnetic resonance imaging (MRI). For plain radiographs, the New York scoring system was applied to assess the SI joints.[12]

Modified New York Criteria for X-ray of Sacroiliitis

Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3 to 4 unilaterally.

- **Grade 0:** normal
- **Grade I:** suspicious changes (some blurring of the joint margins)
- **Grade II:** minimum abnormality (small localized areas with erosion or sclerosis, with no alteration in the joint width)
- **Grade III**: unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis)
- **Grade IV:** severe abnormality (complete ankylosis)

Patient data (the dependent and independent variables) obtained from the hospital charts and information management system were recorded in the case report forms.

The following demographic, clinical, laboratory, radiological, and treatment-related variables were recorded:

Gender and ethnicity, date at diagnosis, age at symptom onset (year), age at diagnosis (year), duration of follow-up (month), consanguinity between parents, human leukocyte antigen B27 (HLA-B27)-related rheumatologic disease in the family (ankylosing spondylitis [AS], enthesitis-related arthritis [ERA], inflammatory bowel disease [IBD], reactive arthritis, acute anterior uveitis), type of disease onset (peripheral arthritis-oligoarticular, peripheral arthritis-polyarticular, axial), peripheral arthritis (knee, ankle, hip, midfoot, wrist, elbow, fingers, toes), enthesitis, sacroiliitis (radiologically confirmed),[8] tarsitis, dactylitis, acute anterior uveitis during the entire follow-up, physician visual analog scale (VAS) on first admission (if done) and acute phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), HLA-B27 status. An elevated CRP was defined as a value above 5 mg/L, while an elevated ESR was defined as greater than 20 mm in the first hour. HLA-B27 was performed either by PCR (polymerase chain reaction) or flow cytometry.

Treatment-related data were also recorded, including the use of nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, conventional disease-modifying antirheumatic drugs (cDMARDs) (methotrexate, sulfasalazine, and leflunomide), biologic DMARDs (bDMARDs) (anti-TNF agents, tocilizumab, and secukinumab), and targeted DMARDs (tDMARDs) (tofacitinib). In addition, current disease status (active, inactive off medication, inactive on medication) was recorded.

All cases were independently evaluated by two expert pediatric rheumatologists (one from Türkiye and one from India) according to the predefined inclusion and exclusion criteria. A total of 24 patients from India and 5 patients from Türkiye were excluded because their follow-up duration was less than 1 year. Consequently, 107 children from India and 391 children from Türkiye were included in the final analysis.

Statistics

The normality of variables was assessed through visual inspection (histograms and probability plots) and analytical tests (Kolmogorov–Smirnov/Shapiro–Wilk). Descriptive

statistics were presented as mean ± standard deviation for normally distributed data, and as median with interquartile range (IQR) for nonnormally distributed data. Categorical variables were summarized as frequencies and percentages.

To compare data from the two countries, the Student-t test was used as a parametric test and the Mann–Whitney U-test as a nonparametric test in numerical data such as age at symptom onset, age at diagnosis, duration of follow-up, ESR, CRP, and physician VAS. Chi-square or Fisher's exact test was used to analyze categorical data such as affected joints, treatments, and disease activity at last follow-up. To identify factors independently associated with sacroiliitis at diagnosis, a multivariable logistic regression analysis was performed including country of origin, sex, age at symptom onset, follow-up duration, parental consanguinity, and HLA-B27 positivity as covariates. A two-sided *P* value of <.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM SPSS Corp.; Armonk, NY, USA).

Ethical Issues

This study was conducted as per the Declaration of Helsinki Principles. Permission to access hospital archives was obtained from all departments in Türkiye and India, and approval was obtained from the local ethics committees of Dokuz Eylül University Non-Interventional Research Ethics Committee and Dr Rajendra Prasad Government Medical College Non-Interventional Research Ethics Committee. (Türkiye ethics committee approval number: 2023/04-31, Dated: 15.02.2023; India ethics committee approval number: HFW-H DRPGMC/Ethics/2023/027, Dated: 06.04.2023). For this retrospective study, the requirement for informed consent was waived by the ethics committee.

Results

Demographic Features

Out of the total 498 patients, 391 were of Turkish (78.5%) and 107 were of Asian-Indian (referred to as Indian) (21.5%) origin. The male gender was predominant in both countries, and age at onset of symptoms and age at diagnosis were comparable (*P* > .05). In the Turkish population, a longer follow-up period was observed, along with a higher prevalence of consanguinity among parents with HLA-B27–related rheumatologic diseases in the family (*P* < .001) (Table 1).

In terms of joint involvement characteristics at the onset of disease, peripheral oligoarticular involvement was most common and comparable in both countries (52.9% in Turks and 51.4% in Indians, *P* = .7). However, peripheral polyarticular involvement was more common in Indians (*P* < .001), and axial involvement was more common in Turks (*P* < .001) (Table 1).

During the entire follow-up period, peripheral joints were most commonly involved in both countries (72.4% in Turks and 84.1% in Indians). This was followed by sacroiliitis (69.6%) and enthesitis (55.5%) in Turks, and enthesitis (37.4%) followed by sacroiliitis (35.5%) in Indians. In both countries, the knee was the most commonly involved peripheral joint.

Peripheral arthritis involvement and dactylitis were more frequent in Indians than in Turks (*P* = .01 for both). Sacroiliitis, enthesitis, and tarsitis were more common in Turks (*P* ≤ .001, .001, .02, respectively [Table 1]).

In Turkish patients (*n* = 212) with peripheral oligoarticular or polyarticular involvement without axial involvement at the time of diagnosis, 43.9% developed sacroiliitis during follow-up (*n* = 93), whereas this rate was 20.7% in Indians (*n* = 18/87) (*P* < .001).

The frequency of acute anterior uveitis on first admission was comparable (*P* = .79). Physician VAS on first admission was higher in Indians (*P* = .01). CRP values were similar (*P* = .14), while ESR levels were higher in Indians (*P* < .001) (Table 1).

Relations Between HLA-B27 Positivity and Joint Involvement

HLA-B27 test was analyzed in 93.3% (*n* = 365/391) of Turkish patients and 91.6% (98/107) of Indian patients (*P* = .5). HLA-B27 positivity was more frequent in Indians (*P* < .001).

In Turkish and Indian patients with axial involvement at the time of diagnosis, HLA-B27 positivity was similar (51.8%, *n* = 85/164; 61.1%, *n* = 11/18, respectively, *P* = .45).

However, in Indian patients with peripheral joint involvement at the time of diagnosis, HLA-B27 positivity was significantly higher compared to Turkish patients (83.8%, *n* = 67/80 vs 60.2%, *n* = 121/201, *P* < .001).

Treatment

In Türkiye, cDMARDs were preferred first (95.9%), followed by NSAIDs, biological agents, and systemic corticosteroids, respectively. In the cDMARD group, methotrexate (MTX) was the most common (68%), followed by sulfasalazine (SSZ) and leflunomide. Among biologic agents, adalimumab (ADA), etanercept (ETN), and infliximab (IFX) were in the first three ranks, respectively.

In India, the most commonly used agent was NSAIDs (99.1%), followed by cDMARDs and tDMARDs, systemic corticosteroids, and biological therapies in the last order. SSZ (50.5%), followed by MTX, tofacitinib, and leflunomide, were the most commonly used cDMARDS and tDMARDs. ADA, followed by IFX and ETN, were the most preferred biological agents.

NSAIDs were used more frequently in India, and DMARDs and biological treatments were used more frequently in Türkiye (*P* < .001, < .001, < .001, respectively).

While MTX was preferred more frequently in Türkiye (68% vs 41.1%, *P* < .001), the two countries were similar in terms of frequency of SSZ use.

Table 1. Demographic and Clinical Features of Patients from Both the Türkiye and India Cohorts

Variables	Türkiye	India	*P* value
Age at symptom onset (year) (mean ± SD)	11.79 ± 2.8	12.3 ± 2.8	.09
Age at diagnosis (mean ± SD)	12.9 ± 3.2	13.2 ± 2.6	.36
Sex, male (*n*) (%)	291/74.4	88/82.2	.09
Duration of follow-up (month) (median, IQR)	37 (23–61)	21 (14–31)	**<.001**
Consanguinity (*n*) (%)	54 (13.8)	1 (0.9)	**<.001**
HLA-B27–related rheumatologic disease in the family (*n*) (%)	83 (21.2)	6 (5.6)	**<.001**
Ankylosing spondylitis	80 (96.4)	6 (100)	**1**
Inflammatory bowel disease	3 (3.6)	0	
Type of disease onset (*n*) (%)			
Peripheral arthritis-oligoarticular	207 (52.9)	55 (51.4)	.77
Peripheral arthritis-polyarticular	22 (5.6)	43 (40.2)	**<.001**
Axial	179 (45.8)	20 (18.7)	**<.001**
Clinical features during the entire follow-up (n) (%)			
Peripheral arthritis	283 (72.4)	**90 (84.1)**	**.01**
Knee	151 (38.6)	**69 (64.5)**	**<.001**
Ankle	138 (35.3)	**49 (45.8)**	**.04**
Midfoot	33 (8.4)	15 (14)	.08
Wrist	17 (4.3)	**15 (14)**	**<.001**
Elbow	14 (3.6)	**10 (9.3)**	**.01**
Fingers	32 (8.2)	13 (12.1)	.2
Toes	24 (6.1)	**18 (16.8)**	**<.001**
Hip	128 (32.7)	**53 (49.5)**	**.001**
Sacroiliitis (confirmed radiologically)	**272 (69.6)**	38 (35.5)	**<.001**
Enthesitis	**217 (55.5)**	40 (37.4)	**.001**
Tarsitis	**44 (11.3)**	4 (3.7)	**.02**
Dactylitis	6 (1.5)	**7 (6.5)**	**.01**
Acute anterior uveitis (n) (%)	23 (5.9)	7 (6.5)	.79
HLA-B27 positivity (n) (%)	206/365 (56.4)	**78/98 (79.5)**	**<.001**
ESR (mm/H) (median, IQR)	19 (9–40)	**38 (20–62)**	**<.001**
CRP (mg/L) (median, IQR)	6 (2–20)	10 (3–24)	.14
Physician VAS on first admission (median, IQR)	5 (4–7)	**7.2 (6–8)**	**.01**
Treatment (n) (%)			
Nonsteroidal anti-inflammatory drugs	335 (85.7)	**106 (99.1)**	**<.001**
Systemic corticosteroids	134 (34.3)	40 (37.4)	.55
Disease-modifying antirheumatic drugs (DMARDs)	**375 (95.9)**	86 (80.4)	**<.001**
Methotrexate	266 (68)	44 (41.1)	**<.001**
Sulfasalazine	226 (57.8)	54 (50.5)	.17
Other DMARDs	16 (4.1)	**10 (9.3)**	**.03**
Leflunomide	**16 (100)**	2 (20)	**<.001**
Tofacitinib	0 (0)	**8 (80)**	
Biologic DMARDs	**207/52.9**	19/17.8	**<.001**
Adalimumab	124 (59.9)	9 (47.4)	.2
Etanercept	**107 (51.7)**	3 (15.8)	**.003**
Infliximab	6 (2.9)	**4 (21.1)**	**.006**
Secukinumab	5 (2.4)	0 (0)	1
Tocilizumab	2 (1)	**5 (26.3)**	**<.001**

Table 1. Demographic and Clinical Features of Patients from Both the Türkiye and India Cohorts (*Continued*)

Variables	Türkiye	India	*P* value
Biologic switching	34 (16.4)	2 (10.5)	.5
Current disease status (n) (%)			
Active	63 (16.1)	27 (25.2)	.08
Inactive off medication	101 (25.8)	27 (25.2)	
Inactive on medication	227 (58.1)	53 (49.6)	
Total (n) (%)	391 (78.5)	107 (21.5)	–

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, human leukocyte antigen B27; IQR, interquartile range; *n*, number; SD, standard deviation.

The most preferred biological agents in both countries were anti-TNFs. Among all biological agents, ETN was more frequently preferred in Türkiye, IFX, and TOC in India (*P* = .003, .006, < .001, respectively) (Table 1).

Current Disease Status

The disease activities of the patients at their last admission were examined. In both countries, patients with inactive disease on medication were first in line. The frequency of patients with active disease in India was slightly higher than in Türkiye (25.2% vs 16.1%), but this difference was not statistically significant (*P* = .08) (Table 1).

Multivariable Logistic Regression Analysis

To address potential confounding factors, a multivariable logistic regression analysis was performed using sacroiliitis at diagnosis as the dependent variable. Country of origin remained independently associated with sacroiliitis at diagnosis (OR 0.25, 95% CI 0.15–0.43, *P* < .001). In contrast, HLA-B27 positivity, sex, age at symptom onset, and parental consanguinity were not independently associated with sacroiliitis. Follow-up duration showed a statistically significant association in the adjusted model (OR 1.01, 95% CI 1.00–1.02, *P* = .018) (Table 2).

Discussion

Enthesitis/spondylitis-related juvenile idiopathic arthritis (E/SpRJIA), which corresponds to juvenile-onset spondyloarthritis and overlaps substantially with ERA and juvenile ankylosing spondylitis, represents a clinically heterogeneous disease entity. The proportion of E/SpRJIA among JIA subtypes has been reported to be higher in Türkiye and India compared with many European populations,[13,14] suggesting potential population-specific disease expression.

In the present multicenter study, clinically relevant differences were observed between Turkish and Indian patients with E/SpRJIA regarding patterns of musculoskeletal involvement and HLA-B27 positivity. Turkish patients more frequently exhibited axial manifestations, including sacroiliitis and enthesitis, whereas Indian patients predominantly showed peripheral polyarticular involvement and dactylitis. These findings support the concept that E/SpRJIA is not a uniform entity and may manifest distinct phenotypic trajectories across populations.

Although axial involvement is a characteristic feature of juvenile spondyloarthritis, its frequency varies across cohorts. Previous studies in Turkish patients have reported relatively high rates of axial disease, including MRI-defined sacroiliitis and spinal involvement.[15,16] In contrast, lower axial involvement has been reported in some Indian pediatric cohorts, although differences in inclusion criteria and study populations likely contribute to this variability.[17,18] Overall, these observations suggest that the burden of axial disease is heterogeneous and may reflect underlying biological differences as well as methodological variability across studies.

Importantly, Turkish patients without axial involvement at diagnosis showed a higher frequency of sacroiliitis during follow-up compared with Indian patients (43.9% vs 20.7%). However, this finding must be interpreted with caution due to a major imbalance in follow-up duration between cohorts. The Turkish cohort had a significantly longer follow-up period, whereas the Indian cohorts were derived from more recently established centers. Given that axial involvement in E/SpRJIA often develops over time, particularly during adolescence and early adulthood, this represents a major source of bias that limits direct comparison of longitudinal outcomes between the two populations.

HLA-B27 positivity was more frequently observed in Indian patients, who predominantly exhibited peripheral disease, whereas Turkish patients showed more frequent axial involvement. Consistent with previous reports, HLA-B27 positivity was higher in Indian patients (80%) compared with Turkish patients (63%).[14,17] These findings indicate that HLA-B27 alone is insufficient to explain the observed phenotypic differences between populations.

Although HLA-B27 plays a central role in disease classification and pathogenesis, E/SpRJIA is increasingly recognized as a multifactorial disease. Genome-wide association studies have identified additional susceptibility loci, including ERAP1, IL23R, TNFRSF1A, and IL1A, which may contribute to disease heterogeneity.[19,20] Furthermore, variation in HLA-B27 subtypes may influence clinical expression; however, subtype-level data were not available in the present study and remain limited in Turkish pediatric cohorts, precluding direct evaluation of this hypothesis. Nevertheless, the observed

Table 2. Multivariable Logistic Regression Analysis for Factors Associated with Sacroiliitis at Diagnosis

Variable	Odds Ratio (OR)	95% Confidence Interval	*P* value
Country of origin (India vs Türkiye)	0.25	0.15–0.43	**<.001**
Male sex	0.67	0.39–1.13	.130
Age at symptom onset	1.05	0.97–1.14	.209
Follow-up duration (months)	1.01	1.002–1.019	.018
Parental consanguinity	1.24	0.60–2.56	.570
HLA-B27 positivity	0.89	0.56–1.40	.604

CI, confidence interval; HLA-B27, human leukocyte antigen B27; OR, odds ratio.

differences persisted even after adjustment for major clinical variables.

Furthermore, in multivariable analysis adjusting for sex, age at symptom onset, follow-up duration, parental consanguinity, and HLA-B27 positivity, country of origin remained independently associated with sacroiliitis at diagnosis, whereas HLA-B27 positivity did not. This finding supports the possibility that factors beyond HLA-B27, including broader genetic and environmental influences, may contribute to population-specific differences in disease expression.

Population-specific genetic factors may also contribute to the observed differences between cohorts. Familial Mediterranean fever (FMF) and MEFV gene variants are highly prevalent in the Turkish population and have been suggested to modulate systemic inflammatory responses in several rheumatic diseases.[21–23] FMF diagnosis and MEFV mutation testing were not routinely available across participating centers. Although FMF diagnosis and MEFV mutation status were not systematically assessed in this retrospective study, their potential contribution represents an important unmeasured confounder, particularly in the Turkish cohort. Therefore, the possible influence of MEFV-related inflammatory background on disease phenotype cannot be excluded and should be investigated in future prospective studies.

In addition, higher rates of parental consanguinity observed in the Turkish cohort may suggest increased familial clustering of genetic susceptibility factors. However, this observation remains hypothesis generating, as no formal genetic linkage or causal analysis was performed.

Differences in treatment strategies were observed between cohorts, with NSAIDs used more frequently in Indian patients, whereas DMARDs and biologic therapies were more commonly used in Turkish patients. These differences are most likely driven primarily by health care system–related factors, including drug accessibility, reimbursement policies, and differences in referral pathways, rather than reflecting intrinsic differences in disease severity alone.[24] Therefore, treatment comparisons between cohorts should be interpreted in the context of systemic health care disparities.

Among the study limitations, the substantial difference in follow-up duration between the two cohorts deserves particular consideration, as it may have influenced the observed rates of sacroiliitis progression and other time-dependent outcomes. The observed differences in disease activity and longitudinal outcomes should therefore be interpreted with caution, as differences in follow-up duration, health care access, and referral patterns between the two countries may have contributed to these findings. These factors could not be fully controlled in the present retrospective multicenter design and represent important sources of potential bias.

Additional limitations include the retrospective nature of the study, heterogeneity in follow-up duration, and lack of systematically collected FMF diagnosis and MEFV mutation data, which may represent an important confounding factor in the Turkish cohort. Furthermore, FMF diagnosis and MEFV mutation testing were not routinely available across participating centers, precluding a formal assessment of their contribution to disease phenotype. Despite these limitations, the multicenter binational design and relatively large sample size are key strengths, allowing a unique comparison of two populations in which E/SpRJIA is relatively prevalent.

In conclusion, this study demonstrates that E/SpRJIA exhibits significant clinical heterogeneity between Turkish and Indian populations. These differences persisted even after adjustment for major clinical covariates, supporting the contribution of population-specific factors to disease expression. However, given the presence of important methodological limitations, particularly differences in follow-up duration and unmeasured genetic modifiers such as FMF-related variants, these findings should be interpreted cautiously. Prospective, standardized, and genetically stratified multicenter studies are needed to further clarify the determinants of phenotypic variability in E/SpRJIA.

Data Availability Statement: *The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.*

Artificial Intelligence Usage Statement: *The authors declared that no Artificial Intelligence Tool was used in the preparation of the manuscript.*

Ethics Committee Approval: *Ethical approval was obtained from the local ethics committees of Dokuz Eylül University Non-Interventional Research Ethics Committee and Dr Rajendra Prasad Government Medical College Non-Interventional Research Ethics Committee. (Türkiye ethics committee approval number: 2023/04-31, Dated: February 15, 2023; India ethics committee approval number: HFW-H DRPGMC/Ethics/2023/027, Dated: April 06, 2023).*

Informed Consent: *N/A.*

Author Contributions: *Concept – R.İ., A.S., B.B.; Design – R.İ., A.S., B.B.; Supervision – T.C., S.G., G.A., P.K.P., S.B., H.C., A.G., J.N., M.Y., E.Ç., B.B.; Resources – R.İ., A.S., Z.K., Y.B., Z.B., Ü.G., C.K., Ş.T., T.C., S.G., G.A., P.K.P., S.B., H.C., A.G., J.N., M.Y., E.Ç., B.S., G.A., S.Ö., E.Ü., B.B.; Materials – R.İ., A.S., Z.K., Y.B., Z.B., Ü.G., C.K., Ş.T., T.C., S.G., G.A., P.K.P., S.B., H.C., A.G., J.N., M.Y., E.Ç., B.S., G.A., S.Ö., E.Ü., B.B.; Data Collection and/or Processing – R.İ., A.S., Z.K., Y.B., Z.B., Ü.G., C.K., Ş.T., T.C., S.G., G.A., P.K.P., S.B., H.C., A.G., J.N., M.Y., E.Ç.; Analysis and/or Interpretation – R.İ., A.S., Z.K., Y.B., Z.B., Ü.G., C.K., Ş.T., T.C., S.G., G.A., P.K.P., S.B., H.C., A.G., J.N., M.Y., E.Ç., B.B.; Literature Search – R.İ., A.S., Z.K., B.B.; Writing Manuscript – R.İ., A.S., B.B.; Critical Review – Z.K., Y.B., Z.B., Ü.G., C.K., Ş.T., T.C., S.G., G.A., P.K.P., S.B., H.C., A.G., J.N., M.Y., E.Ç., B.S., G.A., S.Ö., E.Ü., B.B.*

Declaration of Interests: *The authors declare that they have no competing interests.*

Funding: *The authors declared that this study has received no financial support.*

References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007;369(9563):767-778. [CrossRef].
2. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31:390-392.
3. Tse SML, Petty RE. Enthesitis-related arthritis. In: Petty RE, Laxer RM, Lindsley C, Wedderburn L, eds. *Textbook of Pediatric Rheumatology*. Saunders; 2015; 238-255.
4. Reveille JD. Genetics of spondyloarthritis – beyond the MHC. *Nat Rev Rheumatol*. 2012;8(5):296-304. [CrossRef]
5. Martini A, Ravelli A, Avcin T, et al. Toward New Classification Criteria for juvenile idiopathic arthritis: first steps, Pediatric Rheumatology International Trials Organization International Consensus. *J Rheumatol*. 2019;46(2):190-197. [CrossRef]
6. Zaripova LN, Midgley A, Christmas SE, Beresford MW, Baildam EM, Oldershaw RA. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. *Pediatr Rheumatol Online J*. 2021;19(1):135. [CrossRef].
7. Catarino S, Nunes J, Ganhão S, Aguiar F, Rodrigues M, Brito I. Application of the new PRINTO classification criteria for juvenile idiopathic arthritis in a sample of Portuguese patients. *ARP Rheumatol*. 2024;3(1):11-17. [CrossRef]
8. Ramos-Tiñini P, Menchaca-Aguayo H, Alpizar-Rodriguez D, Mercedes-Pérez E, Faugier-Fuentes E. Application of the new classification proposal for juvenile idiopathic arthritis of the Pediatric Rheumatology International Trials Organization in a group of Mexican patients. *Front Pediatr*. 2024;12: 1476257. [CrossRef]
9. Weiss PF, Brandon TG, Aggarwal A, et al. Do the Provisional Paediatric Rheumatology International Trials Organisation Enthesitis/Spondylitis-Related Juvenile Idiopathic Arthritis Criteria capture youth with axial spondyloarthritis? *Arthritis Care Res (Hoboken)*. 2025;77(6):785-791. [CrossRef]
10. Leung YY, Fong W, Lui NL, Thumboo J. Effect of ethnicity on disease activity and physical function in psoriatic arthritis in a multiethnic Asian population. *Clin Rheumatol*. 2017;36(1): 125-131. [CrossRef]
11. Ghantous N, Heshin-Bekenstein M, Dequattro K, et al. Do geography and ethnicity play a role in juvenile spondyloarthritis? A multi-center binational retrospective study. *Pediatr Rheumatol Online J*. 2021;19(1):4. [CrossRef]
12. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum*. 1984;27(4): 361-368. [CrossRef]
13. Sahin S, Acari C, Sonmez HE, et al. Frequency of juvenile idiopathic arthritis and associated uveitis in pediatric rheumatology clinics in Turkey: a retrospective study, JUPITER. *Pediatr Rheumatol Online J*. 2021;19(1):134. [CrossRef]
14. Demirkaya E, Ozen S, Bilginer Y, et al. The distribution of juvenile idiopathic arthritis in the eastern Mediterranean: results from the registry of the Turkish Paediatric Rheumatology Association. *Clin Exp Rheumatol*. 2011;29(1):111-116.
15. Barut K, Sezen M, Sahin S, et al. Juvenile spondyloarthropathies: a single center experience [abstract]. *Ann Rheum Dis*. 2015;74(suppl 2):390.
16. Demir S, Kasap Cüceoğlu M, Bilginer Y. Enthesitis-related arthritis: a single center experience. *ActaMedica*. 2021;52(4): 303-308.
17. Srivastava R, Agnihotry S, Aggarwal R, Bajpai P, Aggarwal A. HLA-B27 subtypes in enthesitis-related arthritis category of juvenile idiopathic arthritis and ankylosing spondylitis in northern India. *Clin Exp Rheumatol*. 2015;33(6):931-935.
18. Naveen R, Mohindra N, Jain N, Majumder S, Aggarwal A. Hip involvement in children with enthesitis-related arthritis (ERA) is associated with poor outcomes in adulthood. *Clin Rheumatol*. 2021;40(11):4619-4627. [CrossRef].
19. Hinks A, Martin P, Flynn E, et al; Childhood Arthritis Prospective Study-CAPS. Subtype specific genetic associations for juvenile idiopathic arthritis: ERAP1 with the enthesitis related arthritis subtype and IL23R with juvenile psoriatic arthritis. *Arthritis Res Ther*. 2011;13(1):R12. [CrossRef]
20. Díaz-Peña R, Castro-Santos P, Durán J, Santiago C, Lucia A. The genetics of spondyloarthritis. *J Pers Med*. 2020;10(4):151.
21. Yaşar Bilge Ş, Sarı İ, Solmaz D, et al. The distribution of MEFV mutations in Turkish FMF patients: multicenter study representing results of Anatolia. *Turk J Med Sci*. 2019;49(2): 472-477. [CrossRef]
22. Dundar M, Fahrioglu U, Yildiz SH, et al. National Genetics Consortium Study. Clinical and molecular evaluation of MEFV gene variants in the Turkish population: a study by the National Genetics Consortium. *Funct Integr Genomics*. 2022;22(3):291-315. [CrossRef]
23. Cosan F, Ustek D, Oku B, et al. Association of familial Mediterranean fever-related MEFV variations with ankylosing spondylitis. *Arthritis Rheum*. 2010;62(11):3232-3236. [CrossRef]
24. Patra PK, Kumar M. Clinico-epidemiological profile of pediatric rheumatology disorders in Eastern India. *J Nat Sci Biol Med*. 2018;9(1):19-22. [CrossRef]