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EXTRA-ARTICULAR MANIFESTATIONS ASSOCIATED WITH HLA-B27 IN PEDIATRIC PATIENTS, INCLUDING UVEITIS, INFLAMMATORY BOWEL DISEASE AND DERMATOLOGICAL INVOLVEMENT: A SYSTEMATIC REVIEW

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ABSTRACT

Background: HLA-B27 is strongly associated with spondyloarthritis and related conditions. While extra-articular manifestations (EAMs) are well characterized in adults, their prevalence and clinical relevance in pediatric populations remain less clearly defined.
Aim: To systematically review and quantitatively synthesize evidence on the association between HLA-B27 positivity and extra-articular manifestations, including uveitis, inflammatory bowel disease (IBD), and dermatological involvement, in pediatric patients.
Material and methods: A systematic literature search of PubMed, Embase, Scopus, and Google Scholar was performed. Observational studies reporting extra-articular manifestations in HLA-B27–positive pediatric patients were included.
Results: Twenty-five studies met the inclusion criteria and were included in the qualitative synthesis. Uveitis was the most frequently reported manifestation, with consistently higher occurrence in HLA-B27–positive pediatric patients across cohorts. Inflammatory bowel disease and dermatological manifestations were reported less frequently but remained consistent components of the disease spectrum.
Conclusions: HLA-B27 positivity in pediatric patients is associated with a significant burden of extra-articular disease. Early recognition and multidisciplinary management may improve long-term outcomes. Integration of digital health tools and improved healthcare system strategies may play a key role in optimizing early detection and management.

KEYWORDS

HLA-B27, Uveitis, Extra-Articular Manifestations, Psoriasis, Inflammatory Bowel Disease, Pediatric Population

CITATION

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1. Introduction

Human leukocyte antigen B27 (HLA-B27) is a class I major histocompatibility complex (MHC) molecule that plays an important role in immune system regulation. Its presence is strongly associated with a group of chronic inflammatory diseases collectively referred to as spondyloarthritis (SpA), including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease-associated arthritis [1]. In the general population, the prevalence of HLA-B27 varies significantly by ethnicity and geographic region, depending on ethnicity, ranging from approximately 2% to 8% in European populations, while its frequency exceeds 80–90% among patients with ankylosing spondylitis [2].

In pediatric patients, HLA-B27 is most commonly associated with juvenile spondyloarthritis, particularly the enthesitis-related arthritis (ERA) category of juvenile idiopathic arthritis (JIA) [3]. Children with HLA-B27-positive disease often present with peripheral arthritis, enthesitis, and later axial involvement, but their clinical course [2,4].

Compared with adults, pediatric HLA-B27-associated disease is characterized by earlier onset and a predominance of peripheral manifestations, whereas adult-onset spondyloarthritis more frequently presents with axial symptoms, including inflammatory back pain and early sacroiliitis detectable on imaging [2,4]. Importantly, these conditions in children often extend beyond the musculoskeletal system and involve multiple organ systems [4].

Children with HLA-B27-positive disease may experience a higher burden of extra-articular manifestations, particularly uveitis, which may occur earlier in the disease course and sometimes precede musculoskeletal symptoms [3]. Moreover, diagnostic delay is more common in pediatric patients due to less specific early symptoms and limitations of imaging findings in growing skeletons. Differences in immune

system maturation and ongoing skeletal development may further influence disease expression, response to treatment, and long-term outcomes compared with adults.

These age-related differences have important clinical implications, as pediatric patients often require a multidisciplinary approach involving rheumatologists, ophthalmologists, gastroenterologists, and dermatologists, as well as individualized monitoring strategies. Early recognition of extra-articular involvement in children with HLA-B27-associated disease is crucial to reduce long-term complications and improve functional outcomes into adulthood [4].

Extra-articular manifestations (EAMs) are defined as inflammatory conditions affecting organs outside the joints and represent a key component of the disease burden in HLA-B27-associated disorders. The most common EAMs include acute anterior uveitis, inflammatory bowel disease (IBD), and dermatological conditions such as psoriasis.

1.1. Acute anterior uveitis

Acute anterior uveitis is the most frequent extra-articular manifestation associated with HLA-B27-related diseases and represents a major cause of ocular morbidity. In the general population, uveitis has an estimated annual incidence of approximately 17-52 cases per 100,000 persons, as reported in population-based epidemiological studies [5, 6], while pediatric uveitis accounts for 5-10% of all uveitis cases worldwide [7]. Among patients with spondyloarthritis, the prevalence of acute anterior uveitis increases substantially and is reported in 20-30% of HLA-B27-positive adults, compared with less than 5% in HLA-B27-negative individuals [1].

In pediatric populations, uveitis is observed in approximately 10-20% of children with juvenile spondyloarthritis or enthesitis-related arthritis, with a strong association with HLA-B27 positivity [7, 8]. HLA-B27-positive children are reported to have a 2-4-fold higher risk of developing acute anterior uveitis compared with HLA-B27-negative pediatric patients with inflammatory rheumatic diseases [8]. Uveitis in children may be asymptomatic in early stages and is associated with an increased risk of ocular complications, underscoring the importance of early detection and interdisciplinary management [7].

1.2. Inflammatory bowel disease

Inflammatory bowel disease, including Crohn's disease and ulcerative colitis, represents another important extra-articular manifestation associated with spondyloarthritis. In the general population, the prevalence of IBD in Europe and North America is estimated at approximately 0.3-0.5% [9], while pediatric-onset IBD accounts for 20-25% of all IBD cases [10]. Musculoskeletal manifestations, including peripheral arthritis and enthesitis, occur in 10-25% of pediatric patients with IBD, indicating a close interaction between intestinal and joint inflammation [11].

The association between IBD and HLA-B27 is particularly evident in patients with concomitant spondyloarthritis. In adult populations with SpA, IBD is reported in approximately 5-10% of HLA-B27-positive patients, while subclinical intestinal inflammation may be present in up to 50% [2]. In pediatric cohorts, HLA-B27 positivity is observed more frequently in children with IBD-associated arthritis than in those without musculoskeletal involvement, suggesting a shared inflammatory pathway and genetic susceptibility [4].

1.3. Dermatological manifestations

Dermatological involvement, particularly psoriasis and psoriasiform skin lesions, constitutes an important component of extra-articular disease burden in HLA-B27-associated conditions. Psoriasis affects approximately 2-3% of the general population [2], while pediatric psoriasis accounts for up to 30% of all psoriasis cases, with a prevalence of around 0.5-1% in children [3]. In the context of spondyloarthritis, psoriatic and psoriasiform skin lesions represent a clinically relevant extra-articular manifestation [12]. Skin manifestations may precede, coincide with, or follow the onset of musculoskeletal symptoms, complicating early diagnosis.

In patients with spondyloarthritis, psoriasis is reported in 10-20% of adults, with a higher prevalence observed in HLA-B27-positive individuals compared with the general population [2]. In pediatric cohorts, dermatological manifestations are reported in approximately 5-15% of children with juvenile spondyloarthritis or juvenile psoriatic arthritis, and HLA-B27 positivity has been associated with a more extensive or multisystem disease phenotype in selected pediatric cohorts [3]. The presence of skin involvement has important clinical implications, as it may influence disease classification, therapeutic decisions, and long-term outcomes.

Despite increasing recognition of extra-articular manifestations in pediatric HLA-B27-associated diseases, the available evidence remains fragmented, and reported frequencies vary widely across studies. Differences in study design, disease definitions, and patient populations contribute to this heterogeneity, as highlighted in recent narrative and systematic reviews of juvenile spondyloarthritis and related inflammatory conditions [2, 4]. A comprehensive synthesis of the existing literature is therefore needed to better characterize the spectrum and frequency of extra-articular manifestations in HLA-B27-positive pediatric patients and to support improved interdisciplinary care strategies.

1.4. Burden of pediatric chronic inflammatory diseases and implications for healthcare systems

Chronic inflammatory diseases in pediatric populations represent a substantial and growing burden for healthcare systems worldwide. Beyond direct clinical manifestations, these conditions are associated with long-term healthcare utilization, increased costs of multidisciplinary care, and significant impact on health-related quality of life [13]. Children with chronic rheumatic diseases often require ongoing monitoring by multiple specialists, including rheumatologists, ophthalmologists, and gastroenterologists, which places additional strain on healthcare infrastructure and coordination systems [14]. Moreover, delayed diagnosis and subclinical disease courses, particularly in conditions such as uveitis, may lead to preventable complications and increased long-term disability [15]. From a societal perspective, pediatric chronic diseases are associated with school absenteeism, reduced psychosocial functioning, and increased caregiver burden [13]. These challenges highlight the importance of early detection strategies, integrated care pathways, and the potential role of digital health solutions in improving disease monitoring and access to care [14]. In this context, the integration of digital health technologies, including telemedicine and data-driven diagnostic tools, has emerged as a promising approach to enhance healthcare delivery, improve access to specialist services, and support more efficient disease monitoring [16], [17].

1.5. Aim

The aim of this study is to systematically review and synthesize the available evidence on the association between positive HLA-B27 expression and the occurrence of extra-articular manifestations in the pediatric population, and to explore implications for healthcare systems and digital health strategiesand to explore implications for healthcare systems and digital health strategies. In particular, this review focuses on inflammatory conditions such as uveitis, inflammatory bowel disease, and dermatological manifestations, including psoriasis, in children and adolescents with HLA-B27–associated inflammatory diseases.

The analysis evaluates the prevalence, clinical characteristics, and patterns of extra-articular involvement in relation to HLA-B27 statusas reported across different pediatric rheumatologic, ophthalmologic, dermatologic, and inflammatory disease entities. The collected data were carefully analyzed to identify consistent findings, sources of heterogeneity, methodological limitations, and gaps in the existing literature, with the aim of improving clinical understanding and supporting future research in this field.

2. Research materials and methods

2.1. Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and was guided by a PICO-based research framework (Population, Intervention/Exposure, Comparison, Outcomes).

A comprehensive literature search was performed in PubMed and Scopus databases to identify relevant studies. To ensure the inclusion of recent and clinically relevant evidence, a publication year filter was applied in both databases, limiting the search to articles published between 2015 and the december 2025. This time frame was selected to reflect current diagnostic criteria, disease classification, and management strategies in pediatric inflammatory diseases.

The search strategy was based on a combination of controlled vocabulary terms and free-text keywords, including HLA-B27, human leukocyte antigen B27, uveitis, extra-articular manifestations, psoriasis, inflammatory bowel disease, children, young adult, and pediatric population. These terms were combined using Boolean operators to maximize search sensitivity while maintaining relevance to the study objectives.

In the Scopus database, an additional filter for article type was applied to retain research articles only, as this publication type represents the primary source of evidence for systematic reviews. In the PubMed database, a text availability filter was applied, restricting the search results to free full-text articles, to allow full methodological assessment and accurate data extraction.

2.1.1. Eligibility criteria

Eligibility criteria were defined a priori in accordance with the PICO framework. Studies were considered eligible if they included pediatric patients (≤18 years of age) or mixed-age populations with clearly extractable pediatric data. The target conditions comprised juvenile idiopathic arthritis (JIA), enthesitis-related arthritis (ERA), juvenile spondyloarthritis (jSpA), or other HLA-B27–associated inflammatory diseases.

Eligible studies were required to report extra-articular manifestations (EIMs), including uveitis, inflammatory bowel disease (IBD), and/or dermatological manifestations such as psoriasis, either as primary outcomes or as clearly defined secondary outcomes. We included observational studies, clinical and cohort studies, registry-based analyses, and systematic reviews of high conceptual relevance, provided that clinical outcomes were stratified by HLA-B27 status or allowed assessment of the association between HLA-B27 and extra-articular involvement in pediatric patients.

2.1.2. Exclusion criteria

Studies were excluded if they involved exclusively adult populations, or if they were basic science, molecular, genetic, or animal studies without direct clinical relevance. Additional exclusion criteria included case reports, editorials, conference abstracts without full-text availability, and publications lacking sufficient clinical data relevant to the objectives of this review.

Articles that did not demonstrate a clear association with HLA-B27, spondyloarthritis spectrum diseases, or extra-articular manifestations, as well as studies focusing on non-inflammatory or unrelated conditions, were also excluded.

2.3. Data collection and analysis

2.3.1. Study selection (PRISMA-compliant)

The study selection process followed the PRISMA 2020 guidelines and is summarized in the PRISMA flow diagram (Figure 1). A total of 4,661 records were identified through database searching, including 499 records from PubMed and 4,162 records from Scopus. Before screening, several filters were applied to improve the relevance and methodological quality of the retrieved records. A publication year filter (2015–2026) was applied in both databases to ensure inclusion of the most recent and clinically relevant evidence, reflecting current diagnostic criteria, disease classification, and management strategies.

In the Scopus database, article type filters were applied to retain only research articles, as this publication type constitutes the primary evidence base for systematic reviews. In PubMed, a text availability filter was applied, restricting results to free full-text articles, to ensure full methodological assessment and accurate data extraction.

After applying these filters, 401 records remained and were screened by title and abstract. Duplicate records (n = 16) were removed. Based on title screening, 232 records were excluded, followed by exclusion of an additional 96 records after abstract screening. As a result, 57 reports were assessed for eligibility through full-text evaluation. Of these, 30 reports did not meet the eligibility criteria and were excluded due to insufficient quantitative data, narrative or descriptive study design, mixed populations without extractable pediatric data, or lack of primary analysis of extra-articular manifestations. Two reports were excluded at the full-text assessment stage due to unavailability of the full-text articles. Ultimately, 25 studies met all inclusion criteria and were included in the systematic review.

2.3.2. Data extraction

Data extraction was performed independently by two reviewers using a standardized and piloted data collection form developed specifically for this systematic review. The extraction template was tested on a random sample of eligible studies to ensure clarity, consistency, and completeness.

For each included study, the following data were collected: first author, year of publication, country and study setting, study design, sample size, and basic demographic characteristics. Information on the proportion of HLA-B27–positive patients was systematically recorded.

Clinical data focused on extra-articular manifestations and included the presence, type, and reported frequency of uveitis, inflammatory bowel disease, and dermatological involvement. When available, additional information on disease duration, clinical severity, complications, and treatment strategies was extracted to support qualitative comparison between studies.

Disagreements between reviewers during the data extraction process were resolved through discussion. If consensus could not be reached, an independent third reviewer was consulted. All extracted data were cross-checked to minimize transcription errors and ensure accuracy. When multiple publications reported overlapping study populations, the most complete and recent report was included. Due to the heterogeneity of

study designs and outcomes, a formal risk of bias assessment was not performed, which represents a limitation of this review.

Publications that did not meet the inclusion criteria but provided relevant theoretical or clinical background were used to support contextual interpretation.

All retrieved references were managed using Mendeley reference management software to facilitate duplicate removal, literature screening, and systematic data organization. This systematic review was not registered in the PROSPERO database.

2.3.3. AI Statement

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

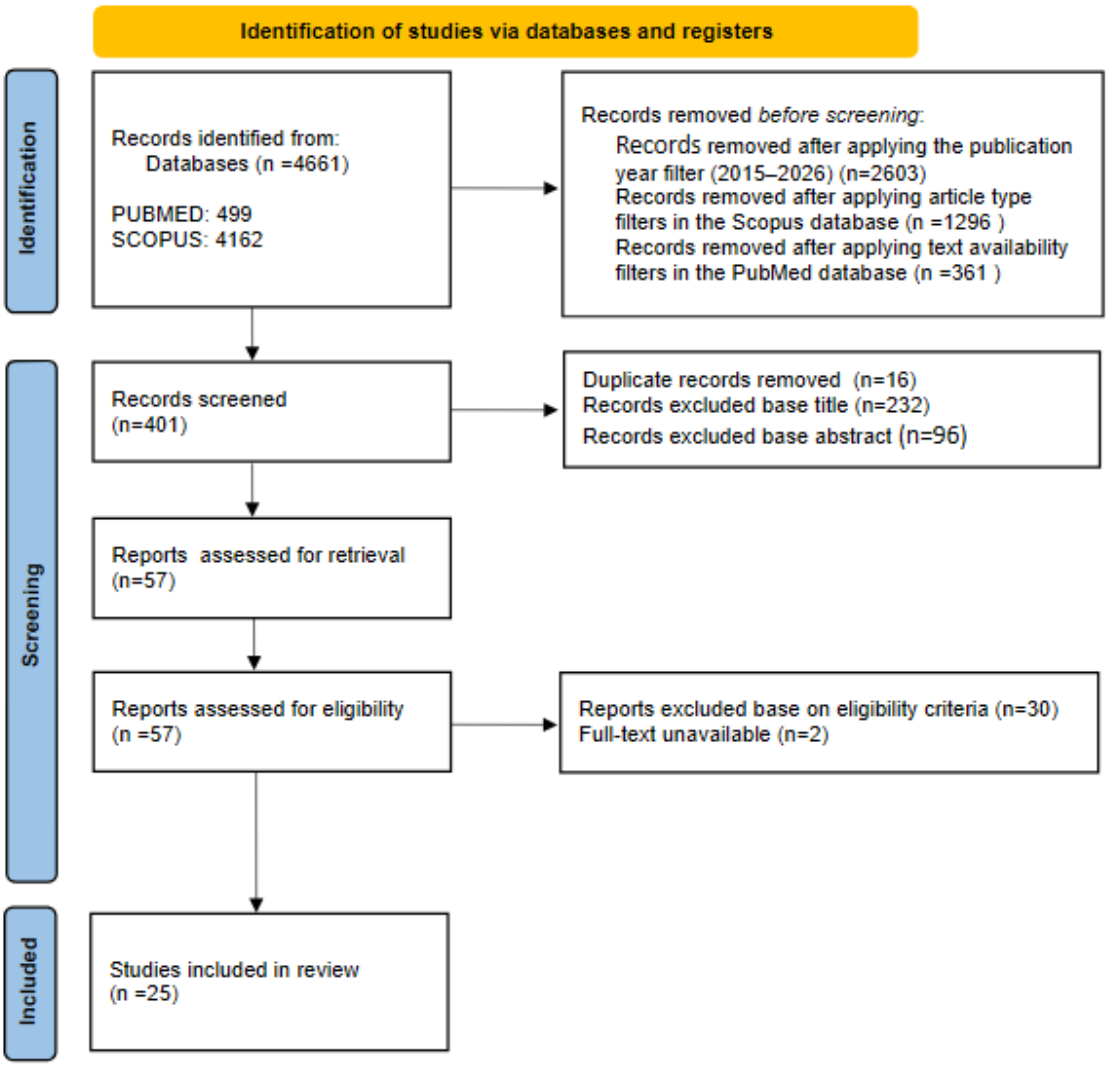

Fig. 1. *PRISMA flowchart.*

3. Results

3.1. Study characteristics

A total of 25 studies met the inclusion criteria and were included in the qualitative synthesis. The analyzed studies comprised predominantly retrospective and prospective cohort designs, as well as registry-based analyses and multicenter observational cohorts. The studies were conducted across diverse geographic regions, including Europe, Asia, and the Middle East, reflecting variability in genetic background and disease expression.

The study populations mainly included children diagnosed with juvenile idiopathic arthritis (JIA), particularly enthesitis-related arthritis (ERA), juvenile spondyloarthritis (jSpA), or mixed pediatric rheumatologic cohorts. In Asian populations, enthesitis-related arthritis represents the most common subtype of juvenile idiopathic arthritis, in contrast to Western cohorts where oligoarticular JIA predominates [13]. Several studies specifically focused on ERA populations characterized by a high prevalence of HLA-B27 positivity and male predominance [18-20]. Enthesitis represents a key clinical feature of ERA, affecting a substantial proportion of patients and contributing to overall disease burden [21].

Across studies, cohort sizes ranged from small single-center analyses to large multicenter datasets, such as cohorts including over 300 patients with JIA-associated uveitis [22] and nearly 1000 pediatric uveitis cases [23].

Juvenile idiopathic arthritis was consistently identified as one of the most common causes of chronic inflammatory joint disease in childhood, representing a major clinical context for the development of extra-articular manifestations [24].

Overall, the included studies demonstrated substantial heterogeneity in study design, patient selection, and outcome definitions.

3.2. Uveitis in HLA-B27–positive pediatric patients

Uveitis was consistently reported as the most frequent extra-articular manifestation across the analyzed studies [25]. Additional studies confirmed that uveitis represents a frequent extra-articular manifestation in juvenile arthritis, although reported prevalence varied across cohorts and disease subtypes [26]. Multiple cohorts confirmed that uveitis commonly occurs in children with JIA and ERA and represents a major source of morbidity, with reported frequencies ranging from approximately 4% to 6.8% in ERA and mixed JIA cohorts and reaching up to 41% in selected pediatric populations [27-29].

Uveitis may develop after the onset of arthritis, with a mean interval of approximately 1.8 years between joint disease and ocular involvement reported in pediatric cohorts ([28]. Uveitis-related complications were observed in a substantial proportion of patients, including cases requiring surgical intervention (14.7%) [28] and ocular hypotony affecting 15.6% of patients [22]. In contrast, ERA classification criteria also recognize acute anterior uveitis as a possible early or defining feature of disease [30].

The clinical phenotype of pediatric uveitis varied between studies, but anterior uveitis was the most common anatomical subtype [7]. A significant proportion of pediatric uveitis cases were associated with systemic inflammatory diseases, particularly JIA, with higher rates of HLA-B27 positivity observed in these patients [7].

Complications of uveitis were reported in a substantial proportion of patients, including ocular hypotony observed in 15.6% of cases and intraocular pressure elevation affecting 33.4% of eyes within 2 years, cataract, glaucoma, macular edema, and structural ocular damage [22],[23]. In one large cohort, ocular hypotony developed in a notable subset of patients and was associated with prolonged disease duration and increased inflammatory activity [22]. Similarly, elevated intraocular pressure and its complications were reported in pediatric uveitis cohorts, particularly in patients receiving corticosteroid therapy [23].

Long-term follow-up studies further demonstrated that uveitis in pediatric patients may be associated with persistent disease activity and unfavorable outcomes over time, including chronic or recurrent inflammation [31]. Specific ocular complications, such as cataract formation, have also been identified as markers of severe or treatment-resistant disease [32]. Genetic factors may also contribute to susceptibility to uveitis, with certain immune-related loci associated with an increased risk of ocular involvement in juvenile idiopathic arthritis [33]. Elevated inflammatory markers at disease onset, including erythrocyte sedimentation rate, have been associated with an increased risk of developing uveitis in children with juvenile idiopathic arthritis [29].

Standardized classification criteria have been proposed to better define juvenile idiopathic arthritis-associated uveitis, reflecting the need for consistent diagnostic approaches across studies [34].

Additional studies highlighted the clinical burden of pediatric uveitis, including its potential to cause long-term visual impairment and the need for systemic immunosuppressive therapy [35].

3.3. Inflammatory bowel disease

Evidence regarding inflammatory bowel disease (IBD) in HLA-B27–positive pediatric populations was more limited compared with uveitis. However, available evidence suggests a potential link between ERA, spondyloarthritis, and intestinal inflammation, supported primarily by clinical classification frameworks and immunological studies rather than direct epidemiological data [21]. There are also reports indicating that the relationship may operate in the opposite direction, with inflammatory bowel disease giving rise to extra-intestinal manifestations such as arthritis and uveitis; moreover, certain HLA phenotypes have been associated with distinct patterns of extra-intestinal involvement, suggesting a shared immunogenetic background rather than a unidirectional pathway [10].

IBD-related immune mechanisms were supported by findings demonstrating altered immune responses to intestinal antigens in children with ERA, including increased IgA reactivity to microbial components such as Prevotella oralis, a constituent of the intestinal microbiota. [36]. These findings suggest a potential link between gut microbiota and systemic inflammation in HLA-B27–associated disease. Alterations in gut microbiome composition, including reduced microbial diversity and decreased abundance of anti-inflammatory bacterial species, have also been described in children with enthesitis-related arthritis [21].

Inflammatory bowel disease is included within the clinical spectrum of juvenile spondyloarthropathies, where gastrointestinal involvement represents a recognized extra-articular component of disease; moreover, pediatric IBD literature supports the presence of extra-intestinal manifestations, including uveitis and musculoskeletal involvement [21], [10].

3.4. Dermatological manifestations

Dermatological involvement, including psoriasis and psoriasiform lesions, was less frequently reported than uveitis and was rarely quantified [21]. It remained a recognized component of the disease spectrum. Moreover, skin manifestations were consistently described as part of the juvenile spondyloarthritis clinical phenotype.

Psoriasis and skin-related features were identified as part of the clinical phenotype of juvenile spondyloarthropathies and psoriatic arthritis in children [21]. In addition, ERA and related conditions may present with dermatologic features such as nail changes, dactylitis, and psoriatic skin lesions, although their prevalence varied across cohorts. These manifestations may occur in association with musculoskeletal symptoms and contribute to the heterogeneity of clinical presentation in pediatric patients.

Immunogenetic factors may partially explain variability in clinical expression, as HLA-B27 and related molecules, including HLA-G and HLA-E, have been shown to influence disease susceptibility and phenotype in enthesitis-related arthritis [37].

Ethnic and population-based differences in disease expression may further contribute to variability in dermatological manifestations, as distinct clinical phenotypes have been reported in different geographic and genetic populations [38].

In broader inflammatory disease contexts, dermatological manifestations were also described as extra-intestinal features of inflammatory bowel disease, including erythema nodosum and pyoderma gangrenosum [10], further supporting the systemic nature of inflammation in HLA-B27-associated conditions.

Additionally, the co-occurrence of dermatological and musculoskeletal manifestations was reflected in classification frameworks of juvenile spondyloarthropathies, where psoriasis and related features may influence disease categorization and clinical phenotype [21]. Despite this, most studies did not provide detailed quantitative data on dermatological involvement, and reporting remained inconsistent across cohorts, limiting direct comparison between studies.

3.5. Heterogeneity of findings

Considerable heterogeneity was observed across studies, including variation in HLA-B27 positivity ranging from 59% in multicenter cohorts [15] to as high as 97% in single-center ERA populations [18].

Immunogenetic studies further highlighted the role of HLA-B27 and related molecules, including HLA-G and HLA-E, in influencing susceptibility and clinical phenotype in enthesitis-related arthritis [37].

Clinical presentation varied between cohorts, including differences in uveitis frequency ranging from approximately 4% in ERA cohorts [27] to 6.8% in mixed JIA populations [28], while higher proportions were reported in longitudinal studies evaluating uveitis development over time [29].

Differences were also noted in geographic distribution and ethnicity, influencing disease phenotype and HLA-B27 prevalence [18-20]. Differences in HLA-B27 subtypes have also been reported between populations, with certain allelic variants more prevalent in Asian compared with European cohorts [18]. Additional variability related to study design, including retrospective versus prospective cohorts, as well as differences in outcome definitions, follow-up duration, and diagnostic criteria, limited direct comparability between studies [20], [28], [34], [25].

For example, the prevalence of ERA and associated clinical features varied between Asian and European cohorts, with studies from Southeast Asia reporting a high prevalence of HLA-B27 and distinct patterns of disease expression, including different risk factors for sacroiliitis and lower rates of drug-free remission [19].

Additional evidence from ethnically distinct populations demonstrated marked variation in HLA-B27 frequency and disease phenotype, further supporting the role of genetic background in shaping disease expression [38].

Similarly, the reported frequency and clinical characteristics of uveitis differed depending on study population and methodology [28], [7].

3.6. Summary of results

Overall, the analyzed studies consistently demonstrated that uveitis was the most frequently reported extra-articular manifestation in HLA-B27–positive pediatric patients. Reported frequencies ranged from approximately 4% to 6.8% across cohorts [27], [28]. Higher proportions exceeding 40% were observed in longitudinal studies assessing uveitis development over time [29]. Inflammatory bowel disease and dermatological involvement were less frequently reported but remained recognized components of the broader spondyloarthritis spectrum. Available evidence suggests a potential link between intestinal inflammation and HLA-B27–associated disease, supported by immunological findings demonstrating altered responses to microbial antigens, including increased IgA reactivity to *Prevotella oralis*, a constituent of the intestinal microbiota [36]. In addition, inflammatory bowel disease has been described as part of the clinical spectrum of juvenile spondyloarthropathies, where gastrointestinal involvement represents a recognized extra-articular component [21]. Furthermore, pediatric IBD studies indicate that extra-intestinal manifestations, including musculoskeletal and ocular involvement, are relatively common and may be associated with specific HLA phenotypes, suggesting a shared immunogenetic background [10]. Dermatological manifestations, particularly psoriasis and psoriasiform lesions, were also described as part of the juvenile spondyloarthritis phenotype, although their frequency was inconsistently reported and rarely quantified across studies[21]. Substantial heterogeneity across studies highlights the complexity of disease expression in pediatric populations. This variability was reflected in differences in HLA-B27 positivity, clinical presentation, and the reported frequency of extra-articular manifestations across cohorts [20], [18], [28]. Geographic variation further contributed to differences in disease phenotype, including higher HLA-B27 prevalence and distinct clinical patterns reported in Southeast Asian cohorts [19]. In addition, heterogeneity in study design, follow-up duration, and definitions of extra-articular manifestations limited direct comparison between studies. These findings underscore the need for standardized definitions and well-designed longitudinal studies to improve the understanding of extra-articular disease in pediatric HLA-B27–associated conditions.

4. Discussion

This systematic review demonstrates that HLA-B27 positivity in pediatric patients is associated with a spectrum of extra-articular manifestations, representing a substantial clinical burden. Among these, uveitis emerged as the most frequently reported and clinically significant manifestation across the analyzed studies. Inflammatory bowel disease and dermatological involvement were less commonly reported but remained consistent components of the disease phenotype. These findings indicate that extra-articular involvement reflects a systemic inflammatory process affecting multiple organ systems in children with HLA-B27–associated diseases. [25], [28], [29].

The strong association between HLA-B27 and uveitis, well established in adult spondyloarthritis, appears to be equally relevant in pediatric populations. In children, uveitis frequently develops after the onset of arthritis, although it may also represent an early disease feature, as reflected in classification frameworks for enthesitis-related arthritis [30]. The clinical course is often characterized by recurrent or persistent inflammation, as demonstrated in longitudinal studies [31]. Importantly, several studies reported a substantial burden of ocular complications, including ocular hypotony, cataract, glaucoma, and intraocular pressure elevation [22], [23], [32]. These findings highlight the clinical importance of early detection and regular ophthalmologic monitoring. In addition, predictive factors such as elevated erythrocyte sedimentation rate and specific genetic variants have been associated with increased risk of uveitis, suggesting that risk stratification may be feasible in clinical practice [29], [33].

The predominance of uveitis across studies was consistent; however, variability in reported frequency and timing of onset likely reflects differences in study design, patient selection, and duration of follow-up [29], [28].

Beyond ocular involvement, the available evidence supports a relationship between HLA-B27–associated disease and intestinal inflammation. Although direct epidemiological data in pediatric populations remain limited, immunological studies indicate altered responses to intestinal antigens in children with enthesitis-related arthritis, including increased IgA reactivity to Prevotella oralis. These observations are consistent with the concept of a gut–joint axis, in which immune responses to intestinal antigens may contribute to systemic inflammation in genetically predisposed individuals [36]. In addition, inflammatory bowel disease is recognized within the clinical spectrum of juvenile spondyloarthropathies, where gastrointestinal involvement represents an extra-articular component of disease [21]. Evidence from pediatric IBD literature further demonstrates that extra-intestinal manifestations, including musculoskeletal and ocular involvement, are common and may be associated with specific HLA phenotypes [10]. Together, these findings indicate an association between intestinal and systemic inflammatory processes.

Dermatological manifestations, particularly psoriasis and psoriasiform lesions, were less frequently reported and rarely quantified across studies. Nevertheless, they were consistently described as part of the clinical phenotype of juvenile spondyloarthritis and related conditions [21]. The co-occurrence of dermatological and musculoskeletal features reflects the overlapping clinical spectrum of inflammatory diseases in childhood. Immunogenetic studies indicate that HLA-B27 and related molecules, including HLA-G and HLA-E, may influence not only articular but also extra-articular disease expression [37]. Furthermore, dermatological manifestations observed in pediatric inflammatory bowel disease, such as erythema nodosum and pyoderma gangrenosum, support the concept of shared inflammatory pathways across organ systems [10]. Despite these observations, the lack of consistent quantitative reporting limits precise estimation of their prevalence.

An important finding of this review is the substantial heterogeneity across studies. Variability was observed in HLA-B27 positivity, clinical presentation, and the frequency of extra-articular manifestations, with differences reported between multicenter cohorts and single-center populations [20], [18]. Geographic and ethnic factors also appear to influence disease expression, as demonstrated in studies from Southeast Asia and ethnically distinct populations with high HLA-B27 prevalence [19], [38]. In addition, differences in study design, diagnostic criteria, and outcome definitions limited direct comparability between studies [34]. These factors should be considered when interpreting the available evidence.

From a clinical perspective, the findings of this review support the need for a multidisciplinary approach to the management of HLA-B27–positive pediatric patients [2]. Given the high frequency and potential severity of uveitis, regular ophthalmologic screening is essential [8]. Similarly, awareness of gastrointestinal manifestations may facilitate earlier recognition of systemic disease involvement and guide appropriate referral and management strategies [11]. Early identification of patients at higher risk of extra-articular disease may influence therapeutic decisions, including the use of targeted immunomodulatory therapies [4].

The findings of this review have important implications for healthcare systems, particularly in the context of increasing burden of chronic inflammatory diseases in pediatric populations. Early diagnosis and continuous monitoring of extra-articular manifestations, especially uveitis, require timely access to specialized care, which remains uneven across regions and healthcare settings, as demonstrated in studies on access to pediatric rheumatology care [39].

Telemedicine has emerged as an effective tool to improve access to pediatric rheumatology and ophthalmology services, enabling remote consultations, early screening, and longitudinal disease monitoring [16]. Digital health solutions may help reduce diagnostic delays, which are commonly observed in pediatric spondyloarthritis due to non-specific early symptoms and limited access to advanced imaging and specialist evaluation.

In addition, artificial intelligence (AI)–based tools are increasingly being explored in ophthalmology, particularly in image-based screening and automated detection of ocular pathologies. Deep learning algorithms have demonstrated high diagnostic accuracy in retinal diseases and show potential for supporting clinical decision-making and risk stratification [40], [41], [42]. Although current applications primarily focus on retinal imaging, these technologies may in the future contribute to improved screening and earlier referral in inflammatory eye diseases, including uveitis.

From a systems perspective, the integration of digital health strategies may contribute to improved efficiency of healthcare delivery, reduced burden on specialized centers, and more equitable access to care. This is particularly relevant in pediatric populations, where early intervention is critical to prevent long-term complications and disability.

4.1. Limitations of the evidence

The included studies were heterogeneous in design, with many based on retrospective cohorts and variable sample sizes. Differences in diagnostic criteria, follow-up duration, and outcome definitions limited direct comparability. In addition, extra-articular manifestations such as inflammatory bowel disease and dermatological involvement were less consistently reported, which may have led to underestimation.

4.2. Limitations of this systematic review

This review has several methodological limitations. The literature search was restricted to selected databases and a defined publication period, which may have resulted in the omission of relevant studies. Only articles with available full-text data were included. Furthermore, not all studies stratified findings according to HLA-B27 status, which may limit interpretation of its independent contribution.

4.3. Future directions

Future research should focus on prospective longitudinal studies to better define the temporal relationship between arthritis and extra-articular manifestations. Standardization of outcome definitions and consistent stratification by HLA-B27 status are needed [34], [25]. Further investigation of underlying immunological mechanisms, including interactions between intestinal and systemic inflammation, may contribute to improved understanding of disease pathogenesis and the development of targeted therapies [36], [21], [8].

4.4. Implications for healthcare systems and digital health strategies

The findings of this review have important implications for healthcare systems, particularly in the context of early diagnosis, access to specialist care, and long-term disease monitoring in pediatric patients. Uveitis, as the most frequent extra-articular manifestation associated with HLA-B27, often presents with an asymptomatic or oligosymptomatic course in children, which contributes to diagnostic delays and increases the risk of irreversible ocular damage. Delayed recognition remains a significant clinical challenge and has been associated with worse visual outcomes and higher rates of complications [15], [43].

Access to specialized pediatric rheumatology and ophthalmology services remains uneven across regions, which may contribute to disparities in diagnosis and management. Limited availability of pediatric subspecialists and differences in healthcare infrastructure have been associated with delays in referral and initiation of appropriate treatment in children with rheumatic diseases [39], [14]. In addition, variability in healthcare organization and access to multidisciplinary care may result in fragmented care pathways and suboptimal disease monitoring. These challenges underscore the need for improved models of coordinated,

multidisciplinary care, as well as standardized screening protocols for high-risk pediatric populations, particularly those at risk of developing extra-articular manifestations such as uveitis [14], [15].

Digital health technologies may offer promising solutions to address these challenges. Telemedicine has emerged as an effective tool for improving access to specialist care, particularly in geographically underserved areas, by enabling remote consultations, follow-up assessments, and timely identification of disease-related complications. Studies in pediatric rheumatology have demonstrated that telehealth interventions are feasible and associated with high levels of patient and caregiver satisfaction, while also supporting continuity of care and reducing the burden on healthcare systems [44], [16].

Furthermore, advances in artificial intelligence (AI) and machine learning have shown significant potential in ophthalmology, particularly in image-based screening and early detection of ocular diseases. AI-assisted analysis of ophthalmic imaging, especially retinal imaging, may support earlier identification of pathological changes and facilitate timely referral to specialists. Although these technologies are still under development in pediatric populations, their integration into clinical practice may improve screening efficiency and potentially reduce diagnostic delays [45], [46].

From a systems perspective, the burden of chronic pediatric inflammatory diseases extends beyond direct clinical care and includes long-term healthcare utilization, costs of immunosuppressive therapies, and management of complications. Implementation of structured screening programs, digital monitoring tools, and coordinated care models may help reduce this burden and improve clinical outcomes. Future healthcare strategies should therefore integrate technological innovations with multidisciplinary care approaches to optimize management of HLA-B27-associated diseases in children.

5. Conclusions

HLA-B27 positivity in pediatric patients is associated with a significant burden of extra-articular manifestations, particularly uveitis, as well as less frequently reported but clinically relevant intestinal and dermatological involvement. The available evidence indicates that these manifestations may occur early in the disease course and contribute to long-term morbidity. Substantial heterogeneity across studies highlights the need for standardized definitions and well-designed longitudinal research. Improved recognition of extra-articular disease and a multidisciplinary approach to care may contribute to better clinical outcomes in this population.

In addition to clinical implications, the findings of this review highlight the need for system-level interventions aimed at improving early detection and long-term management of extra-articular manifestations in pediatric patients. From a public health perspective, policy makers and healthcare planners should prioritize the development of standardized screening strategies for high-risk populations, particularly for uveitis, which may remain asymptomatic in early stages. Integration of digital health tools, including telemedicine platforms and AI-assisted diagnostic systems, may facilitate earlier identification of disease and improve access to specialist care. Such approaches have the potential to reduce diagnostic delays, optimize resource utilization, and ultimately improve long-term outcomes and quality of life in children with HLA-B27-associated diseases [15], [45], [44].

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