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EDITORIAL

Non-Radiographic Axial Spondyloarthritis

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1 | The Concept of Nr-axSpA

Non-radiographic axial spondyloarthritis (nr-axSpA) is a distinct clinical entity characterized by the absence of sacroiliitis on plain radiographs, despite evidence of active sacroiliac inflammation on magnetic resonance imaging (MRI). Khan and colleagues first described this condition in 1985, referring to it as "spondylitic disease without radiologic evidence of sacroiliitis" [1]. Although the concept of nr-axSpA had been recognized prior to this description, the 2009 Assessment of Spondyloarthritis International Society (ASAS) classification criteria brought the entity to the forefront of clinical practice and research. According to these criteria, individuals younger than 45 years with chronic low back pain lasting more than 3 months may be classified as having axial spondyloarthritis if they fulfill either the clinical arm, requiring at least two spondyloarthritis (SpA) features, or the imaging arm, requiring at least one SpA feature in conjunction with imaging evidence of sacroiliitis [2]. The prevalence of nr-axSpA in the United States is estimated to be approximately 0.35%, compared with a combined axial SpA prevalence of 0.9%–1.4% [3, 4]. In contrast, a survey-based study from Japan estimated the prevalence of radiographic axSpA (r-axSpA) to be 0.0026%, with an even lower prevalence of nr-axSpA at 0.0006% [5].

Historically, axial SpA has been regarded as a predominantly male disease; however, more recent data suggest that the male-to-female ratio has narrowed, with several studies reporting near equivalence, particularly within nr-axSpA cohorts [6]. Sex-based differences in clinical presentation have also been observed, with women more likely to report widespread pain, including cervical and upper thoracic symptoms that may not meet traditional definitions of inflammatory back pain [7]. Women additionally tend to exhibit less radiographic damage, a factor that may contribute to the longer diagnostic delays consistently reported among female patients compared with males [7].

Findings from large observational cohorts have further clarified the clinical characteristics of nr-axSpA. In the German Spondyloarthritis Inception Cohort (GESPIC), patients with early nr-axSpA demonstrated active inflammatory disease, with radiographic progression associated with HLA-B27 positivity, elevated C-reactive protein (CRP), and the presence of baseline MRI osteitis [8]. The French Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort showed that most patients with early inflammatory back pain remain non-radiographic over long-term follow-up, with women exhibiting greater pain burden and lower inflammatory markers than men [9]. Data from the Corrona registry in the United States similarly demonstrated sex- and inflammation-related differences, identifying a higher proportion of women, lower CRP levels, and longer diagnostic delays among patients with nr-axSpA despite comparable disease activity to r-axSpA [10]. The Korean Nonradiographic Axial Spondyloarthritis (KONASPA) registry extended these observations to an Asian population, demonstrating comparable functional limitations in nr-axSpA despite lower objective measures of inflammation [11].

2 | Clinical Features

The clinical features of nr-axSpA have been less extensively characterized in isolation than those of r-axSpA; nevertheless, both conditions are regarded as part of a continuous disease spectrum and share substantial clinical overlap. The prevalence of inflammatory back pain (IBP) is similar between the two groups, reported in approximately 75%–82% of patients across cohorts, with no consistent differences in individual IBP features [12]. Several studies have reported a higher prevalence of peripheral inflammatory arthritis in nr-axSpA compared with r-axSpA (35.7% vs. 17.0%, $p = 0.001$) [13], whereas pooled analyses demonstrate comparable overall prevalence between groups (27.9% vs. 29.7%) [14].

Extra-articular manifestations also show substantial overlap between disease subsets. A meta-analysis of patients with axial SpA reported that acute anterior uveitis occurs more frequently in r-axSpA than in nr-axSpA, with pooled prevalences of approximately 23.0% and 15.9%, respectively [14]. In contrast, most available data do not demonstrate consistent differences in the prevalence of enthesitis, dactylitis, or inflammatory bowel disease (IBD) between nr-axSpA and r-axSpA cohorts. Collectively, these differences have been summarized in Table 1.

3 | Approach to Diagnosis

The diagnosis of nr-axSpA is based on the integration of appropriate clinical features and supportive imaging findings. Individuals with suspected axial SpA based on clinical presentation should undergo appropriate imaging evaluation. Although the 2009 ASAS criteria are classification rather than diagnostic criteria and no formal diagnostic criteria exist for nr-axSpA, MRI represents the cornerstone imaging modality in the evaluation of suspected nr-axSpA when interpreted within the appropriate clinical context.

According to definitions established by the ASAS MRI Working Group, MRI studies performed for the assessment of axial SpA should include fat-suppressed sequences, such as short tau inversion recovery (STIR), which are essential for detecting active inflammatory lesions, including bone marrow edema (BME) or osteitis, characteristic of nr-axSpA [16]. A positive MRI, as defined by ASAS, requires the presence of either one area of BME on at least two consecutive slices or at least two areas of BME on a single slice [16]. Maksymowych and colleagues proposed alternative criteria for MRI positivity, defining active inflammation as BME present in four sacroiliac (SI) joint quadrants or on three consecutive SI joint slices. Structural lesions on MRI were defined by the presence of erosions in at least three SI joint quadrants or fat lesions in five SI joint quadrants [17].

Importantly, not all MRI findings consistent with BME should be attributed to nr-axSpA. Several studies have demonstrated a high prevalence of MRI lesions meeting ASAS definitions in asymptomatic individuals, including approximately 23% of healthy military recruits, 30%–35% of recreational runners, 40% of professional hockey players, and up to 60% of postpartum women [18]. Despite these limitations, MRI findings have demonstrated prognostic utility. One study reported a strong correlation between the severity and extent of osteitis on baseline MRI and the subsequent development of radiographic sacroiliitis 8 years later [19]. Additionally, greater extent of osteitis on MRI has been associated with improved responses to tumor necrosis factor–alpha inhibitor (TNFi) therapy [20].

Laboratory markers such as HLA-B27 status and CRP levels provide supportive information but lack diagnostic specificity for nr-axSpA. Approximately 6% of the general US population is HLA-B27 positive, and not all patients with nr-axSpA carry this allele [4]. Elevated CRP levels are more frequently observed in patients with r-axSpA than in those with nr-axSpA, with one study demonstrating CRP levels greater than 5 mg/L in 45.4% of r-axSpA patients compared with 35.6% of nr-axSpA patients (relative risk 1.27; 95% confidence interval 1.16–1.38; $p < 0.001$) [9]. On average, CRP levels are higher in r-axSpA than in nr-axSpA, although CRP reflects systemic rather than localized inflammatory burden [9]. Notably, elevated CRP has been associated with an increased risk of progression to r-axSpA and a more robust response to TNFi therapy among patients with nr-axSpA [8, 9].

4 | Management

Radiographic progression from nr-axSpA to r-axSpA has been reported in approximately 10%–40% of patients and typically occurs slowly over several years [8]. Long-term data from the GESPIC and DESIR cohorts demonstrate that only a minority of patients with nr-axSpA progress to radiographic disease over 8–10 years, reinforcing that many individuals remain non-radiographic despite persistent symptoms [8, 9]. Patients who are HLA-B27 positive and have elevated CRP levels appear to be at higher risk of radiographic progression [20]. The impact of therapeutic interventions on structural progression in nr-axSpA remains incompletely defined. While some studies suggest that TNFi therapy may slow radiographic progression, other data demonstrate a lack of progression in many patients with nr-axSpA, raising the question of whether this phenotype represents a less structurally progressive subset of disease rather than a self-limiting condition [9, 20]. Current evidence does not support withholding treatment solely based on the absence of radiographic changes. The 2019 American College of Rheumatology and Spondylitis Association of America guidelines provide treatment recommendations for axial SpA and do not distinguish between nr-axSpA and r-axSpA. Nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy remain first-line therapies for all patients with nr-axSpA, with biologic agents reserved for those with persistent disease activity. Table 2 summarizes the biologic therapies currently approved for the treatment of nr-axSpA.

5 | Conclusion

Non-radiographic axial SpA is a clinically important subset within the axial SpA spectrum, characterized by the absence of definitive radiographic sacroiliitis. With an estimated prevalence of approximately 0.35% in the general population, nr-axSpA should be considered in patients with chronic back pain of onset before 45 years of age and features of inflammatory back pain. Although prevalence appears similar between men and women, women are more likely to present with nontraditional clinical features, such as widespread pain, which may contribute to diagnostic delay.

There is substantial overlap between the clinical features of nr-axSpA and r-axSpA, and understanding their distribution can aid clinical recognition. Advances in MRI have improved detection of early inflammatory disease; however, nr-axSpA remains under-recognized due to limited awareness and the absence of formal diagnostic criteria. Large observational cohorts, including GESPIC, Corrona, DESIR, and KONASPA, highlight this diagnostic complexity by demonstrating heterogeneous presentations and meaningful disease burden across diverse populations. MRI remains the optimal imaging modality for evaluating early inflammatory lesions and supporting diagnosis, while

TABLE 1 | Clinical features of non-radiographic axial spondyloarthritis and comparison with radiographic axial spondyloarthritis.

Clinical feature	Clinical characteristics	Similarities and/or differences between nr-axSpA and r-axSpA
Inflammatory back pain (IBP)	– Insidious onset before age 40 years – Morning stiffness > 30 min – Improvement with exercise and NSAIDs – No improvement with rest – Nocturnal pain and alternating gluteal pain	– Similar prevalence in both groups (~75%–82%) [12] – GESPIC: nearly universal (ever 100% versus 100%; past 6 months 97.8% versus 94.1%; Calin's criteria 84.6% versus 86.7%; NS) [8] – DESIR: required for cohort entry (no between-group comparison) [9] – KONASPA and CORRONA: high prevalence, not discriminatory [10, 11] – IBP alone has limited specificity for distinguishing nr-axSpA from r-axSpA [12]
Peripheral arthritis	– Asymmetric inflammatory oligoarthritis – Predominantly affects lower extremities	– Some clinical cohorts report higher prevalence in nr-axSpA (35.7% vs. 17.0%, $p = 0.001$) [13] – Meta-analysis shows comparable pooled prevalence (27.9% vs. 29.7%) [14] – GESPIC: 40.9% versus 37.4% (ever); 18.2% versus 14.4% (current); NS [8] – DESIR: 23.0% versus 25.9% ($p = 0.419$) [9] – KONASPA: 49.4% versus 54.8% ($p = 0.567$) [11]
Enthesitis	– Inflammation at tendon or ligament insertion sites – Associated with HLA-B27 positivity	– Axial enthesitis more frequently observed in r-axSpA [15] – Peripheral enthesitis shows variable findings across cohorts – DESIR: 60.1% versus 47.6% ($p = 0.003$) [9] – CORRONA: 47.4% versus 29.0% ($p < 0.001$) [10] – GESPIC: 43.6% versus 39.4% (ever); NS [8] – KONASPA: 32.9% versus 16.7% ($p = 0.070$) [11]
Dactylitis	– Diffuse swelling of an entire finger or toe	– Overall low prevalence in both groups – Some reports suggest slightly higher frequency in nr-axSpA (12.9% vs. 0%) [15] – GESPIC: 4.0% versus 6.3%; NS [8] – DESIR: 14.6% versus 13.5% ($p = 0.731$) [9] – CORRONA: 12.4% versus 9.0% ($p = 0.34$) [10] – KONASPA: 5.5% versus 3.2% ($p = 1.000$) [11]
Uveitis	– Acute anterior uveitis – Associated with HLA-B27	– Cohort data show numerically higher rates in r-axSpA but no significant differences – GESPIC: 12.4% versus 20.9%; NS [8] – DESIR: 8.3% versus 12.0% ($p = 0.148$) [9] – CORRONA: 18.6% versus 16.8% ($p = 0.69$) [10] – KONASPA: 17.2% versus 19.4% ($p = 0.769$) [11]
Inflammatory bowel disease (IBD)	– Crohn's disease or ulcerative colitis	– Some reports suggest higher prevalence in nr-axSpA [13] – Overall low prevalence with no consistent differences across cohorts – GESPIC: 1.8% versus 2.6%; NS [8] – DESIR: 4.1% versus 7.6% ($p = 0.070$) [9] – CORRONA: 6.2% versus 7.4% ($p = 0.68$) [10] – KONASPA: 5.0% versus 3.2% ($p = 1.000$) [11]

Abbreviations: CORRONA, Consortium of Rheumatology Researchers of North America; DESIR, Devenir des Spondylarthropathies Indifférenciées Récentes; GESPIC, German Spondyloarthritis Inception Cohort; HLA-B27, human leukocyte antigen B27; IBD, inflammatory bowel disease; IBP, inflammatory back pain; KONASPA, Korean Non-radiographic Axial Spondyloarthritis cohort; nr-axSpA, non-radiographic axial spondyloarthritis; NS, not statistically significant; NSAID, nonsteroidal anti-inflammatory drug; r-axSpA, radiographic axial spondyloarthritis.

TABLE 2 | Biologic and oral small molecule therapies for nr-axSpA.

Study	Drug class	Inclusion criteria	Total patients	Primary outcome	Comments
Sieper et al.—Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomized placebo-controlled trial (ABILITY-1)	TNF-α inhibitor (adalimumab)	nr-axSpA per ASAS criteria, BASDAI ≥4, back pain ≥4 (VAS), inadequate response/intolerance/ contraindication to NSAIDs.	185 (91 adalimumab, 94 placebo)	% of patients achieving ASAS40 at Week 12	Significantly higher ASAS40 in adalimumab group (36% vs. 15%, $p<0.001$); improved MRI inflammation, CRP.
Dougados et al.—Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early non-radiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial	TNF-α inhibitor (etanercept)	ASAS-defined nr-axSpA, symptom duration 3 months–5 years, BASDAI ≥4, failure of ≥2 NSAIDs.	215 (106 etanercept, 109 placebo)	% achieving ASAS40 at 12 weeks	ASAS40 response significantly higher in etanercept group (32% vs. 16%, $p=0.006$); responses greater in patients with elevated CRP or sacroiliitis on MRI.
Deodhar et al.—A 52-week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis.	TNF-α inhibitor (certolizumab Pegol)	ASAS-defined nr-axSpA, disease duration of >12 m, BASDAI ≥4, objective evidence of inflammation on MRI.	317 (159 CZP vs. 159 placebo)	Proportion of patients achieving ASDAS-major improvement.	ASDAS-MI at Week 52 was achieved in 47.2% of CZP group versus 7% in placebo group ($p<0.0001$)
Sieper et al.—A randomized, double-blind, placebo-controlled, 16-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis	TNF-α inhibitor (golimumab)	ASAS-defined nr-axSpA, age 18–45, symptom duration ≤5 years, BASDAI ≥4, back pain ≥4, inadequate NSAID response, MRI sacroiliitis or HLA-B27+ ≥2 SpA features; excluded prior TNFi use	198 (98 golimumab, 100 placebo)	% achieving ASAS20 at Week 16	ASAS20: 71.1% (golimumab) versus 40.0% (placebo), $p<0.0001$; greater response in patients with MRI/CRP evidence of inflammation.
Deodhar et al.—Improvement of signs and symptoms of nonradiographic axial spondyloarthritis in patients treated with secukinumab: primary results of a randomized, placebo-controlled Phase III study	IL-17A inhibitor (secukinumab)	nr-AxSpA per ASAS criteria with objective signs of inflammation (MRI SI joint lesions and/or elevated hsCRP); TNFi-naive or ≤1 prior TNFi; excluded radiographic sacroiliitis.	555 (185 loading dose, 184 no loading dose, 186 placebo)	ASAS40 at Week 16 (LD) in TNFi-naive patients	ASAS40 significantly higher in secukinumab groups: 41.5% (LD, week 16) versus placebo (29.2%, $p<0.05$); improved BASDAI, BASFI.

(Continues)

TABLE 2 | (Continued)

Study	Drug class	Inclusion criteria	Total patients	Primary outcome	Comments
Deodhar et al.—Efficacy and safety of intravenous secukinumab in patients with active axial spondyloarthritis: results from a randomized, placebo-controlled, Phase 3 study.	IL-17A inhibitor (secukinumab): intravenous form	Patients with nr-axSpA did not meet the modified New York criteria for ankylosing spondylitis based on sacroiliac joint X-ray but fulfilled the ASAS classification criteria for axSpA.	Of the 526 patients, 113 had nr-axSpA. 56 randomized to treatment group and 57 to placebo group	ASAS 40 response at Week 16.	ASAS40 response rate of 40.9% compared with 22.9% ($p < 0.0001$) among patients receiving placebo. No sub-group analysis for nr-axSpA group.
Deodhar et al.—Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): A randomized, placebo-controlled trial	IL-17A inhibitor (ixekizumab)	Adults with nr-axSpA (ASAS criteria), objective signs of inflammation (MRI and/or CRP), BASDAI ≥ 4, back pain ≥ 4, inadequate response or intolerance to ≥ 2 NSAIDs; excluded prior bDMARD use	303 (105 placebo, 96 Q4W, 102 Q2W)	ASAS40 at Week 16 and Week 52	ASAS40 response significantly higher with ixekizumab Q4W (35% at W16) versus placebo (19%, $p = 0.004$); improved ASDAS, BASDAI, BASFI, MRI inflammation.
Baraliakos et al.—Bimekizumab treatment in patients with active axial spondyloarthritis: 52-week efficacy and safety from the randomized parallel Phase 3 BE MOBILE 1 and BE MOBILE 2 studies	Dual IL-17A & IL-17F inhibitor (bimekizumab)	Adults with nr-AxSpA (ASAS criteria), objective signs of inflammation (MRI sacroiliitis and/or CRP ≥ 6 mg/L), no radiographic sacroiliitis (mNY)	254 (128 BKZ, 126 placebo)	ASAS40 at Week 16	ASAS40: 47.7% BKZ versus 21.4% placebo ($p < 0.001$); improved BASDAI, ASDAS, MRI scores.
Deodhar et al.—Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomized, double-blind, placebo-controlled, Phase 3 trial	JAK inhibitor (upadacitinib)	nr-AxSpA (ASAS criteria) with objective signs of inflammation (MRI sacroiliitis and/or hsCRP > 2.87 mg/L); inadequate response/ intolerance/contraindication to ≥ 2 NSAIDs; prior bDMARD use allowed (≤ 1 TNFi or IL-17i)	313 (156 upadacitinib, 157 placebo)	% achieving ASAS40 at Week 14	ASAS40: 45% (upadacitinib) versus 23% (placebo), $p < 0.0001$; r improved ASDAS, SPARCC MRI.

Abbreviations: ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; hsCRP, high-sensitivity CRP; IL-17A/F, interleukin-17A/interleukin-17F; JAK, Janus kinase; JAKi, Janus kinase inhibitor; mNY, modified New York criteria; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, nonsteroidal anti-inflammatory drug; SPARCC, Spondyloarthritis Research Consortium of Canada; TNF/TNFi, tumor necrosis factor/TNF inhibitor.

physical therapy and NSAIDs continue to play central roles in management. Biologic therapies offer additional options for patients with inadequate response to conventional treatment.

Author Contributions

Alexander Alexandrov: conceptualization, supervision, writing – review and editing. **Chen Chao:** conceptualization, supervision, writing – review and editing. **Anand Kumthekar:** conceptualization, supervision, writing – review and editing. All authors have reviewed and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REVIEW

The Asia-Pacific League of Associations for Rheumatology Consensus Recommendations on the Management of Juvenile Idiopathic Arthritis (JIA): Polyarticular Course JIA, Temporomandibular Joint Arthritis, Imaging, and Non-Pharmacologic Therapies

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ABSTRACT

Background: Juvenile idiopathic arthritis (JIA) is one of the most common childhood rheumatic diseases. In the Asia-Pacific region, access to pediatric rheumatology services and therapies remains variable. To address regional disparities and promote evidence-based yet practical care, the APLAR developed consensus recommendations for the management of polyarticular-course JIA (pcJIA), temporomandibular joint (TMJ) arthritis, and non-pharmacologic interventions.

Methods: A multidisciplinary task force of 34 members from 14 countries, including pediatric and adult rheumatologists and patient representatives, was convened. The guideline development followed the GRADE, ADAPTE, and AGREE II frameworks. Existing international guidelines were critically appraised, and a systematic literature review was performed to address 26 PICO questions. Draft statements were discussed and voted upon using a modified Delphi process, with consensus defined as ≥80% agreement.

Results: Four overarching principles and 32 statements were finalized: 16 for pcJIA treatment, 10 for TMJ arthritis, 3 for non-pharmacologic therapies, 2 for imaging, and 1 for disease monitoring. Key recommendations that diverge from Western guidelines include: (1) stronger recommendation for methotrexate as initial therapy before biologic DMARDs; (2) explicit advocacy for TNF inhibitors, including biosimilars, when escalation is required; (3) cautious allowance of short-term systemic glucocorticoids where DMARDs are limited; (4) emphasis on treat-to-target using cJADAS-10; (5) stronger endorsement for physical and occupational therapy; and (6) conditional allowance of traditional and complementary medicine practices under professional supervision.

Conclusion: These consensus statements provide regionally adapted, evidence-based recommendations to improve access, standardize management, and promote equitable care for patients with JIA across the Asia-Pacific region.

For affiliations refer to page 20.

1 | Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common childhood-onset rheumatic diseases encountered in the Asia-Pacific region [1]. It is defined as arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks for which seven distinct subtypes were classified according to the International League of Associations for Rheumatology (ILAR) classification criteria [1, 2]. The classification is based on the number of inflamed joints, and the presence or absence of IgM rheumatoid factor (RF), HLA-B27, psoriasis or a family history in the first-degree relative of psoriasis or other HLA-B27-related disorders [2]. It was estimated that over 2 million children under 16 years of age had JIA, and more than one-half reside in the Asia-Pacific region [3]. Unlike in the West, the JIA subtype distribution in the region varies significantly by geographic area and ethnicity [4, 5]. Since the beginning of the 21st century, there have been notable improvements in the treatment of children with JIA, resulting in better outcomes [6, 7]. Clinical inactive disease (CID) can be achieved in one-half and three-quarters of children and young adults with JIA within the 1st and 2nd year, respectively [8, 9]. Decrease in the frequency of joint and extra-articular damage was also observed [6]. Clearly, these outcome improvements parallel the increased use of biologic disease-modifying anti-rheumatic drugs (bDMARDs) [6, 8–10]. These same trends cannot apply to the Asia-Pacific region, where the majority of the countries are low to middle-income countries (LMICs) with varying cultures, health perceptions, and healthcare delivery systems [11]. Recent reports from Thailand (2019–2021) and India (2021–2022) JIA cohorts revealed the frequencies of joint damage of 37% and 49%, respectively, as compared to 5% from the Greek (2001–2010) and 22% from the Italian multicenter (2002–2017) cohorts [6, 12–14]. Severe pediatric rheumatology workforce shortage remains the key barrier to proper JIA care delivery in the region, for which only 17 out of 51 countries in the Asia-Pacific area have pediatric rheumatologists [15]. Like other patients with childhood-onset rheumatic diseases, children with JIA are commonly managed by general practitioners, pediatricians, and other pediatric subspecialists, adult rheumatologists, orthopedists, and other healthcare professionals [15, 16]. Furthermore, similar to other LMICs around the globe, a lack of awareness in both physicians and the public, poor access to appropriate therapy caused by limited resources of DMARDs, especially bDMARDs, and local financial constraints and different healthcare policy priorities, as demonstrated in the recent regional survey, are among the barriers affecting the poor JIA outcomes in the region [15].

Early diagnosis and prompt initiation of appropriate therapy are critically important in improving JIA outcomes and preventing permanent damage. Several treatment recommendations for patients with JIA were developed by pediatric rheumatology experts from the West or high-income countries (HICs), which cannot be transferred to many countries in the region where healthcare resources are limited, and most of the JIA patients are managed by non-pediatric rheumatologists [15, 17–20]. A practical and regionally appropriate treatment guideline is required to improve JIA outcomes in the Asia-Pacific area, taking into consideration the distinct regional features such as disparities and challenges in healthcare access, diverse cultures and health perceptions, drug adherence, and wide variations in clinical practice, particularly among non-pediatric rheumatology healthcare professionals.

To address regional-specific concerns, the Asia-Pacific League of Associations for Rheumatology (APLAR) developed evidence-based consensus recommendations with the goals of updating and adapting the guidelines published in the preceding 5 years. These consensus recommendations on JIA management are intended to serve as a guide for healthcare professionals in the Asia-Pacific region (target audiences), including specialists, family physicians or general practitioners, specialty nurses/other relevant practitioners who have direct patient care for patients with JIA (these healthcare professionals will be addressed together as "practitioners" throughout this consensus recommendations) and other healthcare stakeholders including patients and caregivers and health authority policy makers. It is imperative to acknowledge that these consensus recommendations are not intended to dictate the care of a particular patient, since the ultimate therapeutic options should be grounded in the individual clinical context and collaborative decision making between the treating practitioner and patient/caregiver, ensuring that informed choices are made in alignment with the best interest of the patient.

These APLAR consensus recommendations on the management of JIA will be divided into 3 sections due to the breadth of the subjects and the notable advancements in our understanding of JIA immunopathogenesis and treatment. Polyarticular course JIA (pcJIA), temporomandibular joint (TMJ) arthritis, and certain non-pharmacologic therapies and conventional radiographic imaging will be covered in the first section. Additionally, this section provides advice on traditional & complementary medicine (T&CM) for JIA, which is widely used in the region [21]. Systemic JIA/Still's disease management will be covered in the second section, and the management of oligoarthritis, sacroiliitis, enthesitis, and psoriatic arthritis (PsA) will be covered in the final section. For the JIA diagnosis and medication toxicity monitoring and immunizations, the readers are referred to the recent "Juvenile Arthritis Management in Less Resourced Countries (JAMLess): Consensus Recommendations from the Cradle of Mankind" and the "2021 American College of Rheumatology (ACR) Guideline for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for Nonpharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging", respectively [18, 22].

2 | Materials and Methods

This consensus recommendation development process followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (www.gradeworkinggroup.org), which involves the process of rating the quality of the best available evidence and developing health care recommendations following the approach proposed by the GRADE Working Group [23] and adhered to the Appraisal of Guidelines for Research and Evaluation II (AGREE II) criteria [24] for consensus recommendation quality and the ADAPTE

Collaboration methodology for existing guideline adaptation (www.g-i-n.net) [25].

2.1 | Task Force Working Group Organization

The APLAR Pediatric Rheumatology Special Interest Group (PR SIG) established the Task Force (TF) working groups in October 2023 (Appendix S1). There were 5 working groups: (1) The *Steering Committee (SC)* chair (TA) nominated by PR SIG convenor (SF) formed TF SC, consisting of 10 expert pediatric rheumatologists and one adult rheumatologist from 10 countries (median years of experience, 19.0 years [IQR 16.0–25.0]). This committee identified and appraised existing guidelines, formulated and finalized clinically relevant Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions, ranked outcomes, supervised and coordinated the entire development process, and, with the APLAR Guideline Committee, refined recommendation statements and drafted manuscripts; (2) *Guideline Development Methodologist* (LD) advised and guided methodology/technical process, checked evidence summaries for correctness of interpretation of evidence, and provided technical assistance to other working groups; (3) *Evidence Review Panel (ERP)*, consisting of 16 pediatric rheumatologists, searched and identified relevant literature, critically appraised and rated the certainty of evidence, and drafted recommendation statements from PICO questions; (4) *Consensus Panel (CP)*, consisting of 14 pediatric rheumatologists, 3 adult rheumatologists (median years of experience 16.5 years [IQR 11.3–18.8]), and 2 JIA patient and parent representatives, from 14 countries, who assisted in formulating and refining PICO questions, identified and prioritized the critical and important outcome measures before finalizing the questions, such that stakeholders' values and preferences could be incorporated, reviewed evidence summaries and voted on the recommendation statements; (5) *Patient and Parent Panel (PPP)*, consisting of 9 adult JIA patients and 7 parents from 6 countries, provided input and opinion on benefits and adverse events of drugs, reviewed evidence summary, and assisted in ranking outcomes and provided input on patient values and preferences related to treatment options, outcomes, and evidence. All task force members declared conflict of interest before all consensus statement development activity, and $>95\%$ of members had no conflict of interest.

2.2 | Determination of Health Questions and Outcomes

The SC met virtually to define the scope of the project, draft the overarching principles (OPs) and the first version of the PICO questions, and determine and rank the outcomes. This was done before the CP and PPP review and then finalized after a dedicated virtual and a face-to-face meeting. The scope of these consensus recommendations was decided to be limited to non-systemic pcJIA and TMJ arthritis, as these phenotypes had a high impact on patient outcomes, and significant therapeutic progress has been made in the past decade. The TF also decided to include radiographic monitoring and non-pharmacologic therapies, including T&CM, which were prevalent in the region.

2.2.1 | Population

The TF decided to classify JIA patients by their clinical course or phenotype for the current APLAR consensus recommendations, regardless of their ILAR classification subtypes, in accordance with the previous 2019 American College of Rheumatology/Arthritis Foundation (ACR/AF) guidelines for the treatment of JIA, since these ILAR subtypes are not entirely clinically or genetically homogenous, and the classification may be changed in the near future [7, 19]. Furthermore, it is more practical in guiding treatment since available data on treatment are classified as such [26].

2.2.1.1 | Polyarticular-Course JIA (pcJIA). Patients with pcJIA are defined as children and young adults (CYA) with arthritis onset <16 years old with ≥ 5 joints involved. This includes CYA from different ILAR JIA subtypes as long as ≥ 5 joints are involved (rheumatoid factor [RF] positive or negative polyarthritis, extended oligoarthritis, and enthesitis-related arthritis (ERA) excluding axial involvement, and undifferentiated arthritis with polyarticular course) [2]. Patients with axial and TMJ involvement are excluded. The consensus recommendations are not intended to apply to CYA with extra-articular manifestations, including uveitis or psoriasis, which may influence treatment decisions. The TF also adopted the poor prognostic risk factors from the 2019 ACR/AF guideline, as early escalation of treatment is indicated, which included the presence of joint damage, positive RF or anti-cyclic citrullinated peptide (CCP) antibodies [19]. The current consensus recommendations adopt the treat-to-target strategy, where the goal of achieving an inactive disease (or, in some cases, low disease activity [LDA]) stage guides treatment decisions, rather than further classifying the disease into high or moderate disease activities (see below). This will simplify and provide more feasible and practical guidance for the target audiences, particularly non-pediatric rheumatologists in busy settings with high clinical loads.

2.2.1.2 | Temporomandibular Joint (TMJ) Arthritis. Patients with TMJ arthritis are defined as CYA from different ILAR JIA subtypes once TMJ is involved. Patients may or may not have active peripheral joint disease and active TMJ arthritis. Active TMJ arthritis is defined as patient-reported symptoms of inflammatory jaw pain, clinical examination findings of reduced mouth opening or tenderness over TMJ, and/or magnetic resonance imaging (MRI) findings consistent with active TMJ arthritis.

2.2.2 | Intervention

Both pharmacologic and non-pharmacologic therapies covered in these consensus recommendations are listed in Table 1. Nonsteroidal anti-inflammatory drugs (NSAIDs) included both selective and non-selective cyclo-oxygenase (COX) 2 inhibitors. Glucocorticoids as bridging therapy were defined as a short course of oral form (≤ 2 mg/kg/day with a maximum of 60 mg/day), preferably less than 3 months, aimed at rapidly controlling disease activity while initiating or adding DMARDs. This duration is the expected duration of most DMARDs to take their therapeutic effects after initiation. Almost a decade since the emergence of biosimilars in the treatment of rheumatic diseases, access

TABLE 1 | Interventions covered in the current APLAR consensus recommendations.

Intervention	Generic name/type
Non-steroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen, naproxen, indomethacin, diclofenac, mefenamic acid, meloxicam, nabumetone, piroxicam, etodolac, etoricoxib, celecoxib
Glucocorticoids	Oral, intravenous, or intra-articular injections
Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)	Methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide
Biologic DMARDs (bDMARDs)	
TNF inhibitors (TNFi) and their biosimilars	Etanercept, adalimumab, infliximab, golimumab, certolizumab pegol
Non-TNFi and their biosimilars	Abatacept, tocilizumab, anakinra, canakinumab, rilonacept, rituximab, secukinumab, ustekinumab, ixekizumab
Targeted synthetic DMARDs (tsDMARDs)	Tofacitinib, baricitinib, upadacitinib, ruxolitinib
Non-pharmacological interventions	Physical therapy and exercise, occupational therapy, and dietary changes. For TMJ arthritis, this also includes mouth guards
Traditional and complementary medicine (T&CM)	*Whole medical system* (Ayurverda, homeopathy, acupuncture, electroacupuncture, reflexology) *Mind body Medicine* (relaxation, guided imagery, biofeedback, hypnosis, Alexander technique) *Biologically based practices* (herbal medicine, antioxidants, vitamins, minerals, diet-based therapy, chelation therapy) *Manipulative and body-based practices* (osteopathic therapy, chiropractic, tuina, massage, yoga, taichi, qigong) *Energy Medicine* (energy healing, meditation, Reiki)

to bDMARDs seems to be possible, particularly in some of the limited-resource countries worldwide [27]. Evidence on efficacy and safety of biosimilars, especially tumor necrosis factor inhibitor (TNFi) biosimilars, in the treatment of JIA has been published in many JIA cohorts in recent years, and they were included in the current consensus recommendations [28–32].

The T&CM merges the terms traditional medicine and complementary medicine, encompassing products, practices, and practitioners. The World Health Organization (WHO) defined traditional medicine as the total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement, or treatment of physical and mental illness and complementary medicine as a broad set of health-care practices that are not part of that country's own traditional or conventional medicine and are not fully integrated into the dominant health care system [21]. Given the rising prevalence of T&CM in the management of chronic diseases globally, especially in the Asia-Pacific region, numerous national policies and regulations regarding T&CM have been established in various WHO member regions where traditional or herbal medicines have been incorporated in their national essential medicine lists, highlighting the significance of T&CM as adjunct therapies. The T&CM in the management of JIA was included in the literature review. The TF decided to cover only conventional radiography since it is widely accessible and used routinely and is uncomplicated to interpret compared to other imaging modalities such as ultrasound and MRI.

2.2.3 | Outcomes

The CP identified and rated the outcomes, which the SC and PPP members subsequently refined. The critical outcomes included quality of life measures, disease activity measures, clinical inactive disease, functional ability, joint damage requiring surgical intervention, significant limb length discrepancy, and significant or life-threatening adverse events. Other important outcomes included arthritis-related pain, preservation of normal growth and development, fatigue, and significant medication side effects leading to medication discontinuation.

Overall, there were 26 PICO questions, for which 12 were for pcJIA, 10 were for TMJ arthritis, and 4 for non-pharmacologic therapies and imaging (Appendix S2).

2.3 | Existing Guidelines Adaptation

The SC adopted the ADAPTE framework with the intention to adapt international guidelines for the current consensus recommendations [25]. The AGREE II instrument (www.agreetrust.org) was used to appraise the quality of 8 international

guidelines that were published in the past 5 years [17–20, 33–36]. Three SC members appraised each guideline. It was decided by SC to set the prioritized domain (domain 3: rigor of development) score of > 70% as the threshold for high-quality guidelines to be adapted for the current project. Six guidelines were selected for adaptation with modification [17–20, 33, 35].

2.4 | Literature Review and Certainty of Evidence Assessment

A systematic literature review was performed by the ERP members, following PRISMA guidelines and registered on PROSPERO (CRD420251036584). The detailed methods and results are reported separately (Appendix S2). In brief, literature searches for each PICO question were conducted across MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception through September 2024, with updates in January 2025. Both randomized trials and observational studies were included. Study selection and data extraction were independently carried out by two reviewers using Covidence software (https://www.covidence.org). Since the current consensus recommendations were adapted from existing international guidelines approved by the SC using the AGREE II tool, the final studies selected did not include those in previous guidelines (before October 2017). The risks of bias in the included studies were independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB2) tool, with the overall certainty of evidence (CoE) graded via the GRADE approach. When possible, meta-analyses were conducted using Cochrane's Review Manager (RevMan) software (https://revman.cochrane.org). The GRADEpro software (https://www.gradepro.org) was then used to generate the GRADE summary of findings (SoFs) tables for each PICO question.

2.5 | Formulation of Recommendations

The literature review/evidence summary and SoF tables depicting the CoE rating were then sent to all TF members. The ERP drafted recommendation statements (RS) considering the CoE from new evidence in addition to the strength of recommendation from existing guidelines. The RS were subsequently refined and finalized by SC. There are four OPs and a total of 32 statements, including 16 for pcJIA treatment, 1 for disease monitoring, 2 for conventional radiography or X-rays, 3 for non-pharmacologic therapies (2 for T&CM and 1 for physical therapy/occupational therapy [PT/OT]), and 10 for TMJ arthritis management. Two-thirds (66%) of the RS are weak recommendations, with 69% of the evidence overall having a low or very low CoE (Appendix S2).

2.6 | Consensus Formation

The CP members, including 2 PPP representatives received the evidence summary, SoF for CoE grading, and RS (each with its strength of recommendation [SoR] and CoE) several weeks before the modified Delphi sessions. The Delphi processes were executed through two virtual meetings and e-mail correspondences, necessitated by comments and disagreements that required modifications to the statements and adjustment of the SoR, taking into account these 4 factors: (1) balance between desirable and undesirable outcomes, (2) the magnitude of estimates of effect of the interventions on critical outcomes (overall quality of evidence for outcomes), (3) patients' values and preferences and their variability, and (4) resource use (cost) [23]. There are 3 categories of SoR. A strong recommendation (RS with word "recommend", "should") indicated that the TF was confident that the desirable effects of the intervention surpass the harms, or vice versa. On the contrary, a weak recommendation (RS with words "suggest", "may" or "might") implied that the beneficial effects of the intervention likely surpass the adverse effects, or vice versa. The circumstances, values, and preferences of each patient must be considered more thoroughly. Shared decision-making discussion between patient/caregiver and practitioner is crucial for the intervention that has a weak SoR. When there was insufficient or no evidence to recommend for or against a certain intervention, then there would be no SoR. The voting responses were dichotomous, as "agree" or "disagree". An agreement with a statement by 80% of the group was defined as consensus. If consensus was not reached, members discussed suggested modifications based on feedback from the initial/previous vote. The statement was modified accordingly, and another vote was conducted. At last, the SC and CP members were asked to rate their impression of each overarching principle and the final consensus recommendation statements, giving the level of agreement (LoA) on a scale of "0" (completely disagree) to "10" (completely agree). The mean and standard deviation (SD) were calculated and reported.

2.7 | External Review

These consensus recommendations were presented in public forums at the 27th Asia-Pacific League of Associations for Rheumatology Congress (APLAR 2025, Fukuoka, Japan), the 23rd National Conference of Pediatric Rheumatology Society of India (Indore, 2025), and the 28th Annual Conference of the Pakistan Society for Rheumatology (Lahore, 2025) for external review, and the first draft was also sent to three pediatric rheumatology experts (see Acknowledgement) for external review.

2.8 | Update

In light of the swift progress in arthritis research and therapy, the TF will revise these consensus recommendations 5 years after publication.

3 | Results

There are four OPs and 32 RS for the current consensus recommendations on the management of JIA (Table 2).

3.1 | Overarching Principles (OP)

In many parts of the Asia-Pacific region, where limited resources in workforce, healthcare, and medication access, and poor disease awareness lead to delays in diagnosis and

TABLE 2 | APLAR juvenile idiopathic arthritis (JIA) consensus recommendations I.

	Consensus recommendations	SoR	CoE	%A
Overarching principles				
1	Early diagnosis and timely treatment of JIA are essential to achieve an overall goal of maximizing growth, development, and quality of life, while preventing long-term joint damage and disability	NA	NA	100%
2	The overall JIA management should be multidisciplinary, including (but not limited to) pediatric rheumatologists, pediatric ophthalmologists, dental practitioners, resource nurses, physical and occupational therapists, among others	NA	NA	100%
3	Treatment target and treatment plan are based on a shared decision between patient/caregiver and treatment team. Treat-to-target by regular assessment of disease activity and modifying treatment strategy accordingly is essential. Ultimate target is drug-free remission, if possible, or clinical inactive disease with minimum therapy	NA	NA	100%
4	Long-term systemic glucocorticoid therapy is discouraged due to its long-term adverse events	NA	NA	100%
For children and young adults with ACTIVE polyarticular course JIA				
Induction therapy				
1	We recommend initial therapy with a conventional synthetic DMARD over NSAID or glucocorticoid monotherapy	1	B	94%
2	We recommend initial therapy with a conventional synthetic DMARD over a biologic DMARD	1	C	94%
3	We suggest methotrexate as first-line therapy over leflunomide, sulfasalazine, or triple therapy (hydroxychloroquine, methotrexate, sulfasalazine). However, in patients with risk factors and high-risk joint involvement, for example, c-spine, hip joint, and wrist joint, or significant joint damage, a combination of methotrexate and biologic DMARD may be considered	2	C	100%
4	Subcutaneous methotrexate is suggested over the oral form, especially in higher doses ($> 15\,mg/m^2$/week) to improve bioavailability	2	B	99%
5	NSAIDs and/or intra-articular glucocorticoid injection might be used as an adjunct therapy	2	D	100%
6	We recommend triamcinolone hexacetonide (TH) over triamcinolone acetonide for intra-articular injection, if feasible	1	B	100%
7	Bridging therapy with a limited course of oral glucocorticoids (< 3 months) might be considered in patients with limited mobility and/or significant symptoms	2	D	93%
8	We suggest against pulse glucocorticoids for any stage of therapy	2	D	87%
For children and young adults with ACTIVE polyarticular course JIA who had failed initial conventional synthetic DMARD therapy				
9	We suggest adding a biologic DMARD over changing to a second conventional synthetic DMARD	2	C	100%
10	Unless there is an intolerance to methotrexate, we suggest a combination of biologic DMARD with methotrexate over biologic DMARD monotherapy	2	B (ADA) C (ABT, IFX, TCZ) D (ETA, GOL)	100%
11	We suggest that TNFi might be considered as a first-line biologic DMARD over other biologic or targeted synthetic DMARDs	2	D	100%
12	TNFi biosimilars are acceptable alternatives for use as initial therapy or when switching biologic DMARDs	2	C	93%

(Continues)

TABLE 2 | (Continued)

	Consensus recommendations	SoR	CoE	%A
13	In patients who failed the first TNFi (primary failure), we recommend switching to a non-TNFi over switching to a second TNFi. In patients receiving the second biologic or targeted synthetic DMARD, practitioners may consider using either intravenous or subcutaneous abatacept, tocilizumab, oral baricitinib, oral tofacitinib, or oral upadacitinib. There is insufficient evidence for the use of anakinra or rituximab	1	B (BAR, TOF) C (ABT) D (TCZ, RTX, ANA)	93%
Maintenance therapy and therapy discontinuation				
For children and young adults with polyarticular course JIA who achieved INACTIVE disease				
14	In patients taking methotrexate, we recommend considering tapering or stopping methotrexate after at least six months of inactive disease	1	A	100%
15	For TNFi, we recommend tapering over the abrupt withdrawal of TNFi after six months of inactive disease, and prolonging the interval of TNFi is preferred to dose reduction	1	B	87%
16	In patients taking a combination of methotrexate and TNFi, there is insufficient evidence to determine the optimal sequence for medication withdrawal after six months of inactive disease	0	C	100%
Monitoring of disease activity				
17	We recommend regular/routine use of cJADAS-10 to monitor disease activity	1	B	100%
18	In patients with positive rheumatoid factor/anti-citrullinated protein antibodies or with adverse prognostic factors[a] regardless of antibody status, we suggest performing routine X-rays of the wrists, hands, forefeet, and other affected joints[b] at diagnosis, one year after disease onset, and during the transition from pediatric to adult healthcare. The use of X-rays during follow-up is at the discretion of the treating practitioners	2	B	83%
19	In patients with negative rheumatoid factor/anti-citrullinated protein antibodies without adverse prognostic factors, practitioners may consider X-ray of the symptomatic joints at their discretion	2	D	94%
Non-pharmacologic therapy				
Physical/occupational therapy				
20	In patients with JIA who have functional limitations, we recommend referring them for physical and occupational therapy, regardless of concomitant pharmacological therapies	1	D	100%
Traditional and complementary medicine				
21	In patients with JIA on medical therapy, practitioners might allow patients to undergo manipulative and body-based practices, such as massage therapy and yoga to improve pain by trained professionals	2	D	80%
22	In patients with JIA and active arthritis, there is insufficient evidence to recommend for or against biologically based products and supplements	0	N	100%

Note: SoR (strength of recommendation): 0 = absence of SoR, 1 = strong recommendation, 2 = weak recommendation; CoE (certainty of evidence): A = high, B = moderate, C = low, D = very low, *N* = no evidence; %A (agreement): percentage of consensus panel members agreeing with the recommendation statement.
Abbreviations: ABT, abatacept; ADA, adalimumab; ANA, anakinra; BAR, baricitinib; cJADAS, clinical Juvenile Arthritis Disease Activity Score; DMARD, disease modifying anti-rheumatic drugs; ETA, etanercept; GOL, golimumab; IFX, infliximab; NSAID: non-steroidal anti-inflammatory drug; RTX, rituximab; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor; TOF, tofacitinib.
[a]Adverse prognostic factors include early involvement of the wrists; distal involvement; symmetrical arthritis, elevated ESR/CRP or bone erosions on previous radiographs.
[b]Affected joints: Joints with active arthritis, limited range of motion or deformities.

treatment, JIA-related disability in CYA is not uncommon [13, 14, 37, 38]. The first OP emphasized the pivotal role of early diagnosis and prompt treatment to achieve an overall goal of maximizing growth, development, and quality of life while preventing long-term joint damage and disability (OP1). A recent survey conducted in the region showed that insufficient training about childhood rheumatic diseases, lack of disease awareness in both healthcare providers and the public, and severe shortage of pediatric rheumatologists were the main barriers to early disease diagnosis [15]. The urgent priority to alleviate these unmet needs is to increase the number of pediatric rheumatologists since they have a pivotal

role in education and training leadership, advocacy, policy formulation, and research, which will affect the development of clinical care [15, 37]. In recent years, many initiatives have emerged, including fellowship training programs and telemedicine hosted by societies or working groups, to educate practitioners and trainees and to raise awareness of the disease in the region [37, 39].

The complex JIA management requires a multidisciplinary collaboration to maintain joint function, monitor extra-articular disease activity (including ophthalmologic, gastrointestinal, dental, and oral systems), and counsel and educate patients and caregivers. This multifaceted approach is to ascertain normal joint function, growth and development, and quality of life (OP2).

The management of patients with JIA must be tailored to the individual, considering each patient's distinct circumstances, values, preferences, health beliefs, and cultural and ethnic backgrounds. This approach enhances treatment adherence and consequently improves outcomes. Treatment target and treatment strategy should be discussed through shared decision-making between the patient/caregiver and treatment team (OP3). Ideally, the treatment target of CID defined as cJADAS—Juvenile Arthritis Disease Activity Score ≤ 2.5 should be attained, as this has been demonstrated to be associated with reduced long-term joint damage and physical disability. However, such a target remains a challenge in this limited-resource region. The TF reached a consensus that low (or minimal) disease activity (defined as cJADAS 2.6–5.0) could be considered an alternative [40]. Treat-to-target denotes a target-oriented strategy for managing chronic diseases, as opposed to the traditional symptom-focused methodology. This involves frequent adjustment of therapy, guided by quantitative indices, and has been shown to improve outcomes in adult rheumatoid arthritis regardless of the therapeutic agents [41–43]. A similar effect was demonstrated in a recent German JIA multicenter cohort study (BiKER cohort) [44].

Chronic use of systemic glucocorticoids is well-recognized to increase long-term extra-articular damage in patients with JIA, particularly in the Asia-Pacific region, where improper therapeutic regimens are prevalent, especially in the setting of limited DMARD access [13–15, 38]. The TF all agreed that long-term systemic glucocorticoid therapy is discouraged (OP4).

3.2 | Consensus Statements on Polyarticular Course JIA Management (Figure 1 and Table 2)

3.2.1 | Induction therapy: the management of ACTIVE polyarticular-course JIA

1. *We recommend initial therapy with a conventional synthetic DMARD over NSAID or glucocorticoid monotherapy. (PICO 1; LoA 9.3 [1.1])*

This statement is consistent with the existing guideline [19]. It is imperative to initiate conventional synthetic DMARD (csDMARD) therapy without delay to prevent joint damage. There is no evidence comparing NSAIDs to placebo or DMARDs. Additional data on the efficacy of different NSAIDs, including three randomized controlled trials (RCTs) and one observational study comparing piroxicam, meloxicam, or celecoxib to naproxen in pcJIA patients, did not show a significant efficacy discrepancy [45–48]. The meloxicam and celecoxib adverse events were comparable to those of naproxen [45, 46, 48]. With the known glucocorticoid toxicity, systemic glucocorticoids are not used as monotherapy in pcJIA treatment at any stage.

2. *We recommend initial therapy with a conventional synthetic DMARD over a biologic DMARD. (PICO 5,8; LoA 9.4 [0.7])*

Treatment initiation for pcJIA patients with a csDMARD is strongly recommended over bDMARD monotherapy. There is no comparative evidence between csDMARDs and bDMARDs. Despite the low certainty of supporting evidence, the statement SoR was upgraded on the following grounds: Firstly, the scarcity of bDMARDs in many countries within the region, as opposed to the wider availability of csDMARDs [15]. Secondly, restricted access to bDMARDs is primarily attributable to their significantly higher cost, with most local health authorities requiring csDMARD failure as a prerequisite for financial assistance for biologics. Thirdly, bDMARD monotherapy is no more efficacious than combination csDMARD and bDMARD therapy or step-up therapy [49, 50]. Furthermore, csDMARD and bDMARD combination therapy has been demonstrated to reduce the risk of bDMARD antidrug antibodies [51].

3. *We suggest methotrexate as first-line therapy over leflunomide, sulfasalazine, or triple therapy (hydroxychloroquine, methotrexate, sulfasalazine). However, in patients with risk factors and high-risk joint involvement, for example, c-spine, hip joint, and wrist joint, or significant joint damage, a combination of methotrexate and biologic DMARD may be considered. (PICO 5; LoA 9.8 [0.4])*

Methotrexate (MTX) is widely available at a reasonable cost and has a long history and a wealth of experience in its use [15]. It is therefore suggested as the first csDMARD for the treatment of pcJIA unless there are contraindications. This is to prevent or minimize csDMARD selection confusion, particularly among non-pediatric rheumatologists. Compared to other csDMARDs, including leflunomide, sulfasalazine, and hydroxychloroquine, data on MTX are abundant. Furthermore, leflunomide lacks small children dosing and long-term safety data, and sulfasalazine contains the risk of severe hypersensitivity reaction, in addition to no available evidence on its head-to-head efficacy and safety study [19]. Regarding DMARD combination therapy, one recent RCT comparing leflunomide combined with MTX to MTX and placebo did not show any outcome differences, but more transaminitis was reported in the former group [52]. Similarly, a previous study (ACUTE-JIA trial) on triple therapy (MTX + sulfasalazine + hydroxychloroquine) also failed to demonstrate superiority compared to MTX monotherapy, with more gastrointestinal adverse events [24].

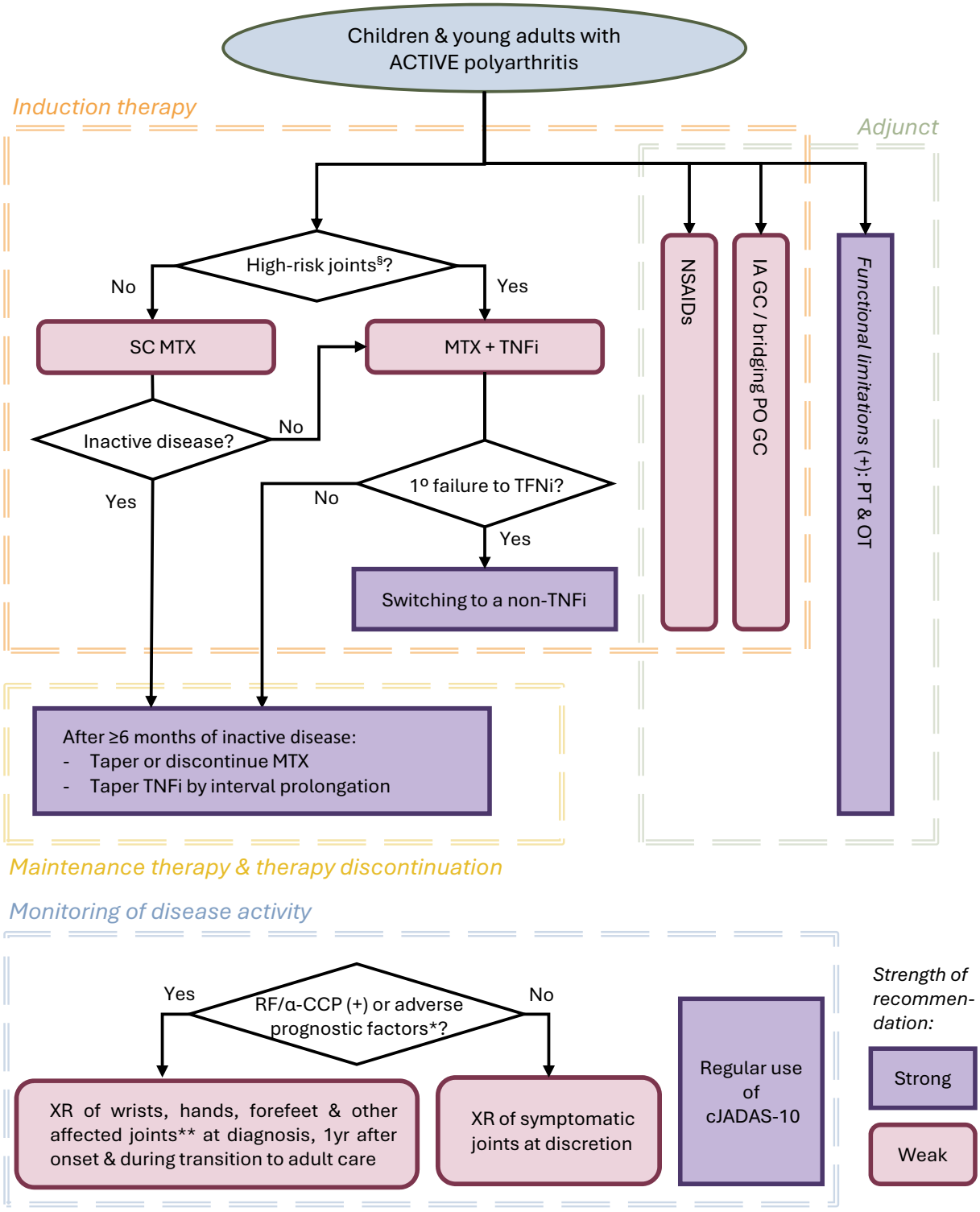

FIGURE 1 | Treatment algorithm for polyarticular-course juvenile idiopathic arthritis (pcJIA). §High-risk joints: C-spine, hip joint, and wrist joint, or significant joint damage. *Adverse prognostic factors include early involvement of the wrists; distal involvement; symmetrical arthritis, elevated ESR/CRP, or bone erosions on previous radiographs. **Affected joints: Joints with active arthritis, limited range of motion, or deformities. α-CCP, Anti-citrullinated peptide; bDMARD, Biological disease-modifying anti-rheumatic drug; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; GC, Glucocorticoid; MTX, Methotrexate; NSAID, Non-steroidal anti-inflammatory drug; OT, Occupational therapy; PO, Oral; PT, Physiotherapy; RF, Rheumatoid factor; SC, Subcutaneous; TNFi, tumor necrosis factor inhibitor.

In patients with risk factors and high-risk joints (c-spine, wrist, hip) or with pre-existing joint damage, the TF suggests an early combination of MTX and bDMARD therapy, if it is feasible in the given patient circumstance. The objective of this escalated treatment regimen is to minimize further joint damage and disability without further delay [49, 50].

4. *Subcutaneous methotrexate is suggested over the oral form, especially in higher doses (> 15 mg/m^2/week) to improve bioavailability. (PICO 5; LoA 8.9 [1.7])*

Both previous Western guidelines recommended subcutaneous injection as the preferred route of MTX administration, underscoring the awareness and concerns about the variable bioavailability of the drug taken by oral route, especially at higher doses (> 15 mg/m^2) [19, 33]. In limited resource settings, enhancing the absorption of MTX is of paramount importance. This approach is crucial for ensuring the optimal efficacy of the drug, particularly in cases where escalating therapy is necessary.

The SoRs of both previous recommendations are weak based on the very low certainty of supporting evidence. A recent German BiKER cohort study reported better outcomes at 24 months favoring the subcutaneous route over the oral MTX despite both groups taking average doses of < 15 mg/m^2. Elevated liver enzymes were observed more in the former group, but no data on folic acid were reported [53]. The quality of evidence was upgraded from low to moderate due to the large effect size. However, considering the preferences of patients and caregivers on the injection, including pain, increased cost for injection (manpower, syringes, and needles, since the majority of caregivers refuse to do the injection at home), anticipatory vomiting, and the availability of healthcare providers to administer in many areas in the region, the SoR was downgraded to a weak recommendation. It is a common practice in this region that patients may receive oral MTX at induction and then be escalated to the subcutaneous route if there is insufficient efficacy.

5. *NSAIDs and/or intra-articular glucocorticoid injection might be used as an adjunct therapy. (PICO 1; LoA 9.8 [0.4])*

This statement concurs with the existing guideline [19]. A recent systematic review and network meta-analysis found no significant differences in efficacy or safety among NSAIDs (meloxicam, naproxen, piroxicam, rofecoxib, tolmetin, aspirin, celecoxib, and diclofenac) [54]. Most patients in the region prefer a trial of oral NSAIDs to alleviate pain and stiffness caused by active joint inflammation. Intra-articular glucocorticoid injection is often indicated once failed NSAIDs and/or a swift control of the severe inflammatory symptoms or disability is needed.

6. *We recommend triamcinolone hexacetonide (TH) over triamcinolone acetonide for intra-articular injection, if feasible. (PICO 2; LoA 9.7 [0.6])*

This is a strong recommendation statement based on the moderate certainty of previous supporting evidence [19]. There is no additional evidence since. Intra-articular glucocorticoid injection offers a rapid control of the inflamed joints. Multiple intra-articular injections have been practiced commonly in patients with pcJIA, while waiting for the full therapeutic effect of DMARD therapy and sparing the use of systemic glucocorticoids. However, there is no evidence comparing systemic glucocorticoids and intra-articular steroid injection. Both are considered adjunct or bridging therapies in acute/active pcJIA management. Triamcinolone hexacetonide (TH) remains the preparation of choice due to its lower solubility, thus offering a longer duration of action [55]. However, in certain areas, TH may not be available, so triamcinolone acetonide may be used with double the usual dose of TH [55].

7. *Bridging therapy with a limited course of oral glucocorticoids (< 3 months) might be considered in patients with limited mobility and/or significant symptoms. (PICO 4; LoA 9.6 [0.8])*

The goal of bridging therapy is to rapidly control the inflammation of the joints so that the patients have less pain and regain their physical function sooner, while anticipating the therapeutic benefits of most DMARDs, which typically require a length of 3 months [56]. The TF suggested using glucocorticoid bridging therapy in patients with severe inflammatory symptoms with a significant impairment of physical function. For disease of lesser severity, NSAIDs may be an alternative. The TF leaves the disease severity judgment to the treating practitioners. Chronic or long-term low doses of oral glucocorticoids should be avoided due to known adverse effects, long-term toxicities of long-term systemic glucocorticoid treatment in children, and the availability of other treatment options. However, in some areas where resources are very limited, this may be inevitable.

8. *We suggest against pulse glucocorticoids for any stage of therapy. (PICO 3; LoA 8.6 [1.9])*

A recent study from India used pulse dexamethasone at 3 mg/kg with a maximum of 100 mg/day for three consecutive days at 0, 6, and 12 weeks, compared to placebo (normal saline), in addition to the standard treatment with MTX, NSAIDs as needed, and bridging therapy with oral glucocorticoids. Bridging oral prednisolone was given to those with persistent disease after 14 days of allocated intervention, at 2 mg/kg/day (max 60 mg/day) for the initial 1 week, followed by tapering over the next 3 weeks (1.0, 0.5, and 0.25 mg/kg/day, over respective weeks). Outcomes were assessed 4 weeks after each pulse of dexamethasone, with the last assessment at week 16. The addition of pulse dexamethasone did not add any advantage regarding ACR responses, the need for intra-articular steroid injection, or use of bridging oral prednisolone [57]. The TF recommended against pulse glucocorticoid therapy in JIA due to the lack of compelling evidence and concerns about the adverse effects associated with elevated cumulative glucocorticoid doses, despite the recommendation being of weak strength due to the very low certainty of supporting evidence.

3.2.2 | For Patients With ACTIVE Polyarticular-Course JIA Who had Failed Initial Conventional Synthetic DMARD Therapy

9. *We suggest adding a biologic DMARD over changing to a second conventional synthetic DMARD. (PICO 6; LoA 9.4 [1.1])*

This statement is a weak recommendation based on low certainty of supporting evidence, and the panel members all agreed without any concern. This also concurs with the

existing guideline [19]. It is suggested that the target of treatment should be CID, if possible, with an adequate duration of MTX trial (~3 months). If CID is not achieved, the next course of action would be to maximize the dose or route of MTX administration, if not already maximized, or to administer an intra-articular glucocorticoid injection. Previous studies comparing MTX monotherapy and MTX combined with bDMARDs (adalimumab in 2008 and the ACUTE-JIA trial (infliximab and MTX) in 2011) demonstrated a better efficacy of the combination regimens with comparable safety profiles [24, 58]. The panel acknowledged that in some very limited resource areas where bDMARDs are not available, a combination of DMARDs like the triple therapy (MTX, 15 mg/m^2 weekly, up to 25 mg + sulfasalazine, 40 mg/kg daily, up to 2000 mg + hydroxychloroquine, 5 mg/kg daily, up to 300 mg in ACUTE-JIA trial) may be considered as compared to other combinations for which there are no convincing efficacy data available and may have more adverse events [24, 52]. This option may have fewer long-term adverse effects compared to adding a variable dose of systemic glucocorticoids to control the inflammation.

10. *Unless there is an intolerance to methotrexate, we suggest a combination of biologic DMARD with methotrexate over biologic DMARD monotherapy. (PICO 8, 9; LoA 9.6 [0.8])*

This statement is a weak recommendation based on moderate (adalimumab), low (abatacept, infliximab, tocilizumab), and very low (etanercept, golimumab) certainty of supporting evidence regarding relative efficacy. However, another concern for the use of bDMARDs is the immunogenicity of the drugs. Anti-drug antibodies (ADAbs) are associated with reduced therapeutic efficacy or treatment failure and hypersensitivity reactions [59]. A recent systematic literature review showed that the prevalence of ADAbs ranged from 0% to 82% across bDMARDs for JIA, with a pooled prevalence of 17% [51]. Concomitant use of MTX or other anti-proliferative agents is associated with a lower incidence of ADAbs across bDMARDs in adult arthritides [59]. In JIA, concurrent use of adalimumab and MTX reduced the risk of ADAb development by 67% in various studies [51]. Given the more restricted availability and higher cost of other bDMARDs, together with the more prevalent and lower expense of TNFi in the region, the TF suggested the concomitant use of MTX to improve the drug survival [15].

11. *We suggest that TNFi might be considered as first-line biologic DMARD over other biologic or targeted synthetic DMARDs. (PICO 7; LoA 9.8 [0.5])*

This statement is a weak recommendation based on the very low certainty of supporting evidence. The panel reached a consensus on recommending TNFi as the preferred bDMARD therapy for pcJIA when indicated, for the following reasons: (1) TNFi is the most available bDMARD as compared to other classes of biologics [15]; (2) TNFi is included in many local and national drug lists for subsidization; (3) The safety and efficacy of TNFi are well-documented compared to other biologic classes, and it has the most extensive experience in the treatment of JIA; (4) TNFi biosimilars are available in many areas in the region; (5) a recent network meta-analysis failed to identify any evidence to suggest that one bDMARD class is more efficacious than another, as well as targeted synthetic DMARDs (tsDMARDs) [26]. This will serve to minimize confusion surrounding drug selection, particularly among non-pediatric rheumatologists.

Targeted synthetic DMARDs or Janus kinase inhibitors (JAKis) are the newest DMARDs in the management of arthritis. One clear attraction for children is that they are available in oral form. Thus far, three JAKis (tofacitinib, baricitinib, and upadacitinib) were US Food and Drug Administration (FDA) approved for patients 2 years and older with pcJIA, who have an inadequate response to one or more csDMARDs or bDMARDs. They all have comparable safety profiles to TNFi. Notwithstanding the appeal of their oral formulation, there has been no direct comparative study between any JAKis and TNFi or other non-TNFi bDMARDs. The cost remains high, especially in comparison to TNFi biosimilars, and they are not readily available across the region. Therefore, their use is limited.

12. *TNFi biosimilars are acceptable alternatives for use as initial or when switching biologic DMARDs. (PICO 26; LoA 9.7 [0.6])*

In recent years, the introduction of biosimilars has significantly improved the accessibility of bDMARDs, particularly TNFi, across various regions in the Asia Pacific, primarily due to their cost-effectiveness. Several JIA cohort studies, including one from China, exploring either head-to-head or non-medical switching of TNFi, have demonstrated comparable safety and efficacy profiles of etanercept and adalimumab biosimilars in comparison with their originators [28–32, 60–62]. The TF expected that the uptake of TNFi biosimilars should be increasing across Asia-Pacific regions in the near future.

13. *In patients who failed the first TNFi (primary failure), we recommend switching to a non-TNFi over switching to a second TNFi. In patients receiving the second biologic or targeted synthetic DMARD, practitioners may consider using either intravenous or subcutaneous abatacept, tocilizumab, oral baricitinib, oral tofacitinib, or oral upadacitinib. There is insufficient evidence for the use of anakinra or rituximab. (PICO 7, 10; LoA 9.2 [0.9])*

This statement is a strong recommendation despite the overall low certainty of supporting evidence (B [baricitinib, tofacitinib], C [abatacept, tocilizumab], D [rituximab, anakinra]). The strength of this statement was upgraded based on data from adult rheumatoid arthritis that have indicated superior outcomes with switching to a non-TNFi once the initial response to the first TNFi has been inadequate or failed (primary failure) [19]. This statement also aims to prevent drug selection confusion. The TF acknowledges the switch to a second TNFi in case of secondary failure (a good initial response, followed by reduced or failed response later), particularly where ADAbs were demonstrated. Once more, there is no specific recommendation regarding the selection of non-TNFi bDMARDs, since other bDMARDs classes and tsDMARDs demonstrated comparable safety and efficacy profiles. The choice will be influenced mainly by factors such as local

availability, cost, and patient values and preferences [26]. A shared decision-making discussion is needed in this selection process. There is insufficient evidence for the use of anakinra or rituximab in the management of pcJIA.

3.2.3 | Maintenance Therapy and Therapy Discontinuation: Patients With Polyarticular-Course JIA Who Achieved INACTIVE Disease

14. *In patients taking methotrexate, we recommend considering tapering or stopping methotrexate after at least 6 months of inactive disease. (PICO 25; LoA 9.3 [1.2])*

This statement is a strong recommendation based on the high certainty of evidence and concurs with the existing guideline [33]. Previous studies have shown that the flare rates between early MTX discontinuation (≤ 6 months) and late MTX discontinuation (> 6 months) were not different [63, 64]. The TF considered patients' and caregivers' preferences regarding the potential MTX toxicity, pain from injection, and its related frequent clinic visits for injection and the frequent blood tests for toxicity monitoring while taking the drug. Some of the TF members had concerns regarding the CID duration before MTX discontinuation, particularly for patients with significant joint damage. After a round of debate, a consensus was reached to soften the CID duration to at least 6 months, instead of 6 months to allow some flexibility. This is supported by another study, but of lower certainty of evidence that the likelihood of a disease flare in follow-up was negatively associated with time in CID under MTX treatment before its discontinuation [65].

15. *For TNFi, we recommend tapering over the abrupt withdrawal of TNFi after 6 months of inactive disease, and prolonging the interval of TNFi is preferred to dose reduction. (PICO 25; LoA 9.3 [1.0])*

Significantly higher flare rate was demonstrated when TNFi was abruptly stopped as compared to the tapering strategy [66]. Moreover, TNFi dose reduction makes no difference in flare rate compared to interval prolongation, thus the TF recommends the interval prolongation as the preferred weaning approach [67]. A recent study from Singapore exploring the weaning regimens found that duration of TNFi (adalimumab) weaning may not affect the rate of flare after TNFi discontinuation [68]. However, recapture rate was almost universal after TNFi reintroduction [68]. Further study is needed to determine the best weaning strategy to minimize the risk of ADAb development and be more cost-effective.

16. *In patients taking a combination of methotrexate and TNFi, there is insufficient evidence to determine the optimal sequence for medication withdrawal after 6 months of inactive disease. (PICO 25; LoA 9.3 [1.1])*

There is no recommendation for this issue as the TF could not come to a definite consensus. The TF recognized that the high cost of TNFi (and other bDMARDs) will have a significant impact on the choice in many areas of the region. The TF recommends a shared decision-making discussion to determine the sequence of the MTX and TNFi withdrawal, considering the associated benefits and harms of each choice.

Stopping MTX first could be the patient and caregiver preference due to the above-mentioned inconveniences, but it could theoretically increase the risk of ADAb development [59, 69]. Although a previous cohort study has shown that discontinuing TNFi first led to a higher flare rate, it was graded as low certainty of evidence [70]. However, incorporating the values and preferences of the patients and caregivers, as well as acknowledging the limited resources of TNFi, is essential.

3.2.4 | Monitoring of Disease Activity

17. *We recommend regular/routine use of cJADAS-10 to monitor disease activity. (PICO 12; LoA 9.4 [0.7])*

The treat-to-target strategy is one of the consensus statements' OPs in the treatment of JIA (see above). An objective outcome measure is required to determine the treatment target. Many outcome measures were developed for JIA; however, the Juvenile Arthritis Disease Activity Score (JADAS), particularly the clinical version, cJADAS, remains the simplest and most practical and feasible to use in routine patient care, especially in a busy clinic setting in the Asia-Pacific region, where the shortage of health care providers is paramount [71]. The tool can be scored without a laboratory test, which is unavailable in many places in the region. The cJADAS is a reliable and validated outcome tool and it comprises only 3 clinical domains: (1) physician's global assessment of disease activity (PGA) visual analogue Scale (VAS) 0-10 cm; (2) parent/patient's global assessment of well-being (PtGA) VAS 0-10 cm; and (3) active joint counts up to 10 joints, with a total score of 30. Clinical inactive disease was defined as cJADAS ≤ 2.5 and low disease activity 2.6–5.0 for pcJIA [40].

18. *In patients with positive rheumatoid factor/anti-citrullinated protein antibodies or with adverse prognostic factors regardless of antibody status, we suggest performing routine X-rays of the wrists, hands, forefeet, and other affected joints at diagnosis, 1 year after disease onset, and during the transition from pediatric to adult healthcare. The use of X-rays during follow-up is at the discretion of the treating practitioner. (PICO 11; LoA 8.1 [1.9])*

This statement had supporting evidence of moderate certainty, according to the existing guideline developed by the French societies for rheumatology, radiology, and pediatric rheumatology in 2018. However, it was downgraded to a weak recommendation based on the patient and caregiver values and preferences, and resource used concerning the cost and radiation exposure to children. The TF underscored that conventional radiography or X-ray is to assess bone and joint damage or to rule out other diseases, not for the diagnosis of arthritis. In many parts of our region, the access and availability of other imaging modalities—musculoskeletal ultrasound (MSUS), computed tomography (CT), or MRI are very limited, and more cost is incurred. Furthermore, many places still lack MSUS technicians

or radiologists with expertise in performing and interpreting the MSUS scans, especially in children. X-rays remain a feasible mode of assessing damage, despite not being as sensitive as other modes.

Studies, particularly focusing on early pcJIA, have shown that joint space narrowing and erosion predominantly occurred in the hands, wrists, and feet [35]. Moreover, these radiographic damages were found in the asymptomatic joints, particularly the hands and feet in relatively high proportion (36% and 39%, respectively) [72]. Patients with *adverse prognostic factors*, including early involvement of the wrists, distal small joint involvement, symmetrical arthritis, elevated ESR/CRP, or bone erosions on previous radiographs are at higher risk of unfavorable outcomes with further joint damage or disability [35, 72–76]. The existing guideline recommended repeating the X-rays at 1 year since radiographic progression was greater during the first year [75]. The X-rays of the wrists, hands, forefeet, and *other affected joints* (joints with active arthritis, limited range of motion, or deformities) at diagnosis were suggested to set as a baseline to monitor progression as well as to guide the treatment, as joint damage may require a swift escalation of therapy (Statement 3). Another time to consider the X-rays is during the transition from pediatric to adult healthcare, for which a thorough damage assessment should be done before the handover procedure [77]. The panel suggests that the follow-up X-ray intervals are determined by treating practitioners given each patient's disease activity and circumstance.

19. *In patients with negative rheumatoid factor/anti-citrullinated protein antibodies without adverse prognostic factors, clinicians may consider X-ray of the symptomatic joints at their discretion. (PICO 11; LoA 9.5 [0.7])*

This statement is a weak recommendation based on a very low level of certainty of supporting evidence, considering the patient and caregiver values and preferences, and the resources used to address cumulative radiation exposure and cost incurred. It is encouraged to have a shared decision-making discussion between patients and caregivers and the treating practitioners.

3.2.5 | Non-Pharmacologic Therapy

3.2.5.1 | Physical/Occupational Therapy.

20. In patients with JIA who have functional limitations, we recommend referring them for physical and occupational therapy, regardless of concomitant pharmacological therapies. (PICO 23, LoA 10.0 [0])

This is a strong recommendation despite the very low certainty of supporting evidence. Studies, including 5 RCTs and 2 observational studies, evaluated the effectiveness of physiotherapy and occupational therapy interventions [78–85]. One RCT assessed an aquatic group exercise program, and the rest assessed a land-based exercise program. Only the former intervention demonstrated a significant improvement in the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) scores and Juvenile Arthritis Functional Assessment Scale scores (JAFAS) [84]. The observational studies produced conflicting results, as one single-arm observational study assessed the feasibility and safety of a 6-month exercise program to increase bone and muscle strength in children with JIA, and another investigated the effects of an 8-week weight-bearing physical conditioning program on disease signs and symptoms in children with chronic arthritis [79, 80]. The former reported no sustained improvements in bone and muscle strength or clinical outcomes, while the latter showed a decrease in mean Articular Severity Index from 28.9 (SD 25) to 17.6 (SD 19.9) and in mean VAS pain scores, 16% from study entry to the post-exercise test. One RCT compared the clinical efficacy of custom foot orthotics, prefabricated shoe inserts, and supportive athletic shoes worn alone in reducing pain and improving function for children with JIA. The orthotics group showed significantly greater improvements in overall pain ($p = 0.009$), speed of ambulation ($p = 0.013$), activity limitations ($p = 0.002$), foot pain ($p = 0.019$), and level of disability ($p = 0.024$) when compared with the other two groups [81].

Although all the evidence thus far was graded from moderate to very low certainty of evidence, depending on the outcomes measured, the TF experience and patients' and caregivers' values and preferences in the significant benefits of physical and occupational therapy (maintaining and improving joint range of motion, muscle strength, and endurance; reversing functional deficits; improving coordination and activities of daily living) outweighed the harms and the statement was upgraded, underscoring the importance of the intervention, particularly in patients with limited physical function or disability [18].

3.2.6 | Traditional and Complementary Medicine

21. *In patients with JIA on medical therapy, practitioners might allow patients to undergo manipulative and body-based practices such as massage therapy and yoga to improve pain by trained professionals. (PICO 24; LoA 8.4 [1.2])*

This statement is a weak recommendation based on very low certainty of supporting evidence. Two studies evaluated the manipulative and body-based practice. A study compared massage therapy (15-min/day massage by trained parents for 30 days) to relaxation therapy (15-min relaxation session with their parents for 30 days) in patients with JIA and noted a significant reduction in pain, number of active joints, and duration of morning stiffness [86]. Another recent study compared yoga therapy to home exercise and showed improvement in rest pain score, six-minute walking distance, and quality of life score in the yoga group but not in the home exercise group [87]. However, the overall quality of evidence is very low due to heterogeneity in the two studies, the small sample size, and the non-randomized nature of the studies (Appendix S2). One observational study for mind-body medicine examined the utility of a psychological treatment package for children with high levels of pain associated with JIA. The package included relaxation training, electromyogram, and thermal biofeedback for the child. Of the

eight children recruited, there was a significant reduction in self-reported pain diary scores and patients who reported high pain periods. However, the overall certainty of the evidence remains very low. A Canadian study assessed the use of various T&CM in patients with JIA over a 1-year period and demonstrated that the use of T&CM was associated with subsequent lower global health and physical functioning, with no improvement in health-related quality of life or decrease in pain or disease severity [88]. The investigators hypothesized that the use of T&CM while continuing conventional or medical treatment may be time- and energy-consuming for the children and the family, and the combination of these therapies could increase the stress and fatigue of both parties [88].

Despite their beneficial effects on the critical outcomes (disease activity and morning stiffness) and important outcome (pain), the TF has concerns about this mode of manipulation practice in the region and strongly advises that only a trained professional perform or supervise these manipulations. A shared decision-making process is encouraged to discuss the benefits and trade-offs of these interventions.

22. *In patients with JIA and active arthritis, there is insufficient evidence to recommend for or against biologically based products and supplements. (PICO 24; LoA 9.8 [0.5])*

There is no recommendation on this statement. The existing guideline strongly recommends against the use of a specific diet to treat JIA and weakly recommends against the use of supplemental or herbal interventions specifically to treat JIA with the main concerns of restricted diets causing malnutrition, delay in medical treatment, and safety concerns on the biologic products [18]. These are based on very low quality of supporting evidence.

Three RCTs and two observational studies were included for biologically based products. One study on vitamin D supplementation showed that vitamin D supplementation (2000 IU/day) for 24 weeks raised serum levels of 25-OH vitamin D in JIA patients but did not reduce disease activity or improve bone mineral density [89]. One study on probiotics failed to show any significant immune or clinical effects over NSAID therapy. However, there were no significant adverse events, and serum IL-6 levels showed a decrease in the probiotic group [90]. One RCT on blueberries demonstrated that blueberries in combination with etanercept resulted in better ACR30/50/70 responses compared to placebo and etanercept [91]. In addition, there were no significant adverse events in the blueberry/etanercept group. Blueberries were also shown to reduce the levels of IL-1 alpha and beta and increase the level of IL-1RA. Two other observational studies on Radix Tripterygium wilfordii Hook F and Kre-Celazine (an oral, non-prescription, nutritional supplement composed of a proprietary alkali-buffered creatine monohydrate and acetylated fatty acids mixture) showed improvement in pain and active joints for patients with JIA, but these are non-randomized studies with small sample sizes; hence, the certainty of evidence remained very low [92, 93].

Without convincing evidence of the biologic products, it is important to consider their safety, drug interactions, and cost. However, it is important to emphasize that under no circumstances will these T&CM be used in isolation without medical therapy to treat patients with JIA.

3.3 | Consensus Statements on the Temporomandibular Joint (TMJ) Arthritis Management (Figure 2 and Table 3)

TMJ arthritis was reported in 17%–87% of patients with JIA [94]. Unfortunately, there is no prevalence data in the Asian population. TMJ arthritis has an impact on orofacial function and interferes with facial growth and development, particularly in skeletally immature children, causing significant impairment in quality of life [20]. Early detection and prompt treatment are pivotal in preventing irreversible damages [95, 96]. Despite an increased awareness of TMJ arthritis, there is a paucity of data to guide treatment [96]. The goal of TMJ arthritis treatment remains inactive disease, preferably documented by a contrast-enhanced MRI [20]. It is unknown if the mild or low degree of inflammation of the TMJ will provide an acceptable normalized mandibular growth [20].

3.3.1 | Patients With ACTIVE Temporomandibular Joint Arthritis

3.3.1.1 | Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

1. *We suggest using NSAIDs as adjunct therapy. There is insufficient evidence on the preferred NSAIDs. (PICO 13, LoA 9.8 [0.4])*

This statement is a weak recommendation based on very low certainty of supporting evidence. This is an expert opinion, as there is no published study. The TF reached a consensus to use NSAIDs to relieve the pain and discomfort of active TMJ arthritis while waiting for the csDMARD to take therapeutic effects.

3.3.2 | Glucocorticoids

2. *There is insufficient evidence to recommend for or against oral glucocorticoids. (PICO 14; LoA 9.7 [0.5])*

There is no recommendation since there is no data on the use of oral glucocorticoids in TMJ arthritis. The TF acknowledged that in some cases, a bridging therapy with glucocorticoids may have beneficial effects. However, under no circumstances will oral glucocorticoids be used for monotherapy (OP4).

3. *Intra-articular glucocorticoid injection may be considered as an adjunct therapy. However, repeated glucocorticoid injections should be cautious. (PICO 14; LoA 9.4 [0.7])*

Existing guidelines conditionally (weakly) recommend intra-articular glucocorticoid injection to TMJ, particularly in active TMJ arthritis with significant orofacial symptoms, but caution

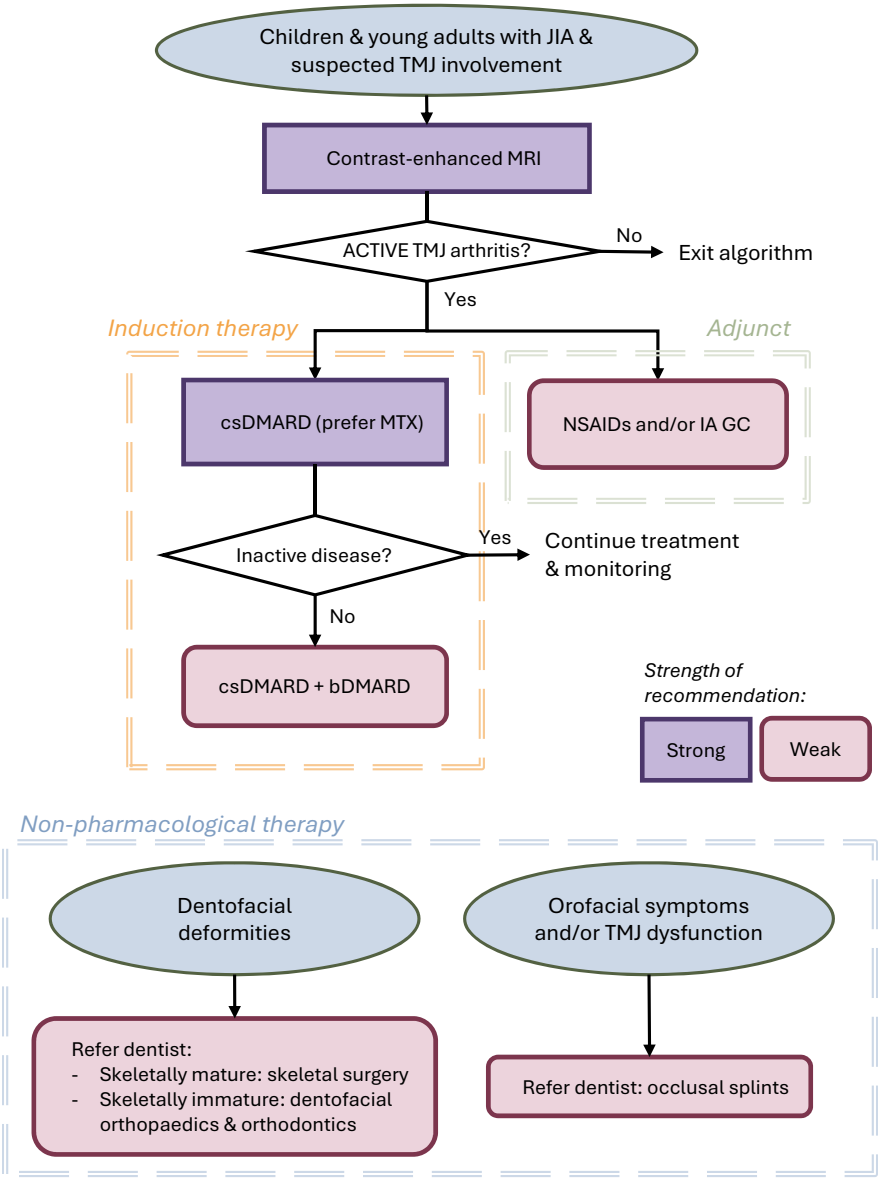

FIGURE 2 | Treatment algorithm for Temporomandibular joint arthritis. bDMARD, Biological disease-modifying anti-rheumatic drug; csDMARD, Conventional disease-modifying anti-rheumatic drug; GC, Glucocorticoid; MTX, Methotrexate; NSAID, Non-steroidal anti-inflammatory drug; TMJ, Temporomandibular joint.

for repeated injections [17, 20]. There is no preferred agent due to a lack of comparative data between different intra-articular glucocorticoid formulations for TMJ injections. Two observational studies were included. One assessed the effects of CT—guided glucocorticoid injection into the TMJ in JIA children with clinical and MRI evidence of TMJ arthritis. Twenty-three were recruited (triamcinolone acetonide [$n = 16$] or triamcinolone hexacetonide [$n = 7$]). About three-quarters had complete resolution of pain, while maximal incisal opening (MIO) improved by at least 0.5 cm in 43% of cases. Patients under 6 years of age at the time of injection showed the best response, with a post-injection MIO similar to that of age-matched healthy children. Resolution of effusion on MRI was noted in 48% of the TMJs involved. No significant adverse events were reported. There was no comparison between patients receiving triamcinolone acetonide and triamcinolone hexacetonide [97].

Another study analyzed the effect of intra-articular lavage in JIA patients with clinical and radiographic evidence of TMJ arthritis compared with intra-articular glucocorticoid injection. Twenty-one patients underwent lavage and intra-articular glucocorticoid injection in at least one TMJ. Notably, these patients may have either undergone no intervention on the other side or a TMJ lavage alone. Eight patients underwent TMJ lavage of at least one TMJ, while 12 patients were followed with no intervention on either TMJ. MRI examination revealed 43% had an improvement at the 6-month follow-up in the lavage with intra-articular glucocorticoid group compared to 31% and 28% in the lavage and no treatment groups, respectively [98]. However, overall certainty of this evidence is very low. Furthermore, there are some potential concerns regarding the mandibular growth arrest, nerve injury, and intra-articular calcification after the injection [96].

TABLE 3 | APLAR consensus recommendations for temporomandibular joint (TMJ) arthritis.

	Recommendation statements	SoR	CoE	%A
Treatment				
For children and young adults with ACTIVE TMJ arthritis.				
NSAIDs				
1	We suggest using NSAIDs as adjunct therapy. There is insufficient evidence on the preferred NSAIDs	2	D	100%
Glucocorticoids				
2	There is insufficient evidence to recommend for or against oral glucocorticoids	0	N	100%
3	Intra-articular glucocorticoid injection may be considered as an adjunct therapy. However, repeated glucocorticoid injections should be cautious	2	D	89%
Conventional synthetic DMARDs				
4	We recommend initial therapy with a conventional synthetic DMARD over NSAID monotherapy. Methotrexate is preferred to other conventional synthetic DMARDs	1	C	100%
5	There is insufficient evidence to recommend for or against conventional synthetic DMARD over biologic DMARD as initial therapy	0	N	100%
6	In patients who failed the first conventional synthetic DMARD, we suggest adding a biologic DMARD over changing to a second conventional synthetic DMARD	2	D	100%
Biologic/targeted synthetic DMARDs				
7	In patients starting biologic DMARDs, there is insufficient evidence for the preferred order of biologic DMARDs. There is also insufficient evidence for the preferred order of targeted synthetic DMARDs	0	N	100%
Non-pharmacological therapy				
8	We suggest referring to the dentist to consider skeletal surgery in skeletally mature patients with dentofacial deformities, as well as dentofacial orthopedics and orthodontics in skeletally immature patients	2	D	100%
9	The use of occlusal splints in patients with orofacial symptoms and/or TMJ dysfunction may be considered as per the dental practitioner's advice	2	D	100%
Disease monitoring				
10	In patients with JIA and suspected TMJ involvement, we recommend contrast-enhanced MRI to detect active TMJ arthritis. There is insufficient evidence to recommend for or against serial MRI to monitor disease activity during follow-up	1	B	100%

Note: SoR (strength of recommendation): 0 = absence of SoR, 1 = strong recommendation, 2 = weak recommendation; CoE (certainty of evidence): A = high, B = moderate, C = low, D = very low, *N* = no evidence; %A (agreement): percentage of consensus panel members agreeing with the recommendation statement.
Abbreviations: DMARD, disease modifying anti-rheumatic drugs; NSAID, non-steroidal anti-inflammatory drug.

3.3.3 | Conventional Synthetic DMARDs

4. *We recommend initial therapy with a conventional synthetic DMARD over NSAIDs monotherapy. Methotrexate is preferred to other conventional synthetic DMARDs. (PICO 15; LoA 9.9 [0.3])*

This statement is a strong recommendation based on low certainty of supporting evidence, but the SoR was upgraded, considering no existing data on TMJ arthritis treatment and the potential of delayed treatment on mandibular growth and development. The TF suggests MTX as the first-line DMARD therapy as an expert opinion recommendation based on the vast experience in using it in JIA management, and the availability and cost of the drug [96, 99]. Moreover, there are some reports on the efficacy of MTX in treating TMJ arthritis in JIA patients compared to other DMARDs [94, 99].

5. *There is insufficient evidence to recommend for or against conventional synthetic DMARD over biologic DMARD as initial therapy. (PICO 16, 19; LoA 9.5 [0.8])*

There is no recommendation on this issue since there is no comparative data to guide therapy. Considering the availability and cost of MTX compared to bDMARDs, and despite the availability of biosimilars, the TF preferred MTX as first-line therapy regardless.

6. *In patients who failed the first conventional synthetic DMARD, we suggest adding a biologic DMARD over*

changing to a second conventional synthetic DMARD. (PICO 16, 17; LoA 9.8 [0.5])

A small descriptive study from Saudi Arabia reported the efficacy of various bDMARDs (infliximab, adalimumab, abatacept, tocilizumab, secukinumab, and ustekinumab) [100]. However, there was no comparison between biologic DMARDs and patients without biologic/targeted synthetic DMARDs. Two retrospective cohorts examined the effect of intra-articular infliximab. There was no significant improvement in the acute findings of TMJ arthritis on MRI imaging after intra-articular infliximab [101]. When compared to intra-articular glucocorticoids, there was no significant difference in MIO, improvement in acute synovitis, or improvement in chronic synovitis [102]. However, patients on intra-articular infliximab (79%) showed substantial improvement in chronic synovitis without adverse events. Overall, these retrospective cohorts were of very low certainty of evidence. The TF remains in favor of adding TNFi, mimicking the management of pcJIA, with the same reason: availability and accessibility, and more affordable cost of TNFi biosimilars or their originals (in some areas) as compared to non-TNFi bDMARDs. Again, adding TNFi to MTX would have not only synergistic effect but also ADAb prevention. The TF expects that more data on TNFi in the management of TMJ arthritis as a combination with csDMARDs, especially MTX, or monotherapy will be available after these consensus statements become public.

3.3.4 | Biologic/Targeted Synthetic DMARDs

7. *In patients starting biologic DMARD, there is insufficient evidence for the preferred order of biologic DMARDs. There is also insufficient evidence for the preferred order of targeted synthetic DMARDs. (PICO 18; LoA 9.7 [0.6])*

There is no recommendation on the sequence of bDMARDs or tsDMARDs since there is no information in this area. For the reasons outlined above, the TF favors TNFi.

3.3.5 | Non-Pharmacological Therapy

8. *We suggest referral to the dentist to consider skeletal surgery in skeletally mature patients with dentofacial deformities, as well as dentofacial orthopedics and orthodontics in skeletally immature patients. (PICO 22; LoA 9.7 [0.8])*

The management of TMJ arthritis should involve a multidisciplinary team of providers involved in dentofacial management, particularly for patients with dentofacial deformities [20]. The TF members all agreed that the treatment of arthritis-related dentofacial deformity requires other disciplines, including dentofacial orthopedics and orthodontics, which may improve facial development, occlusion, and function in skeletally immature patients. In some circumstances, skeletal surgery may be indicated once the inflammation is quiescent. Moreover, screening and monitoring of the oral cavity focusing on dental decay, gingivitis, and ulcerations can be achieved by this multi-disciplinary team.

9. *The use of occlusal splints in patients with orofacial symptoms and/or TMJ dysfunction may be considered as per the dental practitioner's advice. (PICO 20; LoA 9.6 [1.0])*

Oral occlusal splint is one of the most used modalities in TMJ diseases and was reported to improve JIA-related orofacial dysfunction and symptoms significantly [94]. It also has a role in dentofacial deformity management [20]. The splints are designed to provide support and balance to both TMJs, thus helping to prevent further pain and discomfort in the TMJ complex [94]. The TF emphasizes that this modality of treatment will be prescribed exclusively by dental providers.

3.3.6 | Disease Monitoring

10. *In patients with JIA and suspected TMJ involvement, we recommend contrast-enhanced MRI to detect active TMJ arthritis. There is insufficient evidence to recommend for or against serial MRI to monitor disease activity during follow-up. (PICO 22; LoA 9.7 [0.8])*

Despite its higher cost and availability, contrast-enhanced MRI remains the gold standard to diagnose active TMJ arthritis as well as to assess joint damage, as this imaging modality has been extensively studied and validated [103–105]. The readers are encouraged to consult the publications elsewhere for MRI of the TMJ protocol and atlas for detection and grading, since some findings could be a normal variation in a healthy TMJ rather than a sign of active TMJ arthritis [20, 103–105]. Ultrasound of the TMJ has limited sensitivity to detect TMJ inflammation and it is known to be heavily operator dependent [20]. The panel emphasizes that accurate patient history and clinical orofacial examination should precede imaging in the diagnostic sequence for TMJ arthritis [20].

4 | Discussion

This consensus statement marks the first effort by APLAR to provide regional recommendations for the management of pcJIA, TMJ arthritis, and specific non-pharmacologic approaches. Several unique considerations in the Asia-Pacific region influenced the development of this consensus. First, pediatric rheumatologists may not be readily available in certain areas, and this means that many JIA patients are often treated by general pediatricians, general practitioners/internists, adult rheumatologists, or nurses [15]. This calls for simpler management algorithms that avoid unnecessary complexity. Second, healthcare access is limited in some areas, and sociocultural tendencies that normalize pain in children may lead to delayed referrals and a higher disease severity at diagnosis [106]. Third, drug availability and affordability beyond csDMARD remain major issues in many countries in this region. Finally, the Asia-Pacific region encompasses a heterogeneous group of healthcare settings, including both high-income settings with advanced rheumatology services and resource-limited systems. Therefore, recommendations were graded to accommodate local practitioners and resources, giving professionals the flexibility to adapt them to their local availability and affordability.

TABLE 4 | Key differences between the current APLAR consensus recommendations and other Western guidelines.[a,b]

Domains	2025 APLAR consensus statements	Western guidelines/ recommendations
Polyarticular course JIA		
Glucocorticoids	Suggest against pulse glucocorticoid therapy in any disease stage	Not mentioned
DMARDs	Recommend initial therapy with csDMARDs over bDMARDs	Conditionally recommend initial therapy with csDMARDs over bDMARDs
	Suggest MTX as 1st line csDMARD therapy	Mentioned but not clearly stated
	Suggest MTX in combination with bDMARDs, and never use bDMARD monotherapy	Suggest any csDMARDs combination with bDMARDs
	Suggest TNFi as 1st bDMARD	Not explicitly specified
	Recommend switching to a non-TNFi in primary failure	Switching to a non-TNFi is only conditionally recommended
	Suggest that JAKi may be used as second line after TNFi primary failure	Does not include recommendations on JAKi
Biosimilars	Suggest non-medical switching to TNFi biosimilars	Not mentioned
DMARD tapering	Recommend the duration of clinical inactive disease before tapering DMARDs	Not mentioned
	Recommendation on tapering over abrupt discontinuation of TNFi	Not mentioned
Treat-to-target and disease monitoring	Recommend the use of cJADAS for disease assessment routinely	Not mentioned, but used for disease activity stratification
Risk stratification	Do not stratify pcJIA patients into different disease activity	Stratified patients into high-moderate and low disease activity using cJADAS cutoffs
Traditional & complementary medicine	Statements on traditional & complementary medicine	Mentioned specific diets and supplemental or herbal interventions to treat JIA
Physical and occupational therapy	Recommend physical and occupational therapy for children and young adults with JIA who have functional limitations	Conditionally recommend regardless of concomitant pharmacologic therapy.
TMJ arthritis		
NSAIDs	Do not recommend NSAID monotherapy for TMJ arthritis, but start MTX as preferred csDMARDs as initial therapy	Suggest a trial of NSAIDs as part of initial therapy. MTX is only conditionally recommended over other csDMARDs
MTX	Recommend starting MTX as preferred csDMARDs as initial therapy	MTX is only conditionally recommended over other csDMARDs
Glucocorticoids	No recommendation on the use of oral glucocorticoids at initial therapy	Recommend against oral glucocorticoids as part of initial therapy
Initial therapy	No recommendation on the preference of csDMARD or bDMARD as initial therapy	bDMARD is conditionally recommended only after failure of at least 1 csDMARD

Abbreviations: bDMARD, biologic disease-modifying anti-rheumatic drug; cJADAS, clinical Juvenile Arthritis Disease Activity Score; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; JAKi, Janus kinase inhibitor; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; pcJIA, polyarticular course juvenile idiopathic arthritis; TNFi, tumor necrosis factor inhibitor.

[a]Six adapted Western guidelines [17–20, 33, 35].

[b]Strong recommendations are indicated by words "recommend or strongly recommend", and weak recommendations are indicated by words "suggest or conditionally recommend".

One important purpose of this consensus statement is to provide information on where the APLAR consensus aligns with and diverges from Western recommendations (Table 4). Consistent with Western guidelines, MTX remains the preferred csDMARD [19]. However, a notable deviation is the recommendation for csDMARDs as the initial therapy before bDMARDs. Western algorithms now increasingly support early biologic use for high-risk patients with poor prognostic features [19]. In contrast, APLAR's strong recommendation for MTX as the initial therapy takes into consideration its availability and affordability compared to bDMARDs. It also highlights the financial pressures imposed by local health authorities, who often require failure of csDMARDs before approving biologic therapy. However, where feasible, early therapy escalation was also mentioned for high-risk patients.

In patients where bDMARD escalation is required, both the APLAR consensus statements and the Western guidelines favor TNFi as the first-line biologic agent. With new evidence supporting the similar efficacy and safety of biosimilars, along with real-world clinical experiences of switching patients from originator to biosimilars, the APLAR consensus more clearly advocates for the use of TNFi biosimilars as an acceptable alternative [60]. Since biosimilars are significantly less expensive than originators, this recommendation has worthwhile health policy implications for the region, as they may reduce cost barriers and improve access to treatment. Furthermore, the consensus statement serves to strengthen the arguments for inclusion of biosimilars in the national formularies, which will hasten adoption and better bridge the treatment gap between high and low-income countries in this region.

The APLAR consensus statement's recommendations on glucocorticoid use highlight one of the most challenging issues due to resource limitations across the Asia-Pacific region. Western guidelines caution against the long-term use of glucocorticoids due to potential growth issues and cumulative organ toxicity. The APLAR consensus similarly endorses avoiding chronic systemic glucocorticoids and their use as monotherapy. The APLAR consensus notes, however, that for some countries, prolonged steroid exposure will be unavoidable due to insufficient availability of csDMARDs or bDMARDs. In those circumstances, the APLAR consensus encourages the cautious use of the lowest effective dose for the least amount of time and the provision of improved access to DMARDS in an effort to minimize steroid use. The APLAR consensus acknowledges recent efforts by the WHO and the Global Task Force on the Essential Medicines List (EML) to expand the children's section on joint diseases, including the listing of MTX, intra-articular glucocorticoids, and selected TNFi [107]. Our recommendations align with the WHO EML and support their prioritization in national formularies as essential care. Doing so will improve the availability and affordability of these medications in low-resource settings across the Asia–Pacific region and ultimately reduce reliance on long-term glucocorticoids.

TMJ arthritis remains a major clinical conundrum. The 2021 ACR guideline recommends earlier MRI for detection and a treat-to-target aim for inactive disease [20]. The APLAR consensus statement TF acknowledges that MRI is not always available or possible, allowing practitioners to prioritize clinical and radiographic assessments. The APLAR consensus statement also identifies a significant gap in evidence-based management of TMJ arthritis. The absence of high-quality data has two main implications. Firstly, in the Asia-Pacific region, where access to MRI and specialized dental or orthodontic care is already limited, practitioners must make treatment decisions based on extrapolations from peripheral joint disease and expert opinion. This increases variability in care and has a significant impact on facial growth and function. Second, this gap exposes a global research need. Addressing this issue can only occur through ongoing international collaboration to develop evidence-based treatment protocols and outcome measures. Otherwise, TMJ arthritis will continue to be an under-discussed cause of disability and poor quality of life for children with JIA around the world.

Given the deficit of pediatric rheumatologists in the Asia-Pacific region, there is a need for a practical guideline that non-specialist providers can follow. This was taken into consideration while making several adaptations. The TF focused on MTX as the preferred initial csDMARD to reduce treatment complexity for non-pediatric rheumatologist practitioners and adult rheumatologists managing JIA patients. Instead of other outcome measures, the TF recommends using cJADAS-10 because it makes disease activity monitoring easier in busy clinics with limited healthcare staff. Rather than categorizing patients based on their disease activity (high-moderate or low disease activity), the TF adopted the treat-to-target strategy, whereby practitioners change or alter their treatment to achieve the specified target at each patient visit. Furthermore, the consensus also guides DMARD weaning. This approach would simplify and streamline the management of JIA patients in the region. Additionally, there is also a focus on non-pharmacologic interventions, which a broader spectrum of healthcare providers can undertake.

The APLAR guidelines' strong recommendation for physical and occupational therapy referral takes a more assertive stance compared to Western guidelines. While the evidence remains limited due to a lack of robust trials, the recommendation is strong, reflecting the understanding that physical therapy may be one of the few consistently available treatment options in resource-limited Asia-Pacific settings. This recommendation also recognizes the important contribution that physical and occupational therapy makes in preserving joint range of motion, muscle strength, or functional capacity.

In contrast to Western contexts, T&CM is an integral part of the health-seeking behavior of many patients and their patients/caregivers in the Asia-Pacific region [108]. Western guidelines categorically advise against their use. In contrast, APLAR conditionally allows manipulative and body-based practices like massage therapy and yoga when carried out by trained professionals. This acknowledges the prevalent reliance on traditional or alternative treatment in some areas, while also having structures in place to ensure safety. Although the evidence base remains limited, this nuanced approach to T&CM reflects cultural considerations influencing treatment adherence and patient satisfaction throughout the Asia-Pacific region.

The APLAR consensus statement included a thorough review and analysis of evidence, as well as the representation of

practitioners, parents, and patients from multiple countries in the region. This was important to illustrate that this work aims to provide recommendations that incorporate not only scientific evidence but also the lived experiences of patients with JIA from low- and middle-income countries. Nevertheless, over two-thirds of the recommendations are based on low or very low certainty of evidence, reflecting the scarcity of RCTs in pediatric rheumatology, especially within the Asia-Pacific population. Most of the evidence included is derived from Western cohorts. Moreover, important non-pharmacological management areas, including transition to adult care, vaccination, and unmet psychosocial needs, are not covered in this consensus and would require separate and additional work in the future. There is an urgent need for multinational registries, prospective observational studies, and regionally led RCTs to develop evidence that is relevant to Asia-Pacific populations. Instead of looking into bDMARDs and tsDMARDs, which are limited in access in many countries, more efficacious yet acceptable safety profiles, the use of the combination of existing and available csDMARDs may be needed. Notwithstanding that many pediatric rheumatologists in our region already practice this way, this can be achieved by formulating consensus treatment plans with various (combination) protocols to evaluate and compare each regimen within our multi-national JIA cohorts, with the shared objective of establishing safe and effective treatment regimens throughout the region to enhance both short- and long-term JIA outcomes. Moreover, investigation into the optimal timing and methodology for weaning DMARDs, particularly TNFi, is essential to reduce the incidence of ADAb production, hence mitigating the secondary failure rate and enhancing drug survival, as TNFi, along with its biosimilars, constitutes the most cost-effective and accessible bDMARDs in the region. In the meantime, policy advocacy to expand access to biologics, particularly to obtain biosimilar access to the national formulary, and to expand pediatric rheumatology training programs, is critically important for the field.

5 | Conclusion

The APLAR consensus statements on pcJIA, TMJ arthritis, and non-pharmacologic management are an important milestone toward evidence-based yet culturally relevant care for children with JIA in the Asia-Pacific region. For professionals working in the Asia-Pacific region, these recommendations represent both clinical best practice knowledge and a call to action to strengthen health systems, increase access to effective therapies, and enhance regional research.

Author Contributions

T.A., S.F., L.F.D., and K.L.T. conceptualized the study. All authors contributed to drafting, discussing, modifying, and finalizing the consensus statements. T.A. and K.L.T. drafted the manuscript. K.L.T., N.K.B., C.-Y.W., C.M.A., K.A., P.C., M.C.M.C.-C., N.G.U.C., M.T.C., C.H.J., S.C.L., M.J.H.L., B.L., W.S., and M.B.V. did the systematic literature search and review. All authors edited and approved the final manuscript.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

R.A.J. reports honoraria from Pfizer. All other authors declare no competing interests. This work was funded by the APLAR secretariat to support the online voting platform and other secretary supports. There are no commercial conflicts of interest to be declared.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** APLAR consensus statements on the management of juvenile idiopathic arthritis (JIA) task force member list. **Appendix S2:** Evidence report.

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EDITORIAL

Difficult-To-Treat Psoriatic Arthritis: An Evolving Clinical Construct

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Psoriatic arthritis (PsA) is a complex disease with articular, extra-articular, and extra-musculoskeletal manifestations. Despite therapeutic advances, sustained remission remains elusive for a considerable proportion of patients. This editorial examines the multifaceted reasons behind treatment resistance, evolving definitions of difficult-to-treat (D2T) PsA, and emerging strategies that promise to reshape future management [1].

1 | Lack of Treatment Response in PsA—A Challenging Impediment

Lack of treatment response is often multifactorial, involving both inflammatory and noninflammatory factors. A comprehensive assessment of all clinical domains, comorbidities, and psychosocial influences in patients is crucial.

a. Persistent Inflammation Despite Targeted Therapy: Some patients exhibit active inflammation despite multiple targeted therapies, indicating true refractoriness to treatment, potentially due to a failure in targeting the key inflammatory pathway or immune adaptation. Targeting alternative or multiple cytokine pathways may offer benefits to these individuals.

b. Non inflammatory Contributors: Metabolic factors, notably obesity and smoking may blunt therapeutic responses, highlighting the necessity of integrated lifestyle interventions, including weight loss and smoking cessation in the care of PsA. Equally important contributors such as concomitant fibromyalgia and central sensitization can amplify pain perception and mimic inflammatory activity, complicating clinical evaluation. Psychological comorbidities, depression and anxiety further impair treatment adherence and complicate disease perception and evaluation. Structural joint damage and osteoarthritis may masquerade as joint swelling and pain, calling for judicious use of imaging to avoid overtreatment. Moreover, sex and gender differences and socioeconomic inequalities influence disease burden and access to care, with women frequently reporting greater disease activity and lower drug responsiveness. Other concomitant illnesses like renal or hepatic dysfunction, and uncontrolled diabetes may restrict therapeutic options. Genetic and epigenetic factors like polymorphisms in TNF/TNF receptor and NF-κB pathways modulate drug response. Rapid drug clearance, underdosing, or antidrug antibodies can impair response. Furthermore, PsA domain heterogeneity can influence treatment selection; for instance, IL-23 inhibitors may be less effective for axial disease than IL-17 blockers [2].

2 | Difficult-To-Treat PsA—An Evolving Concept

The concept of difficult-to-treat (D2T) PsA is evolving, with frameworks being introduced by the Group for Research and Assessment in Psoriasis and Psoriatic Arthritis (GRAPPA) and the European Alliance of Associations for Rheumatology (EULAR) [3, 4]. While both definitions were developed through expert consensus, they share common elements. However, there are differences in terminology, treatment thresholds, and inclusion of factors beyond inflammation. GRAPPA introduces a broader concept of Complex-to-Manage PsA (C2M), encompassing treatment intolerance,

comorbidities and coexistent medical conditions, fibromyalgia, nociplastic pain, sex and gender constructs, treatment effects, and region-specific challenges such as access to care [3]. D2T or treatment-refractory represents a subset of C2M, with objective signs of arthritis, enthesitis, dactylitis, or active skin or nail disease, or magnetic resonance imaging (MRI) evidence of axial PsA, despite one or more biologic or targeted synthetic Disease-Modifying Antirheumatic Drugs(b/tsDMARDs) with different mechanisms of action. EULAR, on the other hand, uses the term Difficult-to-Manage PsA (D2M) as an umbrella category, aligning with terminology used in axial spondyloarthritis [4]. True treatment refractory state, which requires failure to respond to two or more b/tsDMARDs with different mechanisms of action, is defined by both the groups (Table 1). Comparing the D2T concept between GRAPPA and EULAR, GRAPPA C2M provides a broader inclusion of patients. The treatment resistance criteria in the EULAR definition, which exclude comorbidities, represent more stringent criteria for patient selection in intervention-specific clinical trials.

3 | Managing Difficult-To-Treat PsA

3.1 | Identifying Difficult-To-Treat PsA

Nearly 1 in 6 patients with PsA met the D2T criteria in a multicentric real-world study, with female sex, obesity, extensive psoriasis, axial involvement, inflammatory bowel disease, fibromyalgia, and depression as risk factors [5]. It is important to verify the diagnosis of PsA and ensure that the root cause of persistent symptoms is the disease rather than comorbidities. This also highlights the need for an in-depth discussion with the patients for drug compliance, investigation into the adverse effects of drugs, evaluation of comorbidities, and discussion of the management plan to maximize treat-to-target strategies.

Integrating clinical, imaging, and biomarker data offers a path to personalized care in PsA. While several promising biomarkers have been identified, most lack clinical validation. Emerging predictors of treatment response include the

TABLE 1 | Comparison of GRAPPA and EULAR Definitions for Difficult-to-Manage Psoriatic Arthritis.

Domain	GRAPPA	EULAR
Umbrella term	Complex-to-Manage (C2M)	Difficult-to-Manage (D2M)
Definition of C2M/D2M	a. Persistent symptoms despite ≥1 b/tsDMARD; includes comorbidities, treatment barriers, overlap syndromes b. Disease perceived as problematic by patient or physician	a. Failure of ≥2 b/tsDMARDs with ≥2 modes of action (MOA), per EULAR recommendations, AND b. Impression of this being problematic per physician and/or patient, AND c. At least one of the following: * Failure to achieve low disease activity, regardless of the cause ** Active EMM *** Objective inflammation (clinical/c-reactive protein and/or imaging)
Strict subgroups (Treatment refractory groups)	Failure to respond to ≥3 treatments for PsA with different MOA (including ≥2 b/ts DMARDs) AND Persistent symptoms recognized as problematic by both the physician and the patient AND Presence of objective signs of inflammation	Fulfillment of D2M criteria PLUS ≥2 of A) Failure to achieve a low disease activity state, B) Active EMMs C) Objective signs of inflammation (c-reactive protein and/or imaging) are mandatory D) Obligatory: Exclusion of comorbidities and psychosocial factors
Treatment failure	C2M/TR: ≥3 treatments (≥2 b/tsDMARDs, ≥2 MOAs)	D2M/TR: ≥2 b/tsDMARDs, ≥2 MOAs
Comorbidities	Included in C2M; not excluded in TR	Included in D2M; excluded in TR
Suitability for Trials	Broad criteria in TR (including comorbidities), reduce specificity for targeted intervention trials	Comorbidity exclusion enhance precision for intervention-specific trials.

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; b/ts DMARDs, biologic and/or targeted synthetic disease-modifying antirheumatic drugs; b, biologic; ts, targeted synthetic; DMARD, disease-modifying antirheumatic drug; EMM, extra-muscular manifestations; EULAR, European Alliance of Associations for Rheumatology; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; MOA, mechanism of action; TR, treatment refractory.

presence of specific CD4+ T-cell subsets, such as Th1 and Th17 cells, genetic variants in the TNF/TNF receptor and NF-κB pathways, epigenetic changes like histone modifications, proteomic markers, autoantibodies, as well as insights derived from AI-driven multi-omic analytics [2]. Until these tools are fully validated and implemented in clinical practice, comprehensive clinical assessment and imaging remain indispensable for guiding treatment decisions and evaluating disease activityssss [6].

3.2 | Optimizing Treatment in D2T PsA

- Drug Sequencing: After two b/tsDMARD failures, switching therapeutics with different mechanisms of action should be considered.
- Combination Therapy: Strategies for the use of combination b/tsDMARDs in PsA lack robust evidence. While the combination of csDMARDs with bDMARDs does not improve efficacy in randomized trials, observational data show heterogeneous, agent-specific effects on drug persistence, with no consistent benefit beyond TNF inhibitors. Added treatment burden and csDMARD-related toxicity limit the routine use of such combinations [7]. Dual-targeted therapy (e.g., TNFi + IL-12/23 or IL-17) shows promise from real-world observational data, with remission rates approaching 60% in refractory cases of PsA or spondyloarthritis [8]. Further research is needed to define the optimal combination therapy regimen in PsA.
- Antidrug Antibodies (ADA): Though the use of b/tsDMARDs in PsA is expanding, the loss of efficacy over time remains a challenge. ADAs can dampen pharmacokinetics and clinical response. The utility of ADA monitoring in clinical care, however, is challenged by the assay diversity and accessibility. Also, the presence of ADA does not correspond to clinical responses. Currently, there is more widespread use of ADA therapeutic monitoring in the management of inflammatory bowel disease, but not for PsA [9].
- Management of Comorbidities: Optimizing the management of comorbidities is vital in PsA as they may shape the inflammatory burden, pain mechanisms, and drug survival. Weight reduction and emerging microbiome-modulating approaches may further improve outcomes, as gut dysbiosis can influence TNF, IL-6, and IL-17 pathways, and potentially modify treatment response. Probiotics, prebiotics and phage therapy have been evaluated with varying results. Glucagon-like peptide-1 receptor agonists can show promise in patients with PsO/PsA and obesity by improving metabolic health and indirectly reducing inflammation, though more rigorous evaluation is required [10]. Multidisciplinary care with shared decision-making supports adherence and alignment with patient priorities.
- Emerging Agents: TYK2 inhibitors, JAK1/STAT3 inhibitors, broader JAK inhibitors, and more drugs targeting IL-17, IL-23, and other mechanisms of action are under active investigation.

4 | Future Directions and Conclusion

Key challenges in D2T PsA include marked clinical and biological heterogeneity, the need for clearer phenotypic definition and classification, limited long-term data on novel therapies, insufficient understanding of residual symptoms such as pain and fatigue, and the lack of validated biomarkers. Priority areas for research include precision medicine to guide the prediction of therapeutic response, b/ts DMARDs combination therapies, and the development of new therapies. Managing D2T PsA remains complex due to its heterogeneous presentation and comorbidities. Comprehensive assessment of disease activity in all PsA domains and adherence to treat-to-target strategies remain fundamental. In addition, evaluating various comorbidities and their management through a multidisciplinary approach, as appropriate, is essential. Personalized treatment significantly enhances outcomes and quality of life in PsA.

Author Contributions

I.K.I. – Conceptualization, writing – original draft. Y.Y.L. – Supervision, review and editing. A.J.M. – Conceptualization, supervision, review and editing. All authors have read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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CLINICAL IMAGE

The Disappearing Jawbone

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A 48-year-old man presented to our department with a 20-year history of acne conglobate and mandibular pain. He initially developed left mandibular pain, followed by atrophy of the mandible. The patient's left mandibular pain resolved within months of a single 30 mg dose of pamidronate, and the atrophy appeared to progress more slowly thereafter. However, pain later developed on the right side. By age 45, he reported left elbow pain. Physical examination revealed mandibular asymmetry, extensive cutaneous and eyelid scarring secondary to acne conglobata (Figure 1A–C), as well as tenderness and swelling of the left elbow with limited extension. Skeletal scintigraphy demonstrated osteitis of the right mandible and alveolar bone, along with increased radionuclide uptake in the sternoxiphoid joint, left sternocostal joint, and left elbow (Figure 1D). Computed tomography confirmed osteolysis of the left mandible (Figure 1E). Magnetic resonance imaging revealed osteomyelitis and hyperostosis of the right mandible (Figure 1F), in addition to synovitis of the left elbow. A diagnosis of SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis) was established. Treatment was initiated with weekly methotrexate (15 mg) and biweekly adalimumab (40 mg), resulting in significant symptomatic improvement.

SAPHO syndrome represents a clinical spectrum encompassing osteoarticular and dermatological manifestations. Mandibular involvement occurs in only about 2% of cases and is frequently overlooked by general practitioners [1]. The cause of mandibular osteolysis in this patient is confusing, as both the underlying disease and bisphosphonate therapy could be responsible. However, the onset of bone atrophy prior to bisphosphonate initiation, along with the osteolytic lesion being localized to the ascending ramus—without typical involvement of the tooth-bearing region seen in bisphosphonate-related osteonecrosis of the jaw—points to SAPHO syndrome as the most likely etiology. Beyond conventional treatments such as NSAIDs, glucocorticosteroids, and conventional DMARDs, biologic agents and targeted DMARDs (e.g., Janus kinase inhibitors) are emerging as effective therapeutic options for SAPHO syndrome [2]. This case illustrates the enduring and disfiguring impact of SAPHO syndrome and underscores the importance of early recognition and intervention.

Author Contributions

X.S. and L.J. managed the patient and drafted the manuscript. K.W. provided the radiographic images. Z.Z. critically reviewed and revised the manuscript. The patient provided written informed consent for publication of this Clinical Picture.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Xiaoying Sun and Lanlan Ji contributed equally as joint first authors.

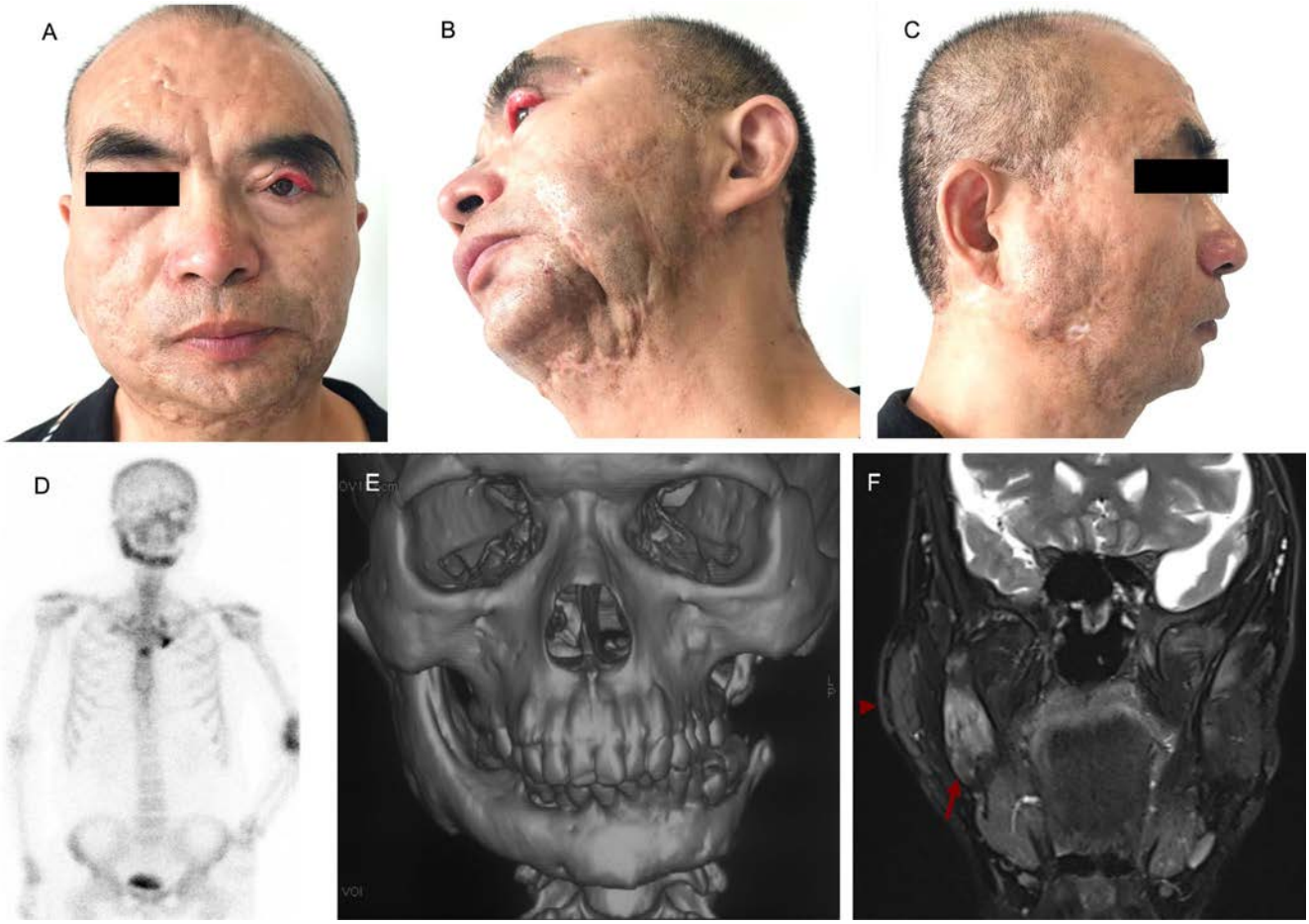

FIGURE 1 | Mandibular osteolysis in a 48-year-old man with SAPHO syndrome. (A–C) Facial asymmetry due to mandibular osteolysis and extensive cutaneous and eyelid scarring (frontal, left, and right views). (D) Skeletal scintigraphy showing osteitis of the right mandible and alveolar bone, along with increased radionuclide uptake in the sternoxiphoid joint, left sternocostal joint, and left elbow. (E, F) CT and MRI revealing osteolysis of the left mandible, bone edema (arrow), and hyperostosis of the right mandible, and inflammatory thickening of the right subcutaneous tissue (arrowhead).

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LETTER TO THE EDITOR

Case Report: IgG4-Related Disease With Isolated Spinal Involvement

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Dear Editor,

IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory condition that can affect multiple organs and tissues [1, 2]. Initially reported in the pancreas, IgG4-RD most commonly involves the pancreas, bile ducts, salivary glands, lacrimal glands, and lungs [3]. Central nervous system (CNS) involvement of IgG4-RD is relatively rare [4]. When the CNS is affected, it mostly manifests as IgG4-related hypertrophic pachymeningitis (IgG4-RHP). Lesions may be located intradural-intramedullary, intradural-extramedullary, dural, or extradural and are typically characterized by dural thickening with enhancement, with or without an associated spinal lesion [5]. In contrast to previously reported cases, the present patient exhibited an isolated spinal lesion without other organ involvement. Spinal infection was initially suspected. However, the markedly elevated serum IgG4 level together with histopathological evidence of IgG4-positive plasma cell infiltration supported the diagnosis of a rare spinal manifestation of IgG4-RD.

A 40-year-old male presented with a four-month history of low back pain. Physical examination revealed lumbar pain with positive percussion tenderness. Pelvic compression and distraction tests were negative, and there was no tenderness over the sacroiliac joints. Neurological examination showed that muscle strength and sensation in all four limbs were intact, muscle tone was normal, and there were no pathological reflexes. Lumbar spine computed tomography (CT) demonstrated osteolytic destruction of the fourth (L4) and fifth (L5) lumbar vertebrae, with more pronounced involvement of the L5 vertebral body (Figure 1a,b). Magnetic resonance imaging (MRI) revealed a mass at the L4-5 intervertebral disc, extending to the inferior border of the L4 vertebral body and progressing toward L5. Additionally, bilateral psoas muscle edema was observed (Figure 1c,d).

Blood tests showed normal white blood cell and neutrophil counts but elevated C-reactive protein (84.6 mg/L; normal: 0.0–6.0 mg/L) and erythrocyte sedimentation rate (54 mm/h; normal: 0–15 mm/h), suggesting an inflammatory mass. A comprehensive microbiological evaluation, including T-SPOT.TB, Xpert MTB/RIF (for *Mycobacterium tuberculosis*), metagenomic next-generation sequencing (mNGS), and fungal and bacterial cultures, ruled out infectious causes. To further characterize the lesion, a CT-guided percutaneous vertebral biopsy was performed. Histopathological analysis of the L5 vertebral lesion revealed marked proliferation of fibrous tissue between trabecular bone structures, scattered hematopoietic cells, and increased plasma cells. Immunohistochemical staining (Figure 2) showed a high density of IgG4-positive plasma cells (approximately 30 per high-power field, with an IgG4+/IgG+ ratio of ~25%). Additionally, serum IgG4 levels were significantly elevated at 4.470 g/L (normal: 0.03–2.01 g/L), strongly suggesting IgG4-related disease (IgG4-RD).

Further immunological tests, including serum assays for anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies (ANA) series, and human leukocyte antigen B27 (HLA-B27) were conducted. All results were negative, ruling out other autoimmune diseases as potential causes, and no evidence of malignancy or multi-segment spinal disease was detected.

Based on the clinical presentation, serological findings, and imaging characteristics, the patient met the 2020 Japanese comprehensive diagnostic criteria for possible IgG4-RD. The patient

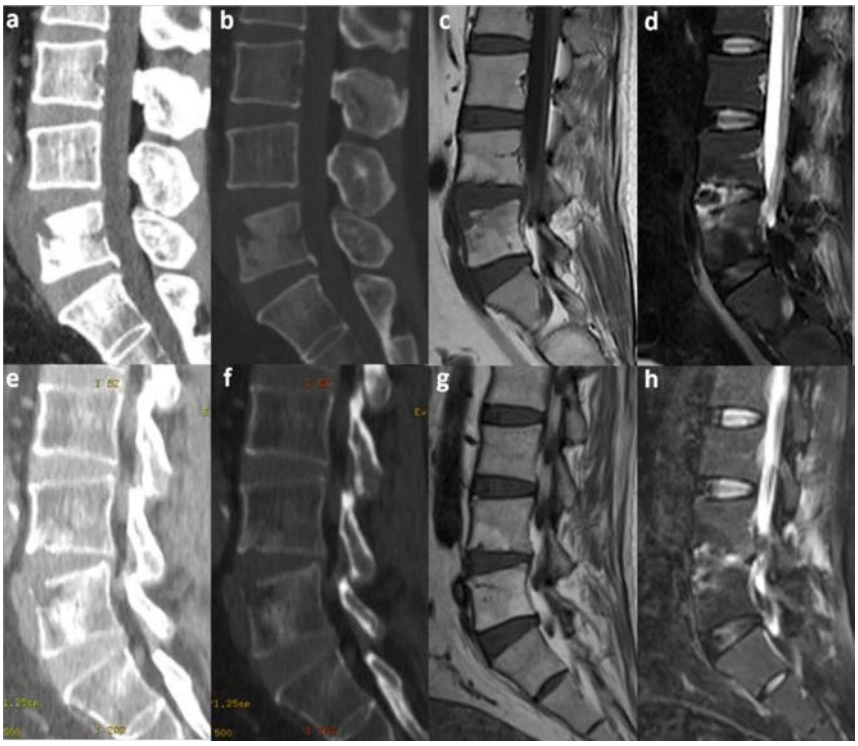

FIGURE 1 | (a–d) showed the initial CT and MRI plain scans; increased bone density was seen in the anterior-middle part of L4-5 vertebra accompanied by focal bone resorption (a, b), the lesion presented as mixed low signal on T1-weighted image (T1WI) and mixed high signal on T2-weighted image (T2WI) (c, d), while the lesion involved the L4/5 intervertebral disc, with blurred edges and mild edema around (a–d). (e–h) showed the follow-up CT and MRIplain scans after three months of standardized treatment; the lesion of L4-5 vertebra was generally increased in density with a slightly shrunken area of bone resorption, of which the T1WI signal was increased, and the T2WI signal was mildly reduced. (a–h) All images are sagittal views: (a, e) CT image (soft tissue window), (b, f) CT image (bone window), (c, g) T1WI, (d, h) FS-T2WI.

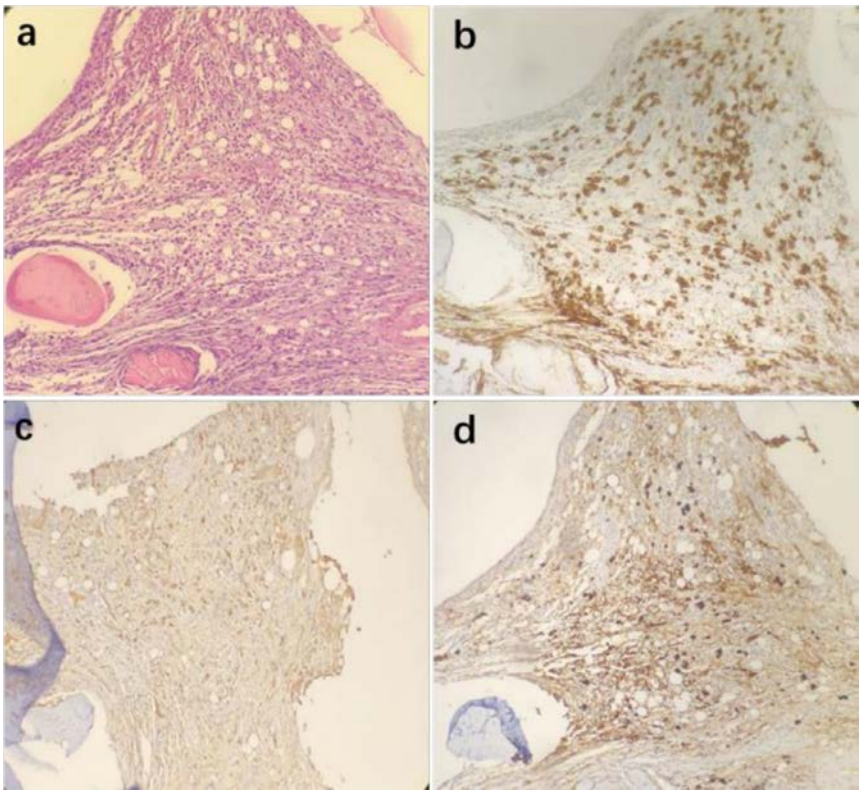

FIGURE 2 | Percutaneous Biopsy: (a) Section showing a dense infiltration of lymphoplasmacytic cells and collagenous fibrosis between bone trabecula ×200; (b) immunohistochemistry showing CD38 staining of plasma cells ×200; (c, d). Section showing the ratio of IgG4+/IgG+ cells 25% and 30 IgG4+ Plasma Cells/HPF ×200.

commenced treatment with oral methylprednisolone (40 mg daily). After two weeks of treatment, he reported significant relief from low back pain. At the three-month follow-up, lumbar spine CT showed increased patchy bone density at the inferior border of L4 and within L5, along with areas of bone destruction (Figure 1e,f). The MRI showed no narrowing of the intervertebral space, but there was heterogeneous signal intensity in the L4-5 vertebral bodies. The adjacent vertebrae exhibited patchy mixed high- and low-intensity signals on T1W1 and T2W1 at their upper and lower margins (Figure 1g,h), indicating an improvement compared to previous scans. Serological indicators, including C-reactive protein (10.5 mg/L), erythrocyte sedimentation rate (10 mm/h), and IgG4 level (1.920 g/L), had decreased, indicating reduced inflammatory activity and an improvement in the patient's condition.

Although IgG4-related disease has been increasingly recognized in recent years, its diagnosis remains challenging because of nonspecific clinical manifestations, overlapping features with other conditions, and the wide spectrum of organ involvement. Spinal involvement in IgG4-RD is particularly rare, especially when presenting as an isolated lesion without concurrent involvement of other organs, which may increase the risk of misdiagnosis or underdiagnosis in clinical practice. Therefore, IgG4-RD should be considered in the differential diagnosis of unexplained spinal lesions, even in the absence of systemic manifestations. Although elevated serum IgG4 levels are not disease-specific, serological testing may provide an important diagnostic clue and prompt further histopathological evaluation.

Author Contributions

Huihui Jin and Xiaoru Xia designed the study; Fei Wang collected the data; Ziyu Guo analyzed the data; Fei Wang and Xiaolan Wang wrote the manuscript. Huihui Jin supervised the research, revised the manuscript critically, and was responsible for all aspects of the work. All authors reviewed and approved the final version.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Ziyu Guo
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LETTER TO THE EDITOR

Monitoring Anti-MDA5 Antibody Titers Associated With Higher GC-Free Maintenance in Patients With Anti-MDA5 Positive RP-ILD

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Dear Editor,

Anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis is a distinct subtype of idiopathic inflammatory myopathy that frequently presents with rapidly progressive interstitial lung disease (RP-ILD) [1]. The current standard of care consists of early triple immunosuppressive therapy—glucocorticoids (GCs), calcineurin inhibitors, and intravenous cyclophosphamide—based on accumulating evidence for improved short-term survival [2]. While induction regimens have become increasingly standardized, the optimal strategy for long-term maintenance remains unclear. Long-term glucocorticoid therapy is associated with considerable toxicity, yet withdrawal is often deferred because of concerns about disease relapse. Observational data on GC-free or drug-free remission remain limited, although a recent study reported such outcomes in a small subset of patients [3]. We, therefore, aimed to describe GC-free maintenance in real-world patients with anti-MDA5 antibody-positive RP-ILD.,

We conducted a retrospective cohort study at Juntendo University Hospital between April 2008 and December 2024, following our previously described methodology [4]. RP-ILD was defined as clinical or radiological deterioration within 1 month after the onset of respiratory symptoms. Anti-MDA5 antibody levels were measured using a commercial ELISA (MESACUP anti-MDA5; Medical & Biological Laboratories, Nagoya, Japan). Patients without ILD or with non-rapidly progressive ILD were excluded. Those who died or were transferred within 12 months of onset were classified as the "early dropout" group and excluded from long-term tapering analyses, as assessment of GC discontinuation requires sufficient follow-up. Analyses of GC discontinuation were conditional on survival and continued follow-up beyond 12 months. This study was approved by the Ethics Committee of Juntendo University Hospital (approval no. E24-0366). Written informed consent was obtained in accordance with the Declaration of Helsinki.

Patients were stratified by calendar era based on the introduction of routine antibody testing at our institution in July 2018. Those diagnosed before July 2018 comprised the pre-monitoring cohort, while those diagnosed on or after July 2018 formed the antibody monitoring cohort. For the pre-monitoring cohort, follow-up beyond July 2018 was censored, with later data analyzed only as Supporting Information. Serum samples collected before commercial assay availability had been routinely preserved at −80°C. The primary endpoint was the time from treatment initiation to GC discontinuation (0 mg/day). GC discontinuation was defined as complete withdrawal of oral GC. Secondary endpoints included GC-free maintenance, defined as GC discontinuation sustained for ≥6 months without re-initiation during that period, overall survival, relapse-free survival, and treatment-related complications. Limited three-level CT scoring was performed [5]. ILD relapses were defined as the recurrence of respiratory symptoms with new interstitial abnormalities on HRCT, after excluding other causes. Organ damage was evaluated using the Myositis Damage Index (MDI) at the final observation [6]. Time-to-event outcomes were analyzed using the Kaplan–Meier method and compared by the log-rank test. As a sensitivity analysis to address potential survivor bias, we performed a 12-month landmark analysis in which follow-up for GC discontinuation started at 12 months after treatment initiation among patients alive and in follow-up at that time. Continuous

and categorical variables were analyzed using the Mann–Whitney *U* and Fisher's exact tests, respectively. Longitudinal GC dose trajectories were assessed by linear mixed-effects models, estimated via restricted maximum likelihood. All analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA).

We identified 61 patients with anti-MDA5 antibody-positive RP-ILD. Two without ILD and 11 with non-rapidly progressive disease were excluded, leaving 48 eligible patients. Twelve patients were classified as early dropouts within 12 months, including nine deaths and three transfers, leaving 36 patients with sufficient follow-up for long-term outcome analyses (13 pre-monitoring, 23 monitoring). Figure S1A shows the overall survival of all 48 patients (including early dropouts). When analyses were restricted to patients with sufficient follow-up, Kaplan–Meier analysis demonstrated no significant survival difference between cohorts (log-rank $p = 0.32$; Figure S1B). Among patients who achieved GC discontinuation and had adequate follow-up, no fatal ILD relapses were observed during follow-up.

Among the nine deaths in the early dropout group, the causes of death were ILD progression ($n = 6$), intestinal perforation (1), iliopsoas hematoma (1), and candidemia (1). Among patients with sufficient follow-up, one patient in the pre-monitoring cohort died of pulmonary adenocarcinoma, and four in the monitoring cohort died of pulmonary adenocarcinoma, acute leukemia, breast cancer, and progressive supranuclear palsy. The latter patient had previously achieved drug-free remission.

Baseline demographics and disease characteristics were generally comparable between cohorts (Table S1), with no significant differences in age, sex, baseline antibody titer, ferritin, or KL-6. The pre-monitoring cohort had higher median creatine kinase levels, but aldolase levels were similar.

Kaplan–Meier analysis showed that the cumulative incidence of GC discontinuation was significantly higher in the monitoring cohort than in the pre-monitoring cohort (log-rank $p = 0.012$; Figure 1A). None of the patients who achieved GC discontinuation required GC re-initiation within 6 months, indicating that discontinuation was sustained during this period. Results were unchanged in the 12-month landmark analysis starting follow-up at 12 months (log-rank $p = 0.012$), consistent with the fact that GC discontinuations occurred predominantly after the first year. Longitudinal trajectories of GC dosing (Figure 1B,C) revealed significantly distinct tapering patterns between groups, which were further characterized using mixed-effects modeling (group effect $F[1, 874.47] = 2356.99$, $p < 0.001$; group × time interaction $F[2, 247.61] = 521.91$, $p < 0.001$). The monitoring cohort showed lower GC use at 12 months and beyond 60 months. Figure S2 illustrates serial anti-MDA5 antibody titers, which declined rapidly after induction in both cohorts without statistically significant inter-group differences at comparable time points where data were available, despite differences in GC tapering patterns. Results were directionally similar after exclusion of patients receiving JAK inhibitors (Figure S3).

In this retrospective cohort, approximately 39% of patients in the antibody monitoring cohort achieved GC-free maintenance,

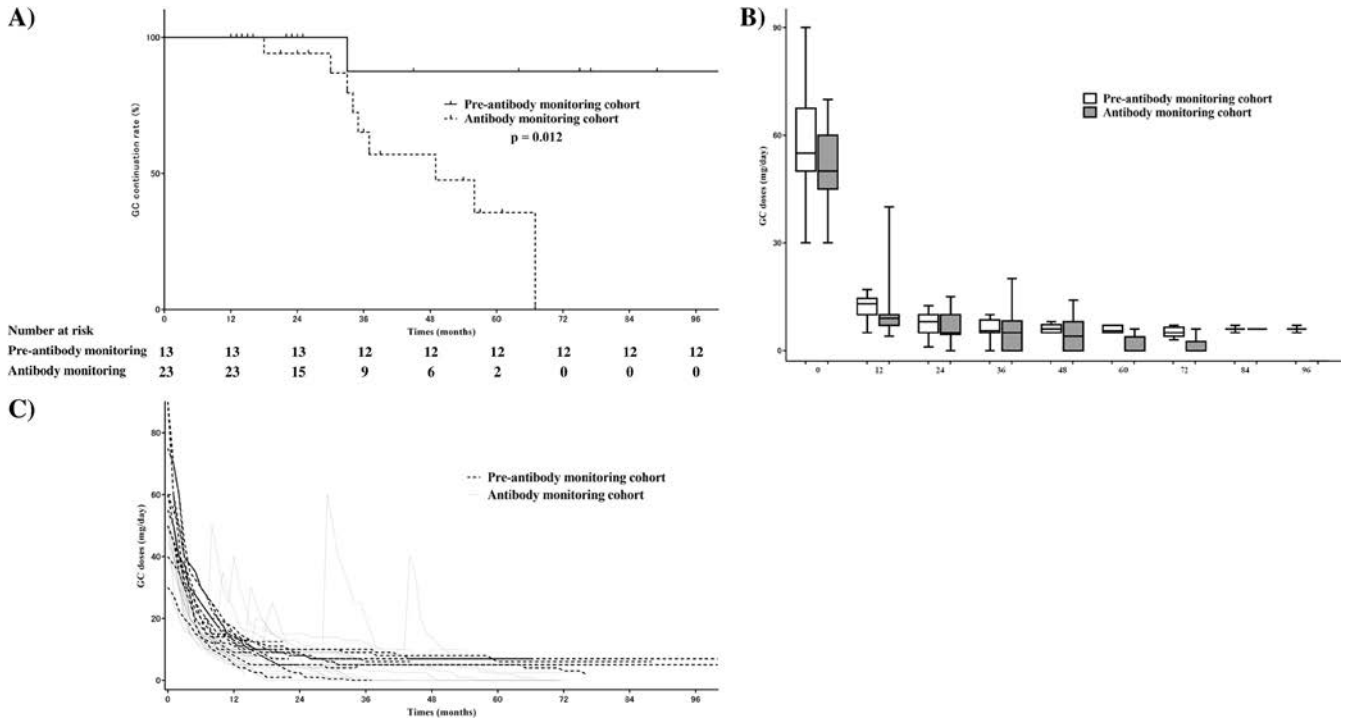

FIGURE 1 | GC tapering between the pre-antibody monitoring and antibody monitoring cohorts. (A) Kaplan–Meier curves for GC discontinuation (0 mg/day). The cumulative incidence of GC discontinuation was significantly higher in the antibody monitoring cohort than in the pre-monitoring cohort (log-rank $p = 0.012$). (B, C) Longitudinal trajectories of daily GC doses in each cohort, demonstrating significantly different tapering patterns (mixed-effects model, $p < 0.001$ for both group and group × time interaction). GC, glucocorticoid.

and 17% reached complete drug-free remission. When considering all long-term survivors, the overall GC-free rate was 28%. After the introduction of routine antibody monitoring, GC tapering was undertaken during a period when serial antibody titers were routinely available in clinical practice. Most discontinuations occurred 30–37 months after treatment initiation, typically at the physician's discretion rather than under a standardized protocol. No fatal or treatment-catastrophic relapses were observed following GC discontinuation during the observation period.

Our findings are consistent with previous studies demonstrating that declining anti-MDA5 antibody levels during remission are associated with prolonged relapse-free intervals, and that re-elevation of titers often precedes clinical relapse, consistent with a role of antibody monitoring as a dynamic marker of disease activity [3, 7–9]. Anti-MDA5 antibody levels were serially assessed during GC tapering in routine clinical practice. Patients who achieved GC-free or drug-free remission generally exhibited low or declining titers, whereas relapses were typically preceded by a titer increase temporally associated with GC re-escalation. This observation supports the hypothesis that serial antibody assessment may serve as a marker of disease activity during long-term management.

This study has several limitations. It was a retrospective, single-center analysis with a small sample size, limiting generalizability. The two cohorts were treated in different calendar periods, and maintenance regimens were determined by physician discretion, introducing heterogeneity; thus, the observed associations may partly reflect evolving practice patterns, including differences in concomitant therapies such as JAK inhibitors. Broader temporal changes in supportive care and clinical decision-making may also have influenced long-term GC management, and residual era-related confounding cannot be excluded. In addition, long-term GC tapering outcomes could only be evaluated among patients who survived and remained in care beyond the first year; therefore, our analysis is conditional and may be subject to survivor bias. However, results were unchanged in a 12-month landmark analysis, supporting the robustness of the observed association.

In conclusion, routine anti-MDA5 antibody monitoring was associated with a higher probability of GC-free maintenance in patients with anti-MDA5 antibody-positive RP-ILD. These findings highlight an association between serologic monitoring and long-term GC tapering in real-world clinical practice.

Author Contributions

Yoshiyuki Abe: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, software, supervision, validation, visualization, writing – original draft. **Motoki Takeuchi:** data curation, formal analysis, investigation, methodology, validation, writing – review and editing. **Takumi Saito:** data curation, formal analysis, methodology, validation, writing – review and editing. **Masahiro Kogami:** data curation, formal analysis, investigation, methodology, validation, writing – review and editing. **Naoto Tamura:** conceptualization, funding acquisition, resources, supervision, writing – review and editing. All authors contributed to the interpretation of the data, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Damage Index (MDI), quantitative Muscle Testing (QMT), myositis Functional Index-2 (FI-2), myositis Activities Profile (MAP), inclusion Body Myositis Functional Rating Scale (IBMFRS), cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI)," *Arthritis Care & Research (Hoboken)* 63, no. Suppl 11 (0 11) (2011): S118–S157, https://doi.org/10.1002/acr.20532.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Overall survival in patients with anti-MDA5 antibody-positive RP-ILD. (A) Kaplan–Meier curve showing overall survival for the entire cohort, including the early dropout group ($n = 48$). (B) Kaplan–Meier survival between the pre-antibody monitoring cohort ($n = 13$) and the antibody monitoring cohort ($n = 23$), excluding early dropout cases. MDA5, melanoma differentiation-associated gene 5; RP-ILD, rapidly progressive interstitial lung disease. **Figure S2:** Longitudinal changes in anti-MDA5 antibody titers. (A) Overall trajectories of anti-MDA5 antibody titers during the entire observation period in both groups. (B) Zoomed-in view limited to patients with titers < 100 to visualize low-titer kinetics. (C) Enlarged view of the first 12 months to illustrate early-phase dynamics. (D) Box-and-whisker plots comparing anti-MDA5 antibody levels between the pre-monitoring and antibody monitoring cohorts at selected time points. In both cohorts, titers declined rapidly after treatment initiation, and no statistically significant between-group differences were observed at comparable time points. MDA5, melanoma differentiation-associated gene 5. **Figure S3:** Kaplan–Meier analysis of time to GC discontinuation after exclusion of patients receiving JAK inhibitors. Sensitivity analysis excluding patients receiving JAK inhibitors. Kaplan–Meier curves for time to GC discontinuation, with patients treated with JAK inhibitors excluded from the analysis. GC, glucocorticoid; JAK, Janus kinase. **Table S1:** The comparison of characteristics, background, treatment, and prognosis between two groups.

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REVIEW

Romosozumab Versus Teriparatide for the Treatment of Postmenopausal Osteoporosis: An Overview of Systematic Reviews With Direct and Indirect Meta-Analyses

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ABSTRACT

Aim: To summarize the evidence of efficacy and safety of romosozumab compared to teriparatide for postmenopausal osteoporosis.

Methods: A literature search was performed in Medline, the Cochrane Library, CRD, and LILACS until November 2023. We included systematic reviews with meta-analyses on the use of romosozumab compared to teriparatide in women with postmenopausal osteoporosis. Two authors performed study selection, data extraction, and quality assessment using AMSTAR-2 and GRADE tools.

Results: A total of 725 records were identified, and 13 studies fully met the eligibility criteria. Regarding efficacy, romosozumab did not show a significant difference in risk of falls (12/24 months), vertebral fractures (12/36 months), non-vertebral fractures (12/36 months), and hip fractures compared to teriparatide. For the safety profile, romosozumab did not show significant change compared to teriparatide for serious adverse events (12/26 months) and composite cardiovascular outcomes (3PMACE and 4PMACE). The overall quality of evidence in the reviews ranged from very low to moderate, primarily due to indirectness and imprecision in the outcomes. Additionally, the reviews were classified as having "low" or "critically low" methodological quality.

Conclusion: Romosozumab demonstrated efficacy and safety similar to teriparatide. However, this overview revealed substantial overlap among primary studies, with most outcomes assessed through indirect comparisons and poor methodological quality. Future research should confirm these findings.

1 | Introduction

Osteoporosis is a skeletal disorder characterized by low bone mass and fragility associated with an increased risk of fractures. It is a substantial public health concern, particularly impacting postmenopausal women, because of the morbidity and mortality linked with vertebral and hip fractures [1, 2]. The global prevalence of osteoporosis is 19.7% and every year, 37 million fragility fractures occur among individuals aged over 55 [3, 4]. Therefore, the primary goal of therapy in patients with osteoporosis is to reduce the risk of fractures and thereby sustain the quality of life for these individuals [5].

Key Points

- Romosozumab demonstrated comparable efficacy and safety to teriparatide in the treatment of postmenopausal osteoporosis, with no significant differences observed in the risk of falls, fractures, and serious adverse events, including cardiovascular events.
- The overall quality of evidence from the systematic reviews ranged from very low to moderate, primarily due to issues of indirectness and imprecision in the outcomes assessed.
- The findings of this overview revealed substantial overlap among primary studies, with most outcomes assessed through indirect comparisons, highlighting the need for further research to confirm these results.

Different drugs are recommended for preventing fractures related to osteoporosis. Among these, bisphosphonates (e.g., alendronate, risedronate, ibandronate, and zoledronic acid) are the most widely used medicines for preventing and managing osteoporosis. However, there are concerns regarding serious adverse events, including atypical femoral fractures and osteonecrosis of the jaw as well as unproven efficacy over 5 years [6]. Moreover, therapeutic failure can occur in 25% of patients [7]. Thus, novel therapeutic agents to reduce the high risk of fractures are emerging, with variable mechanisms of action and effectiveness/safety, such as teriparatide and romosozumab [8].

Teriparatide, a recombinant human parathyroid hormone (PTH) analog, stimulates bone formation on trabecular and endocortical bone surfaces, promoting bone formation and increasing bone mineral density (BMD) [8]. In contrast, romosozumab, a monoclonal antibody targeting sclerostin, increases bone formation and reduces bone resorption, producing marked gains in spine and hip BMD [5]. Studies have demonstrated the same efficacy in reducing the high fracture risk in postmenopausal women for both agents. Although romosozumab offers better dosing convenience compared to teriparatide (monthly by subcutaneous injection for 12 months versus daily by subcutaneous injection for 24 months), their use should not be considered for women at high risk of cardiovascular disease or stroke due to associated cardiovascular risks [5, 6, 8, 9].

The increase in the availability of systematic reviews presents a challenge to healthcare professionals and decision-makers to promote evidence-based healthcare. Moreover, it is important to assess the methodological quality of these systematic reviews before treatment recommendations can be reliably implemented in clinical practice. Currently, there is no overview published on the use of romosozumab versus teriparatide in postmenopausal osteoporosis. Therefore, this overview aimed to summarize the evidence of the efficacy and safety of romosozumab compared to teriparatide in postmenopausal women with osteoporosis and critically appraise the methodological quality of systematic reviews.

2 | Methods

The protocol of this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO number CRD42024499738). This review followed the Preferred Reporting Items for Overviews of Reviews (PRIOR) Statement [10].

2.1 | Databases and Search Strategy

A comprehensive search for relevant literature was conducted in Medline (PubMed), Cochrane Library, Centre for Reviews and Dissemination (CRD), Embase, and Latin American and Caribbean Health Sciences Literature (LILACS) until November 28th, 2023 without data restriction and regardless of the study design and language. The gray literature was also examined for any relevant supplementary literature, using the search engine Google Scholar up to the 40 registries, excluding patents and citations, through the Publish or Perish v.8 software [11]. No language restrictions or publication dates were applied in the strategies search. The search strategies used the Medical Subject Headings (MeSH) and Emtree terms or text words related to postmenopausal osteoporosis and romosozumab. The full search strategies for all databases can be found in Table S1.

2.2 | Study Selection

Manuscripts were considered eligible if they (1) included postmenopausal women with osteoporosis, with or without prior treatment failure; (2) assessed the effect of romosozumab compared to teriparatide; (3) reported at least one of the outcomes of interest of efficacy (vertebral fractures, non-vertebral fractures, hip fractures, or risk of falls) and safety (serious adverse events or cardiovascular adverse events); and (4) were a systematic review of randomized clinical trials (RCT) with direct or indirect meta-analysis. It is worth noting that the most clinically relevant outcomes for the patients were selected. Primary studies design, technical reports, conference proceedings, other types of review, a meta-analysis performed without systematic review, and systematic reviews with meta-analysis that included other population studies, intervention, comparator, and outcomes were excluded. The manuscripts retrieved from the databases were allocated to the Rayyan QCRI web program [12] to exclude duplicate files (Phase 1), analyze the titles and abstracts of the articles (Phase 2), and analyze complete articles whose abstracts were previously selected (Phase 3). Two reviewers (T.M.L. and T.F.G.S.B.) independently reviewed the titles and abstracts of all studies identified by the searches and discussed any discrepancies arising from consensus. When it was impossible to obtain the full text, the corresponding authors were contacted via e-mail and the ResearchGate platform (www.researchgate.net).

2.3 | Data Extraction

The data were collected in a preformatted spreadsheet in Microsoft Excel, including literature search and period, country, target population, intervention, and comparator with the

dosage regimen, outcome measures, number of RCTs and patients included in the meta-analysis, type of comparison of meta-analysis, statistical model used in the meta-analysis, effect size, heterogeneity, inconsistency, and funding source. Two independent reviewers (T.M.L. AND T.F.G.S.B.) extracted data, and disagreements were resolved by a third reviewer (G.B.G.M.). We also used the Elicit online tool (https://elicit.org/) to complement this process.

2.4 | Methodological Quality Assessment

The methodological quality of systematic reviews was assessed using the AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) tool [13]. The AMSTAR-2 consists of a 16-item questionnaire, in which the responses are categorized as "yes," "partial yes," or "no." The overall assessment was based on weaknesses in key domains (items: 2, 4, 7, 9, 11, 13, and 15) as follows: "high," no or one non-critical weakness; "moderate," more than one non-critical weakness but no critical flaws; "low," one critical flaw with or without non-critical weaknesses; and "critically low," more than one critical flaw with or without non-critical weaknesses. One investigator (T.M.L.) evaluated the studies, and a second one (T.F.G.S.B.) verified this evaluation.

2.5 | Quality of Evidence

The quality of evidence for each outcome measured was assessed using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) tool [14]. The quality of evidence was classified into four levels: high, moderate, low, and very low, indicating confidence in the effect estimate. Initially, the quality of evidence starts as high when RCTs are analyzed. Factors regarding the risk of bias (i.e., methodological limitations), publication bias, indirectness, imprecision, and inconsistency can reduce the level of evidence of the outcome. Indirect meta-analyses were evaluated considering the adjustments proposed by Salanti et al. [15]. The evidence profile was created from an explicit assessment of each of these factors using GRADEpro software (https://gradepro.org/). One investigator (T.F.G.S.B.) evaluated the studies, and a second investigator (T.M.L.) verified this evaluation. Any disagreement was resolved by discussion.

2.6 | Overlap of Primary Studies

To assess the overlap of primary studies across included meta-analyses, the Corrected Covered Area (CCA) was calculated as proposed by Pieper et al. [16], using the formula: $CCA = (N - r)/[r \times (c - 1)] \times 100$, where N represents the total number of primary study inclusions across all included meta-analyses, r the number of unique primary studies, and c the number of included meta-analyses. Results were interpreted according to the following thresholds: slight (0%–5%), moderate (6%–10%), high (11%–15%), and very high (> 15%) overlap.

Given that the included reviews may have analyzed multiple outcomes, only RCTs reporting data on the outcomes of interest defined for this overview were considered for matrix construction. Furthermore, for direct meta-analyses, eligibility was restricted to trials that directly compared the intervention of interest (romosozumab) with a comparator of interest (teriparatide). For indirect meta-analyses, only trials reporting at least one direct comparison of either the intervention of interest or the comparator of interest versus placebo were considered eligible.

In addition to the general citation matrix, separate citation matrices were constructed for each outcome of interest, with primary studies in rows and included meta-analyses in columns, enabling both the calculation of outcome-specific CCA values and the visual identification of meta-analyses with substantial overlap.

2.7 | Data Synthesis

The characteristics of systematic reviews, the methodological quality assessment, and the quality of evidence were provided using narrative and structured tables. The original ideas and concepts of the included studies were respected. The estimates of effect size from meta-analysis and the confidence intervals were expressed as odds ratios (OR), relative risk (RR), or hazard ratios (HR), depending on the author's report.

3 | Results

3.1 | Search Results

A total of 725 potentially relevant records were retrieved from databases. After removing duplicates and screening titles and abstracts, 706 records were excluded. Full texts of the remaining 48 articles were assessed. Of these, 13 systematic reviews with meta-analysis were included in the overview [17–29]. The flowchart of the literature search is shown in Figure 1. The excluded studies and the reasons for their exclusion are detailed in Table S2.

3.2 | Characteristics of Systematic Reviews

The characteristics of the systematic reviews are summarized in Table 1. Eight reviews conducted indirect meta-analyses and five direct meta-analyses. All studies were published in English and were reported between 2019 and 2023, with 8 (61.5%) published in 2019 and 5 (38.5%) performed in China. Almost all reviews included primary studies evaluating only women in postmenopause with osteoporosis [17, 19–22, 24–29]. Two reviews also included patients with osteopenia [18] or low bone mass [23].

Romosozumab 210 mg was the intervention strategy most commonly used in the reviews (9; 69.2%) [17, 19–21, 25–28]. Three reviews did not describe any information on the dosage regimen of the romosozumab [18, 22, 23] Almost all reviews included studies with different comparators beyond teriparatide, such as bisphosphonates, estrogen agonists/antagonists, and other PTH-receptor agonists (abaloparatide) [17–20, 22–29]. Only one review included studies that used only teriparatide as the comparator [21].

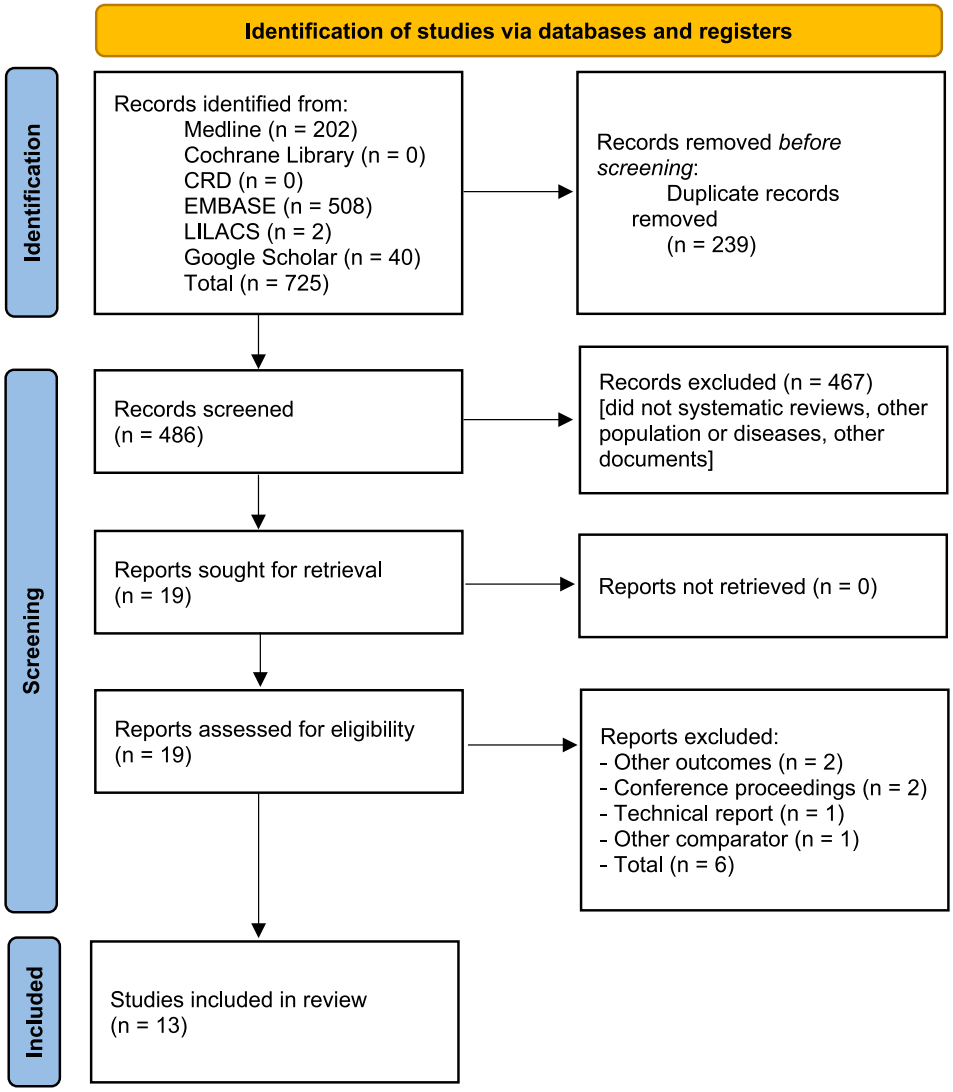

FIGURE 1 | Study selection flowchart through literature search. CRD, Centre for Reviews and Dissemination.

Eleven reviews (84.6%) [17, 19–24, 26–29] assessed the efficacy outcomes, while nine reviews (69.2%) [18, 20, 21, 23–26, 28] evaluated the safety profile of romosozumab versus teriparatide. Other outcomes also assessed in the included reviews, for example, BMD (hip, lumbar spine, or femoral neck), hypersensitivity to local administration, tolerability, and acceptability. Moreover, most reviews did not inform the time point measures for outcome assessment.

Seven studies (53.8%) [17, 19, 20, 22, 24, 26, 28] did not report a source of support for the research, five (38.5%) [18, 21, 23, 25, 27] received research funding from governments, universities, research healthcare centers, or institute organizations, and one (7.7%) [28] received research funding from the industry.

3.3 | Results of Efficacy

Two reviews with direct meta-analyses did not demonstrate a significant reduction in the risk of falling with treatment with romosozumab at 12 months [19] and over 12/24 months [20] in postmenopausal women when compared with teriparatide (low-quality evidence in each). Regarding the risk of vertebral fractures, three reviews with indirect meta-analyses did not show a significant effect of romosozumab compared to teriparatide [22, 27, 28] (low-quality evidence). In addition, one review with indirect meta-analysis did not report a significant difference between the two groups when analyzed over 12/24 months (RR = 0.81 [95% CI 0.19–3.34]) [23] (low-quality evidence). The results were similar for the prevalence of vertebral fractures equal to or greater than 50% (HR = 0.79 [95% CI 0.49–1.40]) and for the prevalence of vertebral fractures less than 50% (HR = 0.98 [95% CI 0.56–1.70]) [24] (low-quality evidence). Moreover, the findings did not show a significant difference between the two groups for the incidence of new vertebral fractures (RR = 0.84 [95% CI 0.41–1.72]) [26] and reduction of non-vertebral fractures at 12 months (RR = 1.75 [95% CI 0.68–3.75]) [29] (low-quality evidence).

Reviews with indirect meta-analyses did not demonstrate a significant reduction in non-vertebral fractures (RR = 0.91 [95% CI 0.67–1.30]) [28] (very low quality evidence) nor in their incidence (RR = 0.79 [95% CI 0.50–1.24]) [26] (very low quality evidence) in treatment with romosozumab in menopausal women

TABLE 1 | Characteristics of systematic reviews with direct and indirect meta-analyses included.

Authors, year	Literature search (period)	Country	Target population (*n*)	Intervention (dosage regimen)	Comparator (dosage regimen)	Outcome measure (time point)	Funding source
Systematic reviews with direct meta-analyses							
Huang et al., 2023 [17]	PubMed, Cochrane Library, NIPH Clinical Trials, International Clinical Trials Registry Platform, and Clinical Trials.gov (the date of database inception to June 18, 2021)	Japan	Women in postmenopause with osteoporosis (12 796)	Romosozumab (70, 140 or 210 mg)	Teriparatide (20 μg), alendronate (70 mg), denosumab (60 mg), or placebo	Vertebral fractures (12 and 24 months), non-vertebral fractures (12 and 24 months), clinical fractures (12 months), changes in total hip BMD (6 and 12 months), changes in lumbar spine BMD (6 and 12 months), changes in femoral neck BMD (6 and 12 months), serious AE (NR), and hypersensitivity to local administration (NR)	NR
Lv et al., 2020 [18]	PubMed, Cochrane Library, and EMBASE (the date of database inception to June 4, 2019)	China	Women in postmenopause with osteoporosis or osteopenia (85 834)	Romosozumab (NR) and denosumab (NR)	Teriparatide (NR), alendronate (NR), ibandronate (NR), risedronate (NR), or zoledronate (NR)	Cardiovascular events—3PMACE, 4PMACE (12 and 36 months)	National Key Research and Development Program
Möckel et al., 2020 [19]	PubMed, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov (the date of database inception to June 2019)	Germany	Women in postmenopause with osteoporosis (12 128)	Romosozumab (210 mg)	Teriparatide (20 μg), alendronate (70 mg), or placebo	Risk of falls (12 and 33–36 months)	NR

(Continues)

TABLE 1 | (Continued)

Authors, year	Literature search (period)	Country	Target population (*n*)	Intervention (dosage regimen)	Comparator (dosage regimen)	Outcome measure (time point)	Funding source
Singh et al., 2021 [20]	Medline (via PubMed), The Cochrane Central Register of Controlled Trials, and clinicaltrials.gov (the date of database inception to May 2020)	India	Women in postmenopause with osteoporosis (11 896)	Romosozumab (70, 140 and 210 mg)	Teriparatide (20 μg), alendronate (70 mg), denosumab (NR), or placebo	Vertebral fractures (24 months), non-vertebral fractures (24 months), clinical fractures (24 months), risk of falls (12 and 24 months), changes in total hip BMD (12 months), changes in lumbar spine BMD (12 months), changes in femoral neck BMD (12 months), total AE (NR), and serious AE (NR)	NR
Tian et al., 2021 [21]	PubMed, Embase, the Cochrane Library, Web of Science, and the Cochrane Controlled Trials Register (the date of database inception to June 2019)	China	Women in postmenopause with osteoporosis (1304)	Romosozumab (210 mg)	Teriparatide (20 μg)	Changes in total hip BMD (6 and 12 months), changes in lumbar spine BMD (6 and 12 months), changes in femoral neck BMD (6 and 12 months), serious AE (12 months), death (12 months), and hypersensitivity to local administration (12 months)	Chinese National Natural Science Foundation, Tianjin Science and Technology, Project in the KeyField of Traditional Chinese Medicine, Tianjin Health Science and Technology Project Research, Tianjin Orthopedic Institute Foundation, Tianjin Natural Science Foundation, Tianjin Enterprise Postdoctoral Innovation Project

(Continues)

TABLE 1 | (Continued)

Authors, year	Literature search (period)	Country	Target population (*n*)	Intervention (dosage regimen)	Comparator (dosage regimen)	Outcome measure (time point)	Funding source
Systematic reviews with indirect meta-analyses							
Albert et al., 2021 [22]	PubMed (January 2018 to February 2021)	United States	Women in postmenopause with osteoporosis (73 862)	Romosozumab (NR)	Teriparatide (NR), alendronate (NR), risedronate (NR), zoledronate (NR), denosumab (NR), raloxifene (NR), abaloparatide (NR), or placebo	Vertebral fractures (12, 18, 24, 36 months), hip fractures (12, 36, 60 months), and non-vertebral fractures (12, 24, 36 months)	NR
Ayers et al., 2023 [23]	MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov (January 2014 to February 2022)	United States	Women with osteoporosis or low bone mass (NR)	Romosozumab (NR)	Teriparatide (20 or 40 μg/dia, SC), alendronate (70 mg/week, or 5 or 10 mg/day, PO), ibandronate (150 mg/month, PO), risedronate (35 mg/week or 5 mg/day, PO), zoledronic acid (5 mg/year, IV), parathyroid hormone (100 μg/day, SC), abaloparatide (80 μg/day, SC), denosumab (60 mg/6 months, SC), raloxifene (60 mg/day, PO), or bazedoxifene (20 or 40 mg/day, PO)	Hip fractures (24, 36, 48 months), vertebral fractures (12, 24, 36 months), clinical fractures (12, 18, 24, 36 months), radiographic vertebral fractures (12, 24, 36, 48 months), serious AE (36 months), drug discontinuation due to serious AE (18, 36 months), atypical or subtrochanteric femoral fractures (3 to 5 years), osteonecrosis of the jaw (2 to 3 years), and atrial fibrillation (NR)	American College of Physicians
Ding et al., 2020 [24]	PubMed, Embase, and the Cochrane Central Register of Controlled Trials (the date of database inception to March 2, 2019)	China	Women in postmenopause with osteoporosis (79 144)	Romosozumab (120 mg/month, SC)	Teriparatide (20 μg/dia, SC), abaloparatide (80 μg/dia, SC), alendronate (35-70 mg/week or 5-10 mg/day, PO), risedronate (5 mg/day ou 35 mg/week, PO), zoledronate (5 mg/1–1,5 year, IV), denosumab (60 mg/6 months, SC), raloxifene (60 mg/day PO), ibandronate (150 mg/month, PO), parathyroid hormone (100 μg/day, SC), or placebo	Vertebral fractures (NR), non-vertebral fractures (NR), and tolerability (NR)	NR

(Continues)

TABLE 1 | (Continued)

Authors, year	Literature search (period)	Country	Target population (*n*)	Intervention (dosage regimen)	Comparator (dosage regimen)	Outcome measure (time point)	Funding source
Seeto et al., 2023 [25]	MEDLINE and EMBASE (July 2017 to December 2020)	Australia, Canada, Ethiopian, and the United States	Women in postmenopause with osteoporosis (136 940)	Romosozumab (210 mg/month, SC)	Teriparatide (20 or 40 μg/dia, SC), abaloparatide (80 μg/day, SC), alendronate (70 mg/week), denosumab (60 mg/6 months, SC), estrogen hormones (NR), risedronate (35 mg/week or 5 mg/day, PO), ibandronate (150 mg/month, PO), or zoledronic acid (5 mg/year, IV)	Cardiovascular events—3PMACE, 4PMACE, 5PMACE (NR), heart attack (NR), stroke (NR), heart failure (NR), atrial fibrillation (NR)	National Health and Medical Research Council Australia Investigator National Heart Foundation Future Leader Amgen, Eli-Lilly e Alexion, and honorarius of the Amgen and Sanofi
Tan et al., 2019 [26]	PubMed, Embase, the Cochrane Central Register of Controlled Trials, and GoogleScholar (the date of database inception to July 16, 2018)	China	Women in postmenopause with osteoporosis (67524)	Romosozumab (210 mg/month, SC)	Teriparatide (20 μg/dia, SC), abaloparatide (80 μg/dia, SC), denosumab (60 mg/6 months, SC), zoledronate (5 mg/year, IV), alendronate (70 mg/week or 5-10 mg/day, PO), risedronate (5 mg/day ou 35 mg/week, PO), etidronate (400 mg/day, PO), strontium ranelate (2 g/day, PO), lasofoxifene (0.25 mg/day, PO), raloxifene (60 mg/day PO), or placebo	Vertebral fractures (NR), non-vertebral fractures (NR), clinical fractures (NR), AE (NR), and serious AE (NR)	NR
Wei et al., 2023 [27]	PubMed, Embase, and the Cochrane Library (the date of database inception to February 15, 2020)	China	Women in postmenopause with osteoporosis (104 580)	Romosozumab (70, 140 or 210 mg)	Teriparatide (20 μg), abaloparatide(80 μg), alendronate (5-10 mg/day or 70 mg/week), calcitonin (20 IU), denosumab (60 mg), parathyroid hormone (100 μg), risedronate (2.5 or 5 mg/day or 35 mg/week), strontium ranelate (0.5, 1 or 2 g), zoledronic acid (5 mg), raloxifene (60 mg), conjugated estrogen (0.625 mg) + medroxyprogesterone (2.5 mg), lasofoxifene (0.25 or 0.5 mg), ibandronate (150 mg), etidronate (400 mg), or bazedoxifene (20 or 40 mg)	Vertebral fractures (12 and 18 months)	Social Talent Fund of Tangdu Hospital and Tangdu Hospital Seed

(Continues)

TABLE 1 | (Continued)

Authors, year	Literature search (period)	Country	Target population (*n*)	Intervention (dosage regimen)	Comparator (dosage regimen)	Outcome measure (time point)	Funding source
Wen et al., 2020 [28]	Cochrane Library, PubMed and Embase (the date of database inception to 17 April 2019)	China	Women in postmenopause with osteoporosis (106 320)	Romosozumab (210 mg/month, SC)	Teriparatide (20 μg/dia, SC), abaloparatide (80 μg/dia, SC), denosumab (60 mg/6 months, SC), parathyroid hormone (100 μg/day, SC), zoledronate (5 mg/1-2 year, IV), raloxifene (60 mg/day PO), alendronate (35-70 mg/week or 5-10 mg/day, PO), ibandronate (150 mg/month, PO), strontium ranelate (2 g/day, PO), lasofoxifene (0.5 mg/day, PO), and bazedoxifene (20 mg/day, PO)	Vertebral fractures (NR), non-vertebral fractures (NR), tolerability (NR), and acceptability (NR)	NR
Willems et al., 2022 [29]	Medline, Medline In-Process Citations, Epubs Ahead of Print & Daily Update, EMBASE, and Cochrane Central Register of Controlled Trials (the date of database inception to September 2, 2020)	Belgium, England, and the United States	Women in postmenopause with osteoporosis (125 165)	Romosozumab (120 mg/month, SC)	Teriparatide (20 μg/dia, SC), abaloparatide (80 μg/dia, SC), alendronate (70 mg/week or 10 mg/day, PO), risedronate (5 mg/day or 35 mg/week, PO), ibandronate (150 mg/month, PO), zoledronate (5 mg/year, IV), denosumab (60 mg/6 months, SC), or raloxifene (60 mg/day PO)	Vertebral fractures (12, 24, and 36 months), non-vertebral fractures (12, 24, 36 months), hip fractures (12, 24, 36 months), changes in total hip BMD (NR), changes in lumbar spine BMD (NR), and changes in femoral neck BMD (NR)	UCB Pharma e Amgen Inc.

Abbreviations: 3PMACE, composite cardiovascular outcomes: death from cardiovascular causes, non-fatal stroke, or non-fatal myocardial infarction; 4PMACE, composite cardiovascular outcomes: 3PMACE and heart failure; 5PMACE, composite cardiovascular outcomes: 4PMACE and atrial fibrillation; AE, adverse events; BMD, bone mineral density; IV, intravenous administration; NR, not reported; PO, oral administration; SC, subcutaneous administration.

when compared with teriparatide. Moreover, two reviews did not show a significant difference between the two groups when analyzed over 12 months (RR = 0.91 [95% CI 0.50–1.54]) [29] (very low quality evidence) and 12/36 months (RR = 1.38 [95% CI 0.88–2.15]) [23] (very low quality evidence).

Finally, the results of a review with indirect meta-analysis performed between romosozumab and teriparatide for the reduction of hip fractures showed no statistical differences ($p = 0.900$) [22] (very low quality evidence). The results of efficacy are displayed in Table 2.

3.4 | Results of the Safety Profile

Two reviews with direct meta-analyses demonstrated no statistical differences between the romosozumab and teriparatide groups in the risk of serious adverse events (RR = 0.78 [95% CI 0.46–1.33], $p = 0.58$; $I^2 = 0.0\%$) [17] (moderate quality evidence), nor in the 12-month follow-up period (RR = 0.78 [95% CI 0.46–1.33], $p = 0.58$; $I^2 = 0.0\%$) [21] (moderate quality evidence). In addition, three reviews with indirect comparisons also did not demonstrate differences between the groups analyzed (RR = 0.97 [95% CI 0.75–1.24]) [27] (moderate quality evidence) over 12 to 36 months (RR = 1.03 [95% CI 0.70–1.51]) [23] (moderate quality evidence) or in the incidence of these adverse events (RR = 1.07 [95% CI 0.87–1.32]) [26] (moderate quality evidence).

Two reviews using direct and indirect meta-analyses that evaluated adverse cardiovascular events (3PMACE and 4PMACE) did not observe statistically significant differences between the groups on the incidence of these outcomes in menopausal women who used romosozumab or teriparatide [18, 25] (moderate quality evidence). In the direct meta-analysis, the adverse event 3PMACE had RR = 2.03 [95% CI 0.37–11.23] ($p = 0.42$) and 4PMACE had RR = 1.88 [95% CI 0.08–45.43] ($p = 0.70$) [18]. In indirect meta-analyses, the adverse event 3PMACE had OR = 0.62 [95% CI 0.25–1.46] (NR), and 4PMACE had OR = 0.51 [95% CI 0.23–1.10] (NR) [25]. The safety profile results are presented in Table 2.

3.5 | Methodological Quality of Systematic Reviews

The methodological quality of the reviews is presented in Table 3. Twelve studies (92.3%) had an "a priori" design, indicating the existence of a protocol or ethical approval [17–21, 23–29]. Nine studies (69.2%) conducted selection [17, 18, 20, 23–25, 27–29] and extraction [17–19, 21, 24–28] in duplicate, resolving differences through discussion. The majority of studies (92.3%) performed a comprehensive review of the literature, including at least two electronic databases, search strategy terms, and a supplemental search [17–21, 23–29]. All reviews included RCTs and described participant characteristics and interventions, and only two (15.4%) provided a list of studies excluded after full-text evaluation [23, 27]. The quality of studies included in all systematic reviews was assessed and documented using validated tools. Ten reviews (76.9%) explained the risk of bias of individual studies when discussing the review results [17, 18, 20, 23–29] or provided a satisfactory explanation for any heterogeneity observed [17, 18, 20, 22–25, 27–29]. Four reviews (30.8%) assessed the publication bias of the main outcome [17, 20, 24, 28]. All studies explicitly disclosed conflicts of interest, and seven [17, 19, 20, 22, 24, 26, 28] did not provide information on funding sources for the systematic review.

This overview found that seven systematic reviews had critically low overall confidence in their results [17, 18, 20, 23, 24, 27, 28], and six had low overall confidence [19, 21, 22, 25, 26, 29] according to the AMSTAR checklist.

3.6 | Overlap of Primary Studies

Tables S3–S5 summarize the distribution of primary studies within the included reviews, limited to those that evaluated the outcomes of interest in this overview. Twelve unique primary studies were identified across 13 included meta-analyses—five pairwise and eight network meta-analyses—yielding an overall CCA of 22.9%, classified as very high overlap. The studies most frequently shared across reviews were Langdahl et al. [30], present in 10 of the 12 meta-analyses (83.3%), followed by Cosman et al. [31] and Neer et al. [32], each appearing in eight meta-analyses (66.6%), and McClung et al. [33], present in seven (58.3%). Outcome-specific analyses revealed consistently high overlap across all evaluated outcomes. For vertebral fracture (CCA = 27.8%), the overlap was primarily driven by Cosman et al. [31] and Neer et al. [32], both of which are present in six of the seven meta-analyses (85.7%), and Langdahl et al. [30], present in four (57.1%). For non-vertebral fracture (CCA = 38.9%), Cosman et al. [31] and Neer et al. [32] were included in all four meta-analyses. For serious adverse events (CCA = 32.1%), Langdahl et al. [30] appeared in four of the five meta-analyses (80%), while McClung et al. [33] and Cosman et al. [31] were each present in three (60%). For 3P-MACE and 4P-MACE (CCA = 25% for both), Langdahl et al. [30] and McClung et al. [33] were the only studies shared between both meta-analyses. Fall risk showed complete overlap (CCA = 100%), as both available meta-analyses included the same two trials—Langdahl et al. [30] and McClung et al. [33].

4 | Discussion

4.1 | Main Findings

To our knowledge, this is the first overview of systematic reviews with meta-analyses of RCTs evaluating romosozumab compared to teriparatide for postmenopausal osteoporosis. Romosozumab demonstrated efficacy and safety similar to teriparatide for all evaluated outcomes. Although 13 studies on this topic have been published since 2019, these findings were derived from systematic reviews supported by only four primary studies [30–33]. Moreover, the quality of evidence for efficacy and safety main outcomes related to efficacy and safety was generally rated as moderate or low, highlighting the need for further research to improve confidence in the estimate of effects.

This overview showed that romosozumab could be an alternative and interesting option as front-line therapy in patients with postmenopausal osteoporosis. The National Institute for Health

TABLE 2 | Results on outcomes evaluated in systematic reviews with meta-analyses on romosozumab compared teriparatide for postmenopausal osteoporosis.

Authors, year	Number of RCT/ patients	Type of comparison	Statistical model	Pooled effect [95% CI] (*p*)	Heterogeneity I^2 (*p*)	Publication bias	Quality of evidence[a]
Risk of falls (12/24 months)							
Mockel et al., 2020 [19]	2/618	Direct	Random effects	RR = 1.19 [0.21–6.74] ($p = 0.85$)	$I^2 = 58.5\%$ ($p = 0.12$)	NR	Low
Singh et al., 2022 [20]	2/818	Direct	Fix effects	OR = 1.59 [0.83–3.02] ($p = 0.16$)	$I^2 = 4\%$ ($p = 0.31$)	Egger's test was not applied as studies were fewer than five	Low
Vertebral fractures							
Albert et al., 2023 [22]	NA	Indirect	Random effects	NR [NR] ($p = 0.973$)	NA	NR	Low
Ayers et al., 2023 [23]	NA	Indirect	Node-splitting	RR = 0.81 [0.19–3.34] (NR)	NA	NR	Low
Ding et al., 2020 [24]	NA	Indirect	Bayesian random effects	HR = 0.79 [0.49–1.40] (NR)	NA	No asymmetry in the funnel plot	Low
Tan et al., 2019 [26]	NA	Indirect	Random effects	RR = 0.84 [0.41–1.72] (NR)	NA	NR	Low
Wei et al., 2023 [27]	NA	Indirect	Frequentist consistency	RR = 0.86 [0.38–1.96] (NR)	NA	NR	Low
Wen et al.,2020 [27]	NA	Indirect	Bayesian random effects	RR = 0.86 [0.56–1.30] (NR)	NA	No asymmetry in the funnel plot	Low
Willems et al., 2022 [28]	NA	Indirect	Bayesian random effects	RR = 1.75 [0.68–3.75]	NA	NR	Low
Non-vertebral fractures							
Ayers et al., 2023 [22]	NA	Indirect	Node-splitting	RR = 1.38 [0.88–2.15] (NR)	NA	NR	Very low
Tan et al., 2019 [25]	NA	Indirect	Random effects	RR = 0.79 [0.50–1.24] (NR)	NA	NR	Very low
Wen et al., 2020 [27]	NA	Indirect	Bayesian random effects	RR = 0.91 [0.67–1.30] (NR)	NA	No asymmetry in the funnel plot	Very low

(Continues)

TABLE 2 | (Continued)

Authors, year	Number of RCT/ patients	Type of comparison	Statistical model	Pooled effect [95% CI] (*p*)	Heterogeneity I^2 (*p*)	Publication bias	Quality of evidence[a]
Willems et al., 2022 [29]	NA	Indirect	Bayesian random effects	RR = 0.91 [0.50–1.54] (NR)	NA	NR	Very low
Hip fractures							
Albert et al., 2023 [21]	NA	Indirect	Random effects	NR [NR] ($p = 0.900$)	NA	NR	Very low
Serious adverse events							
Huang et al., 2023 [17]	2/537	Direct	Random effects	RR = 0.78 [0.46–1.33] (NR)	$I^2 = 0\%$ ($p = 0.58$)	No asymmetry in the funnel plot	Moderate
Tian et al., 2021 [21]	2/537	Direct	Fix effects	RR = 0.78 [0.46–1.33] ($p = 0.37$)	$I^2 = 0\%$ ($p = 0.58$)	NR	Moderate
Ayers et al., 2023 [23]	NA	Indirect	Node-splitting	RR = 1.03 [0.70–1.51 (NR)]	NA	NR	Moderate
Tan et al., 2019 [26]	NA	Indirect	Random effects	RR = 1.07 [0.87–1.32] (NR)	NA	NR	Moderate
Wei et al., 2023 [27]	NA	Indirect	Frequentist consistency	RR = 0.97 [0.75–1.24] (NR)	NA	NR	Moderate
Cardiovascular adverse events (3PMACE)							
Lv et al., 2020 [18]	2/537	Direct	Fix and random effects	RR = 2.03 [0.37–11.23] ($p = 0.42$)	$I^2 = 45\%$ (NR)	No asymmetry in the funnel plot	Moderate
Seeto et al., 2023 [25]	NA	Indirect	Bayesian random effects	OR = 0.62 [0.25–1.46] (NR)	NA	NR	Moderate
Cardiovascular adverse events (4PMACE)							
Lv et al., 2020 [18]	2/537	Direct	Fix and random effects	RR = 1.88 [0.08–45.43] ($p = 0.70$)	$I^2 = 54\%$ (NR)	No asymmetry in the funnel plot	Moderate
Seeto et al., 2023 [25]	NA	Indirect	Bayesian random effects	OR = 0.51 [0.23–1.10] (NR)	NA	NR	Moderate

Abbreviations: 3PMACE, composite cardiovascular outcomes: death from cardiovascular causes, non-fatal stroke, or non-fatal myocardial infarction; 4PMACE, composite cardiovascular outcomes: 3PMACE and heart failure; NA, not applicable; NR, not reported.

[a]The Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

TABLE 3 | The quality assessment results of systematic reviews with meta-analyses included using the AMSTAR-2 tool.

	Amstar-2 item																
Author, year	**1**	**2[a]**	**3**	**4[a]**	**5**	**6**	**7[a]**	**8**	**9[a]**	**10**	**11[a]**	**12**	**13[a]**	**14**	**15[a]**	**16**	**Overall quality**
Systematic reviews with direct meta-analyses																	
Huang et al., 2023 [17]	Y	Y	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Lv et al., 2020 [18]	Y	Y	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Low
Möckel et al., 2020 [19]	Y	PY	N	PY	N	Y	N	PY	Y	N	Y	N	N	N	N	Y	Critically low
Singh et al., 2021 [20]	Y	Y	N	PY	Y	N	N	PY	Y	N	Y	N	Y	Y	Y	Y	Low
Tian et al., 2021 [21]	Y	PY	N	PY	N	Y	N	PY	Y	N	Y	N	N	N	N	Y	Critically low
Systematic reviews with indirect meta-analyses																	
Albert et al., 2021 [22]	Y	N	N	N	N	N	N	PY	PY	N	Y	N	N	Y	N	Y	Critically low
Ayers et al., 2023 [23]	Y	PY	N	PY	Y	N	PY	Y	Y	N	Y	N	Y	Y	N	Y	Low
Ding et al., 2020 [24]	Y	Y	N	PY	Y	Y	N	Y	PY	N	Y	Y	Y	Y	Y	Y	Low
Seeto et al., 2023 [25]	Y	Y	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Critically low
Tan et al., 2019 [26]	Y	PY	N	PY	N	Y	N	PY	PY	N	Y	Y	Y	N	N	Y	Critically low
Wei et al., 2023 [27]	Y	Y	N	PY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Low
Wen et al., 2020 [28]	Y	Y	N	PY	Y	Y	N	Y	PY	N	Y	Y	Y	Y	Y	Y	Low
Willems et al., 2022 [29]	Y	PY	N	PY	Y	N	N	PY	Y	N	Y	Y	Y	Y	N	Y	Critically low

Note: Item 1: Did the research questions and inclusion criteria for the review include the components of PICO?; Item 2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?; Item 3: Did the review authors explain their selection of the study designs for inclusion in the review?; Item 4: Did the review authors use a comprehensive literature search strategy?; Item 5: Did the review authors perform study selection in duplicate?; Item 6: Did the review authors perform data extraction in duplicate?; Item 7: Did the review authors provide a list of excluded studies and justify the exclusions?; Item 8: Did the review authors describe the included studies in adequate detail?; Item 9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?; Item 10: Did the review authors report on the sources of funding for the studies included in the review?; Item 11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?; Item 12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?; Item 13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?; Item 14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?; Item 15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?; Item 16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Abbreviations: N, no; PY, partial yes; Y, yes.

[a]Critical domains.

and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH) recommended the use of romosozumab in the treatment of severe postmenopausal osteoporosis in individuals at high risk of fractures. Moreover, studies conducted in the UK [34], Belgium [35], and Japan [36] indicate that romosozumab is more cost-effective than teriparatide in women with severe osteoporosis. Thus, it is important to consider the price agreement between the manufacturer and the healthcare system for the funding of treatment with the medicine, in addition to the existence of well-defined clinical criteria.

Recent studies have shown the superiority of romosozumab compared to teriparatide for other efficacy outcomes, such as bone mineral density (BMD) [37, 38]. However, these results should be interpreted with caution, as these outcomes do not always translate to a lower risk of falls or fractures. Secondary

outcomes are supplementary measures observed to aid in interpreting the results of the primary outcome, and they are not recommended as the central basis for decision-making [39, 40].

This overview showed that only two systematic reviews [19, 20] with direct meta-analysis assessed an efficacy-related outcome—the risk of falls. Unlike conventional pairwise meta-analysis, which is limited to comparing two interventions at a time, network meta-analysis (NMA) enables the simultaneous comparison of multiple interventions by combining direct and indirect evidence through a common comparator [41]. However, the validity of NMA-derived estimates—which account for most fracture-related outcomes in this overview—depends on three core assumptions that must be critically examined: homogeneity (studies comparing the same treatments are internally comparable); transitivity (potential effect modifiers are similarly distributed across all trials contributing to the network); and consistency, also termed coherence (direct and indirect estimates for a given comparison do not differ beyond what is expected by chance) [42, 43].

Transitivity is particularly critical in the present context, as romosozumab and teriparatide were not compared head-to-head in the primary trials underlying these reviews; instead, indirect estimates were constructed using placebo-controlled trials as the connecting node. This design requires that the placebo arms of romosozumab and teriparatide trials be sufficiently similar in their distribution of key effect modifiers, including baseline fracture risk, prior antiresorptive treatment, disease severity, and follow-up duration—for indirect comparisons to be valid [44, 45]. An empirical analysis of 209 NMA networks found violations of transitivity to be common and multiple statistical tests alone to be insufficient for its detection [46]. Notably, none of the systematic reviews included in this overview reported a formal assessment of transitivity, whether through systematic tabulation of effect modifiers across contributing trials or through graphical diagnostic approaches.

Regarding consistency, although some reviews reported heterogeneity statistics within pairwise comparisons, none explicitly applied tests for global or local inconsistency, such as the decomposition of the Q-statistic or node-splitting analyses in frequentist frameworks or the unrelated mean effects (UME) model in Bayesian approaches [47]. The Cochrane Handbook explicitly cautions that the absence of statistically significant incoherence does not guarantee transitivity in the network [40]. Furthermore, the GRADE Working Group recommends that the certainty of each indirect estimate be rated separately, accounting for transitivity concerns, before being integrated with any available direct evidence [40, 48]. Since this step was not performed in any included review, the certainty ratings for fracture outcomes carry an additional layer of uncertainty beyond what the reported GRADE levels convey. Future research should prioritize head-to-head randomized trials comparing romosozumab and teriparatide directly, and future systematic reviews on this topic should explicitly report transitivity assessments and consistency tests when indirect comparisons are employed.

A significant source of heterogeneity across the included systematic reviews was variability in population characteristics. Several reviews encompassed broader populations with osteoporosis, irrespective of prior treatment history. This inconsistency may introduce clinical heterogeneity that limits the internal validity of pooled comparisons and reduces the precision of subgroup-specific inferences [40]. To address current evidence gaps, future research should prioritize purpose-designed trials and systematic reviews focused on specific treatment scenarios, thereby providing more reliable guidance for clinical decision-making.

Notably, this overview revealed substantial overlap among primary studies, indicating that multiple systematic reviews synthesized largely similar evidence bases [49]. The recurrence of a select cohort of landmark trials [30–33] underscores that RCT evidence remains confined to a few pivotal studies, forming the foundational basis for almost all quantitative syntheses in this domain. This pattern was more pronounced for specific outcomes: two RCTs [31, 32] contributed to all four meta-analyses of non-vertebral fracture, while a single RCT [30] was included in 80% of those examining serious adverse events. The complete overlap in trials assessing fall risk warrants particular caution in interpretation, as both available meta-analyses relied on an identical set of only two trials [30, 33]. This renders their effect estimates statistically dependent and precludes independent corroboration for this outcome. Moreover, all direct meta-analyses relied exclusively on two pivotal studies [30, 33]. Compounding this limitation, inconsistencies in effect estimates emerged even among reviews utilizing the same RCTs. It was not possible to determine whether these discrepancies arose from errors in data extraction or from reliance on secondary data sources. Consequently, these findings underscore the need for cautious interpretation, as study duplication may artificially inflate the strength of the evidence and compromise the independence of the conclusions [40].

4.2 | Methodological Quality of Systematic Reviews

All systematic reviews included in the present overview were judged to have low or very low methodological quality according to the AMSTAR-2 critical appraisal criteria, despite all reviews being published after the update of this tool in September 2017. These results are in line with recent overviews on the impact of traditional Chinese medicine on postmenopausal osteoporosis [50] and the role of vitamin D in preventing falls and fractures [51]. However, these results contrast with the findings of a previous overview that investigated the risks of rare serious adverse effects related to the long-term use of bisphosphonates and applied the first version of AMSTAR [52]. The findings of this overview suggest an urgent need to improve the methodological quality of future reviews.

Among the topics needing improvement, it was noted that only 70% of the reviews conducted selection (item 5) and data extraction (item 6) in duplicate, resolving discrepancies through discussion. This finding contrasts with the studies by Chakhtoura et al. [51] and Zhao et al. [50], which showed high adherence to these items. Conducting these steps in duplicate is crucial for minimizing errors of omission of relevant studies and transcription errors of individual study data. The

practice of performing these steps in duplicate is widely recommended by methodological guidelines, such as those provided by the Cochrane Handbook for Systematic Reviews of Interventions [40].

It is noteworthy that only two systematic reviews (15.4%) provided a list of excluded studies (item 7) after full-text evaluation, which contrasts with other overviews in the field that showed higher adherence to this item [51] This information is essential for the transparency and reproducibility of the review process [53], and it can now be easily included as an electronic supplement to the article.

As observed in the overview by Zhao et al. [50], none of the analyzed systematic reviews disclosed the funding sources of the primary studies included (item 10), raising concerns about potential undisclosed conflicts of interest that could compromise the impartiality of the results. This finding is particularly troubling, as studies sponsored by the pharmaceutical industry tend to report more favorable efficacy results and conclusions than those funded by other sources [54].

Additionally, only four reviews (30.8%) assessed publication bias for the main outcome (item 15), which could distort the overall body of available evidence—a common issue in other reviews in the field [51]. This lack of assessment may be attributed to the small number of RCTs included in the evaluated reviews, as having fewer than 10 studies reduces statistical power and can lead to unreliable results [55]. However, even when statistical tests or graphical aids are not feasible, it would be beneficial to explicitly state the perceived risk of publication bias through a qualitative analysis of the search strategy and sources of evidence, for example [55].

Taken together, these findings reveal a convergent pattern of methodological deficiencies that collectively undermine the reliability of the evidence synthesized in this overview. Among the critical AMSTAR-2 domains—those whose failure directly determines a "critically low" overall rating—the most prevalent flaws were the absence of a list of excluded studies after full-text evaluation (item 7, absent in 84.6% of reviews) and the failure to assess publication bias for the main outcome (item 15, absent in 69.2% of reviews). A third critical domain, the failure to account for risk of bias in individual studies when interpreting the results (item 13), was also absent in 23.1% of reviews. These two critical flaws co-occurred in the majority of reviews rated as critically low, and their combination is particularly consequential: **t**he simultaneous absence of a list of excluded studies, an assessment of publication bias, and adequate discussion of risk of bias creates a setting in which selective inclusion of favorable results cannot be ruled out. This concern is further amplified by the universal failure to disclose funding sources of the primary studies included (item 10), a non-critical domain but one of particular epidemiological relevance, given that industry-sponsored trials in this therapeutic area are the norm. Collectively, these deficiencies suggest that the reported effect sizes for both efficacy and safety outcomes may be subject to systematic overestimation of benefit. These limitations do not invalidate the findings of this overview, but they establish a clear ceiling on the confidence that can be placed in the current evidence base, and reinforce the need for methodologically rigorous future systematic reviews in this field.

4.3 | Opportunities for Future Research

This overview showed that there is room to improve future studies on the use of romosozumab versus teriparatide in postmenopausal women with osteoporosis. Long-term RCTs are essential to provide insights into the efficacy and safety of these treatments beyond the 12–24 months currently studied. In addition to fractures, important outcomes such as quality of life, pain, and mobility in these RCTs could provide a more comprehensive view of the clinical benefits of these therapies. Stratified analyses in specific subgroups of patients, such as those with different levels of disease severity or comorbid conditions, would also be valuable in revealing who might benefit most from each treatment. Finally, more RCTs on the topic with higher quality of conduct and reporting are needed to enhance the scientific evidence, especially regarding efficacy outcomes.

Future systematic reviews on the topic should be appropriately designed and conducted using a quality guide tool, such as the AMSTAR 2 checklist, as all reviews presented low or very low methodological quality. Special attention should be given to the selection and extraction of data in duplicate, the inclusion of a list of excluded studies, the declaration of funding sources for the primary studies included in the review, the explanation of the risk of bias of individual studies when discussing the review results, and the evaluation of publication bias.

4.4 | Limitations

This overview has some limitations. Studies may have been missed because they were not indexed in the databases searched or were published on the websites of institutions or health technology assessment agencies. Moreover, the exclusion criteria applied for systematic reviews without meta-analysis and other clinical outcomes may have led to the omission of significant reviews on this topic. In addition, we were unable to perform a quantitative analysis due to the heterogeneity among populations, interventions, and outcomes across the included reviews. Finally, the fracture-related efficacy outcomes synthesized in this overview derive predominantly from network meta-analyses in which none of the included reviews formally assessed the transitivity assumption—whether through systematic tabulation of effect modifiers across contributing trials or through graphical diagnostic approaches—nor applied tests for global or local statistical inconsistency (coherence). The absence of these assessments represents an additional source of uncertainty in the indirect estimates for vertebral, non-vertebral, and hip fractures, beyond what is captured by the reported GRADE certainty ratings.

5 | Conclusion

Thirteen systematic reviews evaluated the comparative efficacy and safety of romosozumab versus teriparatide for postmenopausal osteoporosis. Although romosozumab demonstrated

effects comparable to teriparatide across key outcomes, including vertebral, non-vertebral, and hip fractures, fall risk, and serious or cardiovascular adverse events, current evidence is insufficient to conclusively establish equivalence between these treatments. The available data are predominantly indirect, derived from reviews of low or critically low methodological quality, characterized by low to very low certainty and marked by substantial overlap among primary studies. Therefore, these findings should be interpreted with caution. Future high-quality, head-to-head randomized controlled trials are required to draw definitive conclusions.

Author Contributions

T.F.G.S.B., P.M.A., C.M.M.V., G.B.G.M., and T.M.L. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. C.M.M.V., G.B.G.M., and T.M.L. designed the study. T.F.G.S.B. and T.M.L. acquired the study data. T.F.G.S.B. and T.M.L. analyzed and interpreted the data. P.M.A., G.B.G.M., and T.M.L. wrote the first draft of the manuscript. P.M.A., G.B.G.M., and T.M.L. revised the manuscript and approved it for publication.

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The authors declare no conflicts of interest.

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The datasets generated during and/or analyzed during this study can be obtained from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Search strategies of the systematic review. **Table S2:** List of excluded studies. **Table S3:** Citation matrix of primary studies across the included systematic reviews. **Table S4:** Corrected Covered Area (CCA) by outcome. **Table S5:** Frequency of primary studies across outcomes.

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LETTER TO THE EDITOR

Case Report: The First Case of Paradoxical Skin Lesions Induced by Xeligekimab in a Patient With SAPHO Syndrome

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Dear Editor,

SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is a rare and complex chronic autoimmune inflammatory disorder characterized by a constellation of cutaneous and osteoarticular manifestations [1]. While it predominantly affects adults with a higher incidence in females [1]. The precise etiology of SAPHO syndrome remains unclear, and no standardized treatment regimen has been established. Given its diverse clinical features, potential molecular and cellular mechanisms, and similarities to ankylosing spondylitis, various therapeutic approaches aimed at controlling pain and inflammation have been proposed, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and conventional disease-modifying antirheumatic drugs (cDMARDs), among others [2]. For patients with SAPHO syndrome who do not respond to conventional therapies, biologic agents such as TNF inhibitors and biologics targeting the IL-17/IL-23 axis are often considered [2]. However, paradoxical skin lesions induced by TNF inhibitors have been extensively reported, and IL-17A inhibitors, including secukinumab and ixekizumab, may also trigger similar paradoxical skin lesions [3]. Xeligekimab (GR1501), developed by Genrix (Shanghai) Pharmaceutical Technology Co. Ltd. and Chongqing Genrix Biopharmaceutical Co. Ltd., is a recombinant fully human IgG4 anti-IL-17A monoclonal antibody [4]. IgG4 is the preferred subclass of therapeutic monoclonal antibodies. Owing to its limited ability to trigger effector functions, it is also an ideal candidate for target blockade in vivo [4]. Fully human antibodies can reduce immunogenicity and the risk of adverse reactions, which confers greater safety to Xeligekimab compared with other IL-17 inhibitors, enabling rapid lesion clearance and long-term stable remission [4]. To date, there have been no reports of paradoxical skin lesions associated with Xeligekimab. However, we herein report the first case of paradoxical skin lesions induced by Xeligekimab in a patient with SAPHO syndrome.

A 63-year-old female patient was diagnosed with SAPHO syndrome one year ago, presenting with erythema, pustules, and desquamation on both palms, accompanied by pain in the left sternoclavicular joint and right elbow joint. [^{99m}Tc]Tc-MDP whole-body bone scan revealed radionuclide uptake in the left sternoclavicular joint and right elbow joint (Figure 1). Treatment with methotrexate and leflunomide for one month improved her skin rash and joint pain. However, the patient's condition began to deteriorate one month later: the erythema, pustules, and desquamation on both palms were more severe than before (Figure 2A), and the pain in the left sternoclavicular joint and right elbow joint was aggravated. Given that previous reports have indicated that both TNF inhibitors and some IL-17A inhibitors are associated with adverse reactions, particularly paradoxical skin lesions, Xeligekimab was selected for administration. After administration of Xeligekimab, the skin rash on the patient's palms significantly improved (Figure 2B), and the joint pain was remarkably alleviated. However, four weeks later, the patient developed paradoxical skin lesions on the right lower limb accompanied by pruritus (Figure 2C), followed by similar but milder eruptions on the left lower limb, which were considered eczematous

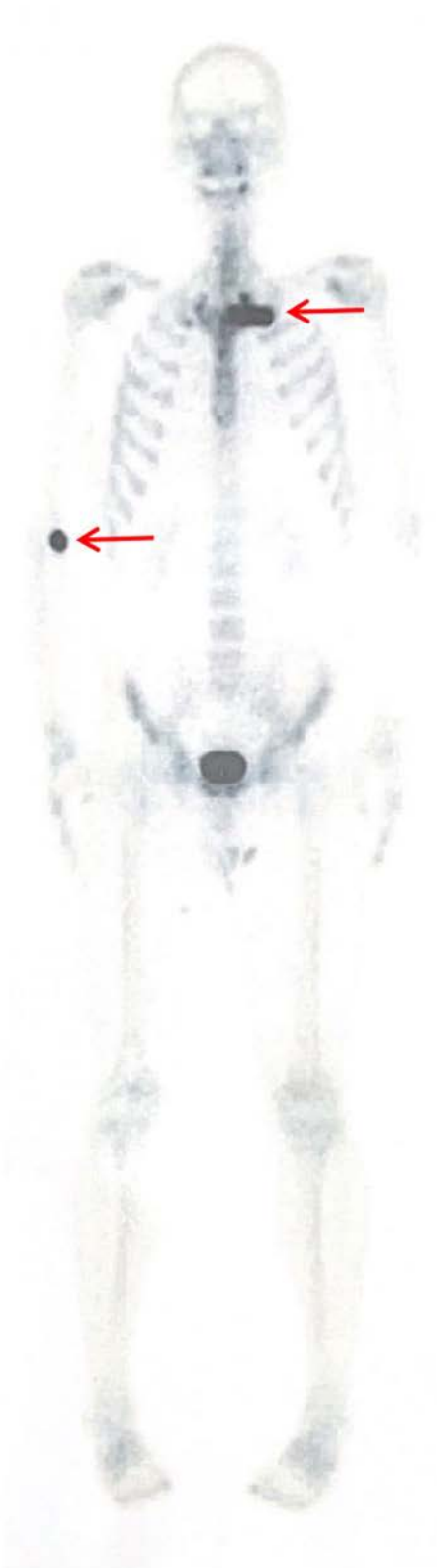

FIGURE 1 | The [^{99m}Tc]Tc-MDP whole-body bone imaging of the patient. The [^{99m}Tc]Tc-MDP whole-body bone imaging showed radiographic concentrations at the left sternoclavicular joint and right elbow joint (as indicated by the red arrows).

dermatitis. Consequently, Xeligekimab was discontinued and switched to tofacitinib. The rash on both lower limbs began to improve one week after the treatment adjustment (Figure 2D). One month later, the patient showed no recurrence of the rash, with only scattered brown pigmentation remaining on both lower limbs and no other discomfort (Figure 2E). During the 11-month follow-up, the SAPHO syndrome remained stable, and the skin rash on the lower limbs exhibited satisfactory recovery without recurrence (Figure 2F).

IL-17, a central cytokine primarily produced by T helper 17 (Th17) cells, plays a pivotal role in the immune processes underlying both cutaneous and osteoarticular inflammation in SAPHO syndrome [3]. Studies have demonstrated elevated levels of proinflammatory cytokines, such as TNF-α, IL-17, and IL-23, in patients with SAPHO syndrome [2]. Consequently, therapies targeting TNF-α, IL-17, and IL-23 are also applicable for addressing the inflammation-mediated pathogenesis in these patients [2]. However, some patients receiving monoclonal antibody therapy have experienced "paradoxical reactions," which refer to the occurrence or exacerbation of new manifestations of the original immune-mediated diseases after the initiation of this medication. Eczematous eruptions occur in 5%–20% of patients receiving anti-TNF-α therapy for various inflammatory diseases [5]. IL-17A inhibitors can also induce paradoxical skin reactions, with eczematous eruptions being the most frequently reported paradoxical event, as documented for both ixekizumab and secukinumab [5]. However, this study presents the first reported case of paradoxical skin lesions induced by Xeligekimab in a patient being treated for SAPHO syndrome.

The pathogenesis underlying paradoxical skin lesions induced by these biologic agents remains incompletely understood. However, emerging evidence suggests that the development of such reactions is associated with an imbalance in type 2 T helper (Th2) immune responses, and given the close interplay between type 1 T helper (Th1) and Th2 pathways, inhibition or downregulation of the Th1 axis may lead to a compensatory upregulation of Th2 activity [6]. IL-17 inhibitors may downregulate the Th1 pathway, leading to a compensatory upregulation of Th2 activity, which subsequently contributes to the development of eczematous eruptions [5]. Furthermore, IL-22 has been demonstrated to promote epidermal hyperplasia and suppress epidermal differentiation [7]. However, IL-17 inhibitors do not reduce serum IL-22 concentrations [8], suggesting that IL-22 may also play a key role in the pathogenesis of eczematous eruptions. Additionally, IL-17 inhibitors may impair dendritic cell maturation by modulating TNF-α levels, potentially leading to sustained IFN-α production, and this process may also involve upregulation of upstream cytokines such as IL-23 and compensatory increases in other IL-17 subtypes (e.g., IL-17C), collectively contributing to the development of eczematous eruptions [3]. Moreover, the skin and gut are intricately connected through the underlying immune system, which coordinately regulates the host's response to foreign antigens, with the microbiota playing an indispensable role in both compartments [9]. IL-17 inhibitors can disrupt the microbial communities in both the gut and skin, potentially leading to pathogenic bacterial infections that may contribute to the development of eczematous eruptions [3].

As a novel anti-IL-17A monoclonal antibody, Xeligekimab represents a valuable therapeutic advancement in clinical practice. We report the first case of its associated paradoxical

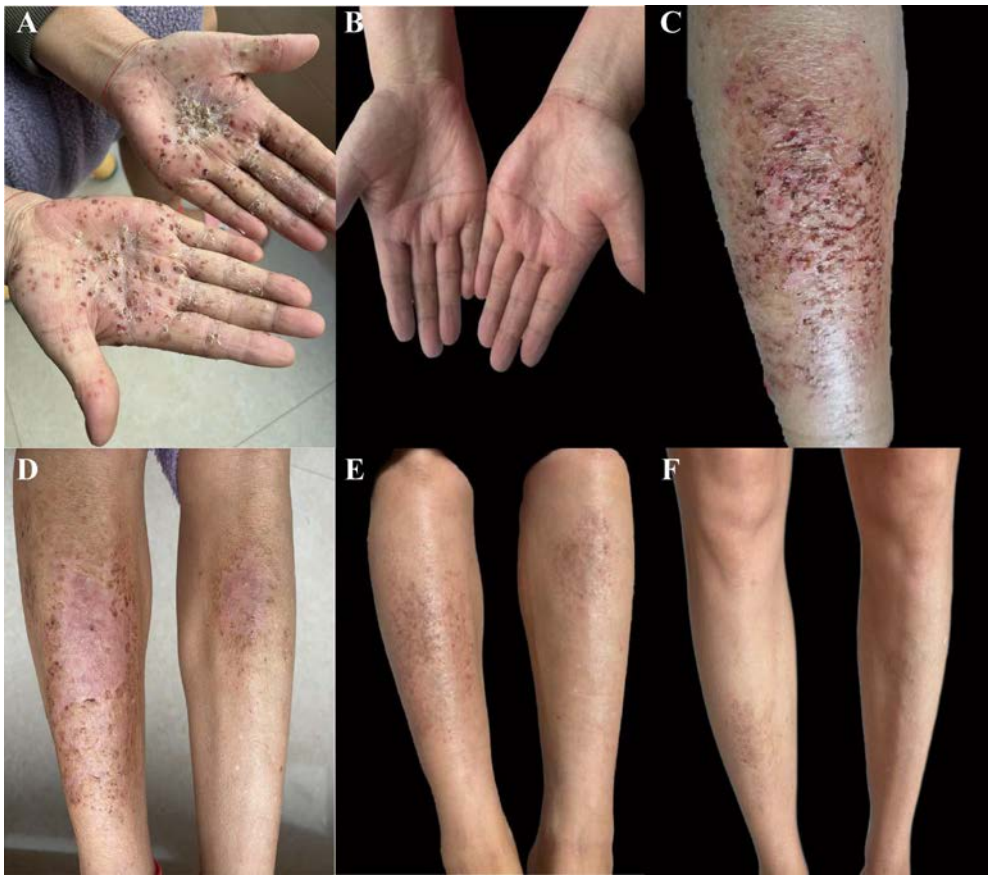

FIGURE 2 | Clinical photographs of the patient. (A) Dense erythema, pustules, and desquamation on both palms. (B) Significant improvement of palmar rash following treatment with Xeligekimab. (C) Paradoxical skin lesions emerging on the right lower limb one month after initiation of Xeligekimab therapy. (D) Improvement of rash on both lower limbs one week after discontinuation of Xeligekimab and initiation of tofacitinib. (E) One month later, showing no recurrence of rash, with scattered brown pigmentation remaining on both lower limbs. (F) At the 11-month follow-up, the skin lesions exhibited satisfactory resolution without recurrence.

skin lesions, aiming to raise awareness in clinical practice. Dermatologists should remain vigilant for the potential development of paradoxical skin lesions in patients treated with Xeligekimab and other IL-17 inhibitors. Early recognition and intervention are critical to halting the progression of adverse reactions. Furthermore, it is recommended that biologic agents be promptly discontinued upon the emergence of paradoxical skin lesions, and alternative therapies that are less likely to induce such responses, such as Janus kinase (JAK) inhibitors. Studies have suggested that JAK inhibitors exert favorable efficacy in SAPHO syndrome by inhibiting the JAK/STAT pathway, which is critical to its pathogenesis [10]. By modulating the signaling of key cytokines such as IL-6 and TNF-α, JAK inhibitors exert potent immunomodulatory effects and alleviate abnormal inflammation, with most patients tolerating treatment well and only manageable adverse events reported [10]. Thus, JAK inhibitors represent a promising and well-tolerated therapeutic option for SAPHO syndrome and may serve as a valuable alternative when other treatments fail or are poorly tolerated.

Author Contributions

Li Chang: Conceptualization, Data curation, Methodology, Writing-original draft, Writing-review and editing (primary contributor). Fanzhang Meng: Conceptualization, Data curation, Methodology, Writing-original draft. Shuli Li: Conceptualization, Methodology, Data curation, Methodology, Writing-original draft. Chen Li: Conceptualization, Methodology, Supervision, Writing-original draft, Writing-review and editing (corresponding author). Jianglin Zhang: Conceptualization, Methodology, Supervision, Writing-original draft, Writing-review and editing (corresponding author). Chen Li and Jianglin Zhang are co-corresponding authors.

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Ethics Statement

Patients' clinical data and images were used anonymously in this study without compromising patient health or privacy. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The details of this case have also been approved for publication by Shenzhen People's Hospital.

Consent

The consent for publication was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Li Chang
Fanzhang Meng
Shuli Li
Chen Li
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EDITORIAL

Adjunctive Dapsone Therapy in Pediatric Systemic Lupus Erythematosus With Cutaneous and Vasculitic Overlap: Implications for Stable Lupus Nephritis

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1 | Introduction

Childhood-onset systemic lupus erythematosus (cSLE) represents a unique phenotype characterized by higher disease activity, earlier multiorgan involvement, and poorer long-term outcomes than adult-onset SLE [1, 2]. Lupus nephritis (LN) develops in up to 60%–70% of pediatric patients and remains the leading cause of morbidity and mortality. International cohort data involving 382 children with lupus nephritis demonstrated significant early disease burden and persistent difficulty in achieving sustained renal remission at 24 months [3]. These findings underscore the unmet clinical need for adjunctive therapeutic strategies beyond conventional immunosuppression. Although corticosteroids, mycophenolate mofetil (MMF), cyclophosphamide, and biologics such as belimumab have improved survival [4, 5], refractory or overlap features including vasculitis, bullous eruptions, and small-vessel inflammation continue to challenge management.

Dapsone, a synthetic sulfone compound (4,4′-diaminodiphenylsulfone) with both antimicrobial and anti-inflammatory activity, has been used for decades in leprosy and dermatitis herpetiformis [6]. Owing to its capacity to inhibit neutrophilic inflammation, dapsone has occasionally been employed off-label in autoimmune diseases such as cutaneous lupus erythematosus (CLE) and vasculitic overlap syndromes. Case-based evidence from the *International Journal of Rheumatic Diseases* and other rheumatology reports suggests its potential role as adjunctive therapy in pediatric SLE, particularly where cutaneous or vasculitic manifestations accompany nephritis. Chinese and Thai populations have been reported to carry a higher risk of dapsone hypersensitivity syndrome (DHS) [7, 8].

2 | Methods

This article was conducted through a focused literature search of PubMed, Embase, and Web of Science up to January 2026. Search terms included "pediatric systemic lupus erythematosus," "childhood-onset SLE," "lupus nephritis," "dapsone," and "steroid-sparing therapy." Case reports, cohort studies, and review articles were included. Articles lacking sufficient clinical data were excluded. This review synthesizes mechanistic rationale and available clinical evidence without performing a quantitative meta-analysis.

3 | Mechanistic Rationale

Dapsone's principal anti-inflammatory mechanism involves inhibition of neutrophil myeloperoxidase and suppression of

Abbreviations: CLE, cutaneous lupus erythematosus; cSLE, childhood-onset systemic lupus erythematosus; DHS, dapsone hypersensitivity syndrome; G6PD, glucose-6-phosphate dehydrogenase; LN, lupus nephritis; MMF, mycophenolate mofetil; NAT2, N-acetyltransferase 2; NETs, neutrophil extracellular traps.

oxidative burst. By reducing neutrophil chemotaxis and complement activation, it limits endothelial injury and tissue damage in immune-complex–mediated disorders. The mechanism differs from that of corticosteroids or antimetabolites and may complement them in conditions dominated by neutrophilic inflammation, such as bullous lupus or small-vessel vasculitis.

Experimental data indicate that dapsone decreases formation of neutrophil extracellular traps (NETs), which contribute to autoantigen exposure and interferon signaling in lupus. It also downregulates adhesion-molecule expression and IL-8-mediated neutrophil recruitment, suggesting an indirect capacity to attenuate vascular injury in lupus nephritis. Although no direct nephroprotective action has been proven, these immunomodulatory effects provide a plausible rationale for its adjunctive use in pediatric LN. However, the human leukocyte antigen *HLA-B*13:01 was reported as an important risk factor for dapsone hypersensitivity syndrome (DHS) in Chinese and Thai populations [7].

4 | Clinical Experience in Pediatric SLE

It is important to emphasize that dapsone is not indicated for induction or maintenance therapy of active lupus nephritis. Rather, its role is limited to an adjunctive, steroid-sparing option in carefully selected pediatric patients with stable renal disease who present with prominent cutaneous or small-vessel inflammatory manifestations. There is currently no evidence supporting a direct nephroprotective effect.

Clinical evidence for dapsone in cSLE remains limited to case reports and small series. In pediatric patients, dapsone is generally initiated at 0.5 mg/kg/day and cautiously titrated to approximately 1 mg/kg/day according to clinical response and tolerability, with a usual maximum dose not exceeding 100 mg per day. Baseline and serial hematologic monitoring are essential, particularly when dapsone is administered concomitantly with mycophenolate mofetil or azathioprine due to the potential risk of additive bone marrow suppression. The decision to initiate dapsone should be individualized and undertaken in consultation with pediatric rheumatology specialists.

In previously published pediatric case reports from East Asia [7, 9], children with leukocytoclastic vasculitis, bullous lupus, or ulcerative lesions refractory to corticosteroids or hydroxychloroquine showed significant improvement within weeks of dapsone therapy. Skin healing allowed corticosteroid tapering without renal deterioration. In several cases, dapsone was introduced in patients with stable class III or IV lupus nephritis on MMF or azathioprine, with no worsening of proteinuria or serum creatinine.

Specific cases in the literature further validate the concept. For instance, a 14-year-old girl with biopsy-proven Class V lupus nephritis and bullous systemic lupus erythematosus (BSLE) achieved rapid clinical remission of skin lesions upon adding dapsone after standard therapies failed [9].

In Western pediatric case reports [10] these observations: in juvenile SLE with urticarial vasculitis or bullous overlap, dapsone achieved resolution of rash and mucosal ulceration while maintaining stable renal indices. We noticed a report, an 11-year-old SLE patient with mild proteinuria successfully utilized dapsone at 1 mg/kg/day as a steroid-sparing agent, maintaining long-term control of both cutaneous and articular symptoms [10]. Improvement in cutaneous and vasculitic symptoms contributed to overall disease control and reduced cumulative steroid exposure. Prior reviews have emphasized that dapsone functions primarily as a steroid-sparing agent rather than a nephroprotective therapy [8].

5 | Safety Considerations and Monitoring

The safety profile of dapsone requires careful surveillance, particularly in children. The most frequent adverse event is dose-dependent hemolytic anemia due to oxidative stress on erythrocytes. Methemoglobinemia, agranulocytosis, and hypersensitivity reactions are rarer but potentially life-threatening [11].

Screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency is essential before initiation. Baseline complete blood count, reticulocyte count, bilirubin, and methemoglobin levels should be obtained and repeated every 2–4 weeks initially. Mild asymptomatic hemolysis can often be tolerated if hemoglobin remains stable.

Dapsone hypersensitivity syndrome manifested by fever, rash, lymphadenopathy, and hepatitis usually appears within 6 weeks and warrants immediate discontinuation. Hepatotoxicity and peripheral neuropathy have also been described with chronic use [8].

In pediatric SLE, concurrent administration with MMF, azathioprine, or tacrolimus necessitates vigilance to prevent additive myelosuppression. Dose titration and individualized monitoring are imperative to maintain safety.

6 | Regional and Pharmacogenetic Perspectives

Pharmacogenetic variation in the N-acetyltransferase 2 (NAT2) gene influences dapsone metabolism. Individuals who are slow acetylators, more commonly observed in certain East Asian populations, may experience higher plasma drug levels and an increased risk of hematologic toxicity.

In addition, *HLA-B*13:01 has been strongly associated with dapsone hypersensitivity syndrome (DHS) in several Asian populations. Pre-treatment *HLA-B*13:01 screening may be considered in regions with high allele prevalence, particularly in East Asia; however, it is not currently mandated by international pediatric rheumatology guidelines and remains a region-specific risk mitigation strategy rather than a universal recommendation.

7 | Asian Clinical Context

Most available pediatric reports of adjunctive dapsone therapy originate from East Asian countries, particularly Taiwan and

TABLE 1 | Clinical implications and mechanistic basis of adjunctive dapsone use in pediatric systemic lupus erythematosus with stable lupus nephritis.

Domain	Revised description
Clinical role	Dapsone may serve as an adjunctive therapy in selected pediatric SLE patients presenting with prominent cutaneous or small-vessel inflammatory manifestations, particularly when lupus nephritis is stable under conventional immunosuppressive therapy
Mechanistic rationale	The therapeutic effect is indirect in lupus nephritis and is mediated primarily through suppression of neutrophil activation, reduction of oxidative burst, and attenuation of immune-complex–driven vascular inflammation
Steroid-sparing potential	Dapsone may facilitate gradual reduction of corticosteroid dosage while maintaining disease control in cases with refractory cutaneous or vasculitic involvement
Level of evidence	Current evidence is limited to case reports and small case series; no randomized controlled trials have demonstrated a direct renal benefit
Clinical considerations	Careful patient selection and regular hematologic monitoring are essential. The role of dapsone should be restricted to adjunctive use rather than induction or maintenance therapy for active lupus nephritis

South Korea. While the data consist primarily of isolated case reports rather than pooled cohort analyses, the consistency of favorable cutaneous responses without renal deterioration supports cautious consideration in selected patients. However, no aggregated pediatric lupus nephritis dataset currently exists to substantiate a regional treatment effect.

8 | Discussion

The current evidence base is insufficient to define dapsone's precise role in pediatric lupus nephritis, yet accumulated clinical experience suggests potential benefit when neutrophilic inflammation dominates. Its anti-neutrophilic and steroid-sparing effects may enhance control of cutaneous and vasculitic manifestations, contributing indirectly to renal stability and improved quality of life.

Future studies should aim to identify biomarkers such as neutrophil activation markers or oxidative-stress indices that predict response to dapsone. Multicenter registries and collaborative case series can provide valuable real-world data on safety and efficacy across diverse ethnic groups. Ultimately, integration of pharmacogenetic testing and standardized monitoring protocols will be essential to maximize benefit and minimize risk.

9 | Conclusion

Dapsone remains an uncommon but valuable adjunct in pediatric SLE, particularly when cutaneous vasculitis or bullous lupus overlaps with nephritis. Its benefit in LN is likely indirect, achieved through suppression of neutrophilic inflammation and attenuation of immune-complex–mediated vascular injury. Evidence remains largely anecdotal, yet its clinical utility as a steroid-sparing option deserves recognition. A summary of the clinical role, mechanistic basis, and safety considerations of adjunctive dapsone therapy in pediatric SLE with stable lupus nephritis is provided in Table 1.

Author Contributions

H.J.C., and S.H.W. writing original draft, review and editing. S.B.Y., X.L.L., and C.Y.W. writing, review and editing.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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LETTER TO THE EDITOR

Case Report: Multiple Arterial Aneurysms Rapidly Developing in a Patient With Systemic Lupus Erythematosus

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Dear Editor,

In February 2021, a 48-year-old woman presented to the hospital with facial edema, accompanied by bilateral lower limb edema and headache. She was diagnosed with systemic lupus erythematosus (SLE) in 2008 because of facial erythema, polyarthritis with morning stiffness and photosensitivity, and tested positive for antinuclear antibody and anti-Sm antibody. Her previous treatments included methylprednisolone, hydroxychloroquine, tacrolimus, and mycophenolate mofetil. Upon admission, blood pressure was 163/102 mmHg; Laboratory tests: ANA > 1:1000; anti-U1-RNP, anti-SSA, and anti-RNP antibodies were positive; Low C3; the antiphospholipid antibody profile and lupus anticoagulant (LA) were negative; urine protein quantification was 9.01 g/24 h; creatinine was 44 μmol/L; and hepatitis B was negative. The patient was treated with methylprednisolone for inflammation and to supplement protein, and symptoms improved.

On March 8, 2021, the patient had acute abdominal pain and vomited. An abdominal CT scan suggested acute pancreatitis, but blood and urine amylase tests were negative. Treatment with digestive enzymes and antispasmodics relieved the pain. The next day, the patient had transient limb convulsions. A head CT scan and cerebrospinal fluid examination revealed no abnormalities. Lupus encephalopathy was suspected, and treatment was adjusted to include methylprednisolone 500 mg qd and intravenous immunoglobulin. The symptoms did not recur. Follow-up blood tests showed a downward trend (Platelets, $182 \rightarrow 87 \times 10^9$/L; CREA: 44 → 163.1 μmol/L). Plasma exchange therapy was initiated. After a few days, developed extensive skin ecchymoses and a significant decrease in hemoglobin (95 to 30 g/L). Repeated detection of abdominal CT scan showed a large number of hematoma in abdominal cavity, suggesting left ovarian aneurysm (Figure 1B,C). On March 16, the patient underwent left ovarian artery embolization, after which hemoglobin and platelet levels improved. On March 19, the patient suddenly experienced massive hematemesis. Emergency gastroscopy suggests middle esophageal artery bleeding. An endoscopic hemostasis procedure was performed, and hemoglobin and platelet levels stabilized. On March 25, a follow-up HGB test showed another drop (from 130 to 91 g/L). An abdominal and pelvic computed tomography angiography (CTA) was performed, revealing edema and thickening of the hepatic artery wall, as well as possible multiple aneurysms in the local area (Figure 1D). Transcatheter hepatic artery angiography and embolization were performed. During the procedure, multiple pseudoaneurysms were observed in the left and right hepatic arteries, and three small aneurysms were observed in a small branch of the superior mesenteric artery (Figure 1E). Postoperative imaging studies of the head and chest vessels showed no abnormalities, and the patient was discharged (Figure 1A).

Long-term use of Telitacicept after discharge controlled the disease and gradually stabilized. CTA in abdominal cavity and pelvic cavity was dynamically checked, and the ovarian aneurysm in the left abdominal cavity had disappeared, and there was no new aneurysm except the changes after embolization of common hepatic aneurysm (Figure 2).

We presented a rare case of multiple aneurysms in a patient with SLE, which is caused by the synergistic effect of many factors, and the core lies in immune-mediated vascular injury. The occurrence and expansion of aneurysm in patients are completely synchronized with the active stage of the disease (high SLEDAI

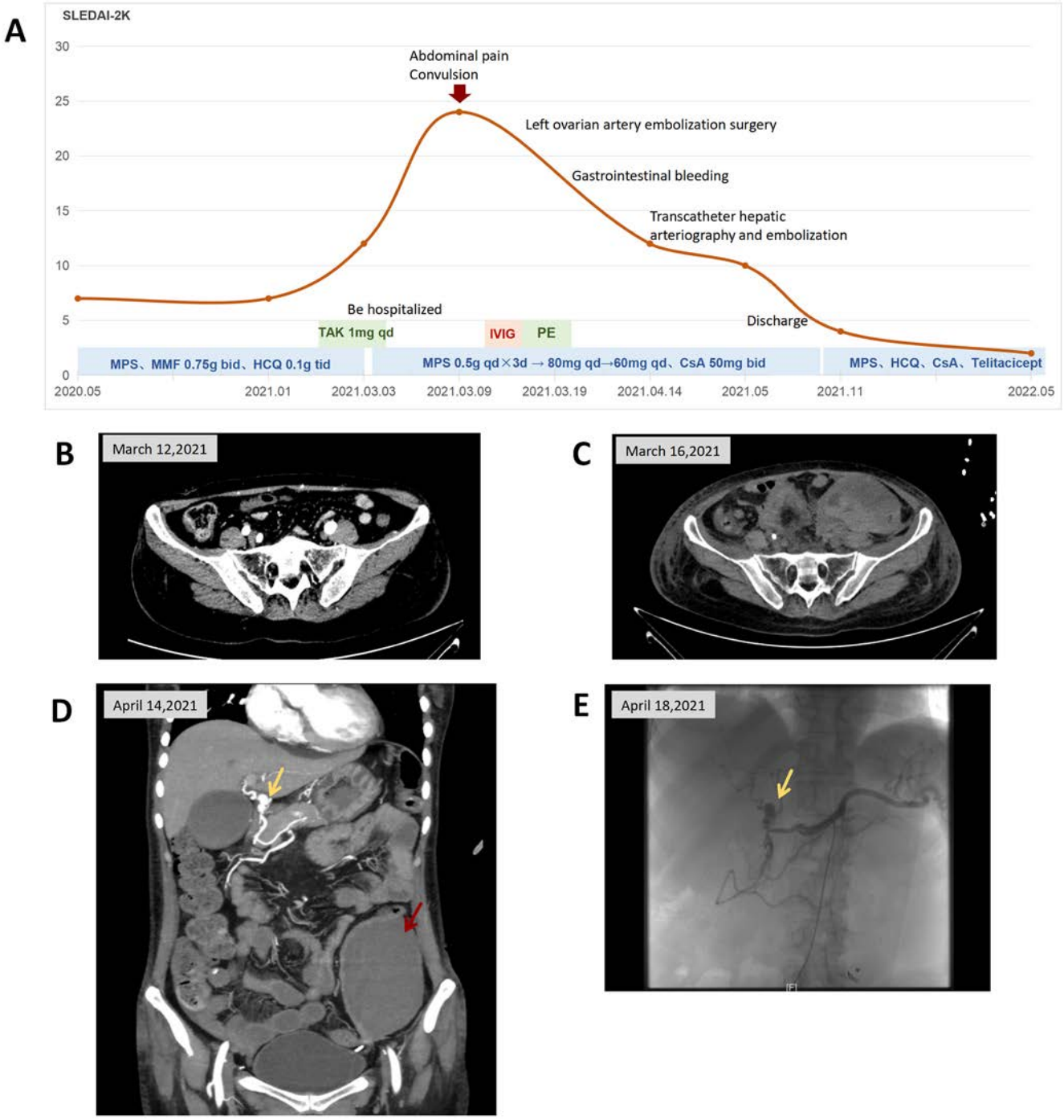

FIGURE 1 | (A) The relationship between the patient's condition and the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). (B) Abdominal CTA on March 12 showed no abdominal hematoma formation. (C) Contrast-enhanced abdominal CT on March 16 suggested pseudoaneurysm formation in the left ovarian artery. (D) On April 14, multiple pseudoaneurysms were found in the hepatic arteries, some small branches of the superior mesenteric artery were aneurysm-like dilated (yellow arrow), and pseudoaneurysm was formed in the left ovarian artery (red arrow). (E) On April 18th, "Transcatheter Hepatic Arteriography and Embolization" was performed. During the operation, the suspicious part of the left ovarian artery was recanalized after embolization. Three tumor-like dilations of different sizes can be seen in some small branches of superior mesenteric artery.

score), but there is no progress after remission. This clear time correlation strongly supports that active immune inflammation is the root cause. Its pathological basis may involve vasculitis directly damaging the vessel wall, inflammatory cell infiltration, collagen degeneration caused by up-regulation of matrix protease activity, elastic fiber destruction, and smooth muscle injury, which together promote vascular remodeling and tumor-like dilatation [1]. In addition, long-term use of steroids may weaken vascular homeostasis by inhibiting repair, promoting atherosclerosis, and mucinous degeneration [2].

Hypertension at the time of onset is probably an important secondary aggravating factor. Although hypertension is more often associated with large aneurysms, it constitutes a continuous

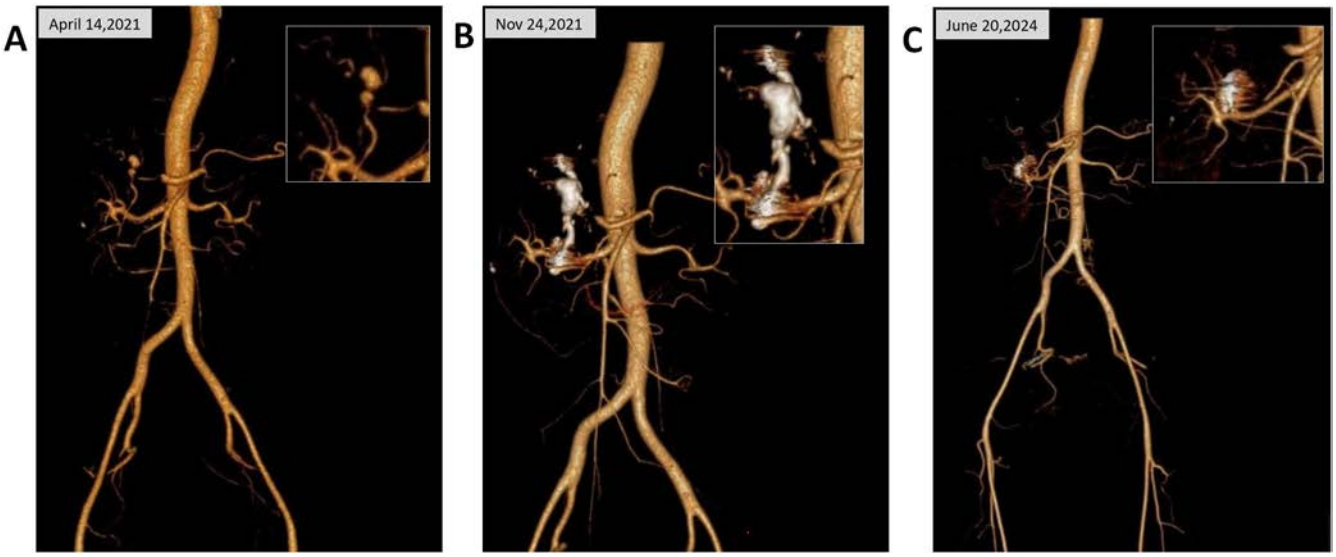

FIGURE 2 | (A) Three-dimensional arterial angiography of the abdomen and pelvis of the patient on April 14. (B and C) There was no new aneurysm formation except for the changes after embolization of the common hepatic aneurysm.

mechanical stress on the vascular wall that has been weakened by inflammation, which may accelerate the expansion and rupture of medium visceral arteries (such as ovarian, esophageal, liver and mesenteric arteries) [3]. Although immunosuppressive patients need to be alert to vasculitis caused by infection (such as Salmonella) [4], this case has no fever and negative pathogenic examination, and there is no basis for infection.

The challenges in diagnosing and treating these patients lie in early identification and timely vascular intervention. The authors suggest that when patients with lupus erythematosus have unexplained abdominal pain, when common acute abdominal diseases such as pancreatitis and gastrointestinal vasculitis are excluded, and when they are combined with rapid decrease of hemoglobin and skin ecchymosis (vascular wall lesions), visceral hemangioma should be highly suspected, and CTA examination of important organs should be performed in time. When the patient can't tolerate transport and the renal load is heavy, contrast-enhanced ultrasound (CEUS) or bedside Doppler ultrasound can serve as a rapid, noninvasive, and repeatable first-line bedside tool to screen for major vascular abnormalities and free fluid [5].

Currently, common treatments for aneurysms include open surgery and endovascular therapy. For unruptured abdominal aortic aneurysms without complex medical comorbidities, open repair is the preferred treatment. However, for high-risk patients, endovascular aneurysm repair (EVAR) or conservative management is recommended, considering the risk of rupture and mortality [6]. For pseudoaneurysms in special populations or at special locations, active treatment is necessary regardless of size [7]. The EVICTUS study found that for aortic lesions in patients with connective tissue disease (CTD), endovascular treatment achieves a high early surgical success rate and a low perioperative mortality rate, with mid-term survival rates comparable to those reported for open aortic surgery in CTD patients.

In this case, the patient underwent MDT discussions and received collaborative treatment involving the ICU, vascular surgery, interventional radiology, and gastroenterology endoscopy departments. For critically ill SLE patients, developing individualized treatment plans following MDT discussions is crucial for improving patient prognosis and survival rates.

Author Contributions

Binbin Chen: conceptualization, data collection, formal analysis, manuscript drafting, literature review. **Hongying Shi** and **Juanjuan Wang:** patient management, follow-up, clinical insights, case interpretation. **Chenglong Fang:** supervision, project administration, manuscript review. **Meiling Li:** case interpretation oversight, validation, final manuscript approval.

Consent

Written informed consent was obtained from the patient for publication of this case report. Patient identity has been anonymized.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting this study are available from the corresponding author upon reasonable request. They are not publicly available due to privacy/ethical restrictions.

Binbin Chen
Hongying Shi
Chenglong Fang
Juanjuan Wang
Meiling Li

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LETTER TO THE EDITOR

Cerebrospinal Fluid IgG4 as a Key Diagnostic Clue in IgG4-Related Spinal Pachymeningitis With Normal Serum Levels

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Dear Editor,

IgG4-related disease (IgG4-RD) is a systemic immune-mediated fibroinflammatory disorder that can involve virtually any organ. Central nervous system involvement is rare, and spinal pachymeningitis represents an exceptionally uncommon manifestation that may lead to spinal cord compression and myelopathy. Early diagnosis is challenging due to nonspecific clinical features and difficulties in distinguishing the disease from infectious or neoplastic conditions. We report the case of a 64-year-old woman who presented with progressive back pain and was found to have extensive IgG4-related spinal pachymeningitis. Despite normal serum IgG4 levels, markedly elevated cerebrospinal fluid IgG4 concentration and intrathecal immunoglobulin synthesis supported the clinical diagnosis of IgG4-related spinal pachymeningitis in the absence of histopathological confirmation. The patient showed a dramatic clinical and radiological response to glucocorticoid therapy followed by rituximab. This case highlights the diagnostic value of cerebrospinal fluid IgG4 analysis and underscores the importance of early immunosuppressive treatment in preventing irreversible neurological sequelae.

A 64-year-old woman presented to the neurosurgery outpatient clinic with a 6-month history of back pain that had significantly worsened over the preceding month. The pain was severe enough to awaken her from sleep and was refractory to nonsteroidal anti-inflammatory drugs. Apart from fatigue and generalized weakness, she denied constitutional symptoms such as fever, weight loss, or night sweats, and there were no clinical features suggestive of a systemic inflammatory rheumatic disease at presentation.

Her past medical history included hypertension, coronary artery stent implantation, a previously detected pulmonary nodule, and varicose vein surgery. Family history was notable for rheumatoid arthritis in a first-degree relative. Physical examination revealed localized tenderness over the thoracic spinous processes. Neurological examination was unremarkable, with full muscle strength, intact superficial and deep sensation, normal deep tendon reflexes, and no pathological reflexes. Joint examination showed no evidence of synovitis or limitation of motion.

Following evaluation in the neurosurgery outpatient clinic, spinal magnetic resonance imaging (MRI) was obtained. Imaging demonstrated diffuse dural thickening extending from the C7 to T12 vertebral levels, predominantly involving the posterior and right lateral aspects of the spinal canal. The lesion was long-segment and partially nodular, with intense contrast enhancement. The maximum dural thickness measured approximately 5.5 mm, with a longitudinal extension of approximately 175 mm, resulting in spinal cord compression. T2-weighted images revealed hyperintense signal changes within the spinal cord at the T6–T9 levels, consistent with myelopathic edema (Figure 1A,B).

Based on these findings, the patient was referred for neurological consultation. Infectious, neoplastic, and inflammatory etiologies were considered in the differential diagnosis. To assess for systemic involvement, fluorodeoxyglucose positron

emission tomography–computed tomography (FDG PET-CT) was performed. This revealed markedly increased metabolic activity within the spinal canal from T1 to T8 vertebral levels, with a maximum standardized uptake value of 7.2. Additionally, a fluorodeoxyglucose-avid lesion extending into the spinal canal from the posterior aspect of the T12 vertebral body was observed. Circumferential thickening of the infrarenal abdominal aorta with increased FDG uptake (maximum standardized uptake value 6.3) was also noted, consistent with periaortitis (Figure 2A,E). Although FDG uptake in the arterial wall can be observed in atherosclerosis, particularly in patients with cardiovascular risk factors, the pattern of uptake in our patient was more suggestive of periaortitis. Unlike the typically patchy and irregular FDG distribution seen in atherosclerotic plaques, our patient demonstrated diffuse, circumferential wall thickening and intense, continuous metabolic activity (SUVmax 6.3) involving the infrarenal abdominal aorta (Figure 2E). This morphological pattern, combined with the absence of significant calcification at the site of maximal uptake, strongly supported an inflammatory

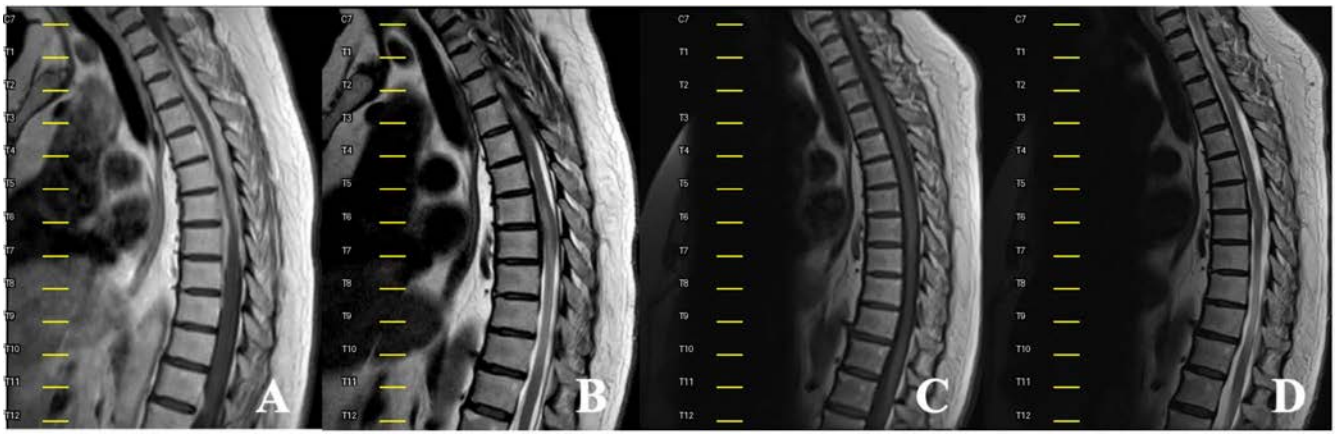

FIGURE 1 | (A, B) Pre-treatment contrast-enhanced T1- and T2-weighted images; (C, D) non–contrast-enhanced T1- and T2-weighted images obtained 1 month after treatment, showing resolution of dural and intramedullary abnormalities.

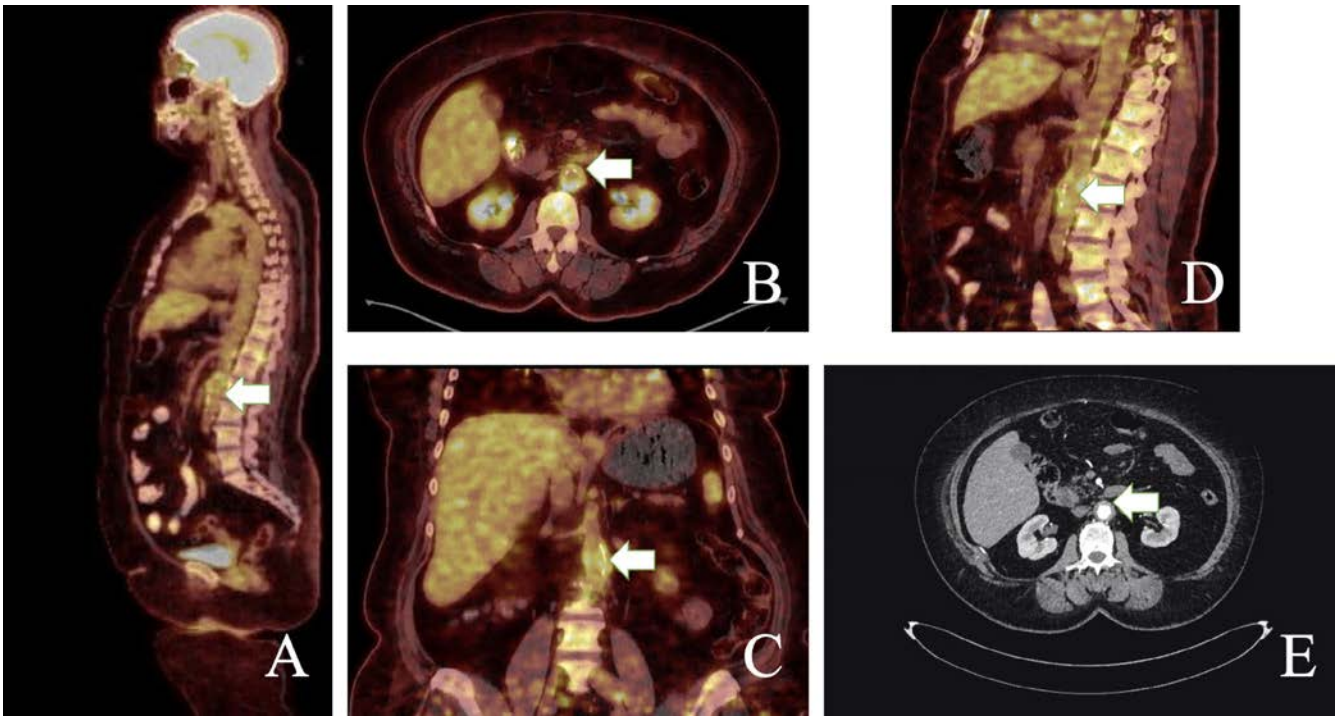

FIGURE 2 | (A) Sagittal FDG PET–CT showing extensive metabolic activity along the dura from T1 to T8 vertebral levels with long-segment dural involvement (arrow). Maximum SUV: 7.2. (B) Axial FDG PET–CT at the T12 level demonstrating an FDG-avid lesion extending from the posterior aspect of the T12 vertebral body into the spinal canal (arrow). (C) Coronal FDG PET–CT showing the lesion extending into the spinal canal from the posterior T12 vertebra and adjacent structures (arrow). (D) Reformatted sagittal FDG PET–CT illustrating the longitudinal extent and upper limits of dural involvement (arrow). (E) Axial contrast-enhanced CT demonstrating circumferential thickening of the infrarenal abdominal aorta consistent with periaortitis (arrow), correlating with increased FDG uptake (maximum SUV: 6.3).

periaortitis—a well-documented extra-neurological manifestation of IgG4-RD—rather than simple atherosclerotic changes [1].

The patient was referred to the rheumatology clinic for further evaluation. Rheumatologic history revealed no additional complaints, and a detailed rheumatologic review of systems was unremarkable. Physical examination did not demonstrate any pathological findings. Muscle strength was intact in all extremities, and sensory examination was normal.

Laboratory evaluation demonstrated elevated inflammatory markers, with a C-reactive protein (CRP) level of 22 mg/L and an erythrocyte sedimentation rate (ESR) of 39 mm/h. While CRP levels are typically within the normal range in IgG4-RD, this elevation necessitated a rigorous exclusion of other inflammatory mimics. Notably, antineutrophil cytoplasmic antibodies (ANCA; MPO and PR3) were negative, significantly reducing the likelihood of ANCA-associated hypertrophic pachymeningitis. Complete blood count and routine biochemical tests were within normal limits. Autoimmune serologic testing, including antinuclear antibodies (ANA), anti–double-stranded DNA antibodies, extractable nuclear antigen (ENA) panel, antineutrophil cytoplasmic antibodies (ANCA; MPO and PR3), and angiotensin-converting enzyme levels, were negative or within normal ranges. Screening for tuberculosis using an interferon-gamma release assay, as well as tests for human immunodeficiency virus and syphilis, were negative. Serum IgG4 concentration was within the normal range.

After multidisciplinary evaluation, infectious and malignant etiologies were considered unlikely, and an inflammatory process was favored. Surgical biopsy was deferred due to the long-segment nature of the lesion and the risk of spinal cord injury. Diagnostic lumbar puncture was therefore performed.

Cerebrospinal fluid (CSF) appeared xanthochromic, in the absence of evidence of hemorrhage, consistent with marked inflammatory changes. CSF analysis demonstrated markedly elevated protein levels, hypoglycorrhachia, and lymphocytic pleocytosis, with cytological examination revealing lymphoplasmacytic cells. CSF cultures, tuberculosis polymerase chain reaction (PCR) testing, neuromyelitis optica antibodies, anti–myelin oligodendrocyte glycoprotein (MOG) antibodies, oligoclonal bands, and a paraneoplastic antibody panel were all negative. The IgG index was markedly elevated (2.41), indicating intrathecal immunoglobulin synthesis, and CSF IgG4 concentration was markedly increased (779 mg/dL). Detailed cerebrospinal fluid parameters are summarized in Table 1. CSF IgG4 concentration was measured using nephelometry. The reference range for CSF IgG4 in our laboratory is 4.2–6.4 mg/dL. It should be noted that the assay has not been formally validated for CSF samples, which may affect the interpretation of absolute values. Nevertheless, the markedly elevated CSF IgG4 level (779 mg/dL) in this case strongly supports intrathecal IgG4 synthesis.

After exclusion of infectious, neoplastic, and alternative inflammatory etiologies, a clinically diagnosed IgG4-related spinal pachymeningitis was considered, based on the clinical presentation, radiological findings, and cerebrospinal fluid evidence of intrathecal IgG4 synthesis.

TABLE 1 | Measured by nephelometry.

Parameter	Patient result	Reference range
Appearance	Xanthochromic	Clear and colorless
Cell count	91/μL (82% mononuclear)	0–5/μL
Protein level	1870 mg/dL	15–45 mg/dL
Glucose level	37 mg/dL	40–70 mg/dL (Blood glucose: 112 mg/dL)
IgG index	2.41	0.20–0.60
CSF IgG4	779 mg/dL	4.2–6.4 mg/dL

Note: The assay has not been formally validated for cerebrospinal fluid samples in our laboratory.

The patient received intravenous methylprednisolone at a dose of 1000 mg/day for three consecutive days, followed by oral prednisolone at 0.5 mg/kg/day with subsequent gradual tapering.

In view of the long-segment spinal dural involvement, the presence of myelopathic spinal cord edema, and the high risk of irreversible neurological injury, rituximab was initiated early as a steroid-sparing agent to achieve rapid and sustained disease control, favoring early B-cell depletion over a stepwise escalation approach. Rituximab was administered at a dose of 1000 mg, with a second infusion given 2 weeks later, for a total cumulative dose of 2000 mg.

Following treatment, the patient experienced complete resolution of back pain, accompanied by normalization of acute-phase reactants. At the 1-month follow-up, contrast-enhanced spinal MRI demonstrated complete resolution of dural thickening and contrast enhancement, along with full regression of spinal cord edema (Figure 1C,D).

IgG4-related disease (IgG4-RD) is a systemic immune-mediated fibroinflammatory disorder characterized by tumefactive lesions, dense lymphoplasmacytic infiltration enriched with IgG4-positive plasma cells, and variable degrees of fibrosis [2, 3]. Although the pancreas, salivary glands, and lacrimal glands are most frequently involved, central nervous system (CNS) involvement is rare, occurring in fewer than 5% of cases, with hypertrophic pachymeningitis representing the most common neurological manifestation [4].

IgG4-related spinal pachymeningitis is an exceptionally rare and underrecognized manifestation of IgG4-RD. Recent reviews indicate that fewer than 21 cases have been reported worldwide, with spinal involvement accounting for only a small proportion [5]. Notably, among the previously reported cases of IgG4-related spinal pachymeningitis, the majority were diagnosed based on elevated serum IgG4 levels and/or histopathological confirmation. Cases presenting with normal serum IgG4 levels represent a particularly challenging diagnostic subset, as serum IgG4 is elevated in only approximately 55% of patients with IgG4-related hypertrophic pachymeningitis [6]. To our knowledge, this case is among the few in which the diagnosis was established solely on the basis of

markedly elevated CSF IgG4 concentration and intrathecal IgG synthesis without tissue confirmation, further underscoring the diagnostic value of CSF IgG4 analysis in seronegative presentations [7, 8]. Clinical presentation is often nonspecific, and radiological findings may closely mimic infectious, neoplastic, or other inflammatory conditions such as lymphoma, tuberculosis, sarcoidosis, or idiopathic hypertrophic pachymeningitis, frequently leading to diagnostic delay [4].

In the present case, the patient presented with isolated progressive back pain without focal neurological deficits, despite extensive long-segment dural involvement and radiological evidence of spinal cord compression and myelopathic edema. This clinicoradiological dissociation has been increasingly recognized in recent series and highlights the importance of considering IgG4-RD in patients with persistent back pain and unexplained dural thickening, even in the absence of overt neurological impairment [9].

Contrast-enhanced spinal magnetic resonance imaging (MRI) remains the cornerstone of diagnosis, typically demonstrating diffuse or nodular dural thickening with intense enhancement [4]. In this case, extensive cervicothoracic involvement strongly favored an inflammatory etiology. Fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET-CT) further supported the diagnosis by revealing metabolically active dural inflammation and concomitant periaortitis, a well-recognized manifestation of IgG4-RD, and proved valuable in assessing systemic disease activity when tissue diagnosis was not feasible [10].

Although elevated serum IgG4 levels are frequently observed in IgG4-RD, their diagnostic sensitivity is limited, and normal serum IgG4 concentrations do not exclude the disease [3]. Recent literature emphasizes that reliance on serum IgG4 alone may result in underdiagnosis, particularly in cases with isolated CNS involvement. In contrast, cerebrospinal fluid (CSF) analysis has emerged as a valuable diagnostic adjunct. Markedly elevated CSF IgG4 concentrations and evidence of intrathecal IgG synthesis has been increasingly reported as supportive diagnostic findings in IgG4-related pachymeningitis [11, 12]. In the present case, the combination of elevated CSF IgG4 concentration and an increased IgG index was instrumental in establishing the diagnosis.

A key challenge in our case was the elevated CRP level (22 mg/L), as IgG4-RD is characteristically associated with normal or only mildly elevated acute-phase reactants. Elevated CRP often points toward alternative etiologies, such as ANCA-associated hypertrophic pachymeningitis (A-HP), particularly those positive for MPO-ANCA, which can radiologically and histologically mimic IgG4-RD [13, 14]. However, the consistently negative ANCA serology, the presence of concomitant periaortitis on PET-CT, and the markedly elevated CSF IgG4 levels (779 mg/dL) with an increased IgG index strongly favored a diagnosis of IgG4-RD over A-HP or other vasculitides. In the absence of tissue confirmation, our case represents a clinically diagnosed IgG4-related spinal pachymeningitis, supported by a constellation of indirect evidence including characteristic imaging, cerebrospinal fluid analysis, and a dramatic response to immunosuppressive therapy. Histopathological confirmation remains the diagnostic gold standard for IgG4-RD; however, biopsy is not always feasible or safe. In cases of extensive long-segment spinal dural involvement, the risk of neurological injury associated with surgical biopsy may outweigh the diagnostic benefit. Recent expert reviews acknowledge that in anatomically high-risk locations, a diagnosis may be established based on characteristic imaging findings, supportive laboratory evidence (including CSF IgG4 analysis), exclusion of alternative etiologies, and response to immunosuppressive therapy [15]. The dramatic clinical and radiological response observed in this patient further supports the diagnostic accuracy of this approach.

Glucocorticoids remain the first-line therapy for IgG4-RD and typically induce rapid clinical and radiological improvement [16]. However, relapse rates are substantial, particularly in patients with CNS involvement or extensive disease burden. Rituximab, through B-cell depletion, has emerged as an effective steroid-sparing agent and has demonstrated high remission rates in refractory or high-risk IgG4-RD, including neurological manifestations [17]. In this patient, early initiation of rituximab resulted in complete symptom resolution and full radiological regression, supporting an early and aggressive treatment strategy in patients at high risk of irreversible neurological sequelae.

In conclusion, IgG4-related spinal pachymeningitis is a rare but potentially reversible cause of spinal cord compression and myelopathy. Normal serum IgG4 levels do not exclude the diagnosis, and CSF IgG4 measurement may provide a critical diagnostic clue when biopsy is contraindicated. Early recognition through a multidisciplinary approach and prompt initiation of immunosuppressive therapy are essential to prevent permanent neurological damage.

Author Contributions

S.C.H.: Conceptualization, clinical management of the patient, literature review, writing of the original draft, and final approval of the manuscript. **S.B.:** Critical revision of the manuscript for important intellectual content, and final approval of the manuscript.

Ethics Statement

Institutional policy of our center does not require formal ethics committee approval for single case reports.

Consent

Written informed consent for publication of this case report and accompanying images was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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LETTER TO THE EDITOR

A Case Series: Real World Data on the Use of Anifrolumab in Patients With Systemic Lupus Erythematosus in Two Private Tertiary Hospitals in the Philippines

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Dear Editor,
It has been one year since anifrolumab was introduced in the Philippines for the treatment of systemic lupus erythematosus (SLE). Anifrolumab is a fully human monoclonal antibody that targets the type I interferon receptor, thereby inhibiting type I interferon signaling and modulating the inflammatory cascade [1].

Clinical trials have demonstrated its efficacy in reducing overall disease activity, particularly improving cutaneous manifestations, arthritis, and allowing glucocorticoid tapering [2–4]. Real-world evidence has also supported its effectiveness and tolerability in routine practice as seen in observational data from the United States, United Kingdom, Greece, and Japan [5, 6].

Since its local introduction, however, no published post-approval case series involving Filipino patients has been published. Given regional differences in disease expression, healthcare access, and genetic backgrounds, documenting local experience is of significant clinical value.

This case series includes eight patients diagnosed with SLE, using the 2019 American College of Rheumatology/European League Against Rheumatism criteria, who were treated with anifrolumab at two private tertiary hospitals. Clinical data, serologic markers (Table 1), and patient images (Figure 1) were collected. Informed consent was obtained for data sharing.

Patient 1 is a 33-year-old female with a four-year history of SLE, presenting with vasculitic rash, joint pain, and photosensitivity, maintained on prednisone with persistence of symptoms. After one dose of anifrolumab treatment, her vasculitic rash and joint pain resolved. By the fifth dose, prednisone was tapered down, and the patient expressed a perceived overall improvement in quality of life. No serious adverse events were observed.

Patient 2 is a 34-year-old female with a four-year history of SLE, presenting with intermittent fever, malaise, joint pain, and vasculitic rash. After one dose of anifrolumab, the rash resolved. Arthritis improved after the third dose. By the fifth dose, steroids were tapered off, and the patient reported full functionality at work. No serious adverse events were observed.

Patient 3 is a 55-year-old female diagnosed with SLE for seven years, presenting with alopecia, discoid rash, joint pain, and fatigue. Prednisone dose below 10 mg caused flares despite other medications. Baseline Cutaneous Lupus disease area and disease Severity Index (CLASI) of the patient prior to anifrolumab infusion was 19. By the fourth dose of anifrolumab, prednisone was discontinued, and the CLASI score was reduced to 9. Thin velus hairs also developed in areas of alopecia, resulting in a reported boost in self-esteem. No serious adverse events were observed.

Patient 4 is a 79-year-old female with a chronic, generalized, erythematous, pruritic, scaly rash from SLE (biopsy-proven) and polyarthralgia. Despite treatment with hydroxychloroquine, methotrexate, and prednisone, symptoms persisted. Her rash resolved after two doses of anifrolumab, improving patients' confidence and overall disposition. No serious adverse events were observed.

TABLE 1 | Clinical presentation, laboratories, previous treatments given, and outcomes of each patient.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Lupus specific manifestation								
Fever	+[1]	+	-[2]	—	—	—	—	—
Body Malaise	+	+	—	—	—	—	—	—
Fatigue	—	—	+	—	+	+	+	—
Rash	+Vasculitic rash over extremities	+Vasculitic rash over left leg	+Discoid rash	+Chronic, persistent pruritic erythematous rash with scaling	—	+Discoid rash	—	—
Alopecia	—	—	—	—	—	+	—	—
Joint Pain	+	+	+	+	+	+	+	+
Raynaud's	+	—	—	—	—	—	—	—
Proteinuria	—	—	—	—	—	+	—	—
Myalgia	—	—	—	—	—	—	+	—
Neuro-Psychiatric symptoms	—	—	—	—	+ with mood swings	—	—	+Seizures, neuropathic pain
SLEDAI[3] prior to Anifrolumab	8	7	13	6	7	10	4	4
Serology/Labs								
ANA[4]	1:320	1:320	1:640	1:640	1:1280	1:160	1:160	1:160
C3 (mg/dL)	64.8	46.9	60	72	38.2	76.6	37.6	66.0
C4 (mg/dL)	12.10	6.85	Not done	Not done	Not done	17.50	21.2	20.8
Anti-SSA	Positive	Positive	Negative	Positive	Negative	Positive	Negative	Negative
Anti-Smith	Negative	Positive	Positive	Negative	Negative	Positive	Negative	Positive
Anti-dsDNA	Negative	Negative	Positive	Negative	Positive	Negative	Negative	Negative
Hgb (g/dL)	11.1	10.1	10.8	11.9	8.6	12.3	14.6	13.4
WBC (/uL)	5,840	8,800	2,060	3,580	2,500	3,450	4,820	14,170
Platelet Count (10^9/L)	254	520	205	200	214	345	347	301

(Continues)

TABLE 1 | (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Medications								
HCQ[5] and dose (mg/day)	Discontinued for retinal toxicity	Taking 400mg	Taking 300mg	Taking 200mg	Taking 200mg	Taking 400mg	Taking400mg	Taking 400mg
MTX[6] and dose (mg/week)	Could not tolerate	N/A	N/A	Taking 10mg/week	Taking 7.5mg/week	N/A	N/A	Took 7.5mg 2 years prior
Tacrolimus ointment	N/A	N/A	Taking ointment	N/A	N/A	N/A	N/A	N/A
RTX (mg/dose)[7]	N/A	N/A	N/A	N/A	s/p 2 doses (500 mg each) - 2 years prior to anifrolumab	s/p 7 doses (500 mg each)-5 years prior to anifrolumab	s/p 2 doses (500mg each)-3 years prior to anifrolumab	s/p 6 doses (500 mg each)-10 years prior to anifrolumab
MMF (mg/day)[8]	N/A	N/A	N/A	N/A	N/A	Taking 1500mg	N/A	Took 1500mg 2 years prior
IVIG[9]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Others	N/A	N/A	N/A	N/A	N/A	Telmisartan 40mg/day	Amitriptyline 25mg/day	Pregabalin 225mg/day
Steroid dose (mg/day) prior to infusion	Prednisone 15	Prednisone 5	Prednisone 40	Prednisone 2.5	Prednisone 2.5	Off steroid	Prednisone 15	Prednisone 10
Steroid dose (mg/day) post infusion[10]	Prednisone 2.5	Off steroids	Off steroids	Prednisone 2.5	Prednisone 2.5	Off steroid	Prednisone 10	Prednisone 10
Weeks to improvement[11]	4 weeks	4 weeks	4 weeks	8 weeks	8 weeks	8 weeks	4 weeks	Still with symptoms
Weeks to maximal improvement[12]	20 weeks	20 weeks	16 weeks	8 weeks	12 weeks	16 weeks	8 weeks	Still with symptoms
CLASI A[13] Before and after anifrolumab	Not done	Not done	19-> 9	Not done	Not done	Not done	Not done	Not done

(Continues)

TABLE 1 | (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Adverse events observed	No events noted 28 weeks post initiation	No events noted 28 weeks post initiation	No events noted 20 weeks post initiation	No events noted 20 weeks post initiation	No events noted 16 weeks post initiation	No events noted 20 weeks post initiation	No events noted 16 weeks post initiation	2 Urinary Tract Infections 4 and 8 weeks after initiation
Others	N/A	N/A	N/A	N/A	FACIT F[14] 19-> 24	50% reduction RUPCR[15]	FACIT F 13-> 20Pain Score 8/10-> 5-6/10	N/A

[1](+) = Present.
[2](–) = Absent.
[3]SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.
[4]ANA = Antinuclear Antibody.
[5]HCQ = Hydroxychloroquine.
[6]MTX = Methotrexate.
[7]RTX = Rituximab.
[8]MMF = Mycophenolate mofetil.
[9]IVIG = Intravenous Immunoglobulin.
[10]Steroid dose (mg/day) post infusion = Steroid dose (mg/day) after fifth cycle of anifrolumab.
[11]Weeks to improvement = Number of weeks until the first clinically observable improvement (e.g., visible improvement of rash, reduction in joint pain).
[12]Weeks to maximal improvement = Number of weeks until the greatest measurable clinical improvement (e.g., reduction in steroid dose, reduction in CLASI-A, reduction in FACIT score).
[13]CLASI-A = Cutaneous Lupus Erythematosus Disease Area and Severity Index.
[14]FACIT-F = Functional Assessment of Chronic Illness Therapy- Fatigue Scale.
[15]RUPCR = Random Urine Protein-to-Creatinine ratio.

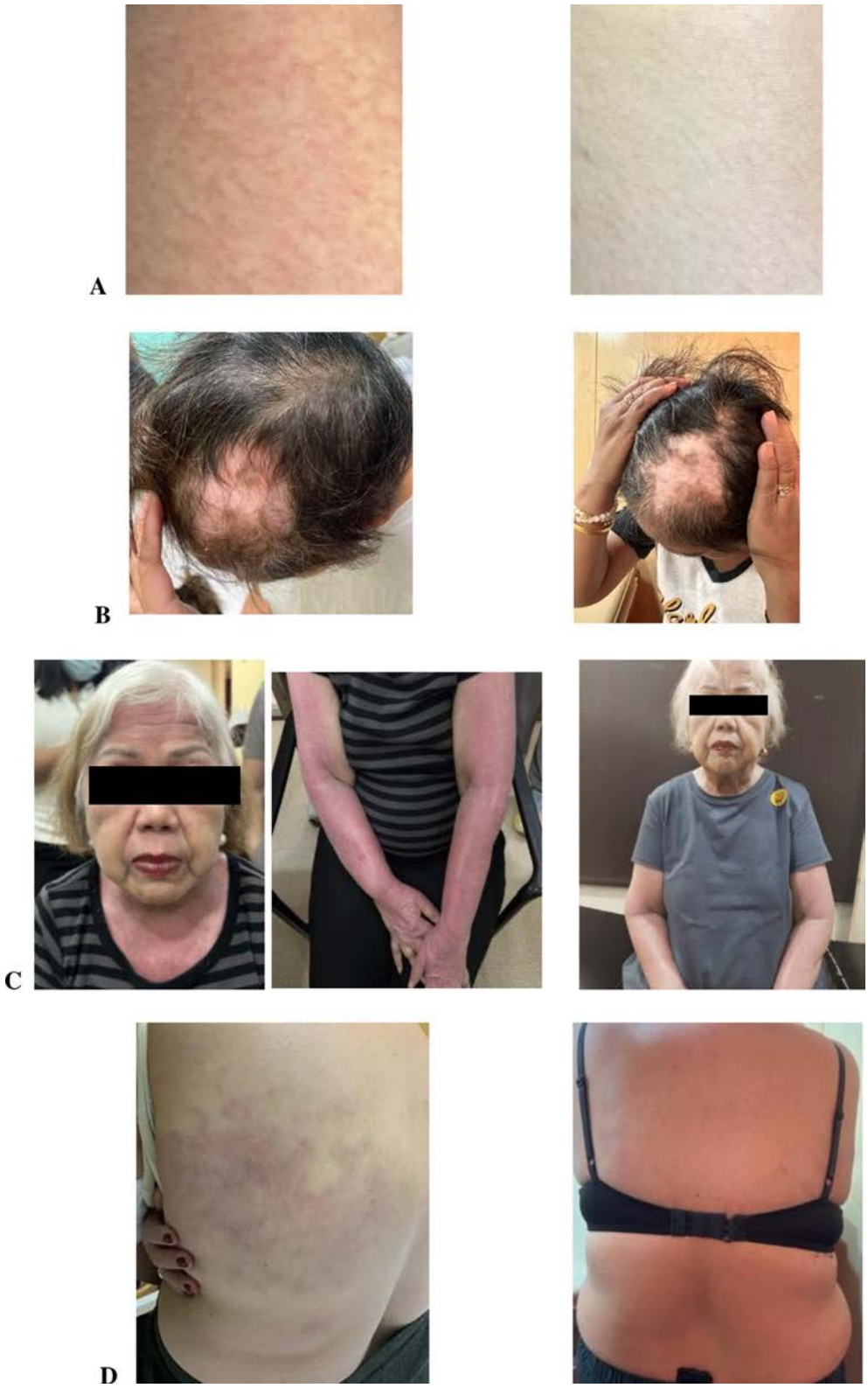

FIGURE 1 | Cutaneous responses of patients treated with anifrolumab. (A) Close-up vasculitic rash of patient 2 over the right thigh before anifrolumab treatment (left) and after the first dose of anifrolumab given intravenously (300 mg) every 4 weeks (right). (B) Comparison of alopecia of patient 3 before the first anifrolumab infusion (left) and after the fourth cycle of anifrolumab (right), with noted development of vellus hair on areas of alopecia. (C) Comparison of the generalized, erythematous, pruritic scaly rash of patient 4 before anifrolumab infusion (left) and after the second dose of anifrolumab (right). (D) Comparison of rash of patient 3 before the first anifrolumab infusion (left) and after the fourth cycle of anifrolumab (right).

Patient 5 is a 30-year-old female with a fourteen-year history of SLE, presenting with arthritis, permanent Jaccoud's arthropathy, fatigue, and mood swings. After three doses of anifrolumab, joint pain resolved, and her Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) increased to 24 from 19. She also noted a decrease in mood swings. No serious adverse events were observed.

Patient 6 is a 39-year-old female with a six-year history of SLE, presenting with discoid rash, arthritis, alopecia, photosensitivity, and lupus nephritis. Despite therapy, cutaneous lesions and proteinuria persisted. After two doses of anifrolumab, rashes resolved, and by the fourth dose, proteinuria decreased by 50%. No serious adverse events were observed.

Patient 7 is a 38-year-old female with a five-year history of SLE, presenting with myalgia, arthralgia, fatigue, and weight loss. She previously received two doses of rituximab and subcutaneous immunoglobulin due to acquired B and T cell deficiencies. After three doses of anifrolumab, fatigue and arthralgia improved. No serious adverse events were observed.

Patient 8 is a 43-year-old female with neuropsychiatric lupus presenting with seizures and neuropathic pain. She had received rituximab 10 years prior, with resolution of seizures, but neuropathic pain persisted. After three anifrolumab doses, a slight improvement in neuropathic pain was noted. Two urinary tract infections occurred during the treatment period.

The efficacy of anifrolumab in SLE was established in pivotal trials such as TULIP-1, TULIP-2, and MUSE, which demonstrated improvements in skin disease, arthritis, fatigue, and glucocorticoid tapering [1–3]. Our local experience mirrors these findings in Filipino patients with varied SLE phenotypes.

Cutaneous responses were consistent with trial data, where a $\geq$50% reduction in CLASI scores was seen by week 12 in nearly half of anifrolumab-treated patients [3]. In our series, three patients had complete resolution of rash within eight weeks, and one patient demonstrated a 50% CLASI reduction after 16 weeks. Glucocorticoid tapering was also comparable: Two patients discontinued steroids, and another reduced the dose to $\leq$7.5 mg/day, aligning with TULIP-2 outcomes [1].

Arthritis improved in most cases by week 12, consistent with trial timelines. In one patient, this was quantified with a 25%–38% decrease in pain score within 4 to 8 weeks. Fatigue, evaluated using the FACIT-Fatigue scale, improved in two patients beyond the minimum clinically important difference, consistent with MUSE trial findings [2].

Though TULIP-LN did not meet its proteinuria reduction endpoint [7], one patient in our series demonstrated a 50% proteinuria decrease by week 16, suggesting a possible renal effect warranting further investigation.

Despite its demonstrated efficacy and safety, the use of anifrolumab in the Philippines presents region-specific challenges. Infection risk remains a key concern, particularly in a setting where tuberculosis is endemic. Accordingly, pre-biologic screening for tuberculosis and hepatitis is essential and routinely performed [8, 9]. Recombinant zoster vaccination is recommended, but often limited by out-of-pocket cost [10]. In our cohort, all patients underwent appropriate screening for tuberculosis and hepatitis prior to initiation of anifrolumab. No serious adverse events were observed; only mild urinary tract infections occurred, supporting the feasibility of anifrolumab use with careful monitoring.

Accessibility represents another major challenge in the Philippine setting. While healthcare funding may come from national and local government, insurance, and donors, most healthcare expenses remain out-of-pocket (roughly 57%) [11]. This creates a substantial barrier, as the monthly cost of anifrolumab and other biologics far exceeds the average Filipino monthly wage (PhP 21 544 or 365.54 USD), restricting access to a limited subset of patients [12]. These financial and logistical constraints may delay treatment initiation and limit real-world applicability.

Overall, this case series confirms the real-world benefits of anifrolumab in Filipino patients with SLE, with response patterns comparable to those observed in global trials. While efficacy and safety are mirrored in international data, high cost and limited accessibility remain significant barriers—challenges likely shared by other low- and lower-middle-income countries in the Asia-Pacific region, where out-of-pocket expenditures make up the majority of healthcare funding.

This case series highlights the real-world benefits of anifrolumab in Filipino patients with SLE, demonstrating clinical benefits across a spectrum of manifestations. Larger studies are needed to confirm long-term efficacy and safety in this population, along with strategies to improve access.

Author Contributions

C.A.D. assisted in collection and analysis of data, created the draft for this paper and participated in revisions. M.L.A.-V. and E.G.S.V. participated in data collection, analysis and provided revisions to the content of the manuscript. A.U.A.-D. and J.J.T.L. conceived the idea for the paper, participated in data collection and analysis and provided revisions to the content of the manuscript.

Conflicts of Interest

Melissa L. Aquno-Villamin, Aileen U. Agbanlog-Dimatulac, Juan Javier T. Lichauco and Evan Glenn S. Vista have received honoraria from AstraZeneca as speakers.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ORIGINAL ARTICLE

The Clinical Role of miR-744-5p in Osteoarthritis and Its Regulation of Chondrocyte Inflammation Through the Modulation of Thrombospondin-2 (THBS2) Expression

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ABSTRACT

Aim: Osteoarthritis (OA) is a common degenerative joint disease that is difficult to diagnose in its early stages, which can easily delay treatment. MicroRNAs (miRNAs) are key regulatory factors in the pathogenesis of OA. This study investigated the clinical diagnostic value of miR-744-5p in OA and its regulatory effect on chondrocyte inflammation through modulation of thrombospondin-2 (THBS2).

Methods: This study included 108 OA patients and 62 healthy controls. Serum levels of miR-744-5p were detected using qRT-PCR. The diagnostic value of miR-744-5p was evaluated using the ROC curve and logistic regression. LPS-induced chondrocyte OA models were used to assess the regulatory effect of miR-744-5p on chondrocyte inflammation via CCK-8 and ELISA. Dual-luciferase assay verified the targeting relationship between miR-744-5p and THBS2.

Results: The serum level of miR-744-5p in OA patients was markedly reduced ($p < 0.001$), showing good diagnostic performance (AUC = 0.860). Logistic regression indicated that it could serve as an independent protective factor for OA (OR = 0.089). miR-744-5p mimic significantly restored the viability of chondrocytes induced by LPS ($p < 0.001$), inhibited the expression of inflammatory factors ($p < 0.001$), and alleviated oxidative stress damage. Dual-luciferase reporter assay confirmed that miR-744-5p directly targets THBS2. Overexpression of THBS2 reversed the protective effects of miR-744-5p.

Conclusion: miR-744-5p is significantly downregulated in OA and is a highly promising diagnostic and predictive molecule for OA. It can alleviate inflammation in chondrocytes by targeting THBS2, thereby inhibiting the progression of OA.

1 | Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by insidious onset and slow progression, featuring degenerative changes in articular cartilage and secondary bone proliferation. It predominantly affects middle-aged and elderly individuals [1]. The most typical symptom of OA is chronic joint pain, which in early stages often manifests as intermittent dull aches that worsen with activity and fail to improve with rest. In advanced stages, it progresses to persistent pain and resting pain, accompanied by joint deformity and functional impairment, severely affecting patients' daily lives [2]. Imaging serves as the core diagnostic tool for OA, but its insidious onset and lack of symptom specificity in early stages, coupled with conventional imaging's low sensitivity to early cartilage damage, result in high rates of misdiagnosis [3]. For patients, cognitive biases regarding OA

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lead to delayed medical consultation, thereby missing the optimal window for intervention [4]. Consequently, there is an urgent need to develop highly sensitive early biomarkers and optimize screening strategies to enhance the efficacy of early diagnosis.

MicroRNAs (miRNAs) are a class of non-coding RNA molecules. As critical post-transcriptional regulators, they finely regulate gene expression by mediating the degradation or translational repression of target mRNAs [5]. miRNAs regulate cell growth, differentiation and apoptosis by targeting hundreds of mRNAs at the same time. miRNAs regulate cell growth, differentiation and apoptosis by targeting hundreds of mRNA at the same time Its dysregulation is closely associated with various pathological states including cancer and degenerative diseases [6]. In recent years, extensive studies have demonstrated that miRNAs play a crucial regulatory roles in the pathological progression of musculoskeletal diseases, particularly OA [7, 8]. miRNAs exert significant pathogenic or protective effects by regulating key pathological processes including chondrocyte homeostasis, inflammatory responses, and apoptosis. For instance, miR-214-3p is significantly downregulated in OA cartilage and accelerates OA progression by targeting IKKβ [9]; while miR-5581 promotes OA development by interfering with chondrocyte proliferation [10].

Recent studies have revealed that miR-744-5p exhibits a significant downregulation trend in skeletal system diseases such as osteosarcoma and multiple myeloma [11, 12], and it can inhibit tumor cell proliferation. These findings suggest its antitumor role in malignant bone tumors. Notably, previous study demonstrated that overexpression of miR-744-5p enhances chondrocyte viability while reducing excessive inflammation and oxidative stress [13]. Furthermore, miR-744-5p levels are significantly downregulated in the early stages of OA [14]. Therefore, this study speculates that miR-744-5p may also play a critical regulatory role in OA. Although direct evidence in OA remains limited, based on the above research background, it may be a key regulator of OA-related inflammation or oxidative stress.

Thrombospondin-2 (THBS2) is a multifunctional glycoprotein secreted by cells into the extracellular matrix. Its structure comprises multiple specific functional domains capable of binding various molecules [15], thereby participating in diverse cellular life activities. It serves as a critical regulatory factor in maintaining tissue homeostasis and participating in disease progression [16]. Studies have found that THBS2 expression significantly increases with cartilage injury [17] and is markedly upregulated in OA [18], suggesting it may be a key regulator of cartilage regeneration. Additionally, studies indicated that THBS2 serves as a direct target of miR-744-5p in pancreatic neuroendocrine tumors [19]. Therefore, we speculate that miR-744-5p may participate in the pathological process of OA by targeting THBS2, but its specific regulatory mechanism needs to be further clarified.

This study explores the diagnostic value of miR-744-5p in OA. Using an LPS-induced chondrocyte OA model, we analyze its regulatory role in chondrocyte inflammation. Furthermore, functional rescue assays will be employed to elucidate the specific molecular mechanisms by which miR-744-5p participates in the pathological process of OA. Ultimately, this research intends to provide new candidate targets for the early diagnosis and targeted intervention of OA.

2 | Materials and Methods

2.1 | Study Subjects

This study enrolled 108 OA patients who presented to the Department of Orthopedics at Linfen Central Hospital from January 2023 to January 2025 as the study group. Concurrently, 62 healthy volunteers without joint-related symptoms were recruited from the community and screened via health examination centers to serve as the control group. The research scheme has been approved by the Ethics Committee of Linfen Central Hospital. Written informed consent has been obtained from all participants before inclusion in the study.

Inclusion criteria:

(1) All patients met the 2019 Osteoarthritis Diagnosis Guidelines [20]; (2) all patients were confirmed to have osteoarthritis via X-ray imaging and had a Kellgren–Lawrence (K–L) grade of ≥ 2.

Exclusion criteria:

(1) Patients also suffer from joint diseases such as rheumatoid arthritis and gouty arthritis; (2) severe dysfunction of vital organs (heart, brain, liver, or kidneys); (3) pregnant or lactating women; (4) incomplete clinical data.

2.2 | Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR)

Fasting peripheral blood was collected from all enrolled participants. After centrifugation at 3000 rpm for 20 min using a 4°C centrifuge, collect the supernatant.

Serum total RNA was extracted using the TRLzol reagent (Invitrogen, USA), and the protocol by the manufacturer was strictly followed. The extracted RNA was treated with DNase I (TaKaRa, Japan) to remove genomic DNA contamination. Subsequently, cDNA was synthesized from 1 μg of total RNA using the PrimeScript RT Reverse Transcription Kit (TaKaRa, Japan). Quantitative PCR analysis was performed on an ABI7500 Real-Time Fluorescent Quantitative PCR System (Invitrogen, USA). Each 20 μL reaction mixture contained 2 μL of cDNA template, 0.4 μM of each forward and reverse primer, and 10 μL of TB Green Premix. The thermal cycling conditions were: 95°C for 30 s, followed by 40 cycles of 95°C for 5 s and 60°C for 30 s, with a final melting curve analysis. Gene expression was normalized to endogenous controls GAPDH (for mRNA) and U6 (for miRNA). The primers used were as follows: miR-774-5p, forward, 5′-AATGCGGGGCTAGGGCTA-3′, reverse, 5′-GTGCAGGGTCCGAGGT-3′; THBS2, forward, 5′-TCCTGCTGGCTCTGTGGGTGT-3′, reverse, 5′-ATGGTCTTGCGGTTGATGTTGCT-3′; GAPDH, forward, 5′-CACCCACTCCTCCACCTTTG-3′, reverse, 5′-CCACCACCCTGTTGCTGTAG-3′;

U6, forward, 5′-CTCGCTTCGGCAGCACA-3′, reverse, 5′-AACGCTTCACGAATTTGCGT-3′. The $2^{-\Delta\Delta C_t}$ method was used for relative quantitative analysis. All the data were from three independent repeated experiments.

2.3 | Cell Culture

Human chondrocytes (YS-C031) used in the cell experiment of this study were purchased from ATCC (USA). To make it grow well in vitro, we put it in DMEM medium and added 10% fetal bovine serum (FBS) to provide nutrition and added 1% penicillin/streptomycin to prevent bacterial pollution. Chondrocytes in the logarithmic growth period were inoculated into 6-well plates at a density of 5×10^4 cells per well. After the cells adhered to the wall, they were replaced with serum-free medium containing 100 ng/mL lipopolysaccharide (LPS) and cultured for an additional 48 h to establish an LPS-induced OA model of chondrocytes for subsequent experiments. All cells were maintained at 37°C in a humidified incubator with 5% CO_2, which provides the optimal temperature for cellular metabolism and maintains the physiological pH necessary for normal growth and function in vitro.

2.4 | Cell Transfection

miR-744-5p mimics, inhibitors, oe-THBS2 overexpression plasmid, and their corresponding negative controls were synthesized and constructed by GenScript (Nanjing, China). Transfection was performed using Lipofectamine 3000 reagent (Invitrogen, USA) according to the manufacturer's instructions. Before transfection, chondrocytes in the logarithmic growth phase were spread in 6-well plates at a density of 5×10^4 cells per well. When cells grow to cover about 60%–70% of the bottom surface, the target gene fragment was introduced into the cell. Briefly, for each well, 2.5 μg of plasmid or 50 nM of miRNA mimic/inhibitor was diluted in 125 μL of Opti-MEM reduced serum medium. In a separate tube, 5 μL of Lipofectamine 3000 was diluted in 125 μL of Opti-MEM. After 5 min of incubation at room temperature, the two solutions were combined and incubated for an additional 20 min to allow complex formation. The transfection mixture was then added dropwise to the cells. The culture medium was replaced with fresh complete medium 6 h after transfection. Cells were collected 48 h after transfection, and the expression level of miR-744-5p or THBS2 was detected via qRT-PCR to verify transfection efficiency.

2.5 | Cell Counting Kit-8 (CCK-8) Assay

To evaluate the cell proliferation ability, CCK-8 assay was used for detection. Chondrocytes were put into a 96-well plate at a density of 5×10^4 cells per well and cultured for 24 h. Then, at the four time points of 0, 24, 48, and 72 h of culture, 10 μL of CCK-8 reagent was added to each well and incubated at 37°C in the dark for 2 h. Finally, the absorbance of each well was measured by enzyme-labeled instrument at the wavelength of 450 nm.

2.6 | Enzyme-Linked Immunosorbent (ELISA) Assay

Chondrocytes were collected, centrifuged at 4°C and 1000 rpm, and the upper liquid part was taken for later use. Levels of inflammatory factors (TNF-α, IL-6, and IL-1β) were analyzed using commercial ELISA kits (R&D Systems, USA). Concurrently, levels of oxidative stress markers (MDA, SOD, GSH-Px) were detected using oxidative stress assay kits (Beyotime, China). All operations were carried out according to the kit instructions.

2.7 | Dual-Luciferase Reporter Assay

The potential binding sites of miR-744-5p and THBS2 were predicted by the online database. The THBS2 3′-UTR fragment containing the predicted binding site was cloned into the pGL3-Basic vector to construct the wild-type reporter plasmid (WT-THBS2). Meanwhile, a mutant reporter plasmid was constructed by site-directed mutagenesis and named MUT-THBS2. Through co-transfection experiment, the reporter plasmid and miR-744-5p mimetic, inhibitor, or corresponding negative control were introduced into chondrocytes, respectively. Forty-eight hours transfection, luciferase activity was determined by Dual-Luciferase Reporter Gene Detection System. The direct targeting relationship between miR-744-5p and THBS2 was validated by comparing the changes of luciferase activity among groups.

2.8 | Western Blot

Cells in the logarithmic growth phase were collected and lysed with RIPA lysis buffer on ice for 30 min. The lysate was then centrifuged at 12 000 rpm for 15 min at 4°C to collect the supernatant. Protein concentration was determined using the BCA assay. Equal amounts of protein samples were separated by 12% SDS-polyacrylamide gel electrophoresis and transferred onto a PVDF membrane. The membrane was blocked with 5% skim milk in TBST at room temperature for 1 h, followed by three washes with TBST. The membrane was then incubated overnight at 4°C with primary antibodies against THBS2 (1:1000) and GAPDH (1:5000). After washing with TBST, the membrane was incubated with HRP-conjugated secondary antibody at room temperature for 1 h, followed by three additional TBST washes. ECL substrate was applied for 1–2 min in the dark, and signals were captured using a chemiluminescence imaging system. Band intensities were analyzed with ImageJ, and THBS2 expression was normalized to GAPDH.

2.9 | Statistical Analysis

In this study, SPSS 23.0 and GraphPad Prism 9.0 were used for all statistical analysis. *T*-test or ANOVA was used for comparison between groups. ROC curve was used to evaluate the diagnostic efficacy of miR-744-5p. Risk factors of OA and the correlation between miR-744-5p and disease severity were analyzed by binary

Logistic regression and Spearman correlation analysis. Pearson correlation analysis was used to evaluate the correlation between miR-744-5p and THBS2. $p < 0.05$ was statistically significant.

3 | Results

3.1 | Expression and Diagnostic Value of miR-744-5p in OA

The clinical baseline data of 108 OA patients and 62 healthy people were evaluated in this study. Baseline data comparisons showed no statistically significant differences in age, sex, body mass index (BMI), diabetes, and hypertension history between the two groups. It showed that the two groups are comparable. All OA patients received K–L grading evaluation including 35 cases of K–L II, 56 cases of III, and 17 cases of IV. The visual analogue scale (VAS) score was 5.47 ± 1.88, which was significantly higher than that of the control group ($p < 0.001$, Table 1).

The results of qRT-PCR revealed that the expression of miR-744-5p in the serum of OA patients was significantly lower than that of the control group ($p < 0.001$, Figure 1A). Additionally, compared with the control group, OA patients with K–L Grades II, III, and IV all showed significantly downregulated levels of miR-744-5p ($p < 0.001$), and their expression levels gradually decreased as the disease severity increased. Specifically, the miR-744-5p level in Grade III was significantly lower than that in Grade II, and the level in Grade IV was significantly lower than that in Grade III ($p < 0.01$, Figure 1B). ROC curve analysis demonstrated that miR-744-5p exhibited good diagnostic efficacy for OA (sensitivity = 75.00%, specificity = 82.26%, AUC = 0.860, Figure 1C).

TABLE 1 | General information of the enrolled participants.

Parameters	Control ($n = 62$)	OA ($n = 108$)	p
Age (years)	56.63 ± 10.90	58.00 ± 9.28	0.386
Gender, *n* (%)			
Male	35 (56.45)	61 (56.48)	0.997
Female	27 (43.55)	47 (43.52)	
BMI (kg/m^2)	23.92 ± 2.03	24.81 ± 3.65	0.078
Diabetes mellitus, *n* (%)			
Yes	28 (45.16)	63 (58.33)	0.097
No	34 (54.84)	45 (41.67)	
Hypertension, *n* (%)			
Yes	26 (41.94)	59 (54.63)	0.111
No	36 (58.06)	49 (45.37)	
K–L grade, *n* (%)			
II	—	35 (32.41)	—
III	—	56 (51.85)	
IV	—	17 (15.74)	
VAS score	1.21 ± 0.77	5.47 ± 1.88	< 0.001

Note: Data were presented as mean ± SD or *n* (%). A *p* value of < 0.05 was considered statistically significant.
Abbreviations: BMI, body mass index; K–L grade, Kellgren–Lawrence grading scale; OA, osteoarthritis; VAS, visual analogue scale.

3.2 | Association of miR-744-5p With OA Severity and Risk

Logistic regression analysis showed that miR-744-5p might act as a potential protective factor against OA (OR = 0.089, 95% CI = 0.038–0.208, Figure 1D).

Furthermore, Spearman correlation results showed that miR-744-5p was significantly negatively correlated with both K–L grade ($r = -0.721$) and VAS score ($r = -0.838$, Table 2).

3.3 | Regulatory Effect of miR-744-5p on Chondrocyte Inflammation

In LPS-treated chondrocytes, miR-744-5p expression was significantly reduced; however, miR-744-5p mimics markedly upregulated its expression ($p < 0.001$, Figure 2A).

LPS can significantly inhibit the viability of chondrocytes, but miR-744-5p mimics can significantly restore the viability of chondrocytes ($p < 0.001$, Figure 2B).

In addition, LPS aggravated the inflammation of chondrocytes and promoted the secretion of inflammatory factors, whereas the overexpression of miR-744-5p significantly inhibited the levels of TNF-α, IL-6, and IL-1β inflammatory factors ($p < 0.001$, Figure 2C–E).

In chondrocytes treated with LPS, the oxidative stress index MDA increased significantly, whereas SOD and GSH-Px markedly reduced. However, the high expression of miR-744-5p reversed the above-mentioned abnormal oxidative stress and alleviated the oxidative stress damage ($p < 0.001$, Figure 2F–H).

3.4 | Expression of THBS2 in OA and Validation of Its Targeting by miR-744-5p

qRT-PCR results showed that THBS2 was significantly upregulated in the serum of OA patients ($p < 0.001$, Figure 3A), and Pearson correlation analysis revealed that miR-744-5p was negatively correlated with the expression level of THBS2 ($r = -0.756$, Figure 3B).

Online prediction tools revealed a specific binding site between miR-744-5p and the 3′-UTR region of THBS2 (Figure 3C). The experimental results indicated that miR-744-5p significantly inhibited the luciferase activity of the wild-type THBS2 reporter vector, but had no significant effect on the mutant vector, which confirmed the direct targeting interaction between them ($p < 0.001$, Figure 3D).

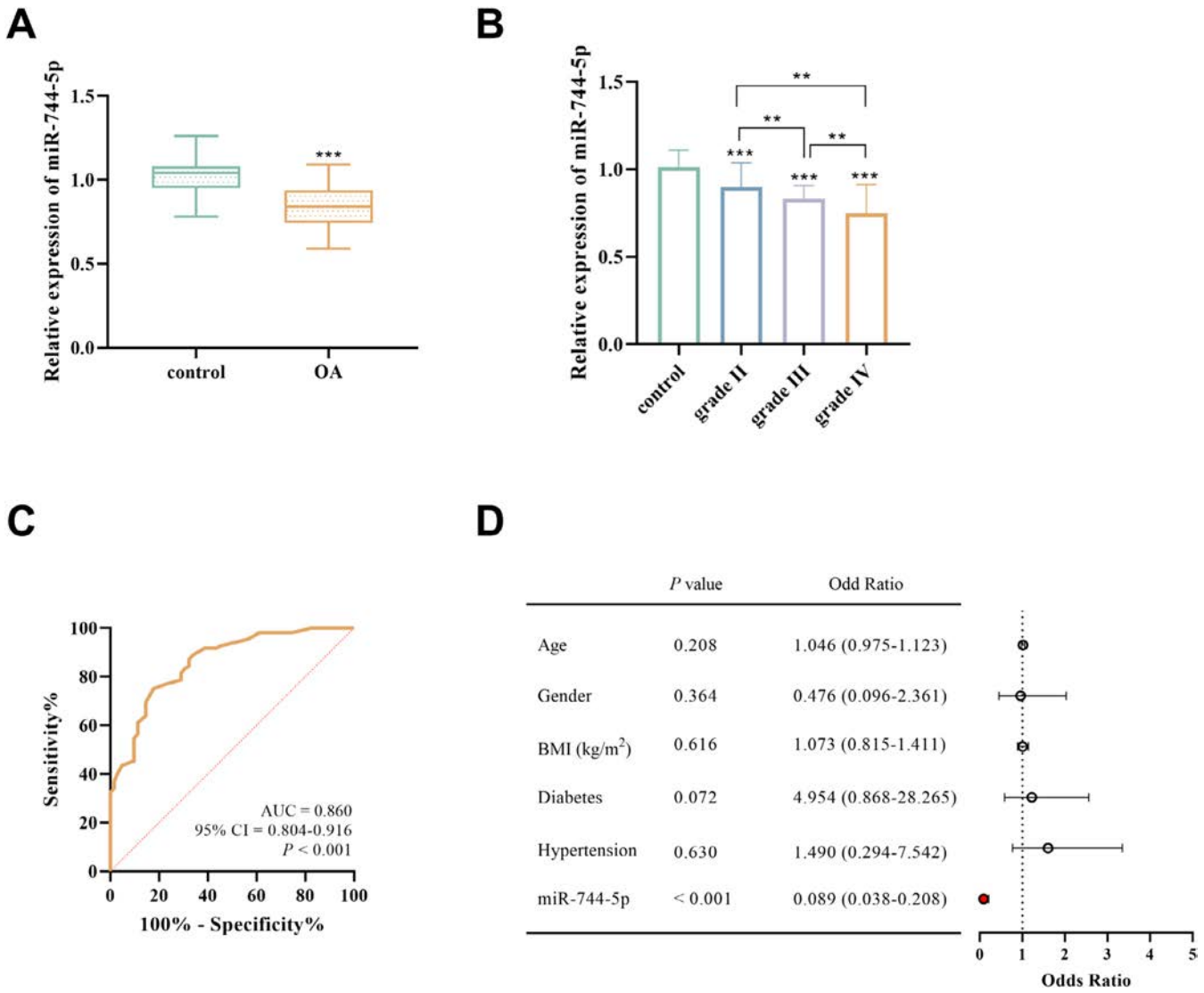

FIGURE 1 | Expression and diagnostic value of miR-744-5p in OA. (A) Relative expression level of serum miR-744-5p in OA patients ($n=108$) and healthy controls ($n=62$). Data are presented as mean ± SD. Statistical significance was determined by unpaired Student's *t*-test. (B) Relative expression level of serum of miR-744-5p in controls ($n=62$) and OA patients stratified by K–L grade: Grade II ($n=35$), Grade III ($n=56$), and Grade IV ($n=17$). Data are presented as mean ± SD. Statistical significance was determined by unpaired Student's *t*-test. (C) Evaluation of the diagnostic efficacy of miR-744-5p for OA via the ROC curve. (D) Logistic regression analysis to evaluate the risk factors of OA. Data are presented as OR with 95% confidence interval. $^{**}p < 0.01$, $^{***}p < 0.001$.

TABLE 2 | Spearman's rank-order correlation between miR-744-5p expression and OA severity scores.

	miR-744-5p	
Parameters	***r***	***p***
K–L grade	−0.721	< 0.001
VAS score	−0.838	< 0.001

Abbreviations: K–L grade, Kellgren–Lawrence grading scale; VAS, visual analog scale.

3.5 | miR-744-5p Regulates Chondrocyte Inflammation by Modulating THBS2 Expression

qRT-PCR results showed that LPS treatment could significantly upregulate the expression of THBS2 in chondrocytes. On the contrary, transfection of miR-744-5p mimic significantly suppressed the expression THBS2, whereas after introduction of THBS2 overexpression. Its expression was successfully reversed and significantly upregulated ($p < 0.001$, Figure 4A). Concurrently, Western blot analysis revealed concomitant alterations in THBS2 protein levels, a trend consistent with the transcriptional data ($p < 0.001$, Figure 4B), indicating that miR-744-5p modulates THBS2 protein expression.

Overexpressed THBS2 substantially reversed the protective effect of miR-744-5p on LPS-induced chondrocyte injury, which is manifested by reducing chondrocyte viability ($p < 0.001$, Figure 4C), elevating the levels of inflammatory factors (TNF-α, IL-6, and IL-1β; $p < 0.001$, Figure 4D–F); and aggravating oxidative stress injury (significantly higher MDA levels and lower SOD/GSH-Px levels, $p < 0.001$, Figure 4G–I).

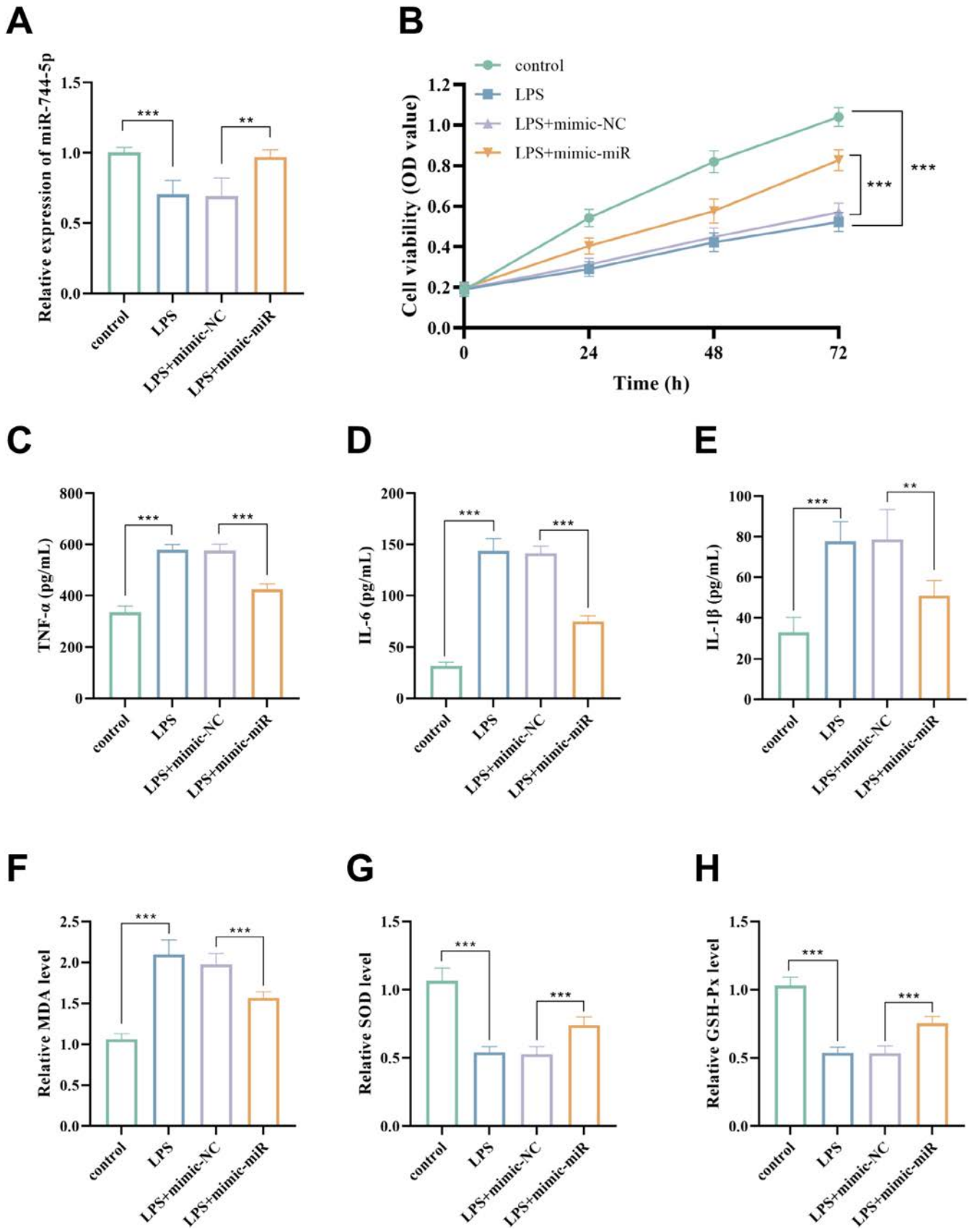

FIGURE 2 | Regulation of miR-744-5p on chondrocyte inflammation. (A) Expression of miR-744-5p in LPS-stimulated chondrocytes. (B) Effect of miR-744-5p mimic on LPS-induced chondrocyte viability. (C–E) Effect of miR-744-5p mimic on inflammatory factors TNF-α (C), IL-6 (D), IL-1β (E). (F–H) Effect of miR-744-5p mimic on oxidative stress markers MDA (F), SOD (G), GSH-Px (H). Data are presented as mean ± SD ($n = 5$ per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test for all panels (A–H). $^{**}p < 0.01$, $^{***}p < 0.001$.

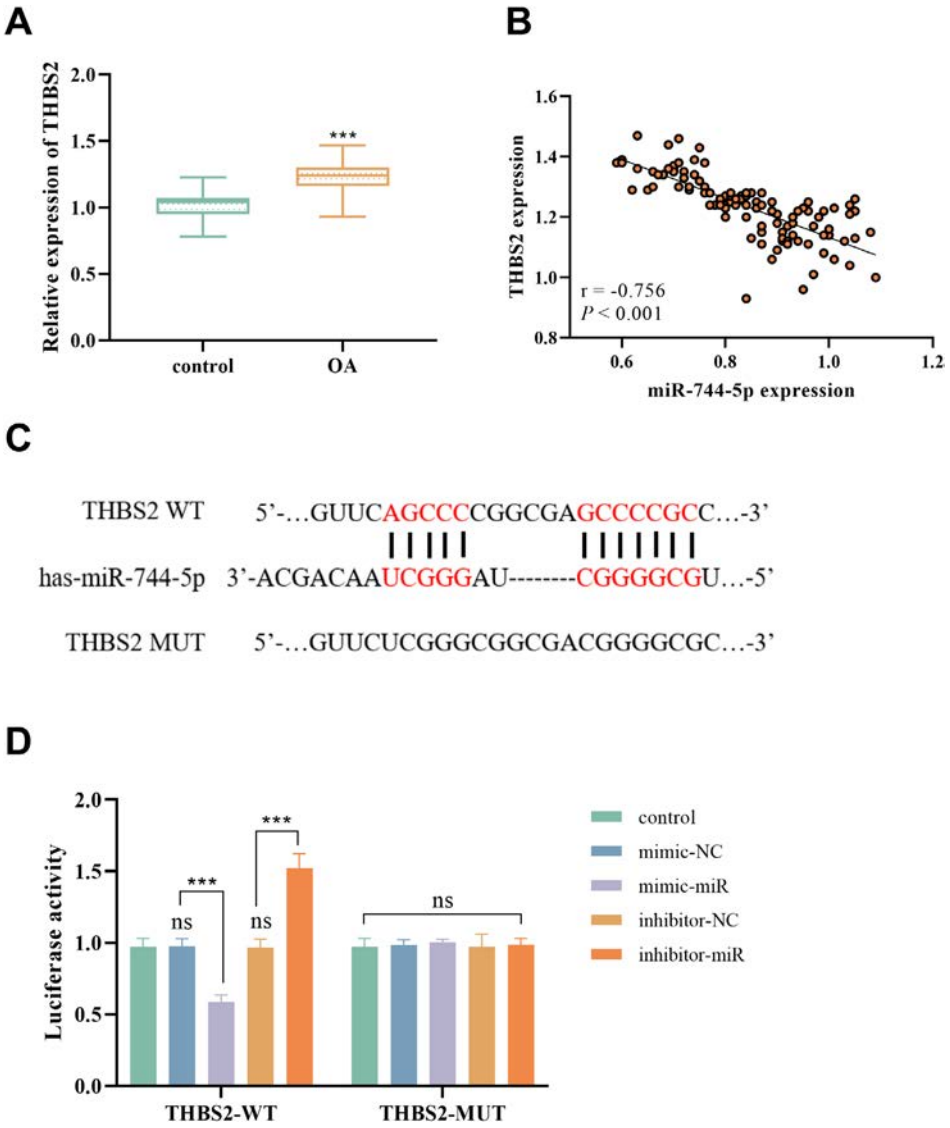

FIGURE 3 | Expression of THBS2 and its targeted binding to miR-744-5p. (A) Expression of THBS2 in OA ($n = 108$) and control samples ($n = 62$). Statistical significance was determined by unpaired Student's *t*-test. (B) Correlation analysis of THBS2 with miR-744-5p. Statistical significance was determined by Pearson correlation analysis. (C) Targeted binding site between THBS2 and miR-744-5p. (D) Dual-luciferase reporter assay validated the targeted binding between THBS2 and miR-744-5p ($n = 5$ per group). Statistical significance was determined by one-way ANOVA followed by Tukey's post hoc test. Data are presented as mean ± SD. ***$p < 0.001$.

4 | Discussion

As a chronic and progressive degenerative joint disease, OA is harmful to many aspects of physiological, psychological and social functions [21]. First, the onset of the disease is hidden, the course of the disease is long, and the early symptoms are mostly intermittent and atypical joint discomfort, which makes patients easily ignore and miss early intervention [22]. Second, with the continuous aggravation of cartilage damage, patients will eventually face progressive pain, dysfunction and even joint deformity [23], which not only seriously reduces the quality of life, but also brings a heavy medical burden to society [24]. Consequently, it is of great significance to develop biomarkers that can realize early and accurate diagnosis for blocking the progress of OA and improving the prognosis of patients. In recent years, miRNAs have shown great potential as a new generation of disease diagnosis markers because of their high stability in serum, easy detection and specific expression fluctuation in the early stage of pathology.

On the basis of previous studies, the work of Baghel et al. showed that miR-744-5p was significantly down expressed in OA and various skeletal system diseases [11, 12, 14]. This finding was highly consistent with the results of this study, suggesting that it may participate in the pathological process of OA. Combined with the abnormal expression of miR-744-5p in early-stage OA, we hypothesized that miR-744-5p may be a promising marker for early OA diagnosis. The ROC curve of this study further supports this possibility, revealing that miR-744-5p has good differentiation ability for OA. In the clinical assessment of OA, the K–L grade is one of the gold standards for the radiological diagnosis of OA, which can clearly define the structural stages of the disease and guide clinical decision-making [25]. The VAS score quantifies the pain symptoms of patients [26]. Both of them reflect the severity of OA from the aspects of structure and symptoms. Our study found that miR-744-5p was negatively correlated with K–L grade and VAS scores, indicating that miR-744-5p was closely related to the severity of OA and may play

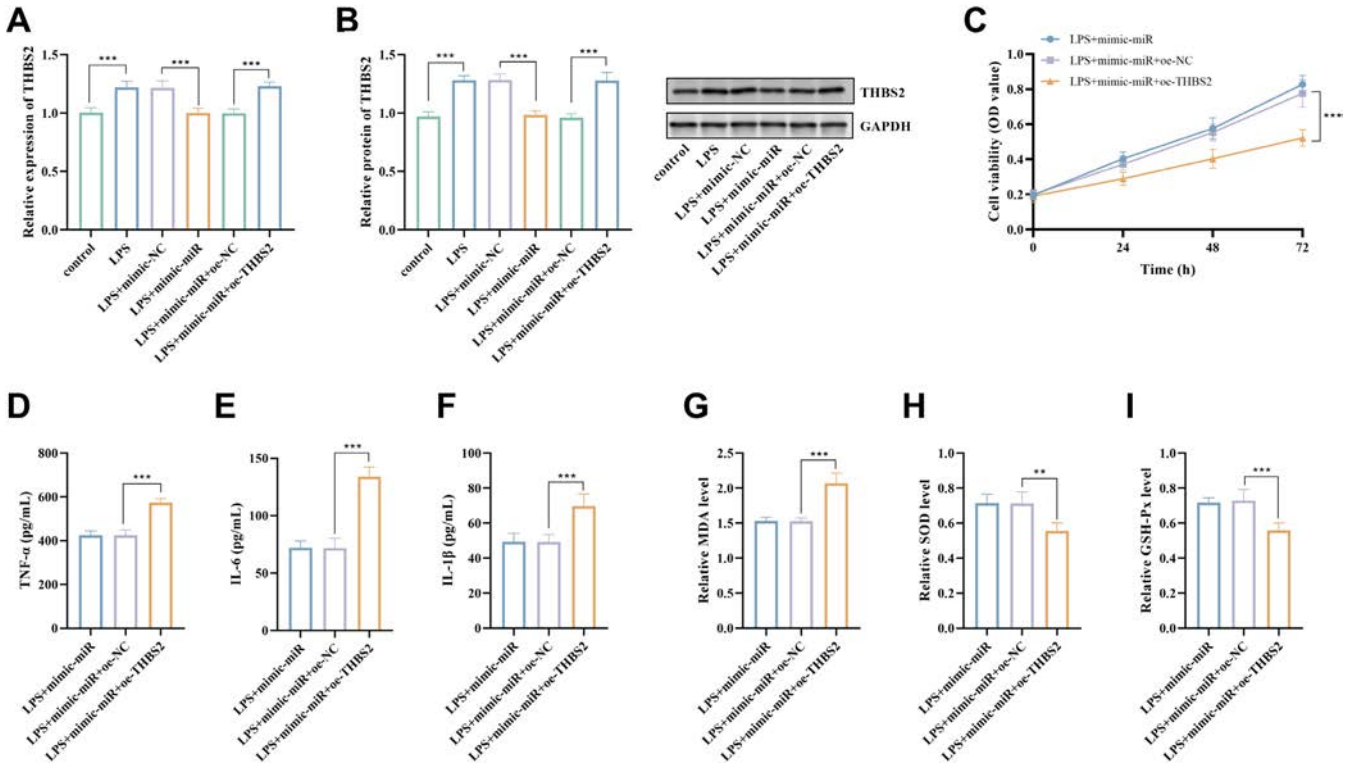

FIGURE 4 | miR-744-5p regulates chondrocyte inflammation by targeting THBS2. (A) miR-744-5p regulated the expression of THBS2. (B) Effects of overexpression or inhibition of miR-744-5p on THBS2 protein expression. (C) miR-744-5p modulates chondrocyte viability by regulating THBS2. (D–F) MiR-744-5p regulates the levels of inflammatory cytokines TNF-α (D), IL-6 (E), and IL-1β (F) by targeting THBS2. (G–I) MiR-744-5p regulates the levels of oxidative stress markers MDA (G), SOD (H), and GSH-Px (I) by targeting THBS2. Data are presented as mean ± SD ($n = 5$ per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test for all panels (A–I). $^{**}p < 0.01$, $^{***}p < 0.001$.

a potential protective role in OA. We further confirmed this speculation by logistic regression analysis, establishing miR-744-5p as an independent protective factor for OA. This study systematically verified that miR-744-5p not only plays a key clinical role in OA, but also has important potential as a diagnostic biomarker.

As a complex degenerative disease, the pathogenesis of OA involves many pathological processes such as metabolic imbalance of chondrocytes, inflammatory reaction, and oxidative stress [2]. Chondrocytes are the only functional cells in normal articular cartilage. Stimulated by the pathological environment of OA, they release a large number of pro-inflammatory factors and matrix degrading enzymes, leading to joint structure damage and dysfunction [27]. Among them, TNF-α, IL-6, and IL-1β are core proinflammatory factors that induce chondrocyte dysfunction [28]. In addition, oxidative stress is also the core pathological link parallel to inflammation [29], and the level of MDA directly reflects the severity of oxidative stress injury, whereas the levels of key antioxidant enzymes such as SOD and GSH-Px are closely related to the progress of cartilage degeneration and the intensity of the inflammatory reaction.

Previous studies have shown that after LPS induction of chondrocytes, an inflammatory response is triggered, elevating the levels of transforming growth factor-β1 (TGF-β1), TNF-α, IL-6, matrix metalloproteinase-13 (MMP-13), and a disintegrin and metalloproteinase with thrombospondin type 1 motif 5 (ADAMTS-5), thereby exacerbating extracellular matrix (ECM) degradation [30]. These alterations in markers are closely associated with the pathological progression of OA. Therefore, in this study, we selected LPS to induce the construction of a chondrocyte OA model to simulate the inflammatory microenvironment of OA. Cell experiments showed that LPS induction led to typical pathological characteristics of OA: cell viability was significantly reduced, inflammatory factor levels were significantly increased, and oxidative stress damage was significantly aggravated. On this basis, we found that transfection of miR-744-5p mimic can effectively alleviate the above pathological injury. Not only can it enhance the cell viability, but it also can downregulate the expression of inflammatory factors and alleviate oxidative stress injury, showing a clear cartilage protection effect.

Previous studies have established that THBS2 was very important for cartilage development and regeneration. Notably, THBS2 expression is significantly upregulated in OA patients and correlates positively with disease severity [17]. This is consistent with the results of this study. Further studies have identified that THBS2 is the key hub gene of OA and has significant clinical implications [18]. Additionally, THBS2 has been shown to promote the expression of IL-6 in synovial fibroblasts of OA and play an important role in the pathogenesis of OA [31]. In this study, the targeted binding relationship between miR-744-5p and THBS2 was verified. Further, through the functional rescue experiments, it revealed that overexpressed THBS2 significantly reverses the anti-inflammatory and protective effects of

miR-744-5p in LPS-induced chondrocytes. These results suggest that miR-744-5p plays a protective role on chondrocytes through the targeted regulation of THBS2 expression.

There are still the following limitations in this study. First, the clinical sample size was relatively limited, and samples of different OA subtypes were not covered, so the universality of the results needs to be further verified by a larger multi-center cohort study in the future. Second, although the direct targeting relationship between miR-744-5p and THBS2 was confirmed, the specific signal pathway downstream of THBS2 to regulate OA inflammation or matrix metabolism remains unclear. A more systematic experimental exploration will be carried out for this part in the future. However, we fully recognize the inherent limitations of the in vitro cell model used in this study: current in vitro simulations only achieve static replication of temperature and acid–base environments, making it difficult to replicate the dynamic and complex microenvironmental factors within the human body such as the combined effects of multiple factors including mechanical stress (joint mechanical loading), age-related cellular functional decline, and autoimmune responses. Consequently, they fail to comprehensively reproduce all the complex pathological features of OA. Future studies need to integrate multiple inducing factors to construct an in vitro system that more closely mimics the in vivo pathophysiological environment. Additionally, it is planned to develop OA mouse models for in vivo experiments to further validate the role and functional positioning of the miR-744-5p/THBS2 regulatory axis within the complex pathological network of OA. Furthermore, future research should validate these findings in primary chondrocytes from OA patients and elucidate the precise cellular origins and regulatory mechanisms underlying changes in serum levels.

5 | Conclusion

To sum up, miR-744-5p is significantly down regulated in the serum of OA patients, which is negatively correlated with the severity of the disease and has diagnostic potential. miR-744-5p acts as an independent protective factor against OA by alleviating chondrocyte inflammation through targeting THBS2, thereby participating in the regulation of OA progression and providing new evidence for diagnosis and treatment.

Author Contributions

Baoping Du, Yao Hao, Hao Lu, Renwei Wang, Zhihui Xu, Weidong Hao, Fan Shi, Wenge Wang, and Shichen Li made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, and draft of the manuscript. Yuhong Wang and Simin Li revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Acknowledgments

The authors have nothing to report.

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Ethics Statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Linfen Central Hospital.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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LETTER TO THE EDITOR

Pulmonary Arterial Involvement Due to Behçet's Syndrome in a Pregnant Patient Diagnosed Previously as Hughes–Stovin Syndrome: A Case Report From a Tertiary Referral Center

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Dear Editor,

Behçet's disease (BD) is a chronic inflammatory disease characterized by oral and genital ulcers, uveitis, and skin lesions; in addition, it may also affect the joints, cardiovascular, neurologic, and gastrointestinal systems. Pulmonary arterial aneurysms and thrombosis are characteristics of lung involvement and significant causes of morbidity and mortality. In this report, we present a patient with pulmonary arterial involvement due to BD diagnosed during pregnancy and her treatment course.

A 34-year-old woman, 14 weeks pregnant, presented to the emergency room with dyspnea and massive hemoptysis, resulting in respiratory failure. She was intubated and admitted to the intensive care unit. She had a history of idiopathic pulmonary thromboembolism and aneurysms, which were diagnosed as Hughes–Stovin syndrome (HSS) 2 years ago and treated with intravenous/oral methylprednisolone (Figure 1). Additionally, she experienced recurrent oral aphthae almost once a month last year. Upon examination, her body temperature was 36.6°C, heart rate was 103 beats per minute, blood pressure measured 110/70 mmHg, and breath sounds were diminished bilaterally in the lungs. Otherwise, her physical examination was normal and showed no evidence of arthritis or skin lesions. She had no visual complaints, red eye, or history of uveitis. Baseline laboratory examination revealed an erythrocyte sedimentation rate (ESR) of 93 mm/h, a C-reactive protein level (CRP) of 44 mg/L, and a D-dimer of 323 ng/mL. Liver and kidney tests were normal. Transthoracic echocardiography revealed that the pulmonary artery pressure was 50 mmHg and the ejection fraction was 65%. The chest CT scan and pulmonary CT angiography showed signs of an aneurysm coming from the left pulmonary artery, along with a blood clot around it and an uneven internal structure that is about 30 mm wide. A minimal dimensional increase was observed in the aneurysm, as well as in the left pulmonary artery, in comparison to the previous imaging 2 years before. She was diagnosed with BD and lung involvement and was treated with pulse methylprednisolone (1000 mg per day, 3 days), oral methylprednisolone (0.8 mg/kg), and infliximab (IFX) 400 mg (5 mg/kg, with a scheduled duration of 0–2–6 weeks). She was extubated and admitted to the Gynecology and Obstetrics Department after a week. Physicians specializing in intensive care, gynecology, and rheumatology advised the patient to undergo a medical abortion, which the patient consented to, and she was discharged with oral steroid treatment, with IFX treatment planned.

She had been receiving IFX treatment every 6 weeks and was referred for treatment for hemoptysis that had persisted for 2 days 3 weeks following the fifth infliximab treatment. Her CRP level was 27.6 mg/L, and her ESR was 50 mm/h during her examination. Thoracic CT and CT angiography revealed a reduction in the diameter of the right main pulmonary artery, chronic thrombosis in the right lower lobe pulmonary artery, and filling deficiencies indicative of acute embolism in the left lower lobe and anterior segment branches of the left upper lobe. She was admitted to the rheumatology department and administered pulse methylprednisolone (1000 mg per day, 3 days), oral

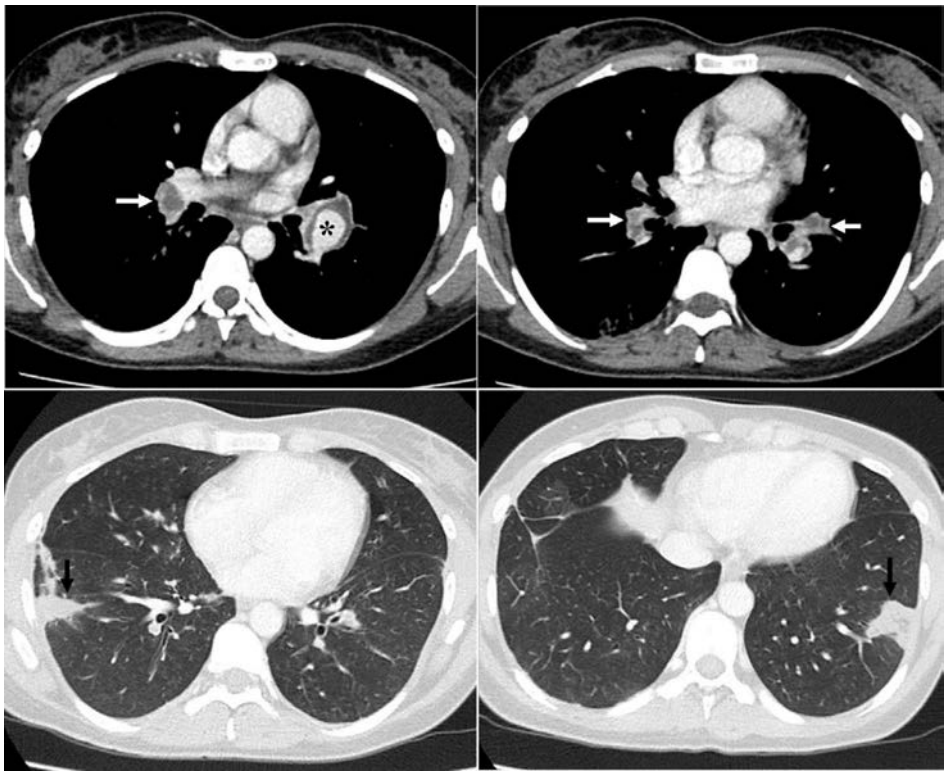

FIGURE 1 | Contrast-enhanced transverse CT images. Left pulmonary artery aneurysm (*) is seen as a fusiform dilation in the left hilus, bilateral pulmonary arterial thrombosis (white arrows) is seen as vascular filling defects and pulmonary infarcts are seen as peripheral wedge-shaped opacities in both lower lobes of the lungs (black arrows).

methylprednisolone (0.8 mg/kg), and cyclophosphamide (CYC) (1000 mg/month). CYC treatment was concluded in six cycles. She was prescribed oral methylprednisolone and azathioprine (AZA) for maintenance treatment during the follow-up.

At the third-year visit, she had a fever, cough, and high acute phase levels. A 5 × 5.5 cm thick-walled, lobulated-shaped cavitary lesion was identified in the lower lobe of the right lung, with air-fluid leveling in her thoracic CT. She underwent bronchoscopy, revealing non-tuberculosis mycobacterial development in the cultured sample. Consequently, AZA therapy was discontinued, and a quadruple anti-tuberculosis regimen was initiated.

HSS is an uncommon disorder characterized by aneurysm and thrombosis in the pulmonary arteries and distinguished from BD by the absence of skin and mucosal manifestations [1,2]. In a recent study, researchers compared patients with HSS and those with pulmonary artery issues from BD, finding that both groups shared many similar characteristics and referred to HSS as an 'incomplete form of BD.' The fact that our case initially presented with HSS and developed recurrent oral aphthae in the follow-up supports that these two diseases may not be distinct entities. However, it should be highlighted that the International Criteria for Behçet's disease criteria may not account for all atypical or incomplete Behçet's disease presentations [3]. In such circumstances, clinical judgment based on typical vascular findings and disease progression is critical.

In a recent case report and literature review, patients diagnosed with BD during pregnancy were presented. Glucocorticoids were the most frequently used treatment, but anti-TNF medications were also preferred in some patients with organ-threatening involvement, such as uveitis [4]. In this case, it is important to acknowledge that the interpretability of inflammatory markers such as ESR and D-dimer may have been limited by the physiological alterations associated with pregnancy.

This case highlights the unique clinical presentation of BD that may be underdiagnosed. IFX therapy might be an option for severe involvement in pregnant patients. Additionally, following up is crucial for identifying relapses as well as any treatment-related problems, particularly those involving infections in this group of patients.

Author Contributions

E.D.E., A.Ö.: conceptualization. A.Ö., Ö.G., Ş.K.: investigation. E.D.E.: writing – original draft. S.A.: writing – review and editing. S.A.: supervision.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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EDITORIAL

Advancing Toward the Precision Medicine in Rheumatoid Arthritis: Current Progress and Critical Challenges

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1 | Introduction

Around 8.5% of the global population suffers from autoimmune diseases, which cause significant impairments and health issues. In different communities of the world, rheumatoid arthritis (RA) is a common inflammatory condition. The progressive nature of RA eventually results in pannus development and joint destruction if not treated timely. RA is a prototypical autoimmune illness that is characterized by a prolonged preclinical phase in which immunological abnormalities may develop years before the onset of clinically apparent disease. RA has the complicated pathophysiology, which involves both environmental and genetic variables. Cancer is one of the major reasons for mortality among patients of RA [1]. Although disease-modifying antirheumatic drugs (DMARDs) are the first-line treatment for the newly diagnosed cases of RA, nonsteroidal anti-inflammatory medicines (NSAIDs) are also used for the treatment of symptoms like pain and inflammation.

2 | Current State of RA Management

2.1 | Standard Therapies and Treatment

Methotrexate (MTX) is one of the most often prescribed DMARDs to RA patients, among other medications. It is considered the gold standard first-line treatment for RA and serves as the prototype of conventional synthetic DMARDs (csDMARDs). bDMARDs like adalimumab, tocilizumab, and etanercept, are recommended to patients with moderate-to-severe RA which doesn't respond to csDMARDs, especially MTX. Janus kinase (JAK) inhibitors are classified as the targeted synthetic DMARDs (tsDMARDs), which include tofacitinib, baricitinib, and upadacitinib, JAK inhibitors are suggested as alternative options to bDMARDs in patients [2]. The therapeutic options for managing RA, before MTX, were limited. In recent years, attention has been increasing toward individualized treatment planning that includes complementary therapies and alternative pharmacological strategies. The major cause of this shift is due to the high prevalence of chronic, treatment-refractory pain in RA and growing concerns regarding the long-term adverse effects. Despite all these advancements, the cure for the illness is still elusive [3].

2.2 | Limitations of the "One-Size-Fits-All Model"

Adopting the disease continuum framework enables a shift away from the traditional "one-size-fits-all" model of care toward more personalized, precision medicine approaches. This paradigm supports tailored therapeutic strategies which have the potential to improve long-term outcomes. Furthermore, standardized treatment models are unlikely to be appropriate for patients with rare autoimmune rheumatic diseases, given the variation in healthcare settings where care is provided. The requirement for adhering to specific cultural norms and a "one size fits all" model approach for palliative care prevents people from diverse cultural backgrounds [4].

3 | Advanced Precision Medicines for RA

3.1 | Identification of Biomarkers and Their Clinical Utility

Recent advances in RA research highlight the role of biomarkers in the disease diagnosis, prognosis, and therapeutic monitoring. Systematic traditional serological biomarkers such as

rheumatoid factor (RF), anti-citrullinated protein antibodies (anti-CCP), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), as well as emerging molecular, genetic, and proteomic markers which reflect underlying treatment response [5]. The biomarkers are quantified using techniques like enzyme-linked immunosorbent assays (ELISA), while protein expression is explored through western blot analysis. Biomarker discovery also includes mass spectrometry (MS) and two-dimensional gel electrophoresis (2D-GE), which have been increasingly applied to plasma and synovial fluid samples to identify markers that are associated with disease activity and drug response (shown in Figure 1) [6].

3.2 | Role of Artificial Intelligence and Data Integration

In recent years, the integration of AI into medicine has triggered a significant transformation in patient care, diagnostics, and treatment strategies. AI provides a framework for the integration of heterogeneous data sources in RA that include clinical characteristics, imaging features, laboratory parameters, and multi-omics profiles. AI-driven models support the transition from population-based treatment strategies to precision rheumatology by facilitating satisfaction of patients and individualized therapeutic decision-making [7].

4 | Clinical Trials and Real-World Data

A comparison between clinical trials and real-world data is summarized in Table 1.

5 | Barriers to Implementation

AI has established significant potential in RA; however, the clinical adoption of this technology depends on model interpretability. Deep learning approaches such as automatic detection of joint damage in RA show high predictive performance and appropriate external validation, but their "black-box" nature, which lacks explanation, is the challenge for its routine clinical

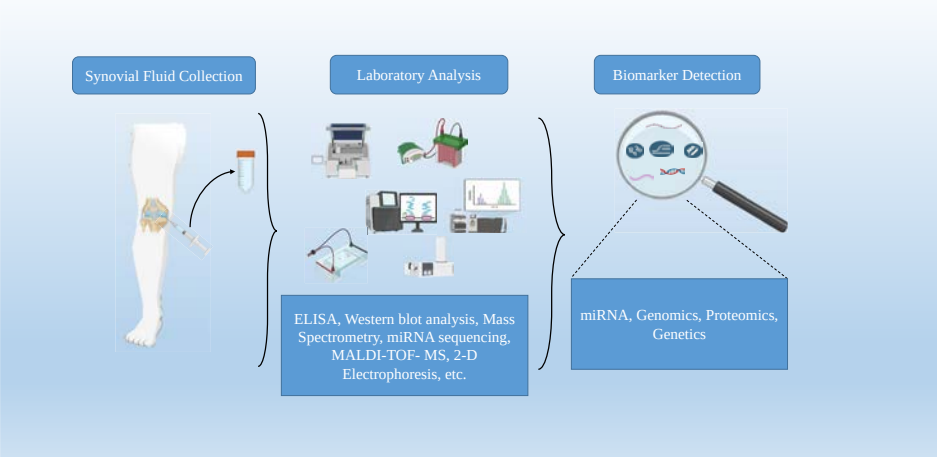

FIGURE 1 | Overview of synovial fluid-based biomarker discovery in RA, demonstrating synovial fluid collection, laboratory analytical techniques (including ELISA, Western blotting, MS, and miRNA sequencing), and downstream detection of molecular biomarkers such as miRNAs, genomic, proteomic, and genetic signatures.

TABLE 1 | Comparison of Clinical Trials and Real-World Data in RA.

Aspect	Clinical Trials	Real-World Data
Setting	Controlled, randomized environments	Routine clinical practice, observational
Patient Selection	Restrictive, with exclusion criteria and strict inclusion criteria	Broader, more diverse populations
Sample Characteristics	Younger, shorter disease duration, fewer comorbidities	Older, longer disease duration, and more comorbidities.
Data collected	Efficacy, safety, ACR response rates (ACR20/50/70), DAS-28, CRP, ESR	Effectiveness, safety, remission rates, adherence, patient-reported outcomes
Outcome Assessed	Treatment efficacy, placebo effect, and drug approval	Real-world effectiveness, long-term safety, quality of life
Limitations	Limited generalizability, short duration	Confounding factors, variable data quality
Example	Baricitinib trial, Newcastle trial	Upadacitinib registry, Hong Kong Biologics Registry

implementation [8]. For clinicians to trust in the utilization of AI-driven predictions, it becomes essential that these models provide transparent outputs, such as disease patterns and imaging features. Interpretability is also crucial in longitudinal disease monitoring. In the emerging technology, including nanotechnology-enabled gene therapy for RA, AI-based design and optimization should be interpretable for biological safety and regulatory acceptance [9].

6 | Ethical and Social Considerations

The development of in vitro trials, such as 3D co-culture synovial tissue models depends on primary cells that are obtained from patients. Therefore, for that ethical oversight, informed consent and transparent governance of biological samples are mandatory. Participants established an ongoing negotiation between established responsibilities and social roles, along with the physical limitations imposed by diseases like RA [10].

7 | Future Prospects and Ongoing Research

Integration of the precision medicine tools into RA care is still a challenge, with the limitation of compatibility with the existing hospital IT infrastructures and clinical workflows. Electronic health record systems, workflow disruption, and data interoperability issues hinder the acceptance of AI-driven decision support. Current research rapidly applies machine learning models that include random forest algorithms and neural networks for the prediction of treatment responses of RA patients to bDMARDs and tsDMARDs. Clinical translation will depend on the alignment of predictive models with hospital IT systems, interpretability and their embedment into clinician-friendly workflows to support real-time decision making.

8 | Conclusion

Precision medicines approach for RA management is rapidly advancing, which offers potential shift from the traditional trial-and-error models toward treatment strategies that are more individualized, which consider each patient's unique molecular, genetic, and clinical profile. Recent developments in biomarker identification, molecular profiling, and data integration, including AI, have enabled clinicians to identify RA as a heterogeneous disease and for the development of targeted therapies to improve efficacy, minimize adverse effects, and enhance patients' quality of life. Among various challenges related to data standardization, clinical implementation, and ethical issues, is the convergence of innovations like multi-omics analysis, predictive development of biomarkers, and various AI-supported decision tools.

Author Contributions

Dherya Guleria: Methodology and Writing – original draft preparation, Navjot Kaur Sandhu: Writing – reviewing and editing manuscript.

All authors contributed equally to preparing the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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ORIGINAL ARTICLE

Large Language Model Use and Training Needs Among Rheumatologists: An APLAR Young Rheumatologists International Survey

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ABSTRACT

Aim: Currently, global rheumatology training programs lack structured frameworks to address the digital literacy and governance of large language models (LLMs) use. This study aimed to assess the use and educational gap related to LLMs in rheumatology.

Methods: The Asia-Pacific League of Associations for Rheumatology (APLAR) Young Rheumatologists (AYR) conducted an international cross-sectional survey to assess the familiarity, usage patterns, perceptions, and educational unmet needs regarding LLMs among rheumatologists and trainees.

Results: A total of 767 participants completed the survey, with 89.6% reporting prior use of LLMs. ChatGPT was the most adopted tool (68.7%), followed by DeepSeek (37.2%) and Google Gemini (21.9%), with a subset of respondents integrating multiple LLMs platforms. While usage is widespread, only 9.9% reported established institutional policies on LLMs use. LLMs users were significantly younger and expressed higher confidence in verifying LLMs-generated information compared to nonusers. Although both groups shared concerns regarding the potential loss of traditional clinical skills (81.1%), active users significantly favored the integration of mandatory LLMs training into core rheumatology curricula.

Conclusion: There is a significant disparity between the high prevalence of LLMs adoption in rheumatology and the absence of formal educational guidelines or institutional governance. These findings underscore an urgent need for the development of competency frameworks to ensure the safe, critical, and effective application of LLMs in clinical practice.

1 | Introduction

The emergence of large language models (LLMs) represents a foundational shift in medical knowledge synthesis and clinical workflow management. Unlike earlier rule-based clinical decision support systems, contemporary LLMs such as ChatGPT, Google Gemini, DeepSeek, and Claude employ transformer architectures trained on extensive databases enabling contextual understanding and generation of medical text with unprecedented fluency [1]. These systems have demonstrated performance approaching specialist-level competency on standardized medical examinations and can synthesize clinical literature with coherence that was unattainable through traditional information retrieval methods [2].

Large language models (LLMs) are rapidly permeating every facet of medicine, and rheumatology is no exception, offering opportunities for improved diagnostic support and patient education while simultaneously posing challenges in ensuring evidence-based practice [3]. Many diagnostic and therapeutic decisions in rheumatology involve abductive reasoning—inferring the most probable explanation from incomplete information—rather than the pattern-matching or probabilistic inference at which current AI/LLM systems excel. At present, LLMs lack genuine causal understanding and cannot reliably distinguish correlation from causation, a distinction essential when evaluating whether multisystem symptoms represent a unifying autoimmune process or coincidental comorbidities. Furthermore, these models exhibit documented tendencies towards overconfident generation of plausible but inaccurate information, a phenomenon termed "hallucination," which poses particular risks in specialties like rheumatology where rare presentations may not be well-represented in training data. Despite these constraints, LLMs are being rapidly deployed in clinical environments, often without corresponding educational frameworks to support their appropriate use [4]. Surveys of medical trainees reveal substantial deficits in AI/LLM literacy, including inability to evaluate algorithmic outputs, unfamiliarity with concepts such as training data bias, and lack of understanding regarding the distinction between statistical associations and clinical causality [5].

In rheumatology specifically, where trainees must develop expertise in diagnostic reasoning for conditions with overlapping presentations and evolving classification criteria, uncritical reliance on LLM-generated differentials could undermine the development of clinical acumen [6]. The current educational landscape in rheumatology training programs worldwide provides minimal structured exposure to AI/LLM technologies [7]. Traditional competency frameworks emphasize acquisition of clinical knowledge, procedural skills, and scholarly activity, but rarely address digital literacy or critical evaluation of AI/LLM-generated content.

Moreover, institutional policies regarding LLM use in clinical documentation, medical education, and research remain inconsistent, creating uncertainty about appropriate boundaries for these technologies. Several fundamental questions remain unexplored regarding the interface between LLMs and rheumatological practice. We lack empirical data on how rheumatologists across diverse practice settings currently engage with these technologies, what specific applications they find valuable versus problematic, and how their perceptions vary based on prior exposure or training.

Regional disparities in technology infrastructure, regulatory frameworks, and cultural attitudes towards AI/LLM adoption may substantially influence these patterns, yet no systematic assessment has examined these variations globally. Furthermore, the educational interventions most likely to foster appropriate LLM literacy—distinguishing beneficial applications from inappropriate use cases, developing skills in prompt engineering and output verification, understanding model limitations—remain poorly characterized for the rheumatology context.

This study addresses these gaps through a global survey of rheumatologists and trainees, examining current familiarity with and utilization of LLMs, perceptions of their impact on practice, confidence in evaluating LLM outputs, educational needs and preferred training modalities, and concerns regarding future integration.

The Asia-Pacific League of Associations for Rheumatology (APLAR) Young Rheumatologists (AYR) has conceptualized this global scoping survey to capture these international variations, ensuring representation from diverse practice settings, resource levels, and cultural contexts. By engaging a heterogeneous group of rheumatologists across career stages and geographic regions, this survey aims to provide insights that can inform the development of globally relevant educational frameworks.

2 | Methods

2.1 | Study Design and Participants

We conducted an international survey study between April 2025 and November 2025 to assess knowledge, attitudes, perceptions, and educational needs regarding artificial intelligence and large language models among rheumatologists. The study was conceptualized and coordinated by AYR, with oversight and approval from the AYR Board for scientific validity, and was reported in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines [8]. The target population included practicing rheumatologists (consultants/attendings) and rheumatology trainees (fellows/registrars) worldwide. Participants were eligible if they were currently practicing rheumatology or in rheumatology training. Responses with incomplete demographic data that would prevent regional or role-based analysis were excluded from the final dataset.

2.2 | Survey Development and Validation

A dedicated steering committee (LG, KM, VV, CE, CX) developed the survey instrument through an iterative process involving 27 revisions over several months. The survey content was validated by rheumatology education leadership (CE) to ensure alignment with current educational frameworks and competency standards. Face validity and clarity were assessed

through pilot testing with five rheumatologists not involved in the survey design, who provided feedback on question comprehension, relevance, and estimated completion time. The final 22-item instrument comprised five sections: Demographics (4 questions covering country of practice, current role, and years in practice), Familiarity & Usage of LLMs (4 questions assessing familiarity status, usage patterns, specific platforms used, and institutional adoption), Perceptions About LLMs (7 questions exploring impact on practice, educational necessity, confidence in evaluation, and verification practices using 5-point Likert scales), and Training & Future Aspects (7 questions examining institutional policies, previous training, preferred modalities, perceived impacts, and concerns using multiple response and ranked options).

The survey assessed familiarity with specific LLMs including ChatGPT (OpenAI), Google Bard/Gemini, DeepSeek, Grok (xAI), Microsoft Bing Chat/Copilot, Anthropic Claude, and medical-specific AI/LLM tools. Perceptions were measured using 5-point Likert scales ranging from "strongly disagree" to "strongly agree" for attitudinal items, and "not confident" to "extremely confident" for self-assessment items. The survey was translated into Chinese using a standardized forward-backward translation protocol with reconciliation by bilingual rheumatologists (CX and YD) to ensure linguistic and cultural equivalence across all versions.

2.3 | Survey Distribution and Data Collection

Given the exploratory nature of this global scoping survey and the absence of prior estimates for LLM familiarity among rheumatologists, we aimed for a convenience sampling of respondents to enable meaningful subgroup analyses across geographic regions and career stages. The survey was distributed through multiple complementary channels to maximize global reach and diversity of respondents. Professional society partnerships facilitated direct email invitations to members of national and regional rheumatology organizations. Country liaisons, including AYR ambassadors and designated collaborators listed in the acknowledgments, disseminated the survey through national rheumatology networks across multiple countries representing diverse geographic regions and economic development levels. Additional distribution occurred through targeted professional groups on social media platforms including WeChat official account, national rheumatology society, professional networks of AYR members, and patient advocacy organizations that shared the survey with their networks of treating rheumatologists. Participants were recruited using a snowball sampling approach, with surveys distributed to an initial pool and subsequently shared by respondents. No financial or other incentives were offered for participation to minimize response bias.

2.4 | Ethical Considerations

The study protocol received ethical approval from Combined Military Hospital (CMH), Dhaka Cantonment Institutional Review Board (IRB) (approval number: CMH Dhaka/ECC/185). The survey was further endorsed by the AYR board. Given the minimal-risk nature of this professional online survey, the IRB granted a waiver of written documentation of consent. Before starting the survey, participants were shown an information statement outlining the study purpose and confidentiality safeguards. Participation was voluntary, and respondents proceeded to the questionnaire only if they agreed to take part. The study was conducted in accordance with the Declaration of Helsinki and applicable data protection regulations.

2.4.1 | Pretreatment of the Collected Data

The data collected by Google Forms was scrutinized for accuracy, validation, clarification, and competence. The typographical errors of free-text responses were corrected by Microsoft 365 Copilot. Free-text responses were manually re-classified into standardized categories based on the specific AI engine used, such as ChatGPT, Google Gemini, and DeepSeek, to ensure an accurate tool landscape analysis. Data cleaning included cross-validating usage reports; for participants who identified a specific platform in open-ended fields but initially reported no prior usage, the primary status was corrected to maintain internal consistency. Furthermore, geographic regions were mapped to the United Nations-defined M49 regions for standardized reporting of international participation. The 2023 Human Development Index (HDI) from the United Nations Development Programme was used for each country.

2.4.2 | Statistical Analysis

Data are presented as mean ± SD for continuous variables and *n* (%) for categorical variables. *p* values were computed using one-way ANOVA for continuous outcomes and chi-square tests with continuity correction for categorical outcomes. Percentages exclude missing values unless otherwise stated. Comparison table was computed by R package tableone version 0.13.2.

3 | Results

3.1 | Demographics and LLM Adoption

In Table 1, demographic characteristics and baseline LLM adoption patterns of the 767 participants are summarized. The mean age was 42.5 ± 9.8 years, with the study cohort comprising 409 (55.1%) women. Geographically, the majority of respondents originated from Asia (582, 75.9%), followed by Africa (91, 11.9%), the Americas (75, 9.8%), Europe (17, 2.2%), and Oceania (2, 0.3%). Regarding professional roles, 698 (91.1%) were specialists and 68 (8.6%) were trainees. Participants reported a mean of 15.7 ± 10.0 years since their primary degree and 11.1 ± 8.9 years since completing specialty training.

The cohort of respondents was predominantly engaged in clinical practice, with 72.7% ($n = 558$) of respondents reporting a primary focus on direct patient care, followed by research-focused roles (16.7%, $n = 128$) and mixed clinical–research practice (10.6%, $n = 81$). In terms of work environment, 43.3% ($n = 332$) were based in academic institutions, 36.5% ($n = 280$) practiced

TABLE 1 | Demographic and professional characteristics, LLM use, and perceptions among survey respondents ($n = 767$).

Characteristic	Overall ($N = 767$)
Demographic and professional background	
Age—yr	42.5 ± 9.8
Gender—no. (%)[a]	
Woman	409 (55.1)
Man	322 (43.4)
Non-binary	3 (0.4)
Prefer not to disclose	8 (1.1)
Region—no. (%)	
Asia	582 (75.9)
Africa	91 (11.9)
Americas	75 (9.8)
Europe	17 (2.2)
Oceania	2 (0.3)
Years after specialty training—mean ± SD	11.1 ± 8.9
LLM Familiarity and Usage Patterns—no. (%)	
Familiarity with LLMs	455 (59.3)
Use of LLMs	687 (89.6)
Institutional Context and Training—no. (%)	
Institutional policy on LLMs exists	76 (9.9)
Taken any AI/LLM courses	67 (8.7)
Preferred training format[b]	
Online courses	564 (73.5)
Hands-on workshops	519 (67.7)
Conference sessions	395 (51.5)
Key Perceptions and Readiness—no. (%)[c]	
Knowledge of LLMs will be essential (Score 4 or 5)	542 (70.6)
AI skills should be core training (Score 4 or 5)	495 (64.5)
Confidence in evaluating LLM outputs[d]	
Moderately confident	351 (45.8)
Very or extremely confident	215 (28.0)
Concerns about AI and LLMs — no. (%)[b]	
Loss of clinical skills	622 (81.1)
Over-reliance on technology	616 (80.3)
Quality of care	308 (40.2)
Job security	291 (37.9)

[a]Missing data: $n = 25$ for gender.
[b]Respondents were permitted to select multiple options for this category.
[c]Perception and readiness items were assessed using a 5-point Likert scale; percentages represent respondents selecting "Agree" (score 4) or "Strongly agree" (score 5).
[d]Confidence levels represent the combined total of "Very confident" and "Extremely confident" responses, reported together as a single category.

in nonacademic settings, and 20.2% ($n = 155$) worked in private practice. Correspondingly, the clinical workload was substantial, with respondents reporting a mean patient volume of 64 ± 35 patients per week.

Of the 767 participants, 455 (59.3%) reported being familiar with large language models (LLMs), and 687 (89.6%) stated they had used them. In terms of specific tools, 527 (68.7%) respondents used ChatGPT, 285 (37.2%) used DeepSeek, 168 (21.9%) used Google Bard/Gemini, 82 (10.7%) used Microsoft Bing Chat/Copilot, 80 (10.4%) used medical-specific AI/LLM tools, 77 (10.0%) used Perplexity AI, 40 (5.2%) used Grok (xAI), 25 (3.3%) used Anthropic Claude, and 60 (7.8%) reported using other tools.

3.2 | Patterns of Tool Utilization

The landscape of AI/LLM adoption was characterized by a clear hierarchy of tool preference. Figure 1 provides a heatmap visualization of these adoption profiles, illustrating that while ChatGPT serves as the foundational tool for the majority of users, there are distinct clusters of respondents exploring alternative platforms such as DeepSeek, Gemini, and medical-specific AI/LLM tools. Further analysis of usage behaviors, presented in the UpSet plot in Figures 1,2, reveals substantial concurrency in tool adoption.

3.3 | Comparative Analysis: AI Users versus Nonusers

3.3.1 | Demographic Characteristics and AI/LLM-Related Adoption

As shown in Table 2, comparison of AI/LLM users ($n = 687$) and non-users ($n = 80$) revealed distinct demographic and attitudinal profiles (Table 2). AI users were significantly younger than non-users (42.17 ± 9.65 vs. 45.22 ± 10.55 years, $p = 0.009$), though no significant differences were observed regarding gender, region, professional role, or years of experience.

In terms of familiarity and engagement, users demonstrated markedly higher baseline familiarity with LLMs (64.0% vs. 18.8%, $p < 0.001$) and were significantly more likely to report that their institutions had adopted these technologies (19.1%

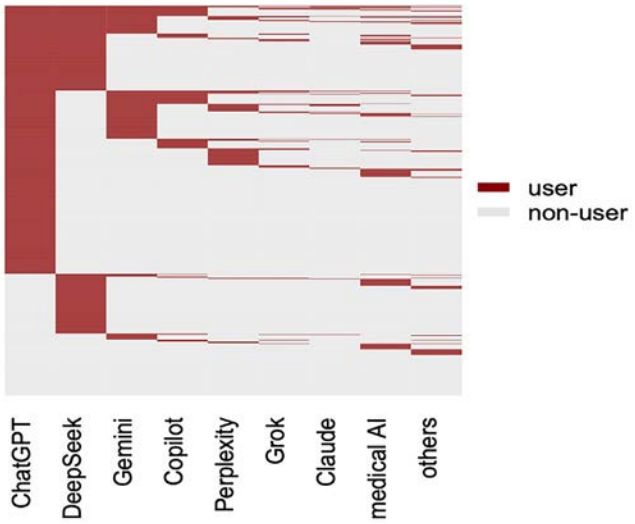

FIGURE 1 | Heatmap visualization of large language model (LLM) adoption profiles across the study cohort. This heatmap illustrates the landscape of AI tool utilization among respondents. Each column represents a specific AI tool (e.g., ChatGPT, DeepSeek, Gemini), while the rows represent individual participants or clustered usage patterns. The color intensity or presence (indicated by the dark/light contrast) denotes the usage status, distinguishing between active users and nonusers for each specific platform. This visualization highlights the dominance of certain tools (such as ChatGPT) while revealing clusters of participants who engage with multiple, less common platforms (e.g., Perplexity, Claude, or medical-specific AI), effectively grouping respondents based on the breadth of their technical adoption.

vs. 5.0%, $p = 0.007$). This exposure appeared to correlate with a more proactive and confident approach to AI integration: users expressed greater confidence in evaluating LLM-generated information ($p < 0.001$) and reported verifying AI outputs with external sources more frequently than nonusers ($p < 0.001$). Overall, 45.8% of respondents reported being moderately confident in evaluating LLM-generated information, while 28.0% reported being very or extremely confident.

3.3.2 | Perceptions of AI Impact, Training Preferences, and Governance Structures

Users held a significantly more positive outlook on the role of AI in rheumatology. They were more likely to agree that LLMs will significantly impact practice ($p < 0.001$), that knowledge of these tools will become essential ($p < 0.001$), and that AI skills should be integrated into core training curricula ($p = 0.001$). Specifically, users perceived a greater impact of LLMs across clinical decision-making (65.4% vs. 47.5%, $p = 0.003$), medical education (77.4% vs. 60.0%, $p = 0.001$), and patient communication (51.4% vs. 35.0%, $p = 0.008$). Consequently, users strongly favored mandatory LLM training (31.4% vs. 17.5%, $p = 0.018$), preferring it be led by regional societies or national organizations. As shown in Table 1, despite widespread use of LLMs, formal training exposure was uncommon, with only 67 respondents (8.7%) reporting having undertaken any prior AI- or LLM-related courses. Similarly, only 76 respondents (9.9%) reported the presence of a formal institutional policy governing the use of LLMs, while the majority reported either no policy (472, 61.5%) or uncertainty regarding institutional

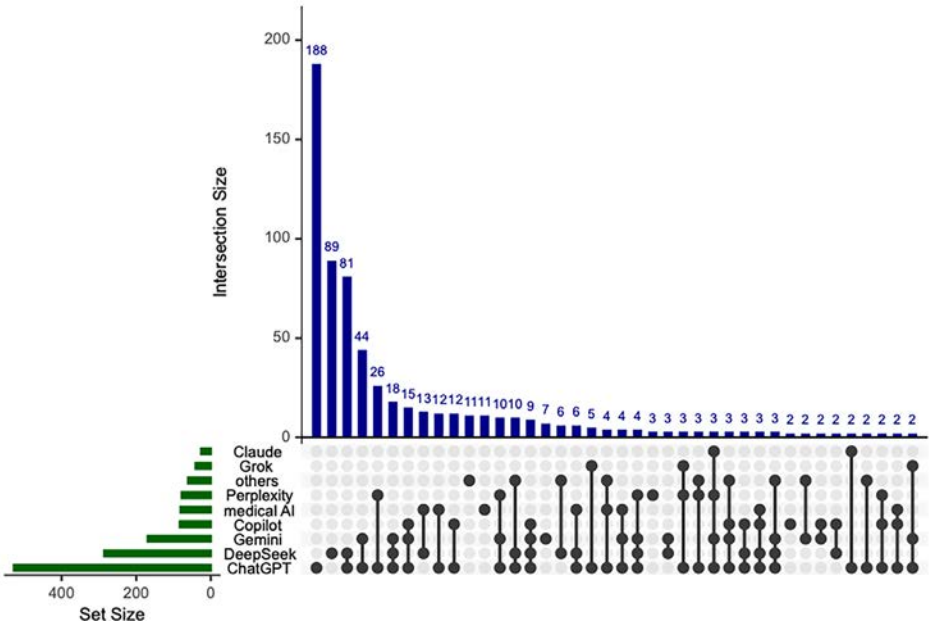

FIGURE 2 | UpSet plot characterizing the intersectionality and concurrency of LLM tool usage. The UpSet plot provides a detailed breakdown of multiplatform adoption, visualizing the overlaps between different LLMs. The horizontal bars on the left (Set Size) display the total number of users for each individual tool, confirming ChatGPT and DeepSeek as the most widely adopted platforms. The vertical bars (Intersection Size) represent the number of respondents falling into specific usage combinations. The matrix below the vertical bars uses connected dots to indicate the exact combination of tools for each group. The plot highlights that while a significant portion of users rely on a single platform (predominantly ChatGPT), there is a subset of respondents integrating multiple LLM platforms, most frequently combining ChatGPT with DeepSeek or Gemini.

TABLE 2 | Associations between respondent subgroups and perceptions, confidence, and training preferences related to large language models.

Characteristic	Group 1	Group 2	*p*
Panel A: LLM Users vs. Non-users	**Users (*N* = 687)**	**Non-users (*N* = 80)**	
Age—yr.[b]	42.17 ± 9.65	45.22 ± 10.55	0.009
Familiar with LLMs—no. (%)	440 (64.0)	15 (18.8)	< 0.001
LLMs could replace tasks (Score 4 or 5)—no. (%)[c]	352 (51.3)	26 (32.6)	0.004
Belief that training should be mandatory—no. (%)	216 (31.4)	14 (17.5)	0.018
Confidence in evaluation (Score 4 or 5)—no. (%)[d]	203 (29.5)	13 (16.3)	0.002
Panel B: Human Development Index (HDI) status	**HDI > 0.8 (*N* = 201)**	**HDI < 0.8 (*N* = 566)**	
Age—yr.[b]	41.08 ± 9.63	43.00 ± 9.80	0.019
Institution has an AI/LLM policy—no. (%)	24 (11.9)	52 (9.2)	0.019
Belief that training should be mandatory—no. (%)	55 (27.4)	175 (30.9)	0.055
AI skills should be core (Score 4 or 5)—no. (%)[c]	118 (58.7)	377 (66.6)	0.089
Confidence in evaluation (Score 4 or 5)—no. (%)[d]	42 (20.9)	173 (30.6)	0.011
Panel C: Professional Role[a]	**Specialists (*N* = 698)**	**Trainees (*N* = 68)**	
Age—yr.[b]	43.62 ± 9.46	30.94 ± 3.91	< 0.001
Current use of LLMs—no. (%)	626 (89.7)	60 (88.2)	0.869
Knowledge is essential (Score 4 or 5)—no. (%)[c]	492 (70.5)	49 (72.1)	0.434
Years after primary medical degree—mean ± SD	17.84 ± 9.46	4.54 ± 3.23	< 0.001
Confidence in evaluation (Score 4 or 5)—no. (%)[d]	200 (28.7)	21 (30.9)	0.777

[a]Missing data: $n = 1$ for professional role.
[b]Age and years are reported as mean ± standard deviation.
[c]Perception items were assessed using a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree); percentages represent respondents selecting "Agree" (score 4) or "Strongly agree" (score 5).
[d]Confidence in evaluating LLM-generated information represents the combined total of respondents reporting "Very confident" or "Extremely confident".

governance (219, 28.6%). When asked about preferred educational formats, respondents most frequently endorsed online courses (73.5%), hands-on workshops (67.7%), and conference-based sessions (51.5%) as suitable modalities for LLM training.

As detailed in Table 2, stratification by national development status revealed modest differences between groups. Respondents practicing in high-HDI countries reported the presence of an institutional policy governing LLM use in 11.9% of cases compared with 9.2% among those from lower-HDI settings ($p = 0.019$). Support for mandatory incorporation of LLM training into core rheumatology curricula did not significantly differ between groups (27.4% in high-HDI vs. 30.9% in lower-HDI countries, $p = 0.055$). Similarly, the proportion agreeing that AI competencies should form a core component of training (scores 4–5) was comparable (58.7% vs. 66.6%, $p = 0.089$). In contrast, respondents from lower-HDI settings more frequently reported high confidence in evaluating LLM-generated information than their counterparts in high-HDI countries (30.6% vs. 20.9%, $p = 0.011$).

3.3.3 | Concerns Regarding AI/LLM Use and Future Skill Priorities

Interestingly, while the groups diverged on adoption and utility, they shared similar concerns regarding the potential downsides of AI. There were no statistically significant differences in the proportions of users and nonusers who worried about the loss of traditional clinical skills (81.1%), over-reliance on technology, or job security ($p > 0.05$ for all). However, users were significantly more likely to identify "understanding and applying AI" (83.8% vs. 66.2%, $p < 0.001$) and "digital health integration" (67.8% vs. 53.8%, $p = 0.016$) as essential technical skills for the future rheumatologist. Concerns regarding potential impacts on quality of patient care were also commonly reported, affecting 40.2% of respondents.

4 | Discussion

Rheumatologists globally are already engaging with LLMs, yet this survey highlights a profound mismatch between rapid adoption and formal preparedness to use these tools safely and effectively in practice. A large majority of respondents reported using LLMs, most commonly ChatGPT and DeepSeek, and many integrate multiple platforms concurrently, suggesting that AI-assisted workflows are emerging organically at the clinician level rather than being strategically planned or governed by institutions. Despite this high uptake, institutional policies, structured training, and clear expectations around verification of AI outputs remain inconsistent, leaving individual clinicians to self-navigate issues of accuracy, bias, and clinical responsibility.

The contrast between users and nonusers underscores that familiarity and hands-on experience with LLMs are associated with more optimistic attitudes towards their impact, higher confidence in appraising outputs, and stronger support for embedding AI/LLM skills within core rheumatology training. However, this attitudinal divide coexists with striking convergence in underlying fears: Both groups expressed similar levels of concern about loss of traditional clinical skills, over-reliance on technology, and potential threats to job security, indicating that AI/LLM is perceived as simultaneously enabling and destabilizing. This duality reinforces that digital competency frameworks must address not only technical literacy (e.g., prompt design, verification strategies, understanding bias and hallucination) but also professional identity, ethics, and the preservation of core bedside skills [9].

These findings support an urgent need for rheumatology-specific educational strategies that move beyond ad hoc exposure to AI/LLM tools towards structured, competency-based training across career stages. Respondents' preferences for delivery through regional or national rheumatology societies, academic institutions, and blended formats (online learning, workshops, and conference sessions) point toward a multi-stakeholder model that can be rapidly scaled and locally adapted. Given the strong belief that AI/LLM and LLM literacy will become essential technical skills for future rheumatologists, there is an opportunity for societies such as EULAR, ACR, and APLAR to define minimum AI competencies, develop curricula, and advocate for aligned institutional policies that promote safe, transparent, and equitable use of LLMs in clinical care, education, and research [10, 11].

Finally, the global scope of this survey, with predominant representation from Asia and meaningful participation from Africa and the Americas, underscores both the promise and the risk of AI/LLM in widening or narrowing existing inequities in rheumatology. Variations in infrastructure, access to paid tools, language availability, and local regulation will shape how LLMs are deployed and who benefits from them. Future work should therefore prioritize longitudinal and qualitative studies that explore how different rheumatology communities integrate AI/LLM into daily practice, evaluate patient-level outcomes, and test educational interventions designed to strengthen AI/LLM literacy while safeguarding clinical reasoning, professionalism, and patient trust [12]. A recent systematic review identifies five essential competency domains—AI/LLM fundamentals, ethical and legal considerations, data analysis and management, communication and teamwork, and the evaluation of AI/LLM tools—that healthcare professionals must acquire to effectively and safely integrate artificial intelligence into clinical practice. It also underscores the need to systematically collect and disseminate best-practice examples to facilitate shared learning and adoption.

This study has several limitations. First, the cross-sectional, self-selected design and reliance on online distribution introduce selection and response bias, likely over-representing digitally engaged rheumatologists and limiting generalizability to clinicians with lower access to or interest in AI. Second, all variables were assessed using self-report, which captures perceived familiarity and confidence rather than observed competence; the survey did not include objective testing of AI/LLM knowledge, and attitudes may therefore not translate into safe, effective use in practice. Third, the sample was heavily weighted toward Asian respondents, with relatively few participants from Europe, Oceania and some low-resource settings, so regional comparisons and inferences about global equity in AI readiness should be interpreted cautiously. Finally, although latent class analysis identified distinct attitudinal profiles, unmeasured factors such as institutional culture, local regulation, and prior informal exposure to AI/LLM were not captured and could influence both class membership and educational preferences.

This global survey shows that LLMs are already embedded in rheumatology practice, but their use is advancing faster than formal training, governance, and objective competence assessment. Building on predominantly self-reported familiarity and attitudes, these data highlight a clear mandate for rheumatology societies, academic institutions, and regulators to co-develop structured, equitable AI/LLM curricula that preserve core clinical reasoning while enabling safe, critical, and context-appropriate use of LLMs across diverse settings.

5 | Conclusion

Large language models are already widely adopted by rheumatologists across diverse regions and career stages, yet their integration into clinical practice and training is occurring in the absence of consistent educational frameworks, institutional policies, or formal competency standards. This global survey demonstrates a clear gap between high levels of use and variable confidence in critically evaluating LLM-generated outputs, alongside strong support for structured training and guidance tailored to the rheumatology context. While rheumatologists recognize the potential of LLMs to enhance clinical decision-making, education, and communication, they also share concerns regarding over-reliance on technology and erosion of core clinical skills.

These findings underscore the need for rheumatology-specific, competency-based educational initiatives that promote safe, transparent, and critical use of LLMs while preserving fundamental principles of clinical reasoning and professional judgment. Collaborative leadership from rheumatology societies, academic institutions, and regulators will be essential to define minimum AI literacy standards, develop scalable curricula, and ensure equitable adoption across regions. As LLMs continue to evolve and embed themselves in healthcare workflows, proactive investment in education and governance will be crucial to harness their benefits while safeguarding patient care, clinician autonomy, and trust.

Author Contributions

L.G. Conceptualization, methodology, recruitment oversight, project administration, writing – original draft, and writing – review & editing. M.K. Methodology, data analysis and interpretation, and writing – review & editing. K.M.Z. Conceptualization, methodology, recruitment oversight, project administration, and writing – review & editing. S.K. Data analysis and interpretation, project administration, writing – review & editing. Y.D. Methodology, recruitment oversight, project administration, and writing – review & editing. V.V. Methodology, and

writing – review & editing. D.D., W.B.M. Recruitment oversight, and writing – review & editing. T.Y. Recruitment oversight, and writing – review & editing. A.E.M. Recruitment oversight, and writing – review & editing. M.R. Recruitment oversight, writing – review & editing. G.H. Recruitment oversight, and writing – review & editing. C.E. Conceptualization, methodology, writing – review & editing. C.X. Conceptualization, methodology, recruitment oversight, project administration, and writing – review & editing.

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Disclosure

L.G.: The views and opinions expressed are solely those of the author and do not represent or reflect those of any affiliated institution.

Ethics Statement

Combined Military Hospital (CMH), Dhaka Cantonment Institutional Review Board (IRB) approval number: CMH Dhaka/ECC/185.

Consent

Given the minimal-risk nature of this professional online survey, the IRB granted a waiver of written documentation of consent. Before starting the survey, participants were shown an information statement outlining the study purpose and confidentiality safeguards. Participation was voluntary, and respondents proceeded to the questionnaire only if they agreed to take part.

Conflicts of Interest

All other authors declare no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Detailed Breakdown of Large Language Model (LLM) Platform Utilization among Respondents. **Survey S1:** Perceptions and Need for Large Language Models (LLMs) in Rheumatology Training—Current Fears and Future Hope.

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EDITORIAL

A Unified, Stratified Approach to the Large Vessel Vasculitis Spectrum and Imaging Implications

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1 | Reconsidering Large Vessel Vasculitis (LVV): From Dichotomy to Spectrum?

Mikito Takayasu described his eponymous "pulseless" arteritis in 1908, while Bayard Horton presented the first histologically defined cases of temporal arteritis in 1932. Although both conditions describe systemic arterial inflammation, they are considered separate diseases based on age of onset (giant cell arteritis [GCA] in the elderly versus Takayasu arteritis [TAK] in the young), geography (GCA in Caucasians versus TAK in non-Caucasians), and vascular involvement (GCA cranial versus TAK extra-cranial). However, this dichotomous view may be oversimplistic.

Large vessel (LV) involvement in cranial GCA was described in 1946. Since then, numerous studies conducted across diverse geographic regions, using various diagnostic modalities and endpoints, have reported LVV in GCA in up to 83%. LV involvement is observed in relatively younger GCA cases, often associated with relapsing disease and a relatively poor response to glucocorticoids (GC) [1, 2]. On the other hand, the age cutoff for TAK has moved from 50 to 60 years, posing the semantic question for patients with LV involvement in their 50s—young GCA or old TAK [3]. Cranial GCA is increasingly reported among non-Caucasian populations [4], whereas LV-GCA is commonly identified on imaging in both GCA and PMR (GPSD) [1].

Should we therefore transition from a dichotomous to a spectrum concept as we plan novel trials and therapies for these conditions, be deviled by conventional GC toxicity? This cautious migration in our outlook is encouraged by pathophysiological and imaging overlaps. Our proposal to consider both disorders within a unified clinical spectrum does not imply identity. However, there is sufficient similarity to warrant trials of common treatment targets employing similar protocols and a common imaging approach.

Both GCA and TAK cause granulomatous inflammation of large and medium-sized vessels, although the vascular distribution differs [5, 6]. GCA is genetically associated with HLA-class II alleles, whereas the major risk factor for TAK is HLA-B*52, a class I allele [1, 6], resembling other MHC-I-opathies [7]. In both conditions, a common *IL-12B* gene polymorphism is present, and $CD4^+$ and $CD8^+$ T cells contribute to pathogenesis, alongside monocytes/macrophages, natural killer cells, and dendritic cells [2, 6]. The similarities (notwithstanding the differences) suggest that they could be regarded as separate phenotypes within the LVV spectrum. Isolated idiopathic aortitis (IA) is an example of the spectrum since it is often classified as either GCA or TAK, depending on the patient's age and where it is diagnosed. Despite variations in disease pathology and distribution, multiple studies highlight clinical features of TAK that may also manifest in GCA [6]. These include musculoskeletal complaints, arthralgia, synovitis, myalgia, visual disturbances, vision loss, and constitutional symptoms.

The inclusion of TAK with GPSD within the LVV spectrum would address a unified approach in clinical trials, classification criteria, and treatment strategies.

2 | Common Threads and Divergent Roots: Pathobiology Across the LVV Spectrum

There are shared and divergent immunopathophysiological mechanisms too between GCA and TAK (Figure 1). The HLA

associations differ: HLA-B*52 in TAK versus HLA-DRB1*04 in GCA. The Th1 and Th17 pathways, mediated by macrophages, play key roles in both diseases, and common cytokine pathways (IL-6, IL-12/23, and IFN-γ) contribute to disease amplification [6]. Proteomic signatures of the two diseases were very similar, including cytokines, chemokines, and tissue remodeling proteins [8]. The key steps for disease initiation are thought to be similar to vascular dendritic cell activation and granulomatous inflammation [6].

3 | Imaging as a Unifying Lens: From Vessel Wall to Clinical Decisions

While imaging findings vary in detail—reflecting TAK's anatomical distribution and higher incidence of stenotic disease—the diagnostic approaches bear notable similarities, with ultrasonography, PET/PET-CT, and CT/MR angiography playing central roles. In particular, POCRUS—the sequential application of clinical pretest probability, such as the Southend GCAPS, followed by targeted ultrasound using standardized assessment, such as eight-vessel ultrasound to compute Halo count, Halo score, and OGUS—may assist diagnosis, disease assessment (remission, smoldering disease, and vascular remodeling), and disease stratification [9]. This suggests that a unified diagnostic strategy could be applied to both conditions. Such targeted imaging can therefore be seen as a unifying step that links the state of the vessel wall to clinical decision-making. In practice, there is considerable variation in resource availability/access, and POCRUS can provide a scalable solution to underpin LVV management.

4 | Stratified Therapeutics: Aligning Treatment With LVV Phenotypes

There is emerging evidence for the limited efficacy of GC within the LVV spectrum. For example, although cranial GCA may often respond to GC alone, LV-GCA and relapsing PMR require additional therapeutic agents, either synthetic disease-modifying antirheumatic drugs (DMARDs) or biologics [10]. Treatment strategies, therefore, need to be tailored to disease phenotype, implying early disease stratification that would then lead to early, stratified therapy. Early stratification would also provide impetus for a proactive rather than a traditional reactive approach, in which complex therapies are escalated based on whether the patient has a remitting or relapsing disease.

5 | A Global Registry for a Global Disease: Toward Standardized Data Across the LVV Spectrum

We call for a harmonized international data collection effort. There is an unmet need for real-world phenotype data, treatment

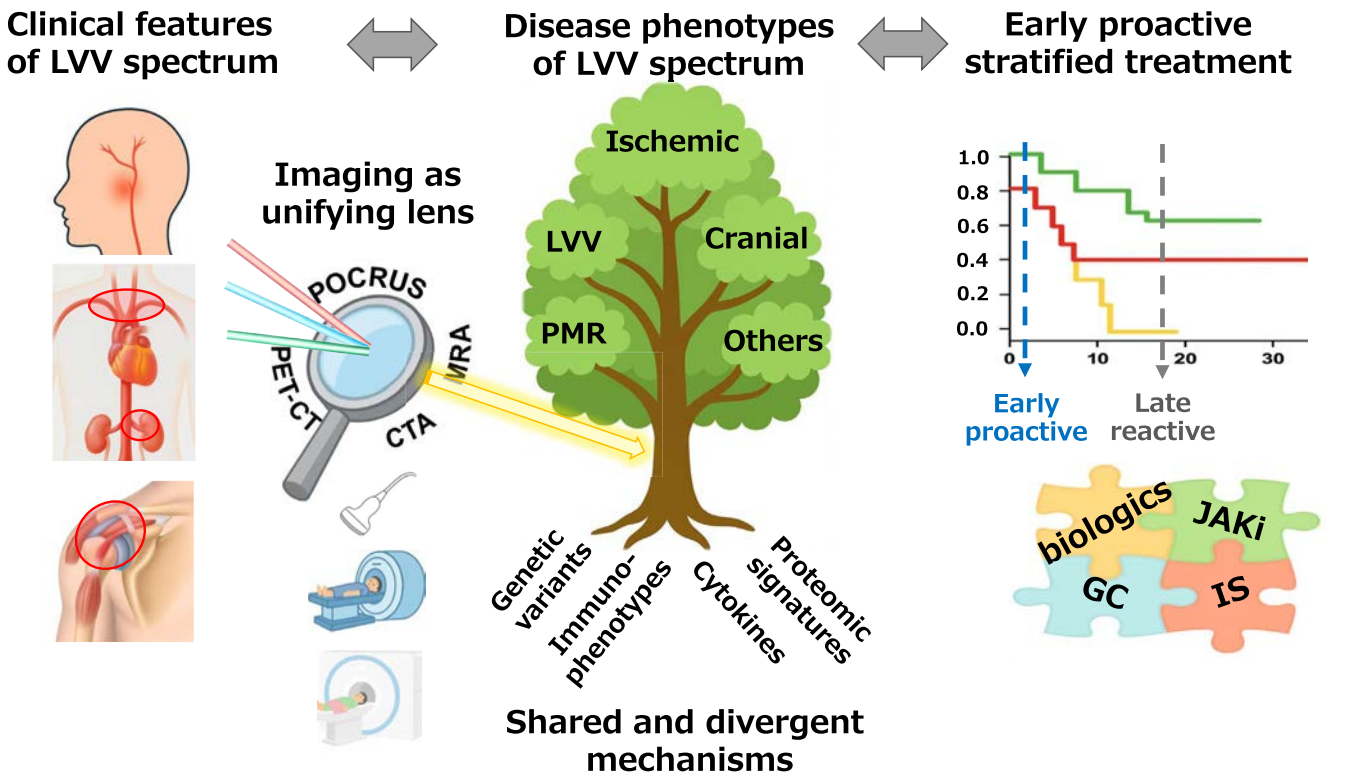

FIGURE 1 | A unified, stratified approach to the LVV spectrum. LVV including giant cell arteritis, PMR, and Takayasu arteritis can be regarded as distinct disease phenotypes within the LVV spectrum. These phenotypes stem from shared and divergent immunopathophysiological mechanisms. A similar diagnostic approach involving POCRUS, CTA/MRA, and PET/PET-CT can be applied as a unifying lens for various clinical features of LVV. Early proactive and stratified treatment tailored to each disease phenotype is expected to improve treatment outcomes and the quality of care for patients with a disease within the LVV spectrum. If the initial treatment fails, or if the clinical features of a patient change during treatment, a physical examination and imaging should be repeated, and the treatment should be adjusted according to the results. CTA/MRA, computed tomography/magnetic resonance angiography; GC, glucocorticoid; IS, immunosuppressant; JAKi, Janus kinase inhibitor; LVV, large vessel vasculitis; PET, positron emission tomography; PMR, polymyalgia rheumatica; POCRUS, point-of-care rheumatology ultrasound.

response, imaging follow-up, and long-term outcomes. Several existing national registries (e.g., the JPVAS, Chinese, and Turkish TAK registries) require harmonization. There needs to be an international effort to outline core dataset elements: demographics, imaging findings, treatment, response definitions, and patient-reported outcome measures. This effort should align with and collaborate with the OMERACT, EULAR, ACR, and APLAR working groups.

6 | Challenges and Future Directions

There is a lack of validated treat-to-target endpoints and response criteria for clinical trials. There is an urgent need for imaging endpoints in clinical trials, as only a few GCA, PMR, or TAK trials to date have investigated imaging for diagnosis, stratification, or response. In this era of personalized precision medicine, we need an international research effort to coordinate the search for biomarkers for diagnosis, prognosis, stratification of treatment targets, response, and damage.

Author Contributions

All authors contributed to the conception of the article, drafting and critical revision of the manuscript, and approved the final version for submission.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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ORIGINAL ARTICLE

Certolizumab Pegol Reduced Anterior Uveitis Flares Compared With Standard Non-Biologic Treatment: Results From an Overlap Weighting Analysis in High-Risk Patients With Axial Spondyloarthritis

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ABSTRACT

Objective: Acute anterior uveitis (AAU) is the most common extra-musculoskeletal manifestation of axial spondyloarthritis (axSpA). This study compared the effect of the tumor necrosis factor inhibitor (TNFi) certolizumab pegol (CZP) with standard non-biologic care, on AAU flare rate in patients with axSpA and high risk of recurrent uveitis flares.

Methods: C-VIEW (NCT03020992) was an open-label, multicenter study in which patients with radiographic or non-radiographic axSpA and high risk of uveitis flares received CZP for 96 weeks. Here, AAU flare rate was compared between patients in C-VIEW (up to 120 weeks) and high-risk patients with axSpA receiving standard non-biologic treatment from the University of California, San Francisco (UCSF) and University Health Network Toronto Western Hospital (UHN). Overlap weighting (OW) was utilized to adjust for potential confounders, followed by Poisson regression to evaluate the effect of CZP on AAU flare rate.

Results: Eighty-seven patients from C-VIEW were compared to 75 axSpA patients with comparative disease activity and not on biologic treatment (UCSF $n = 40$; UHN $n = 35$). After OW, there were no significant differences between groups in baseline characteristics included in the model. The AAU flare rate was significantly lower for patients treated with CZP than in the comparator population: after OW, a 70.9% lower AAU flare rate was associated with CZP treatment (risk ratio [95% confidence interval]: 0.29 [0.18, 0.47]; $p < 0.001$).

Conclusion: This study supports the findings of C-VIEW and demonstrates the benefit of CZP over standard non-biologic treatment as a promising therapeutic option in reducing AAU flares among high-risk patients with axSpA.

Nigil Haroon and Lianne S. Gensler were co-senior authors/dual first authors and contributed equally to this work.

Significance and Innovations

- There is a paucity of studies which compare the effectiveness of TNFis for the treatment of Acute Anterior Uveitis (AAU) flares in patients with axial spondyloarthritis (axSpA) versus non-biologic therapies
- This study explored the incidence of AAU flares in patients with axSpA in the C-VIEW study who were treated with certolizumab pegol (CZP) versus comparator patients treated with non-biologic therapy
- Using overlap weighting and Poisson regression, this study demonstrated that a substantially lower AAU flare rate was associated with the treatment of patients with axSpA with CZP in C-VIEW versus comparator patients treated with non-biologic therapy
- The findings position CZP as a promising therapeutic option for managing AAU flares among high-risk patients with axSpA

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that affects the axial and peripheral skeleton [1]. Although predominantly affecting the musculoskeletal system, extramusculoskeletal manifestations (EMMs) such as acute anterior uveitis (AAU), psoriasis, and inflammatory bowel disease are common in axSpA and additionally contribute to disease burden [2].

The most common EMM in axSpA is AAU, a non-infectious, acute inflammation of the anterior uveal tract and adjacent structures [3]. Sometimes, an attack of AAU can be the first presenting symptom leading to a diagnosis of axSpA [4]. AAU flares are typically sudden, unilateral episodes of photophobia, ocular pain, and blurred vision [4, 5]. AAU flares are common and can be unpredictable, with up to 40%–50% of patients with axSpA experiencing at least one anterior uveitis flare during the course of their disease [4], and recurrent AAU flares being experienced in approximately 50% of patients [6, 7]. AAU flares also have increasing incidence with increasing disease duration and affect both radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA) subpopulations [4]. Furthermore, active AAU flares have been associated with a significant reduction in health-related quality of life (HR-QoL) in patients with previously undiagnosed axSpA [8]. Thus, the burden of AAU on affected patients is high and compounds that of axSpA itself.

Some biologic disease-modifying antirheumatic drugs (bDMARDs), especially tumor necrosis factor inhibitors (TNFis), have demonstrated efficacy for decreasing the number of AAU flares in patients with axSpA [9–11], and have been recommended for treatment of uveitis over other biologics within guidelines of the American College of Rheumatology-Spondylitis Association of America-Spondyloarthritis Research and Treatment Network (ACR-SAA-SPARTAN) and the Assessment of SpondyloArthritis international Society-European League Against Rheumatism (ASAS-EULAR) [12, 13]. Whilst a few prospective studies in r-axSpA have demonstrated a decreased recurrence rate of anterior uveitis during treatment with TNFis, such as adalimumab, certolizumab and golimumab [14–16], the majority of evidence supporting this recommendation to date is limited to indirect comparisons in clinical trials or observational studies, rather than from direct comparisons [12].

Additionally, although several monoclonal antibodies are recommended by ASAS-EULAR for the management of active axSpA with recurrent AAU [17], some patients continue to experience recurrent AAU flares [18]. Hence, there is a continued need for an effective treatment that simultaneously reduces the risk of AAU flares while targeting axSpA symptoms [1, 4].

Certolizumab pegol (CZP) is a PEGylated Fc-free TNFi indicated for the treatment of adult patients with active r- and nr-axSpA [19, 20]. Previous studies have shown CZP to be safe and efficacious in treating axSpA, as well as in improving EMM in both r-axSpA and nr-axSpA populations [19]. Additionally, CZP is currently approved in two EMM indications (Crohn's disease [20], and psoriasis [20, 21]). Furthermore, a growing body of evidence has demonstrated that CZP leads to sustained reductions in the incidence of AAU flares across both subpopulations of axSpA patients [4, 11, 15, 22]. Although a direct comparison of the ability of sulfasalazine to reduce rate of uveitis flares in axSpA has been reported compared to etanercept [23], such direct comparisons of the effectiveness of CZP versus other treatments are lacking. Hence, further data are required to support the effectiveness of CZP for the treatment of this important facet of disease burden.

Here, findings are presented from a propensity score weighting analysis that evaluated AAU flare rate in patients with axSpA and high risk of recurrent AAU. AAU flare rate in patients treated with CZP in the C-VIEW study were compared to the rate experienced by comparator patients treated with standard non-biologic care.

1 | Patients and Methods

1.1 | Study Design

C-VIEW (NCT03020992) was an open-label, single-arm, phase 4, multicenter study conducted across five European countries (the Czech Republic, Germany, the Netherlands, Poland and Spain) that prospectively investigated the impact of CZP on the frequency of AAU flares in patients with both active axSpA (r-axSpA and nr-axSpA) and a recent history of recurrent AAU [15]. The trial comprised a 96-week open-label phase, plus an 8-week safety follow-up (Figure 1A) [15]. Eligible patients received a loading dose of 400 mg CZP at Weeks 0, 2, and 4, followed by subcutaneous 200 mg CZP every 2 weeks (Q2W) up to Week 96. The study was approved by institutional review boards and independent ethics committees at participating sites and was conducted in accordance with local regulations and the International Conference on Harmonization Good Clinical Practice requirements, based on the Declaration of Helsinki. All patients provided written informed consent. Participant race and ethnicity were self-reported by patients through selection from a fixed set of categories.

In this analysis, the rate of AAU flares experienced by patients in the C-VIEW study were compared to those seen in comparator

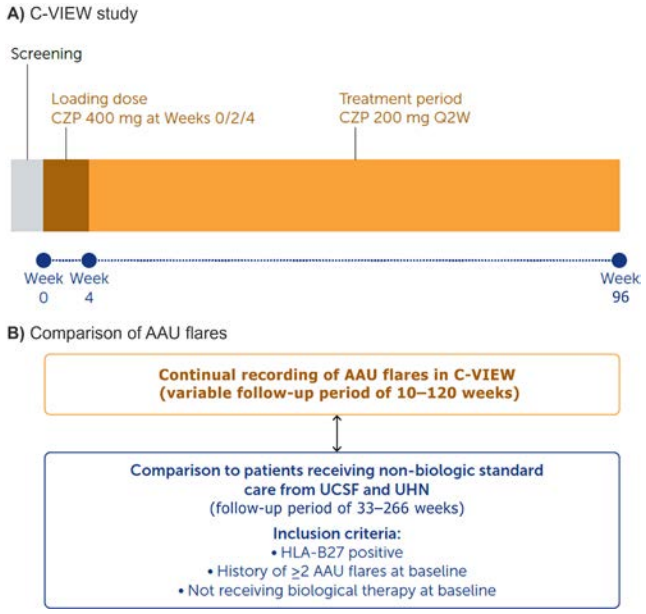

FIGURE 1 | C-VIEW study design and comparison to UCSF and UHN. (A) In C-VIEW, axSpA patients with a high risk of uveitis received CZP for 96 weeks. (B) Follow-up data up to 120 weeks are reported and compared with patients receiving non-biologic standard care from UCSF and UHN. AAU, Anterior acute uveitis; axSpA, Axial spondyloarthritis; CZP, Certolizumab pegol; HLA-B27, Human leukocyte antigen-B27; Q2W, Every 2 weeks; UCSF, University of California, San Francisco; UHN, University Health Network Toronto Western Hospital.

high-risk patients who received non-biologic standard care from the University of California, San Francisco (UCSF) and University Health Network, Toronto Western Hospital (UHN) (Figure 1B). AAU flares were assessed in the C-VIEW study over a mean follow-up period of 101 weeks (standard deviation [SD]: 17 weeks), of which 95.4% of patients were followed for more than 48 weeks. In the comparator group, AAU flares were observed for a mean follow-up period of 86 weeks (SD: 43 weeks), of which 89.3% of patients were followed for more than 48 weeks (Table S1). The number of AAU flares observed in each group is presented in Table S2.

1.2 | Patients

Full inclusion and exclusion criteria for the C-VIEW study have been reported previously [24]. In brief, patients included in C-VIEW were ≥ 18 years old, human leukocyte antigen (HLA)-B27 positive with a diagnosis of axSpA fulfilling ASAS classification criteria with active disease (defined as a Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥ 4 and spinal pain [BASDAI item 2] ≥ 4). Patients also had a documented history of AAU diagnosed by an ophthalmologist (with a history of ≥ 2 AAU flares in total and ≥ 1 AAU flare in the year prior to study entry) and previous inadequate response to ≥ 2 non-steroidal anti-inflammatory drugs (NSAIDs). Patients were excluded if they had been exposed to > 1 TNFi prior to baseline (infliximab, adalimumab and golimumab exposure was not permitted in the 3 months prior to baseline and use of etanercept was not permitted in the 28 days prior to baseline) and were considered as primary non-responders (defined as no response within the first 12 weeks of TNFi treatment).

Adult patients from UCSF and UHN with a diagnosis of axSpA fulfilling ASAS classification criteria (r-axSpA or nr-axSpA), and those with r-axSpA who satisfied the modified New York classification criteria, and were not on biologic therapy at baseline, were compared against C-VIEW patients based on HLA-B27 positivity, a previous history of ≥ 2 AAU flares, and ≥ 1 AAU flare in the year prior to baseline. Comparator patients from UCSF had no recorded history of biologic treatment use; patients at UHN had no recorded history of biologic use for at least a year prior to baseline. For comparator patients, baseline was defined as the first visit instance the patient met all eligibility criteria in addition to having at least one follow-up visit where AAU was assessed, up to an interval of 104 weeks between follow-up visits (the median risk-time in the C-VIEW study). Compared to C-VIEW, the comparator patients may have added or changed NSAID therapy with active axSpA, but did not initiate biologic therapy.

1.3 | Outcomes

The primary outcome of this analysis was the comparison of the mean rate of AAU flares observed over the clinical trial follow-up time in CZP-treated patients from C-VIEW versus eligible comparator patients who received standard non-biologic care, using a rate ratio (RR). In C-VIEW, AAU flares were confirmed by an ophthalmologist. Flares on the same eye were counted as one flare if the time interval between two subsequent flares was < 3 months, since recurrence of the first flare due to premature tapering of AAU treatment could not be excluded. AAU flares occurring on different eyes were considered separate episodes [15].

One outlying value was identified in the comparator group, with an unusually high number of AAU flares in the previous 12 months prior to baseline. Hence, to minimize the impact of this outlier and prevent potential instability in the estimates, a log transformation was applied to the number of flares in the previous 12 months.

1.4 | Statistical Analysis

Overlap weighting (OW) propensity score analysis was performed based on the methods of Li et al. [25] using the 'WeightIt' R package [26], to balance the cohorts. In this approach, the average treatment effect for the overlap population (ATO) serves as the estimand. The ATO refers to the treatment effect in a target population where both treatments are equally applicable to eligible patients, that is, a population at clinical equipoise. Thus, OW emphasizes the target population with the most overlap in observed characteristics between treatment groups, where treatment decisions are most uncertain [27]. This approach assigns weights to patients that are proportional to the probability of being in the opposite treatment group, ensuring that all available patients contribute to the analysis while achieving exact balance in the mean of all covariates included in the model.

OW was chosen over inverse probability of treatment weighting (IPTW) as it provides a more robust method designed to handle comparator groups that are very different [28]. The following variables were included in the OW propensity score analysis: years since axSpA diagnosis, classification (r-axSpA versus nr-axSpA), age category (18–50 years versus 51–80 years),

sex (female participants versus male participants), number of AAU episodes in 12 months prior to baseline (log transformed), disease-modifying anti-rheumatic drugs (DMARD) usage history at baseline (no versus yes), psoriasis or inflammatory bowel disease (IBD) history at baseline (no versus yes) and axSpA Disease Activity Score (ASDAS) category at baseline (< 2.1 versus ≥ 2.1, whereby ASDAS < 2.1 was considered inactive to low disease activity and ASDAS ≥ 2.1 was considered high to very high disease activity). The covariate balance diagnostics were performed using the cobalt R package [29], where the absolute standardized mean differences (aSMD) for these characteristics were assessed to ensure they were below the 0.1 threshold. The effective sample size (ESS), which is a measure of the sample size needed in a non-weighted sample to achieve the same precision as the weighted sample, was provided [30, 31].

All statistical analyses were performed in R (v4.3.2; 2023-10-31 Universal C Runtime) [32]. Following OW, a multivariable Poisson model was fitted and adjusted for patient follow-up times using an offset parameter, to account for the variability in follow-up times (and therefore time at risk) of patients (Table S1, Figure S1). Because the number of AAU flares in the 12 months prior to baseline ('AAU pre12m') was a strong predictor of the outcome, log(AAU pre12m) was included as an interaction term with treatment in the outcome regression. Moreover, statistical differences between the two comparator groups, UHN and UCSF, were assessed, and variables found to be significantly different were also included in the outcome regression model as interaction terms with treatment. The marginal treatment effect estimate (rate ratio: RR) was then calculated using the avg_comparisons function from the 'marginaleffects' R package [33], performing G-computation, a method for comparing expected outcomes under different treatment assignments [34]. This was applied with OW weights to the 'glm_weightit' object, following the guidance in the 'WeightIt' vignette [35]. 95% confidence intervals (CIs) were calculated using the fractional-weighted bootstrap method [36]. These statistical methods reduce potential confounding factors by balancing the distributions of covariates between CZP-treated cases (C-VIEW) and comparator cohorts, and they provide the RR, which reflects the treatment effect after adjusting for baseline differences.

Given the small sample size, the primary propensity score analysis was limited to variables deemed most critical for estimating the outcome. However, as demonstrated in Table 1, several other baseline variables were imbalanced between the treatment and comparator groups prior to OW. To assess how including these variables in the propensity score model affects the outcome, a sensitivity analysis was conducted by carrying out an additional propensity score analysis that included the following additional baseline variables: TNFi medication history, NSAID usage history (binary variable), C-reactive protein (CRP) (mg/L), BASDAI, tender joint count ≥ 1, and swollen joint count ≥ 1.

2 | Results

2.1 | Patient Disposition and Baseline Characteristics

Eighty-seven CZP-treated patients from C-VIEW were included in the analysis. A total of 1648 patients from UHN and 526 patients from UCSF were subsequently reviewed for eligibility as comparators, with 75 patients not on biologic treatment (40 from UCSF and 35 from UHN) and at high risk of AAU flares according to criteria above, ultimately being included. Thus, a total of 162 patients were included in the analysis.

Baseline characteristics are presented in Table 1. Overall, baseline demographics were generally similar between C-VIEW patients treated with CZP and those in the comparator groups. In both groups, the majority of patients were male (CZP: 55/87 [63.2%]; comparator: 49/75 [65.3%]) and classified with r-axSpA (CZP: 74/87 [85.1%]; comparator: 66/75 [88.0%]). Mean time since diagnosis [years, SD] was 9.0 (8.7) years in CZP-treated patients and 10.2 (10.5) years in the overall comparator group.

Few patients in either group had prior DMARD or TNFi use at baseline (CZP: 21/87 [24.1%] and 5/87 [5.7%], respectively; comparator: 21/75 [28.0%] and 8/75 [10.7%], respectively). In both treatment arms, the majority of patients reported previous NSAID use (CZP: 83/87 [95.4%]; comparator: 56/75 [74.7%]).

2.2 | Overlap Weighting Propensity Score Weighting

Before OW propensity score weighting, there were significant differences between C-VIEW patients treated with CZP and comparator patients in critical variables included in the propensity score analysis such as having psoriasis or IBD history at baseline (CZP versus comparator: $p = 0.022$) and ASDAS category (< 2.1 [inactive–low disease activity] or ≥ 2.1 [high–very high disease activity] at baseline; CZP versus comparator: $p < 0.001$; Table 1). In addition to these, the age and number of years since diagnosis were unbalanced according to aSMD criteria, prior to overlap propensity score weighting (aSMD > 0.1; Figure S2 and Table S3).

After OW, the aSMD in the unbalanced baseline characteristics included in the model between the CZP-treated and comparator patients was zero (Figure S2; the balanced characteristics are shown in Table S3). The ESS was 38 for the comparator and 66 for the CZP-treated group. Within the overall comparator group, the UHN and UCSF cohorts had significant differences in disease classification ($p = 0.04$), number of years since diagnosis ($p < 0.001$), and ASDAS disease state ($p < 0.01$) variables at baseline; these variables were therefore included in the final model to correct for them (Table S4).

2.3 | AAU Flare Rate

In the final model after OW, the predicted average rate of AAU flares over the follow-up time was notably lower in CZP-treated patients than in the comparator population, with a mean (SD) of 0.43 (0.09) versus 1.48 (0.19) flares per follow-up time, respectively (Figure 2). A significantly lower AAU flare rate was associated with CZP treatment versus comparator (70.9% lower; RR [95% CI]: 0.29 [0.18, 0.47], $p < 0.001$).

The sensitivity analysis, which included additional baseline variables in the Poisson regression, also demonstrated a significant

TABLE 1 | Patient demographics and baseline characteristics.

	CZP: C-VIEW ($N=87$)	Comparator			CZP vs Comparator p-value
		UCSF ($n=40$)	UHN ($n=35$)	Overall ($N=75$)	
Sex, male *n* (%)	55 (63.2)	24 (60.0)	25 (71.4)	49 (65.3)	0.91[a]
Age, *n* (%)					0.55[a]
*n**	87	40	34	74	
18–50	55 (63.2)	29 (72.5)	22 (64.7)	51 (68.9)	
51–80	32 (36.8)	11 (27.5)	12 (35.3)	23 (31.1)	
Disease classification, *n* (%)					0.75[s]
r-axSpA	74 (85.1)	32 (80.0)	34 (97.1)	66 (88.0)	
nr-axSpA	13 (14.9)	8 (20.0)	1 (2.9)	9 (12.0)	
Years since diagnosis (years), mean (SD)	9.04 (8.69)	7.19 (9.02)	13.73 (11.07)	10.20 (10.47)	0.72[b]
*n**	87	40	34	74	
Previous DMARD use, *n* (%)	21 (24.1)	10 (25.0)	11 (31.4)	21 (28.0)	0.70[a]
Previous TNFi use, *n* (%)	5 (5.7)	0 (0.0)	8 (22.9)	8 (10.7)	0.39[a]
Previous NSAID use, *n* (%)	83 (95.4)	22 (55.0)	34 (97.1)	56 (74.7)	<0.001[c]
ASDAS disease state, *n* (%)					<0.001[c]
*n**	87	39	34	73	
<2.1	3 (3.4)	28 (71.8)	12 (35.3)	40 (54.8)	
≥ 2.1	84 (96.6)	11 (28.2)	22 (64.7)	33 (45.2)	
BASDAI, mean (SD)	6.50 (1.49)	2.43 (2.10)	3.18 (2.11)	2.78 (2.12)	<0.001[b]
BASFI, mean (SD)	5.09 (2.40)	1.28 (1.90)	2.52 (2.29)	1.82 (2.15)	<0.001[b]
*n**	87	37	28	64	
TJC, *n* (%)					<0.001[a]
*n**	87	40	34	74	
≥ 1	58 (66.7)	7 (17.5)	6 (17.6)	13 (17.6)	
SJC, *n* (%)					<0.001[c]
*n**	87	40	34	74	
≥ 1	32 (36.8)	1 (2.5)	1 (2.9)	2 (2.7)	
AAU pre12m, mean (SD)	1.48 (0.71)	1.57 (0.81)	1.69 (1.92)	1.63 (1.43)	0.76[b]
CRP, mg/L, mean (SD)	13.98 (27.50)	4.21 (4.38)	8.57 (12.50)	6.24 (9.32)	0.12[b]
Psoriasis or IBD history, *n* (%)	3 (3.4)	4 (10.0)	7 (20.0)	11 (14.7)	0.022[c]

Note: The p-value compares the treatment (CZP) group with the pooled comparator groups.

Abbreviations: AAU pre12m, number of AAU flares in the 12 months prior to baseline; AAU, acute anterior uveitis; ASDAS, axSpA Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; Chi Sq, chi squared; CRP, C-reactive protein; CZP, certolizumab pegol; DMARD, disease-modifying antirheumatic drugs; IBD, inflammatory bowel disease; nr-axSpA, non radiographic axial spondyloarthritis; NSAID, non-steroidal anti-inflammatory drugs; r-axSpA, radiographic axial spondyloarthritis; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor; UCSF, University of California, San Francisco; UHN, University Health Network, Toronto Western Hospital.

*n excluding missing.

[a]Chi Squared.

[b]Wilcoxon Rank Sum.

[c]Fisher Exact. ASDAS <2.1 refers to inactive disease activity to low disease activity and ASDAS ≥ 2.1 refers to high disease activity to very high disease activity.

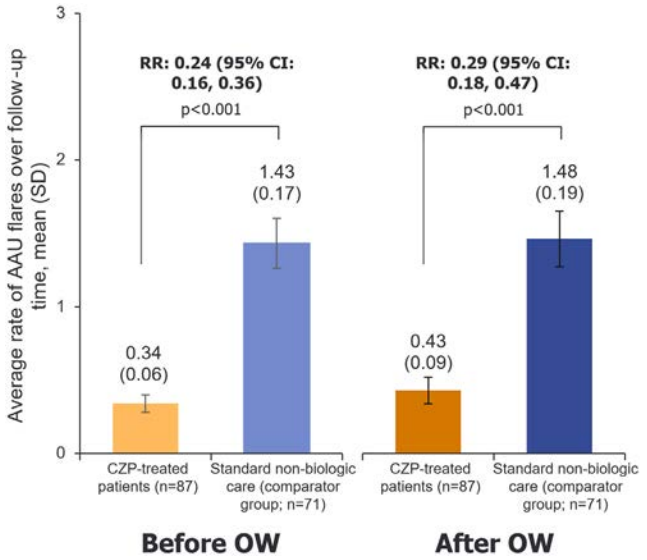

FIGURE 2 | Predicted average rate of AAU flares over follow-up time in CZP-treated and standard non-biologic-treated patients, before and after overlap propensity score weighting. AAU flare rates were predicted using OW to adjust for potential confounders, followed by Poisson regression (as described in the methods), adjusted for follow-up time. The results presented are based on a complete case analysis, whereby missing data are excluded: For the comparator group, there was one missing data point for age (UHN), one missing for number of years since diagnosis (UHN), and two missing for ASDAS (one UHN; one UCSF). In the final analysis to calculate RR, since all these variables were used in PS analysis, they were excluded. Hence, the comparator population was reduced from $N=75$ to $n=71$ ($n=4$ missing). All patients were HLA-B27 positive and had a history of AAU with at least one episode in the preceding year. AAU, acute anterior uveitis; ASDAS, axSpA Disease Activity Score; CI, confidence interval; CZP, certolizumab pegol; OW, overlap weighting; RR, rate ratio; SD, standard deviation.

73.0% reduction in the AAU flare event rate with CZP treatment versus comparator (RR [95% CI]: 0.27 [0.13, 0.55]; $p<0.001$).

3 | Discussion

C-VIEW was a pivotal study which investigated the reduction of AAU flares in a broad axSpA population, encompassing both r-axSpA and nr-axSpA, in patients with HLA-B27 positive disease [15, 24]. To date, there has been a lack of studies presenting comparisons of the effectiveness of TNFis for the treatment of AAU flares in axSpA patients versus comparator treatments. Furthermore, few studies have reported on the incidence of AAU flares in patients with axSpA treated with non-biologic therapies. For the first time, this study reports that in patients with axSpA, those treated with CZP experienced a significantly lower rate of AAU flares per follow-up time compared with comparator patients receiving standard non-biologic treatments, with an overall 70.9% lower AAU flare rate. These results apply to a population where patients are at clinical equipoise for receiving either treatment option, with all measured covariates balanced across treatment groups through OW (Table S3). When additional baseline variables were included in the sensitivity analysis, a similar reduction in the AAU flare event rate as the main analysis was found (73.0% lower flare rate with CZP versus comparator), demonstrating the robustness of the approach.

In C-VIEW, CZP-treated patients saw a significant 87% reduction in AAU flares by Week 48 of treatment versus pre-baseline, and an 82% reduction by Week 96 [15, 24]. The results of the present study support the findings of the primary analysis of the C-VIEW trial [15, 24] and suggest that CZP treatment is associated with a sustained reduction of AAU flare rate in a high-risk population, for whom effective treatment of both axSpA symptoms and AAU flares is highly desirable and may have important HR-QoL implications. Together, these data contribute to the growing body of evidence supporting possible effectiveness of CZP for the reduction of AAU flares in axSpA patients.

These results expand upon previous randomized controlled trial data where CZP-treated patients in both axSpA subpopulations experienced lower AAU flares compared to patients receiving placebo. Results from the phase 3, randomized, double-blind, placebo-controlled trial RAPID-axSpA (NCT01087762) showed that CZP-treated patients with both nr- and r-axSpA displayed lower rates of anterior uveitis flares than placebo-treated patients [4]. In that study, the rate of anterior uveitis flares remained low to Week 96, with the authors noting that flare rates in the CZP-treated patients were comparable to those reported for patients receiving other TNFis in similar studies [10, 37, 38]. Furthermore, when patients were followed to 4 years with open-label CZP treatment, improvements in the rate of uveitis were sustained across both axSpA subpopulations, with no new safety signals identified [11]. Similarly, results from the open-label, phase 3b, C-OPTIMIZE study (NCT02505542) reported improvements in EMMs, including uveitis [22].

Additionally, the 87% reduction in AAU flare rate relative to pre-baseline rates aligns with findings from studies of other monoclonal antibody TNFis. In prior studies of patients with spondylarthropathies, adalimumab demonstrated reduction in AAU flares of 51%–68% from baseline [10], and a reduction in event rate from 60.5 flares/100 patient-years before treatment to 0.0 flares/100 patients years during treatment [9]. Similarly, infliximab demonstrated a reduction in event rate from 47.4 flares/100 patient-years pre-treatment to 9.0 flares/100 patient-years during treatment, corresponding to a similar rate of reduction as the present study [9]. Conversely, the soluble receptor TNFi etanercept has demonstrated minimal impact on AAU flare rate in prior studies of patients with spondylarthropathies [9, 39]. Direct cross-study comparisons should be interpreted with caution due to differences in study design and cohort characteristics.

Beyond direct clinical implications, AAU flares have been shown to significantly affect physical aspects of HR-QoL, especially in patients with pre-existing, undiagnosed spondyloarthritis. Specifically, during active AAU flares, patients report significantly reduced physical and social functioning and score significantly lower on the physical and mental components of the 36-item Short Form Health Survey compared with the general population [8]. Therefore, identifying efficacious treatments for reducing AAU flares in patients with axSpA is crucial to improving the HR-QoL of these patients.

This study was not without limitations; a small proportion of both C-VIEW patients and comparator patients included in the analysis had received prior treatment with biologics, which could have impacted the recurrence rates observed. Nevertheless, given the substantial wash-out period for biologics employed in this study (C-VIEW patients who received any dose of infliximab, adalimumab, or golimumab within 3 months, or etanercept within 28 days prior to baseline were excluded; and comparator patients were not on biologic medication for at least a year prior to baseline), this is unlikely to have been a contributory factor.

Furthermore, this study was not designed to capture safety data from patients in the comparator cohort. As such, it was not possible to directly compare the safety profile of CZP in this analysis with that of patients receiving standard non-biologic treatment. However, this must be considered in the broader context of studies demonstrating the safety and efficacy of CZP for the treatment of AAU in both r-axSpA and nr-axSpA populations [1].

Finally, the OW approach used in the present study, like all other propensity score methods, cannot control for baseline characteristics that are not collected or added to the propensity score calculation, which means there is potential for bias due to unmeasured factors. Additionally, propensity score analyses were not performed to directly match two comparator groups before pooling them. Instead, the differences in baseline characteristics were addressed by incorporation directly into the outcome analysis. However, this approach may not fully eliminate bias that could arise from underlying differences between the two comparator groups. Of note, the proportion of patients with high disease activity as measured by ASDAS scores ≥ 2.1 were different between the groups (96.6% in the C-VIEW cohort vs. 45.2% in the comparator cohort, respectively). This may impact the accuracy of results, given the wider impact disease activity may have on AAU flares.

In this study, a high-risk population of CZP-treated patients with both r-axSpA and nr-axSpA experienced a significantly lower rate of AAU flares (70.9% lower) compared with patients treated with standard non-biologic treatment. Building upon the findings of the primary C-VIEW analysis and the established efficacy of CZP for the treatment of axSpA, these data suggest that CZP treatment is associated with a reduction in AAU flare rate, which could have important ramifications for improving HR-QoL in high-risk patients with axSpA and recurrent AAU. These findings may help to inform treatment decisions for these patients suffering from this important extra-musculoskeletal manifestation of axSpA.

Author Contributions

Substantial contributions to study conception and design: N.H., Z.B., T.C., R.D.I., T.K., R.T., M.K., I.v.d.H.B., L.S.G.; substantial contributions to analysis and interpretation of the data: N.H., Z.B., T.C., R.D.I., T.K., R.T., M.K., I.v.d.H.B., L.S.G.; drafting the article or revising it critically for important intellectual content: N.H., Z.B., T.C., R.D.I., T.K., R.T., M.K., I.v.d.H.B., L.S.G.; final approval of the version of the article to be published: N.H., Z.B., T.C., R.D.I., T.K., R.T., M.K., I.v.d.H.B., L.S.G.

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Conflicts of Interest

N.H.: Consultant for AbbVie, Eli Lilly, Novartis and UCB; Z.B., T.C.: Nothing to disclose; R.D.I.: Consultant for AbbVie, Janssen, Novartis and UCB. T.K., M.K.: Employees and stockholders of UCB; R.T.: Former Veramed statistical consultant for UCB; I.v.d.H.B.: Consultant for AbbVie, Eli Lilly, MSD, Novartis, and UCB; unrestricted Grants received for investigator-initiated studies from AbbVie, MSD, Pfizer, and UCB; fees received for lectures from AbbVie, BMS, MSD, and Pfizer; L.S.G.: Grants from UCB paid to institution; consulting fees from Acelyrin, Eli Lilly, Janssen, Novartis, Pfizer, and UCB.

Data Availability Statement

Data from non-interventional studies is outside of UCB's data sharing policy and is unavailable for sharing.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Histogram of follow-up times in the CZP and comparator. **Figure S2:** Balance analysis for all variables before and after implementing. **Table S1:** Time at risk (of AAU flare) in CZP and comparator groups. **Table S2:** The number of AAU flares in CZP and comparator groups. **Table S3:** Baseline characteristics for all variables before and after. **Table S4:** Comparison of UHN and UCSF cohort baseline characteristics.

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ORIGINAL ARTICLE

Real-World Data of Tofacitinib Versus Tumor Necrosis Factor Inhibitors in Taiwanese Patients With Rheumatoid Arthritis From a Drug-Based Cohort Study

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ABSTRACT

Aim: To assess the long-term effectiveness and safety of, and persistence/adherence to, tofacitinib (an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis [RA]) and tumor necrosis factor inhibitors (TNFi) in Taiwanese patients with RA in real-world settings.

Methods: This was a 5 year, prospective cohort study in Taiwanese patients with RA newly initiating tofacitinib or TNFi. Patients received standard care per treating rheumatologists and fulfillment of National Health Insurance reimbursement criteria. Effectiveness outcomes (baseline and every 24 weeks) included: Disease Activity Score in 28 joints, erythrocyte sedimentation rate; Clinical Disease Activity Index; Health Assessment Questionnaire-Disability Index; and Work Productivity and Activity Impairment-RA. Differences between groups were compared using mixed logistic regression models. Safety and persistence/adherence were assessed throughout.

Results: In total, 267 patients were included (tofacitinib, $n = 145$; TNFi, $n = 122$). No significant differences in effectiveness outcomes for tofacitinib versus TNFi were reported before or after propensity score adjustment. In patients receiving tofacitinib and TNFi, rates of adverse events (AEs; 56.6% vs. 55.7%), serious AEs (20.0% vs. 21.3%), major adverse cardiovascular events (0% vs. 0.8%), malignancy (2.1% vs. 0.8%), and deaths (1.4% vs. 3.3%) were similar. Serious infections/herpes zoster occurred in 13.1%/12.4% and 8.2%/3.3% of patients receiving tofacitinib and TNFi, respectively. No venous thromboembolism events were reported. Persistence/adherence was comparable between tofacitinib and TNFi.

Conclusion: Tofacitinib effectiveness and persistence/adherence were generally similar to TNFi in this real-world analysis in Taiwanese patients with RA. Safety outcomes were consistent with the known safety profiles of tofacitinib and TNFi.

Trail Registration: EUPAS13431.

1 | Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by joint stiffness, swelling, and pain [1]. Tofacitinib, an oral Janus kinase (JAK) inhibitor for the treatment of RA, is a small, targeted synthetic molecule that works at the intracellular level mimicking adenosine triphosphate and binding to a site within the kinase domain of JAK to inhibit phosphorylation and activation of JAK. This prevents activation of Signal Transducer and Activator of Transcription and gene transcription, and subsequently decreases cytokine production pathways critical to the pathogenesis of RA, modulating the immune response [2].

The efficacy and safety of tofacitinib 5 and 10 mg twice daily have been demonstrated in patients with moderately to severely active RA in global Phase 2 [3–7], Phase 3 [8–14], and Phase 3b/4 [15] trials of up to 24 months in duration. In Taiwan, tofacitinib was approved under the National Health Insurance (NHI) reimbursement system in December 2014 for the treatment of patients with moderately to severely active RA and with an inadequate response to two disease-modifying antirheumatic drugs (DMARDs), including methotrexate. According to Taiwan's NHI reimbursement guidelines, a reduction in dose is mandated when a patient has been treated with an advanced therapy, such as tofacitinib or a tumor necrosis factor inhibitor (TNFi), for 24 months and has achieved remission, defined as a Disease Activity Score in 28 joints, erythrocyte sedimentation rate (DAS28-ESR) < 2.6, for > 6 months. Prior to May 1, 2019, a reduction in dose was indicated for patients achieving low disease activity (LDA; assessed as DAS28-ESR ≤ 3.2, ESR ≤ 25 mm/h, and C-reactive protein ≤ 1 mg/dL) for > 6 months.

Currently, there are limited data describing the characteristics of patients who receive tofacitinib in the real-world setting in Taiwan, as well as the long-term clinical effectiveness and safety of tofacitinib. Therefore, the objective of this study was to assess the long-term effectiveness and safety of, and persistence and adherence to, tofacitinib and TNFi in Taiwanese patients with RA in a real-world setting.

2 | Materials and Methods

2.1 | Study Design

This was a 5 year, prospective, non-interventional, observational cohort study that enrolled patients with RA from 7 centers in Taiwan. The study consisted of a 24 month enrollment period and a ≥ 36 month follow-up period (August 2016 to May 2021). Follow-up was continued for at least 36 months or until death, withdrawal from study, or loss of follow-up, whichever occurred first.

Patients aged > 20 years, and those aged 18–20 years who provided consent with their legal guardian, with clinically diagnosed RA who newly initiated tofacitinib or a TNFi (etanercept, adalimumab, or golimumab) were eligible to participate. Patients received standard care for RA according to the treating physician's judgment and fulfillment of the NHI reimbursement criteria. Treatments were provided under the NHI, independent of the study sponsor. Despite NHI reimbursement criteria, dose reduction or weaning off treatment could have occurred at any time during the study when patients met LDA criteria, per the treating physician's judgment.

The study was conducted voluntarily by Pfizer in accordance with Good Pharmacoepidemiology Practice and Good Epidemiology Practice guidelines, and was registered on the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance with the EU Post-Authorisation Studies Register Number EUPAS13431. Written informed consent was provided by patients prior to being enrolled in the study.

2.2 | Outcomes

The primary effectiveness outcomes included DAS28-ESR LDA (< 3.2) and remission (< 2.6), Clinical Disease Activity Index (CDAI) LDA (≤ 10) and remission (≤ 2.8), and mean change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) and Work Productivity and Activity Impairment-RA (WPAI-RA; absenteeism, presenteeism, overall work impairment due to RA, and activity impairment due to RA). Data for the primary outcomes were collected at the enrollment visit when treatment was first initiated (baseline), 1 week after treatment initiation (CDAI and HAQ-DI only), and approximately every 6 months thereafter during regular treatment visits. Additional efficacy assessments were conducted after 4 and 12 weeks for patients who had their dose reduced or discontinued treatment; thereafter, assessments continued at the standard 6 month intervals. Efficacy outcomes are presented for time points at which data were available for ≥ 53 patients (disability and disease activity endpoints) or ≥ 25 patients (WPAI-RA) per treatment group.

Secondary outcomes, assessed for the entire study period, included safety outcomes, treatment patterns, persistence, and adherence. Adverse events (AEs), serious AEs (SAEs), and AEs of special interest (including serious infections, herpes zoster, malignancies, major adverse cardiovascular events [MACE], and venous thromboembolism) were recorded at each occurrence. No adjudication of AEs of special interest was conducted. AEs were collected throughout the study, starting from the incident dose of the medication until 28 days following the last administration of the drug under study. Prescriptions were used to calculate persistence and adherence; persistence was defined as the total number of days between first and last refill date plus the number of days' supply in the last refill, and adherence was assessed using the proportion of days covered.

2.3 | Analyses

The full analysis set comprised all enrolled patients providing written, informed consent and at least one opportunity for data collection. The effectiveness analysis set comprised patients in the full analysis set who received tofacitinib or TNFi and did not switch treatment during the study period. The safety analysis set consisted of patients who received at least

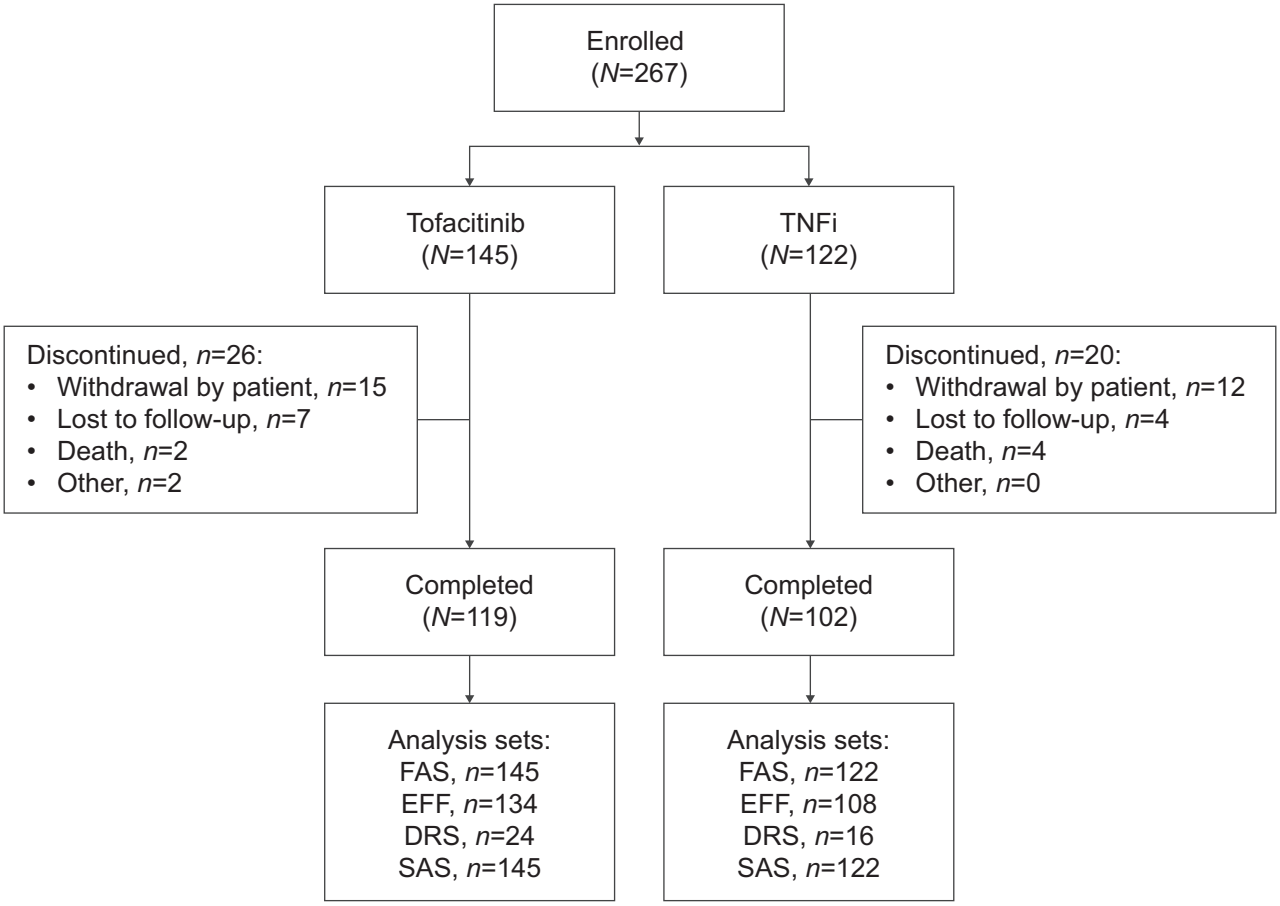

FIGURE 1 | Patient disposition. DRS, dose reduction analysis set; EFF, effectiveness analysis set; FAS, full analysis set; *N*, total number of patients in the analysis; *n*, number of patients in each category; SAS, safety analysis set; TNFi, tumor necrosis factor inhibitor.

one dose of study drug (tofacitinib or TNFi) and was analyzed according to the index treatment arm. Effectiveness outcomes were also assessed specifically in patients who underwent dose reduction or weaning off per NHI requirements (dose reduction analysis set).

Demographics and baseline characteristics were compared between groups using Chi-squared tests (categorical variables) and two-sample *t*-tests (continuous variables), with no multiplicity adjustment. Missing effectiveness or safety data were not imputed, and data were analyzed and presented as recorded in the database. Mean values for effectiveness outcomes are reported over time at each visit. Differences in effectiveness outcomes between groups were compared using mixed-effect logistic regression models (for all visits combined), with dichotomous outcome variables for HAQ-DI, CDAI, DAS28-ESR, and Question 1 of the WPAI-RA (currently employed or not). Baseline HAQ-DI was included as an independent variable for the change from baseline in HAQ-DI outcome in the mixed logistic regression. Given the non-random assignment of treatment in this observational study setting, propensity scores (PS) were included in the model. The PS were previously and separately estimated using a logistic regression model where treatment was the dependent variable, that is, the model estimated the probability of being on tofacitinib; the confounders were baseline clinical and treatment characteristics, including baseline values of time since RA diagnosis, prior number of TNFi/bDMARDs, DAS28-ESR, CDAI, and tender/swollen joint counts. Estimated odds ratios for the exposure effect (tofacitinib vs. TNFi) were calculated along with associated 95% confidence intervals (CIs).

For time to discontinuation analyses, crude and adjusted survival curves were calculated. Crude survival estimates were presented graphically using Kaplan–Meier survival curves, whereas the adjusted survival curves were estimated by a Cox regression model and adjusted for treatment group, age, sex, previous bDMARD use, previous csDMARD use, baseline DAS28-ESR score, baseline WPAI-RA, and comorbidity (Charlson Comorbidity Index score).

3 | Results

3.1 | Patients

In total, 267 eligible patients were enrolled from 7 sites and were included in the full analysis set; of these, 145 received tofacitinib (mostly tofacitinib 5 mg twice daily) and 122 received TNFi (Figure 1). Overall, 221 patients completed the study (82.8%; tofacitinib, $N = 119$; TNFi, $N = 102$), and 46 patients (17.2%) discontinued from the study, because of withdrawal by the patient

TABLE 1 | Demographics and baseline disease characteristics (full analysis set).

	Tofacitinib (*N* = 145)	TNFi (*N* = 122)	*p*
Age (years), mean (SD)	55.4 (12.1)	55.1 (13.4)	0.8059
≥ 65 years, *n* (%)	33 (22.8)	30 (24.6)	0.7255
Female, *n* (%)	124 (85.5)	101 (82.8)	0.5416
Height, cm, mean (SD)	158.4 (7.4)	158.7 (7.5)	0.7196
Weight, kg, mean (SD)	58.8 (12.0)	59.3 (13.8)	0.8051
Smoking status, *n* (%)			0.4287
Never	111 (76.6)	83 (68.0)	
Former	5 (3.4)	6 (4.9)	
Current	4 (2.8)	3 (2.5)	
Time since RA diagnosis (years), mean (SD)[a]	8.0 (9.7)	5.4 (6.7)	0.0212
Pre-specified medical conditions, *n* (%)[b]			
Hypertension	32 (22.1)	33 (27.0)	0.3469
Hyperlipidemia	24 (16.6)	15 (12.3)	0.3206
Diabetes mellitus	12 (8.3)	19 (15.6)	0.0682
Hepatitis B	17 (11.7)	11 (9.0)	0.4671
Renal insufficiency	12 (8.3)	8 (6.6)	0.5916
Herpes zoster	12 (8.3)	2 (1.6)	0.0095
Number of prior bDMARDs, *n* (%)[a]			< 0.0001
0	95 (65.5)	116 (95.1)	
1	34 (23.4)	6 (4.9)	
≥ 2	16 (11.0)	0	
Number of prior TNFi, *n* (%)[a]			< 0.0001
0	102 (70.3)	120 (98.4)	
1	35 (24.1)	2 (1.6)	
≥ 2	8 (5.5)	0	
Prior bDMARD therapy, *n* (%) [average duration of use, years]			
Adalimumab	20 (13.8) [1.8]	2 (1.6) [2.6]	< 0.0001
Etanercept	21 (14.5) [4.1]	0	< 0.0001
Golimumab	10 (6.9) [1.6]	0	0.0010
Tocilizumab	9 (6.2) [0.5]	1 (0.8) [3.6]	0.0128
Abatacept	6 (4.1) [1.3]	3 (2.5) [0.4]	0.4388
Rituximab	6 (4.1) [3.4]	0	0.0124
Prior csDMARD therapy, *n* (%) [average duration of use, years]			
Methotrexate	131 (90.3) [3.7]	110 (90.2) [3.1]	0.9604
Hydroxychloroquine	112 (77.2) [3.4]	101 (82.8) [3.0]	0.2557
Sulfasalazine	95 (65.5) [3.9]	70 (57.4) [3.7]	0.1726
Leflunomide	51 (35.2) [2.3]	37 (30.3) [2.0]	0.3994
Cyclosporine	21 (14.5) [2.4]	11 (9.0) [1.4]	0.1618

(Continues)

TABLE 1 | (Continued)

	Tofacitinib (*N* = 145)	TNFi (*N* = 122)	*p*
Azathioprine	5 (3.4) [2.2]	8 (6.6) [2.6]	0.2504
Cyclophosphamide	1 (0.7) [3.5]	3 (2.5) [1.0]	0.2572
Chloroquine	3 (2.1) [7.1]	0	0.0801
Prior steroid therapy, *n* (%) [average duration of use, years]			
Prednisone	50 (34.5) [0.6]	42 (34.4) [0.6]	0.9923
Methylprednisolone	23 (15.9) [1.2]	11 (9.0) [0.3]	0.0863
Other	55 (37.9) [0.9]	51 (41.8) [1.0]	0.5197
Concomitant csDMARD therapy, *n* (%)			
Methotrexate	104 (71.7)	95 (77.9)	0.2465
Hydroxychloroquine	81 (55.9)	78 (63.9)	0.1779
Sulfasalazine	54 (37.2)	50 (41.0)	0.5325
Leflunomide	34 (23.4)	28 (23.0)	0.9236
Cyclosporine	8 (5.5)	9 (7.4)	0.5397
Azathioprine	1 (0.7)	5 (4.1)	0.0761
Concomitant bDMARD therapy, *n* (%)			
Adalimumab	0	0	—
Etanercept	0	0	—
Golimumab	0	0	—
Tocilizumab	11 (7.6)	11 (9.0)	0.6740
Abatacept	5 (3.4)	6 (4.9)	0.5527
Rituximab	5 (3.4)	4 (3.3)	0.9389
Concomitant steroid therapy, *n* (%)			
Prednisone	27 (18.6)	19 (15.6)	0.5084
Methylprednisolone	29 (20.0)	17 (13.9)	0.1842
Prednisolone	77 (53.1)	70 (57.4)	0.4836
DAS28-ESR, mean (SD)[a]	5.6 (1.3)	6.1 (1.1)	0.0049
CDAI, mean (SD)[a]	28.8 (12.6)	34.1 (12.0)	0.0009
HAQ-DI, mean (SD)[c]	1.0 (0.8)	1.0 (0.8)	0.7148
Tender joint count, mean (SD)[a]	11.1 (6.7)	13.5 (6.9)	0.0046
Swollen joint count, mean (SD)[a]	5.8 (4.3)	7.1 (4.3)	0.0152
Baseline WPAI-RA			
Currently employed, yes, *n* (%)	64 (44.1)	52 (42.6)	0.8035
Percent work time missed due to RA, mean (SD)	5.7 (17.3)	2.9 (7.0)	0.2703
Percent overall work impairment due to RA, mean (SD)	43.4 (27.5)	46.4 (28.2)	0.5857
Percent impairment while working due to RA, mean (SD)	42.0 (25.7)	44.5 (27.5)	0.6271
Percent activity impairment due to RA, mean (SD)	49.7 (23.6)	50.4 (25.2)	0.8005

Note: N may vary for each outcome.
Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-ESR, Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; *N*, total number of patients in the analysis; *n*, number of patients with each demographic/disease characteristic; PS, propensity scores; RA, rheumatoid arthritis; SD, standard deviation; TNFi, tumor necrosis factor inhibitor; WPAI-RA, Work Productivity and Activity Impairment-Rheumatoid Arthritis.
[a]Included as confounders to generate the PS.
[b]Reported by > 5% of overall study patients at baseline.
[c]Baseline HAQ-DI was included as an independent variable in the mixed logistic regression. model for the change from baseline in HAQ-DI outcome.

($n = 27$; 10.1%), being lost to follow-up ($n = 11$; 4.1%), death ($n = 6$; 2.2%), or other reasons ($n = 2$; 0.7%) (Figure 1). The effectiveness analysis set included 242 patients (tofacitinib, $n = 134$; TNFi, $n = 108$).

In general, baseline demographics were similar between groups (Table 1). Overall, most patients were female ($n = 225$; 84.3%), never smokers ($n = 194$; 72.7%), and had not received prior bDMARDs ($n = 211$; 79.0%) or TNFi ($n = 222$; 83.1%). However, significant differences between groups were reported for some baseline disease characteristics, including time since RA diagnosis, number of prior bDMARDs, number of prior TNFi, and baseline CDAI (Table 1).

Pre-specified comorbidities of interest reported by > 5% of overall study patients at baseline included: hypertension ($n = 65$; 24.3%); hyperlipidemia ($n = 39$; 14.6%); diabetes mellitus ($n = 31$; 11.6%); hepatitis B ($n = 28$; 10.5%); renal insufficiency ($n = 20$; 7.5%); and herpes zoster ($n = 14$; 5.2%) (Table 1).

3.2 | Effectiveness

Mean DAS28-ESR, CDAI, and HAQ-DI scores showed improvement from baseline over time with tofacitinib and TNFi by Week 24, with improvements maintained through Week 192 (Figure 2A–C). The proportion of patients achieving DAS28-ESR LDA (< 3.2) at Week 24 and Week 48, respectively, was 20.9% ($n = 28$) and 22.4% ($n = 30$) in the tofacitinib group, and 17.6% ($n = 19$) and 18.5% ($n = 20$) in the TNFi group. DAS28-ESR remission (< 2.6) was achieved by 11.2% ($n = 15$) and 9.0% ($n = 12$) of patients in the tofacitinib group compared with 7.4% ($n = 8$) and 3.7% ($n = 4$) of patients in the TNFi group, at Week 24 and Week 48, respectively.

At Week 24 and Week 48, respectively, CDAI-defined LDA (≤ 10) was achieved by 32.1% ($n = 43$) and 35.1% ($n = 47$) of patients in the tofacitinib group, and by 20.4% ($n = 22$) and 36.1% ($n = 39$) of patients in the TNFi group. CDAI remission (≤ 2.8) was observed for 3.7% ($n = 5$) of patients receiving tofacitinib at Week 24, and for 4.5% ($n = 6$) of patients receiving tofacitinib and 1.9% ($n = 2$) of patients receiving TNFi at Week 48.

Improvement in HAQ-DI (i.e., no increase in score from baseline) was shown by 70.9% ($n = 95$) of tofacitinib initiators and 68.5% ($n = 74$) of TNFi initiators.

At baseline, similar proportions of patients in each treatment group were in current employment (i.e., working for pay): tofacitinib, 44.0% ($n = 59$); and TNFi, 42.6% ($n = 46$). For these patients, percent WPAI-RA work time missed due to RA remained generally consistent throughout the study (Figure 2D).

For the WPAI-RA outcomes of percent impairment while working due to RA, percent overall work impairment due to RA, and percent activity impairment due to RA, improvements were observed at Week 24 and were generally maintained over time with both tofacitinib and TNFi (Figure 2E–G).

From the results of the mixed logistic regression model, which compared differences in effectiveness outcomes between groups across all visits, no significant differences in the effectiveness outcomes for tofacitinib versus TNFi before or after PS adjustment were observed (Figure 3).

3.3 | Safety, Persistence, and Adherence

Overall, 82 (56.6%) and 68 (55.7%) patients in the tofacitinib and TNFi groups, respectively, reported at least one AE. Rates of SAEs and deaths were similar in both treatment groups (Table 2).

Infections and infestations, respiratory, thoracic, and mediastinal disorders, musculoskeletal and connective tissue disorders, and gastrointestinal disorders were the most commonly reported AEs by System Organ Class (SOC), and these were reported more frequently with tofacitinib than with TNFi (Table 2). Most AEs were mild or moderate in severity.

In both groups, the most frequently reported SAE by SOC was infections and infestations (Table 2). A higher proportion of patients in the tofacitinib group reported SAEs of infections and infestations than in the TNFi group (13.8% [$n = 20$] vs. 9.0% [$n = 11$], respectively). In both the tofacitinib and TNFi groups, respectively, the most common SAEs by Preferred Term were pneumonia (2.1% [$n = 3$] and 1.6% [$n = 2$]), herpes zoster (2.8% [$n = 4$] and 0%), and urinary tract infections (1.4% [$n = 2$] and 1.6% [$n = 2$]).

In terms of AEs of special interest, serious infections occurred more frequently with tofacitinib than TNFi (13.1% [$n = 19$] vs. 8.2% [$n = 10$], respectively). Similarly, more patients reported herpes zoster with tofacitinib than TNFi (12.4% [$n = 18$] vs. 3.3% [$n = 4$], respectively). Malignancies were reported for 2.1% ($n = 3$) of patients receiving tofacitinib (breast cancer, hepatocellular carcinoma, and renal cell carcinoma; $n = 1$ each) and 0.8% ($n = 1$) of patients receiving TNFi (gastric cancer). No MACE or venous thromboembolism events were reported in the tofacitinib group. MACE (non-fatal) was reported for 0.8% ($n = 1$) of patients in the TNFi group (Table 2).

Persistence and adherence to treatment were comparable in patients receiving tofacitinib versus TNFi (Table 2). Mean persistence (SD) was 996.2 (498.3) and 986.0 (537.2) days, and adherence, assessed as mean proportion of days covered, was 80.5% and 78.4% with tofacitinib and TNFi, respectively.

Overall, 31.0% ($n = 45$) of patients receiving tofacitinib and 33.6% ($n = 41$) of patients receiving TNFi discontinued or switched treatment. From the survival curves (Figure 4), the mean time to treatment discontinuation or switch was 17.4 months with tofacitinib users and 16.7 months with TNFi. The hazard ratio for treatment discontinuation or switch was 0.89 (95% CI 0.54, 1.44) for tofacitinib versus TNFi.

In the full analysis set, dose change or interruption was more frequent in patients receiving tofacitinib compared with TNFi (77.9% [$n = 113$] and 49.2% [$n = 60$], respectively). Reasons for dose change or interruption in patients receiving tofacitinib and TNFi included AEs (21.4% [$n = 31$] and 14.8% [$n = 18$] of the full analysis set, respectively), NHI requirements (15.9% [$n = 23$] and

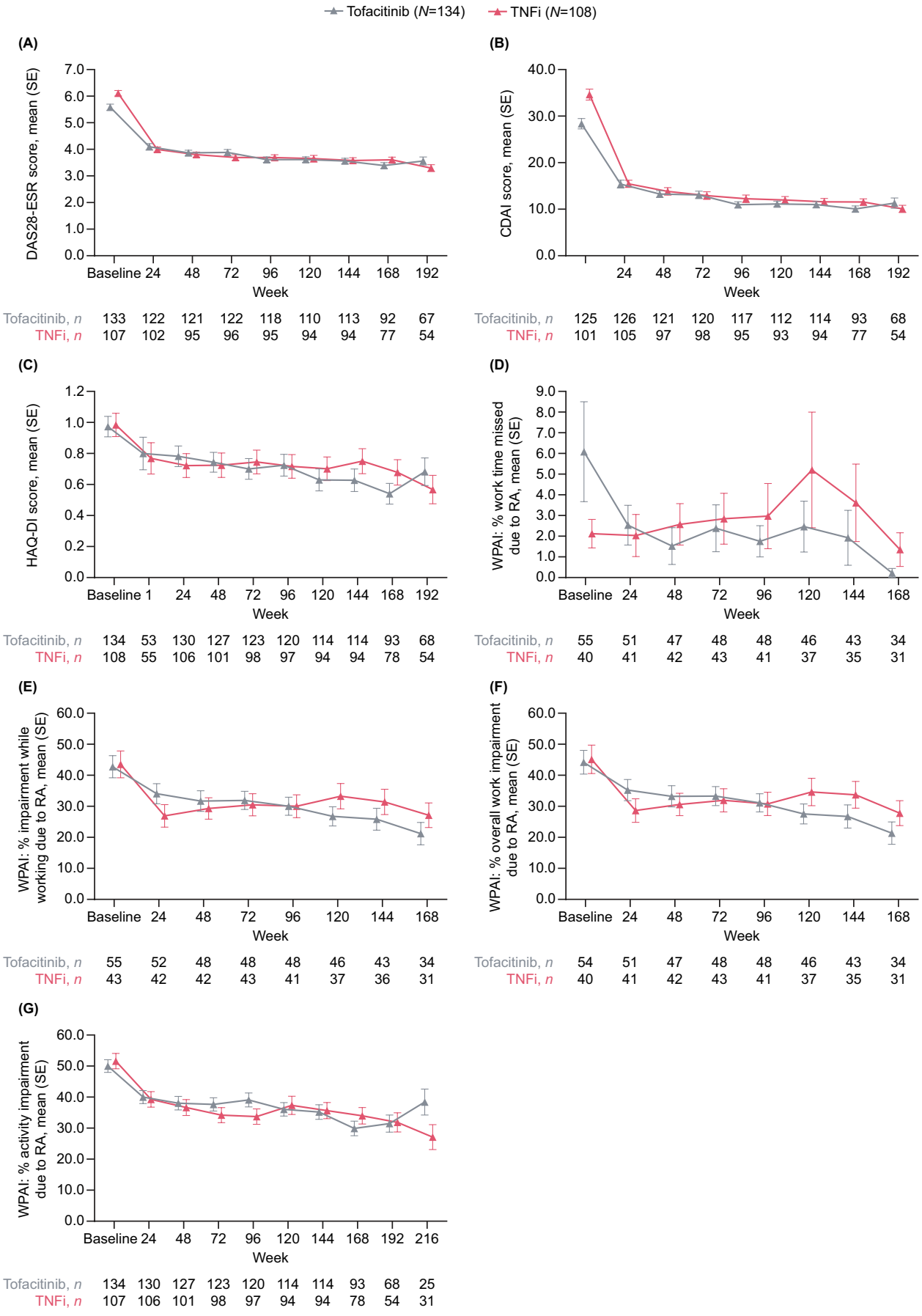

FIGURE 2 | Legend on next page.

FIGURE 2 | Mean (SE) DAS28-ESR (A), CDAI (B), and HAQ-DI (C) scores over time with tofacitinib and TNFi; and percent WPAI-RA work time missed (D), impairment while working (E), overall work impairment (F), and activity impairment (G), due to RA, in patients in current employment at baseline (effectiveness analysis set). Results for DAS28-ESR, CDAI, and HAQ-DI are shown for time points at which data were available for ≥53 patients per treatment group. Results for WPAI-RA outcomes are shown for time points at which data were available for ≥25 patients per treatment group. CDAI, Clinical Disease Activity Index; DAS28-ESR, Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; *N*, number of patients in analysis set; *n*, number of evaluable patients; SE, standard error; TNFi, tumor necrosis factor inhibitor; WPAI-RA, Work Productivity and Activity Impairment-Rheumatoid Arthritis.

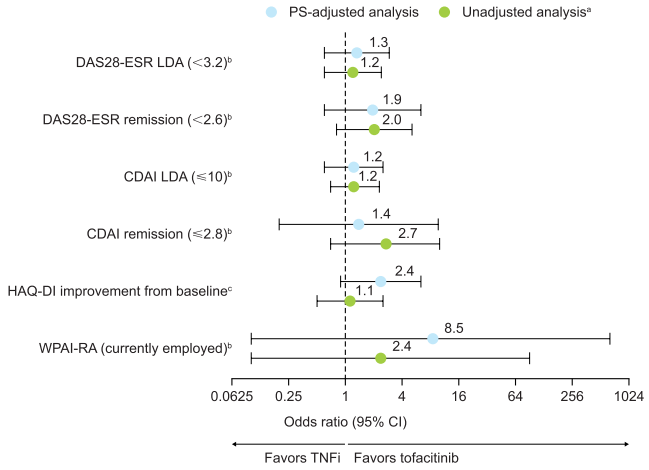

FIGURE 3 | Odds ratios for effectiveness outcomes across all visits (effectiveness analysis set). [a]Crude odds ratio and the corresponding 95% CI were generated by the original model and excluded PS. [b]PS-adjusted analysis includes treatment group, visit, and PS as covariates, and baseline clinical and treatment characteristics (Table 1) as confounders. [c]PS-adjusted analysis includes treatment group, visit, baseline HAQ-DI score, and PS as covariates, and baseline clinical and treatment characteristics (Table 1) as confounders. CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28-ESR, Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; PS, propensity scores; TNFi, tumor necrosis factor inhibitor; WPAI-RA, Work Productivity and Activity Impairment-Rheumatoid Arthritis.

13.1% [*n* = 16], respectively), lack of efficacy (12.4% [*n* = 18] and 9.0% [*n* = 11], respectively), and other reasons (59.3% [*n* = 86] and 28.7% [*n* = 35], respectively). Of the 86 tofacitinib users changing dose due to other reasons, 36 switched to tofacitinib extended release 11 mg once daily (Table 2).

3.4 | Clinical and Patient-Reported Outcomes Following Tofacitinib or TNFi Dose Reduction or Weaning Off

In patients who underwent a dose reduction or weaning off of tofacitinib (*N* = 24) or TNFi (*N* = 16) (dose reduction analysis set), disability and disease activity were generally higher at the time of dose reduction with TNFi than with tofacitinib on the basis of mean HAQ-DI, CDAI, and DAS28-ESR scores, and percent overall work impairment.

HAQ-DI scores were increased at 4 and 12 weeks post-dose reduction in 27.3% (*n/N*: 6/22) and 40.9% (*n/N*: 9/22) of patients, respectively, in the tofacitinib group with dose reduction, and in 38.5% (*n/N*: 5/13) and 46.2% (*n/N*: 6/13) of patients, respectively, in the TNFi group with dose reduction. RA disease activity was increased post dose-reduction for both groups. The proportions of patients with CDAI score > 10 at time of dose reduction, and 4 and 12 weeks post-dose reduction, respectively, were 25.0% (*n/N*: 6/24), 36.4% (*n/N*: 8/22), and 45.5% (*n/N*: 10/22) for tofacitinib, and 43.8% (*n/N*: 7/16), 46.2% (*n/N*: 6/13), and 53.8% (*n/N*: 7/13) for TNFi. For DAS28-ESR, the proportions with score ≥3.2 at the corresponding time points were: 25.0% (*n/N*: 6/24), 38.1% (*n/N*: 8/21), and 50.0% (*n/N*: 11/22) for tofacitinib, and 37.5% (*n/N*: 6/16), 53.8% (*n/N*: 7/13), and 66.7% (*n/N*: 8/12) for TNFi.

The percentage of patients employed was stable over time (for tofacitinib 33.3%, 31.8%, and 36.4%; for TNFi 43.8%, 46.2%, and 46.2%, at time of dose reduction, and at 4 and 12 weeks post-dose reduction, respectively). The percentage work impairment increased slightly from the time of dose reduction to 4 and 12 weeks post-dose reduction in both groups, but the overall increase was greater in the TNFi group (24.3%, 28.3%, and 30.0%) than in the tofacitinib group (15.0%, 22.0%, and 17.5%).

4 | Discussion

This cohort study demonstrated that the long-term effectiveness and persistence of and adherence to tofacitinib and TNFi were generally similar in Taiwanese patients with RA.

Demographic and disease characteristics of patients enrolled in the study were generally similar between treatment groups; however, some significant differences between groups were noted, including the time since RA diagnosis (longer in patients receiving tofacitinib than TNFi), higher CDAI and DAS28-ESR scores in the TNFi group, and a number of prior bDMARDs and TNFi (higher in patients receiving tofacitinib than TNFi). This is reflective of Taiwan's NHI reimbursement policy, which states that patients with RA who demonstrate a poor response to bDMARD treatment should switch to another bDMARD with an alternative mode of action or to tofacitinib [16]. In addition, compared with the TNFi group, a higher proportion of patients in the tofacitinib group had a medical history of herpes zoster, which may be due to the non-random assignment of the tofacitinib and TNFi groups.

The effectiveness of tofacitinib and TNFi (assessed using HAQ-DI, DAS28-ESR, CDAI, and WPAI-RA) over time was similar in this study, and no significant differences in the effectiveness outcomes for tofacitinib versus TNFi before or after PS adjustment were observed. These effectiveness results are generally consistent with the findings of previous randomized controlled trials of tofacitinib

TABLE 2 | Safety summary (safety analysis set), and persistence, adherence, and dose changes (full analysis set).

	Tofacitinib (*N* = 145)	TNFi (*N* = 122)
Safety		
Patients with ≥ 1 AE, *n* (%)	82 (56.6)	68 (55.7)
Patients with ≥ 1 SAE,[a] *n* (%)	29 (20.0)	26 (21.3)
Deaths, *n* (%)	2 (1.4)	4 (3.3)
Most frequently reported AEs[a] (≥ 5% in any treatment group) by MedDRA SOC, *n* (%)		
Infections and infestations	52 (35.9)	37 (30.3)
Respiratory, thoracic, and mediastinal disorders	24 (16.6)	12 (9.8)
Musculoskeletal and connective tissue disorders	23 (15.9)	15 (12.3)
Gastrointestinal disorders	21 (14.5)	9 (7.4)
General disorders and administration site conditions	12 (8.3)	8 (6.6)
Nervous system disorders	14 (9.7)	11 (9.0)
Injury, poisoning, and procedural complications	11 (7.6)	8 (6.6)
Investigations	10 (6.9)	7 (5.7)
Metabolism and nutrition disorders	9 (6.2)	4 (3.3)
Skin and subcutaneous disorders	9 (6.2)	12 (9.8)
Most frequently reported SAEs[a] (≥ 2.5% in any treatment group) by MedDRA SOC, *n* (%)		
Infections and infestations	20 (13.8)	11 (9.0)
Respiratory, thoracic, and mediastinal disorders	5 (3.4)	2 (1.6)
Musculoskeletal and connective tissue disorders	5 (3.4)	4 (3.3)
Nervous system disorders	3 (2.1)	3 (2.5)
AEs of special interest, *n* (%)		
Serious infections[b]	19 (13.1)	10 (8.2)
Herpes zoster (non-serious and serious)	18 (12.4)	4 (3.3)
Tumor/malignancy	3 (2.1)	1 (0.8)
Breast cancer	1 (0.7)	0 (0.0)
Gastric cancer	0 (0.0)	1 (0.8)
Hepatocellular carcinoma	1 (0.7)	0 (0.0)
Renal cell carcinoma	1 (0.7)	0 (0.0)
MACE[c]	0	1 (0.8)
Venous thromboembolism	0	0
Persistence, adherence and dose changes		
Persistence (days), mean (SD)	996.2 (498.3)	986.0 (537.2)
Proportion of days covered (%), mean (SD)	80.5 (30.3)	78.4 (33.2)
Proportion of days covered ≥ 0.8, *n* (%)	103 (71.0)	87 (71.3)
Patients remaining on therapy, *n* (%)		
End of Year 1	117 (80.7)	96 (78.7)

(Continues)

TABLE 2 | (Continued)

	Tofacitinib ($N=145$)	TNFi ($N=122$)
End of Year 2	104 (71.7)	80 (65.6)
End of Year 3	79 (54.5)	70 (57.4)
Dose changed/interrupted,[d] *n* (%)	113 (77.9)	60 (49.2)
Reasons for changed/interrupted dose, *n* (%)		
AE	31 (21.4)	18 (14.8)
NHI requirements[e]	23 (15.9)	16 (13.1)
Lack of efficacy	18 (12.4)	11 (9.0)
Other[f]	86 (59.3)	35 (28.7)

Abbreviations: AE, adverse event; DAS28-ESR, Disease Activity Score in 28 joints, erythrocyte sedimentation rate; MACE, major adverse cardiovascular events; MedDRA, Medical Dictionary for Regulatory Activities; *N*, total number of patients in the analysis; *n*, number of patients having an event or with characteristic of interest; NHI, National Health Insurance; SAE, serious adverse event; SD, standard deviation; SOC, System Organ Class; TNFi, tumor necrosis factor inhibitor.
[a]An SAE is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, results in persistent or significant disability or incapacity, or results in congenital anomaly or birth defect.
[b]Requiring hospitalization or parenteral antibiotics.
[c]MACE includes non-fatal events of myocardial infarction, stroke, transient ischemic attack, cardiovascular-related deaths due to myocardial infarction, congestive heart failure, arrhythmia, sudden cardiac death, pulmonary embolism, stroke/cerebrovascular accident, and other cardiovascular-related deaths.
[d]The reasons for dose(s) changed or interrupted were summarized only for index treatment. For patients who had more than one reason of dose change or interrupted, patients were counted once for each type of reason.
[e]A weaning off policy of advanced therapy was introduced in the treatment guideline for rheumatoid arthritis since 2014 under the NHI in Taiwan, which requested that patients achieving low disease activity (DAS28-ESR ≤ 3.2, ESR ≤ 25 mm/h, and C-reactive protein ≤ 1 mg/dL) after 24 months of treatment have a reduction in dose of tofacitinib or TNFi and discontinued in the following 12 months. In 2019, the policy was updated to mandate a reduction in dose when a patient had been treated with an advanced therapy for 24 months and had achieved remission (DAS28-ESR < 2.6) for > 6 months.
[f]A total of 36 tofacitinib users with dose change due to other reasons switched to tofacitinib extended release 11 mg once daily.

versus TNFi. In the 12 month Phase 3b/4 ORAL Strategy study, tofacitinib in combination with methotrexate was non-inferior to the TNFi adalimumab plus methotrexate [17]. Similarly, in the 12 month, Phase 3 ORAL Standard trial, the efficacy of tofacitinib was similar to adalimumab [13]. More recently, in the post-authorization safety study, ORAL Surveillance, which compared tofacitinib and TNFi in a cardiovascular risk-enriched population, similar efficacy (evaluated as secondary outcomes) was reported between treatments [18].

Moreover, the similar effectiveness of tofacitinib and TNFi shown in our study is consistent with the findings of other real-world studies. Pappas et al. used United States registry data to evaluate the effectiveness of TNFi versus non-TNFi (including tofacitinib) in patients with RA initiating treatment following csDMARDs. No significant differences were noted in the achievement of efficacy outcomes (including CDAI LDA and remission and modified DAS28 remission) after 12 months of treatment [19]. Likewise, comparable effectiveness between tofacitinib and bDMARDs was shown in an Australian retrospective cohort study in patients with RA in real-world settings [20].

Overall, similar proportions of patients experienced AEs and SAEs with tofacitinib and TNFi in this study. The most commonly reported AEs and SAEs with tofacitinib were infections and infestations. These included herpes zoster, which occurred at a numerically higher frequency with tofacitinib (12.4%, non-serious and serious; 2.8%, serious) than with TNFi (3.3%, all non-serious). This finding is consistent with the known safety profile of tofacitinib in RA [21]. Herpes zoster vaccine was not routinely used in Taiwan at the time of the study, and none of the patients in the study were vaccinated against herpes zoster at baseline.

Findings from ORAL Surveillance, a post-authorization safety study, showed that risks of MACE and malignancies were higher with tofacitinib than with TNFi in patients with RA who were cardiovascular risk-enriched [18]. In our study, four malignancy events were reported (tofacitinib, $n=3$; TNFi, $n=1$). No MACE was reported in the tofacitinib group, and one non-fatal MACE was reported in the TNFi group.

Persistence and adherence in our study were comparable for patients initiating tofacitinib or TNFi. Several other real-world studies have evaluated the persistence of tofacitinib and bDMARDs/TNFi in patients with RA. Similar persistence between tofacitinib and bDMARDs was shown in the real-world cohort study in Australia versus bDMARDs [20]. In contrast, in a retrospective longitudinal study in Taiwan, drug survival with tofacitinib and other non-TNFi was higher than with etanercept (TNFi) [16]. Similarly, an observational cohort study using Swiss registry data demonstrated higher drug maintenance with tofacitinib than with TNFi [22].

In patients who underwent a dose reduction or weaning off of treatment in our study due to meeting LDA criteria, disability and disease activity were generally higher with TNFi than with tofacitinib at the time of dose reduction. At 4 and 12 weeks post-dose reduction, more patients in the TNFi group had increases in HAQ-DI score, and CDAI scores > 10 or DAS28-ESR scores ≥ 3.2, compared with the tofacitinib group. However, it should be noted that the sample size for these analyses was small, as few patients underwent a dose reduction or weaning off.

Limitations of this observational cohort study that should be considered when interpreting these findings include the small

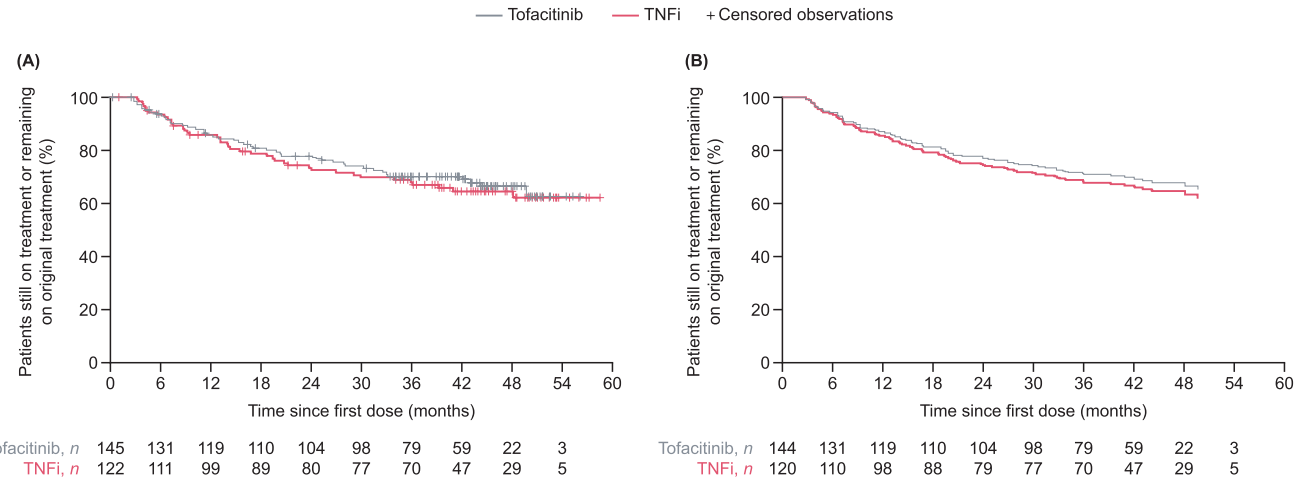

FIGURE 4 | Survival curves for time to discontinuation or switch to tofacitinib or TNFi: (A) crude[a] and (B) adjusted[b] (full analysis set). [a]The crude survival curve for time to discontinuation or switch with tofacitinib or TNFi is shown using the Kaplan–Meier estimate. [b]The adjusted survival curve is estimated by a Cox regression model, adjusting for treatment group, age, sex, previous bDMARD use, previous csDMARD use, baseline DAS28-ESR, baseline WPAI-RA, and comorbidity (Charlson Comorbidity Index score). bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-ESR, Disease Activity Score in 28 joints, erythrocyte sedimentation rate; TNFi, tumor necrosis factor inhibitor; WPAI-RA, Work Productivity and Activity Impairment-Rheumatoid Arthritis.

sample size that limited the statistical power to detect potential differences in the effectiveness of treatment with tofacitinib compared with TNFi. Therefore, future studies would benefit from collaboration across more centers to increase the sample size. In addition, the observational, non-randomized nature of the study means that residual confounding could not be ruled out for between-group comparisons. The effectiveness of tofacitinib and TNFi was assessed using patient- and physician-reported outcomes; therefore, these may be subject to information bias. Furthermore, data for treatment duration and treatment exposure were not available, which limits the interpretation of the safety results, including treatment group comparisons and risk of long-latency events such as MACE and malignancy. The criteria for dose reduction or weaning were based on an LDA definition that has since been updated to DAS28-ESR remission in the Taiwan NHI reimbursement guidelines, and this may be considered a limitation of the study findings. Also, some information on baseline demographic and disease characteristics, such as steroid dose and lifestyle characteristics (e.g., diet and exercise), was not collected, and may have impacted the study findings.

5 | Conclusion

In this analysis of real-world data from Taiwan, the effectiveness, persistence, and adherence of tofacitinib and TNFi were generally similar in patients with RA. Safety outcomes were consistent with the known safety profiles of tofacitinib and TNFi, including higher rates of serious infections and herpes zoster events with tofacitinib than TNFi. The results of this analysis can inform treatment decisions in patients with RA in Taiwan.

Author Contributions

Study conceptualization/design: E.K. Data acquisition: S.-C.H., W.-S.C., J.-C.H., W.-Y.S., W.-C.T., H.-C.C., C.-M.H., and Y.-H.C. Data analysis: S.-C.H. and E.K. Data interpretation: S.-C.H., W.-S.C., J.-C.H., W.-Y.S., W.-C.T., H.-C.C., E.K., D.G., and Y.-H.C. All authors (S.-C.H., W.-S.C., J.-C.H., W.-Y.S., W.-C.T., H.-C.C., C.-M.H., E.K., D.G., and Y.-H.C.) contributed to the interpretation of the data, were involved in drafting the article or reviewing it critically for important intellectual content, and approved the final version to be submitted for publication.

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Conflicts of Interest

S.-C.H., W.-S.C., J.-C.H., W.-Y.S., and H.-C.C. have nothing to disclose. W.-C.T. has acted as a consultant for AbbVie, Novartis, Pfizer Inc., and Roche. C.-M.H. has acted as a consultant for AbbVie, Eli Lilly, and Pfizer Inc. E.K. was an employee of Pfizer Ltd. and stockholder of Pfizer Inc. at the time of the analysis. D.G. is an employee and stockholder of Pfizer Inc. Y.-H.C. has received grants and/or research support from AbbVie, Agnitio Science & Technology, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharma Taiwan, GlaxoSmithKline, Johnson & Johnson, MSD, National Yang-Ming University, Novartis, Pfizer Inc., Roche, Sanofi, Taichung Veterans General Hospital, Taiwan Department of Health and Welfare, Taiwan Ministry of Science and Technology, and UCB; has acted as a consultant for AbbVie, Astellas, AstraZeneca, Bristol Myers Squibb, Chugai Pharma Taiwan, Eli Lilly, GlaxoSmithKline, Inova Diagnostics, Johnson & Johnson, MSD, Novartis, Roche, Sanofi, Thermo Fisher Scientific, UCB, and United Biopharma; and has received other financial or material support from AbbVie,

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Data Availability Statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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EDITORIAL

Breakthrough Biologics: Charting the Course for Sjögren's Syndrome Treatment in 2024

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Sicca complex, characterized by dry eyes and mouth, is distinct from primary Sjögren's syndrome (pSS), which is associated with keratoconjunctivitis sicca and xerostomia as part of a broader autoimmune disease affecting multiple organs. This distinction is essential for accurate diagnosis and treatment planning, as pSS can significantly impact a patient's quality of life.

Sjögren's syndrome is classified into two types: primary and secondary. Primary Sjögren's syndrome occurs independently, while secondary Sjögren's syndrome is associated with other autoimmune conditions like systemic lupus erythematosus (SLE) or rheumatoid arthritis. Diagnosis of pSS requires fulfilling at least two of the following three criteria:

1. Positive serum anti-SSA and/or anti-SSB antibodies, or positive rheumatoid factor and antinuclear antibody titer greater than 1:320.
2. Ocular staining score exceeding 3.
3. Presence of focal lymphocytic sialadenitis with a focus score greater than 1 focus per 4 mm^2 in labial salivary gland biopsy samples [1].

It is important to note that pSS affects not only exocrine glands but also vital organs such as the lungs, kidneys, and blood cells. Currently, there is no gold standard treatment or universally effective drug for pSS, as various immune pathways and mechanisms are implicated in its progression, not all of which are directly associated with disease advancement.

A multicenter retrospective cohort study showed that comorbidities such as male sex, older age, interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), high European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI), thrombocytopenia, anemia, high IgA level, and glucocorticoid treatment instead of pSS related organ damage, were the main causes of death in Chinese patients. And hydroxychloroquine (HCQ) use might improve the long-term survival observed [2].

Research from Taiwan's National Health Insurance Research Database highlighted that patients diagnosed with SLE at least 1 year after being diagnosed with primary Sjögren's syndrome were identified as cases. HCQ has been used to treat patients with pSS and has shown potential in delaying the onset of SLE; however, its use in pSS patients appears to correlate with a lower likelihood of developing SLE in the future [3].

As of 2023, numerous clinical trials have been conducted to explore potential treatments for Sjögren's syndrome. Unfortunately, several clinical drug trials targeting pathways such as interferon (IFN), tumor necrosis factor (TNF) inhibitors, interleukin (IL)-1 receptor antagonists, IL-6 receptor inhibitors, and anti-ICOSL antibodies have either failed or been terminated. However, monoclonal antibodies targeting B-cell activating factor (BAFF), CD20, CD38, and IL-2 show promise, indicating that longer and larger sample trials may be necessary to achieve success [4].

For that reason, we have compiled a list of ongoing or completed clinical trials. The European Alliance of Associations for Rheumatology 2024 congress brought exciting updates on several clinical trials for Sjögren's syndrome (SjS) treatments, offering hope for patients with this challenging autoimmune disease.

TABLE 1 | Ongoing or completed clinical trials and drugs for Sjögren's syndrome.

Author and year	Drug	Study design	Sample size	Results
Gottenberg et al. (2024)	Nipocalimab	Phase 2 randomized, placebo-controlled	163	Significant improvement in ClinESSDAI score vs. placebo at 24 weeks ($p = 0.002$). 70% relative average improvement in primary endpoint for 15 mg/kg dose
Amgen (2023)	Dazodalibep	Phase 2 randomized, double-blind, placebo-controlled crossover	Not specified	Met primary endpoint in both patient groups (systemic disease and severe symptomatology) at Day 169
Fisher et al. (2024)	Iscalimab	Phase 2b dose-ranging	273 (173 in cohort 1, 100 in cohort 2)	Significant improvements in ESSDAI maintained at 48 weeks in cohort 1. Improvements in salivary flow rate and PROs in both cohorts
Baer et al. (2021)	Ianalumab	Phase 2b randomized, placebo-controlled	190	Statistically significant dose–response for ESSDAI score. Maximal ESSDAI score change from baseline in 300 mg group
Ongoing	Rituximab	Various ongoing studies	N/A	No clear evidence of efficacy in previous trials
Ongoing	Abatacept	Various ongoing studies	N/A	Results not reported in provided search results

Nipocalimab, an anti-neonatal Fc receptor monoclonal antibody, showed significant promise in the Phase 2 DAHLIAS study. The 15 mg/kg dose group demonstrated a statistically significant improvement in the primary endpoint of ClinESSDAI score at 24 weeks compared to placebo ($p = 0.002$). Patients receiving this dose experienced over 70% relative average improvement in the primary endpoint. Secondary endpoints, including organ assessments and physician evaluations, also showed clinically meaningful improvements [5]. Iscalimab, an anti-CD40 monoclonal antibody, continued to show positive results in its Phase 2b dose-ranging trial. At 48 weeks, all iscalimab doses demonstrated further improvements in ESSDAI, unstimulated salivary flow rate, and patient-reported outcomes. These improvements were maintained in patients who continued iscalimab treatment and improved in those who switched from placebo [6]. Dazodalibep, another promising agent, met its primary endpoint in both patient groups (systemic disease and severe symptomatology) at Day 169 in its Phase 2 trial. Amgen reported the first findings showing dazodalibep improved major biomarkers in Sjögren's disease [7]. Ianalumab, a BAFF-targeting antibody, is currently in Phase 3 trials and shows promise for becoming one of the first licensed treatments for Sjögren's disease. The 52-week safety and efficacy data indicated that the 300 mg dose group continued to provide clinical benefits [8]. However, not all trials yielded positive results. These developments represent significant progress in the search for effective Sjögren's syndrome treatments. The positive results from nipocalimab, iscalimab, dazodalibep, and ianalumab trials offer hope for patients who currently have limited treatment options. As research continues, these emerging therapies may lead to a paradigm shift in treating the underlying processes of Sjögren's syndrome, potentially improving the quality of life for millions of patients worldwide (Table 1).

In summary, it is important to focus on the ongoing clinical trials and the need for new drugs targeting autoantibodies in Sjögren's syndrome. The increasing number of clinical trials across various medical fields highlights the urgency of addressing this condition. Continued research is vital to improve treatment options and ultimately enhance the quality of life for those affected by this challenging autoimmune disease.

Author Contributions

T.-C.H. drafted the manuscript. J.C.-C.W. critically revised the manuscript. Both authors approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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LETTER TO THE EDITOR

Case Report: Steroid Responsive Pompe Like Inflammatory Myositis With Complete Recovery After Allogeneic HSCT

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Dear Editor,

Idiopathic inflammatory myositis (IIM) is a group of diseases characterized by muscle weakness due to immune-mediated muscle damage [1]. They are all diagnoses of exclusion; patients should be carefully evaluated for the presence of many conditions such as neurogenic, metabolic, endocrine disorders, malignancies, infectious diseases, and drug-associated myositis before diagnosis [2]. Here, we report a 27-year-old woman with chronic myeloproliferative neoplasm hospitalized for allogeneic hematopoietic stem cell transplantation (HSCT) who suffered from severe muscle weakness. She was successfully treated with corticosteroid and IVIG therapy despite having muscle biopsy findings that mimicked glycogen storage disease and underwent allogeneic HSCT.

A 27-year-old woman was evaluated for leukocytosis and abdominal pain. Contrast enhanced computed tomography revealed hepatosplenomegaly accompanied by multiple enlarged lymph nodes in the bilateral axillary and abdominal regions. Bone marrow biopsy demonstrated hypercellular marrow with features overlapping myeloproliferative and myelodysplastic morphology. Molecular analysis identified a CALR mutation, while JAK2 V617F, MPL W515L/K, and BCR-ABL1 (t[9;22]) were negative. Based on these findings, a diagnosis of myelodysplastic/myeloproliferative neoplasm (MDS/MPN) overlap syndrome was considered, and cytoreductive therapy with hydroxyurea was initiated. Hydroxyurea was discontinued in less than a month, and she was hospitalized for allogeneic HSCT. During this period (about 1 month), she developed progressive weakness starting in the upper limbs and extending to the lower limbs, ultimately resulting in an inability to walk. She reported that mild lower limb weakness had already begun around the time of HSCT admission, shortly before hydroxyurea discontinuation. Serum creatine kinase was measured for the first time during this clinical worsening and was found to be markedly elevated; baseline CK levels prior to hydroxyurea exposure were not available.

On admission, her vital signs were stable, and she was alert, oriented, and cooperative. Neurological examination revealed symmetric proximal muscle weakness (Medical Research Council grade: upper limbs 3/5, lower limbs 1/5), hypoactive deep tendon reflexes, and preserved sensation without fasciculations or muscle atrophy. Laboratory evaluation revealed severe anemia with a hemoglobin level of 6.5 g/dL (reference 11.9–14.6 g/dL), a white blood cell count of $4.9 \times 10^3/\mu L$, and a platelet count of $154 \times 10^3/\mu L$ (reference $170–390 \times 10^3/\mu L$). Serum enzyme levels were markedly elevated: creatine kinase (CK), 8323 U/L (reference < 145 U/L); creatine kinase–MB (CK-MB), 294 U/L (reference 0.6–6.3 U/L); lactate dehydrogenase (LDH), 1441 U/L (reference < 247 U/L); and aspartate aminotransferase (AST), 165 U/L (reference < 35 U/L), with normal renal function. Thyroid function tests and serum vitamin B12 levels were within normal limits. Autoimmune serology, including antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), rheumatoid factor (RF), anti cyclic citrullinated peptide (anti-CCP), and extractable nuclear antigen (ENA) antibodies, all negative except for anti–Scl-70 positivity, was evaluated. The myositis antibody

panel, including Mi-2α, Mi-2β, TIF1γ, MDA5, NXP2, SAE1, Ku, PmScl-100, Jo-1, SRP, PL-7, PL-12, EJ, OJ, and Ro-52, was also negative.

The patient developed dysphagia. This prompted the immediate start of pulse methylprednisolone (250 mg/day for 3 days) and intravenous immunoglobulin (400 mg/kg/day for 5 days), followed by oral methylprednisolone (40 mg/day). Magnetic resonance imaging (MRI) of the thighs revealed mild atrophy and intra and parafascial edema of the bilateral thigh and gluteal muscles, along with diffuse bone marrow signal alterations but without overt leukemic infiltration. Electromyography (EMG) showed short duration, low amplitude motor unit potentials and fibrillation potentials, consistent with active myopathic involvement. Shortly after treatment, a muscle biopsy was performed from the biceps brachii.

Muscle biopsy unexpectedly demonstrated polygonal fiber disarray, round atrophic fibers, scattered necrotic fibers, and subsarcolemmal vacuoles with PAS-positive glycogen and acid phosphatase reactivity, but no inflammatory infiltrates (Figure 1). These findings initially suggested a glycogen storage disease, such as Pompe disease. However, both α-glucosidase and chitotriosidase activities were within normal limits, and the lysosomal storage disorder screening panel was negative.

Because the biopsy suggested a possible glycogen storage disorder, targeted next-generation sequencing (NGS) for glycogen storage diseases was performed, but no pathogenic variants were identified. Whole exome sequencing (WES) was then initiated to further explore an immune mediated or secondary autophagic mechanism; however, the WES analysis is still in progress.

Her muscle strength improved noticeably within 2 weeks after treatment, her swallowing difficulty resolved, and her creatine kinase levels declined progressively (Figure 2). After a multidisciplinary discussion with hematologists and neurologists, her corticosteroid dose was gradually tapered according to the HSCT protocol, and she subsequently underwent allogeneic HSCT from an HLA-matched sibling donor. After HSCT, her laboratory values normalized, and she experienced complete and sustained recovery of muscle strength, with no recurrence of myopathic symptoms. At her most recent follow-up, she remained clinically stable and fully functional.

Here we reported a case with myositis who rapidly responded to immunosuppressive treatment despite having an uncontrolled malignancy and a muscle biopsy compatible with glycogen storage disease. After recovery of myositis, we were able to perform allogenic HSCT for her hematologic malignancy which also helped to control the activity of myositis.

At the beginning, we put our patient on steroid and IVIG treatment with preliminary diagnosis of malignancy or drug associated IIM. Though both hematologic malignancies and hydroxyurea have been reported as causes of myositis, to our

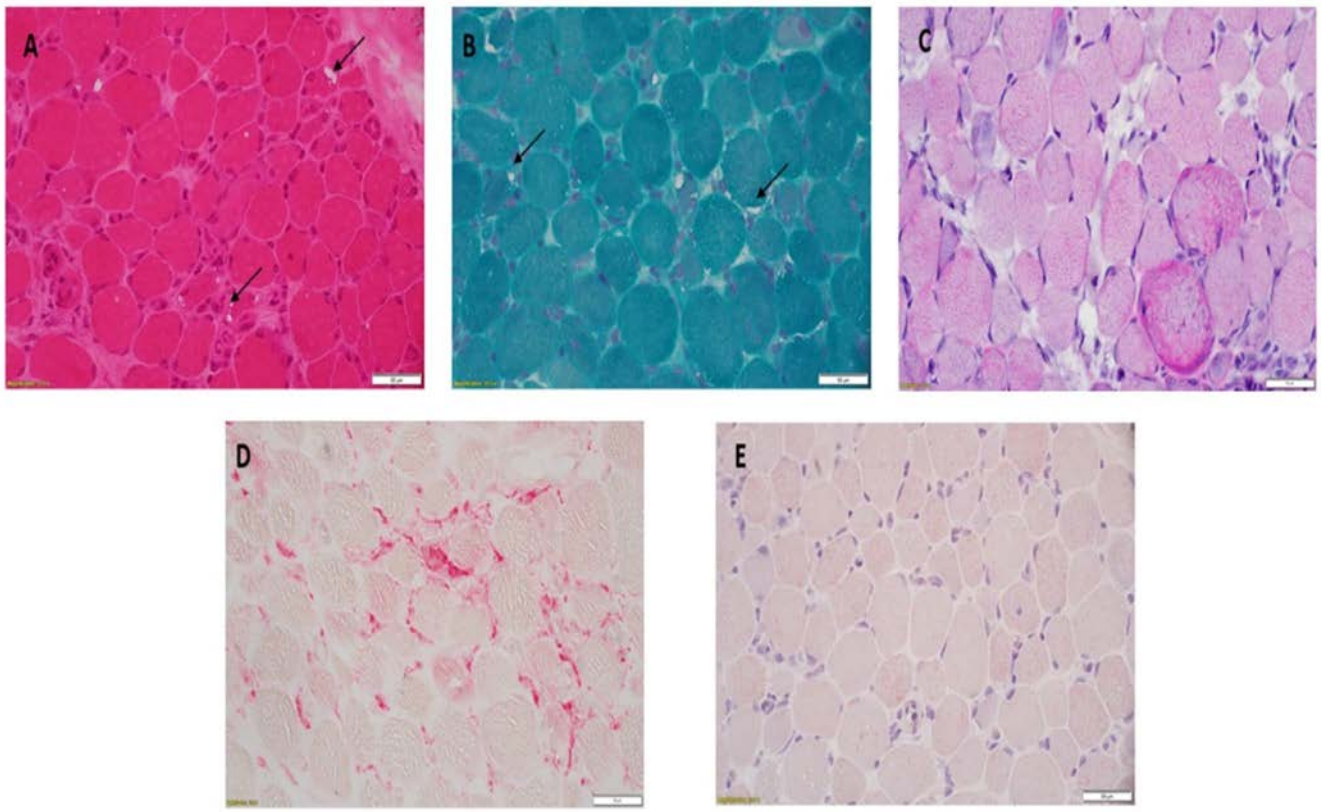

FIGURE 1 | Hematoxylin–eosin (A) and modified Gomori Trichrome (B) stainings of the left biceps brachii biopsy revealed variability in fiber size and the presence of vacuoles (vacuoles are shown by arrows). Periodic acid-Schiff (PAS) staining highlighted fibers with increased glycogen content (C). Additionally, acid phosphatase staining demonstrated heightened lysosomal activity (D). Oil-Red-O staining (E) revealed no evidence of lipid accumulation. All images were sourced from the Hacettepe University Neuromuscular Diseases Research Laboratory archive.

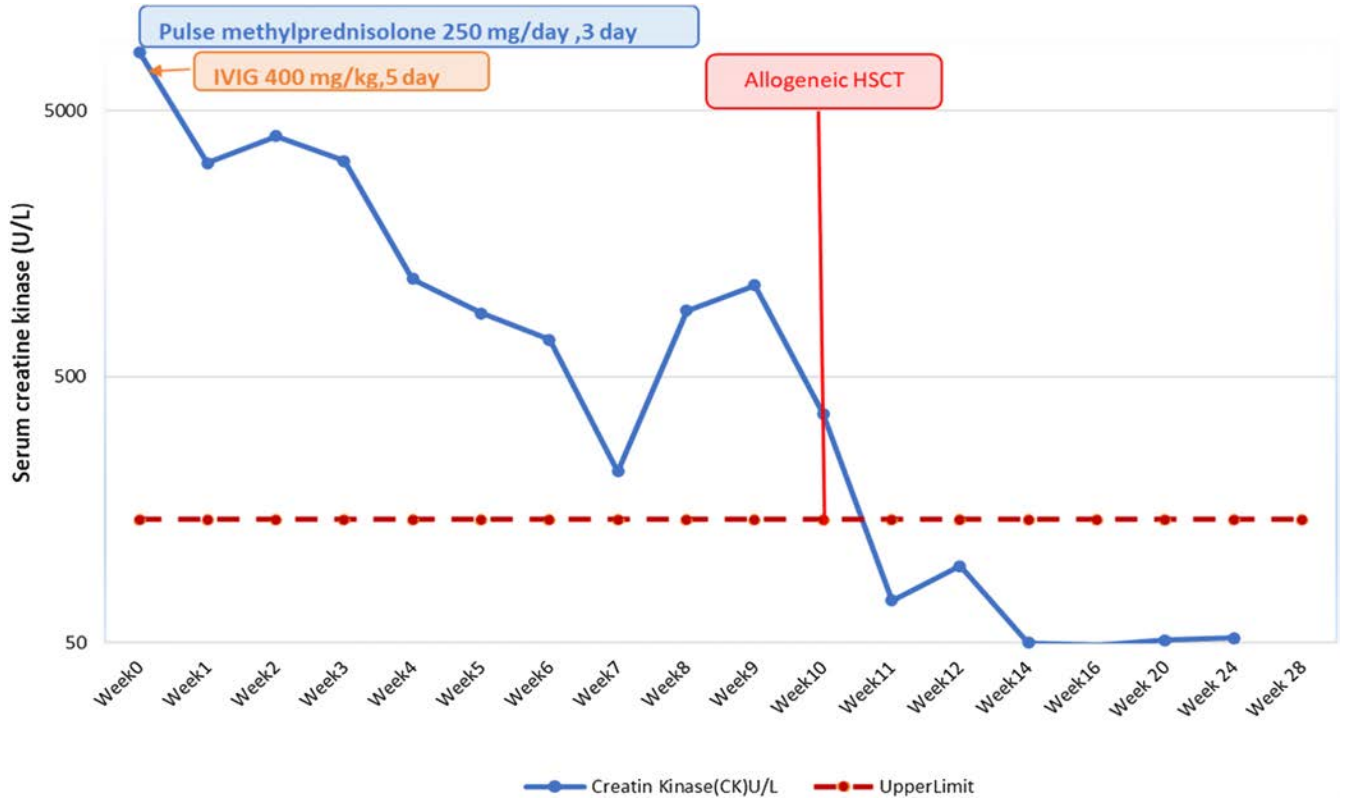

FIGURE 2 | Time course of serum CK levels after pulse steroids, IVIG, and allogeneic HSCT.

knowledge, there are no cases associated with MDS/MPN, and our patient was exposed to hydroxyurea for a very short period [3, 4]. In patients with myelodysplastic and myeloproliferative neoplasms, several mechanisms have been proposed to explain associated inflammatory or immune mediated myopathies, including dysregulated cytokine networks and immune cross reactivity driven by the underlying clonal hematopoietic disorder. Cancer related myopathies are thought to occur when the immune system reacts to antigens that are shared by tumor cells and regenerating muscle fibers [5]. Although we cannot demonstrate this mechanism clearly in our case, a very good response to immunosuppressive treatment supports immune-mediated muscle damage. In our patient, anti–Scl-70 antibody positivity also raised the possibility of a systemic sclerosis (SSc) related or overlap syndrome. However, she did not have clinical findings suggestive of SSc, such as Raynaud's phenomenon, skin thickening, gastrointestinal involvement, or abnormal nailfold capillaroscopy. In the absence of supportive clinical features, we did not consider an overlap connective tissue disease diagnosis to be likely. Therefore, anti–Scl-70 positivity was considered an isolated serological finding and was not supported by clinical features of an overlap syndrome. The muscle biopsy result surprised us, demonstrating subsarcolemmal vacuoles with PAS positive glycogen and acid phosphatase activity, which strongly resembled a glycogen storage disorder. She did not have a family history of myositis and blood enzyme levels were in normal range that made a primary metabolic defect such as Pompe disease unlikely. We decided to continue treatment with a diagnosis of immune-mediated myositis. Similar observations have been reported in vacuolar myopathies where altered autophagy and secondary lysosomal activation are consequences of immune-mediated muscle injury instead of a primary enzyme defect [6]. We also did not identify any pathogenic variants by genetic tests. Absence of prominent inflammation in muscle biopsy may be explained by initiation of treatment before procedure.

A distinctive aspect of this case is the clinical course after allogeneic hematopoietic stem cell transplantation (HSCT). The patient underwent allogeneic HSCT from HLA-matched sibling donor for her hematologic disease, and thereafter she experienced complete and sustained recovery of muscle strength with no recurrence of myopathic symptoms. HSCT, particularly autologous HSCT, has been increasingly used in severe autoimmune diseases such as systemic sclerosis and refractory inflammatory myopathies, where immune reset and reestablishment of self tolerance are believed to underlie long term remission [7]. The current understanding of HSCT in autoimmune diseases suggests that the elimination of autoreactive lymphocyte clones and the regeneration of a more regulated immune repertoire may play a central role in these outcomes [8]. The steady improvement in her muscle strength and CK levels following the transplant suggests that immune recovery probably helped to bring her myositis under long term control.

Overall, this case highlights a few important points. First, the presence of Pompe-like vacuoles on muscle biopsy does not confirm a metabolic glycogen storage disorder on its own; these findings must be interpreted together with enzyme assays, genetic testing, and the patient's clinical response. Second, in patients with hematologic malignancies who develop muscle weakness and marked CK elevation, clinicians should consider paraneoplastic or immune-mediated myositis, even if the biopsy is not typical for an inflammatory myositis. Finally, the strong and sustained improvement after HSCT in this patient suggests

that treating the underlying hematologic disease and reestablishing immune balance may help achieve long-term remission of immune-mediated muscle involvement in selected cases.

Author Contributions

G.S.K.-B. and B.F.-Y. contributed to data organization and drafting of the manuscript. C.E.B.-K. contributed to the collection and interpretation of pathological data and preparation of the images. E.A.-K. contributed to clinical data collection. A.A. and C.E.B.-K. critically reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ORIGINAL ARTICLE

Clinical Characteristics and Management for Flares in Patients With Rheumatoid Arthritis Treated With Biologic and Targeted Synthetic Disease-Modifying Antirheumatic Drugs

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ABSTRACT

Objective: To evaluate the frequency and management of flares in rheumatoid arthritis (RA) patients treated with biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs).

Methods: Data were analyzed from the KOrean nationwide BIOlogics (KOBIO) registry, which includes RA patients initiating b/tsDMARDs therapy. Flares were defined as an increase in DAS28 (>1.2, or >0.6 if DAS28 ≥ 3.2) requiring medication changes. Patients were stratified by flare occurrence, and predictive factors and management strategies were assessed.

Results: Of the 2745 RA patients, 386 (14.1%) experienced flares over a median follow-up period of 5.4 years (IQR, 1.7–11.4). Flares were associated with a significantly higher incidence of shoulder swelling compared with non-flare patients (14.2% vs. 13.7%, $p=0.01$). Predictive factors for flares included a higher swollen joint count (HR: 1.125, $p=0.003$) and shoulder swelling (HR: 2.810, $p=0.002$). Eight patients switched to an alternative b/tsDMARD during flare episodes, while 168 added or modified conventional synthetic DMARDs (csDMARDs). The remaining 210 patients made no changes to their csDMARD regimen. The 12 month retention rate of b/tsDMARDs did not significantly differ between patients who adjusted their csDMARDs and those who did not (86.7% vs. 82.1%, $p=0.23$). However, the mean steroid dose over 12 months was lower in the group that adjusted csDMARDs.

Conclusions: Flares occurred in approximately 14% of RA patients during b/tsDMARD treatment, with baseline joint involvement, particularly shoulder swelling, being a predictor. While the adjustment of csDMARDs was associated with reduced steroid use during flare management, it did not significantly affect b/tsDMARD retention rates.

1 | Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder primarily affecting the joints, often resulting in significant disability and a diminished quality of life [1]. The disease is characterized by symmetrical involvement of synovial joints, with a predilection for the small joints of the hands and feet, commonly presenting with swelling, pain, and impaired function. Over recent decades, advancements in biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) have markedly transformed the treatment landscape of RA, enabling more effective control over disease progression [2, 3]. Despite these therapeutic breakthroughs, RA remains marked by the occurrence of

flares—periods of increased disease activity that accelerate joint damage, impair physical function, and worsen long-term prognosis [4–7]. Flares are a major concern in RA management; however, the clinical characteristics, risk factors, and predictors of flares in patients undergoing b/tsDMARD therapy have not been fully elucidated. Furthermore, optimal strategies for managing these flares during b/tsDMARD treatment remain unclear [8, 9].

The Korean nationwide Biologics (KOBIO) registry was established to monitor the long-term outcomes of patients with RA receiving b/tsDMARD therapy across South Korea [10]. This large-scale, observational study captures comprehensive data on clinical manifestations, treatment responses, and disease progression in patients with RA treated with b/tsDMARDs. Utilizing data from the KOBIO registry, this study aims to investigate the incidence and predictors of RA flares under b/tsDMARD treatment, with a particular focus on joint involvement patterns, clinical outcomes, and drug retention.

2 | Methods

2.1 | Study Population

This study utilized data from the KOBIO nationwide registry, a multicenter, hospital-based observational cohort established by the Korean College of Rheumatology (KCR) [10]. The KOBIO registry includes patients with RA who are initiating b/tsDMARD therapy or switching to a different b/tsDMARD. Patients were recruited from 47 tertiary academic and community rheumatologic centers across South Korea, with follow-up assessments conducted at 12-month intervals. All patients were diagnosed with RA by their treating rheumatologists and met the 2010 American College of Rheumatology criteria for RA [11].

The study protocol was approved by the Institutional Review Board of each participating hospital, including Asan Medical Center (approval #2022–0891), and informed consent was obtained from all enrolled patients.

2.2 | Data Collection

Comprehensive medical records were extracted from the KOBIO registry. Variables included age, sex, disease duration, and comorbidities. Laboratory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, and anti-cyclic citrullinated peptide (CCP) were recorded. Joint assessments were conducted on 66/68 joints to evaluate swelling and tenderness at enrollment and during annual follow-up visits. Disease activity was measured using standardized tools, including the Disease Activity Score of 28 joints (DAS28) and the Simple Disease Activity Index (SDAI) [12]. Medication data were also documented, including the use of conventional synthetic DMARDs (csDMARDs), glucocorticoids (GC), history of previous b/tsDMARDs therapies, and current b/tsDMARD regimen. Concomitant use of csDMARDs or GC was defined as the prescription of these medications at the time of registry enrollment.

2.3 | Assessments for RA Flare

An RA flare was defined as an increase in DAS28 by more than 1.2 from baseline or by more than 0.6 if the concurrent DAS28 was $\geq$3.2, requiring treatment modification [4, 13]. Patients were categorized into two groups: those who experienced a flare during the follow-up period and those who did not. Baseline and follow-up disease characteristics, particularly joint involvement, were compared between the two groups. For patients who experienced multiple flares during the follow-up period, only the first episode was included in the analysis to ensure statistical independence and to evaluate baseline predictors and subsequent management outcomes.

Management strategies during flare episodes were also analyzed, specifically focusing on the proportion of patients who switched to a different b/tsDMARDb/tsDAMRD or had csDMARDs added or modified in their treatment regimen. Patients who switched b/tsDMARDs due to flare were excluded from subsequent analyses. The remaining patients were further classified into two groups: those whose csDMARD regimen was adjusted (through the introduction of a new csDMARD or an increase in dosage of an existing one) and those whose regimen remained unchanged. The mean GC dosage over 1 year and b/tsDMARD retention rates between these two groups were compared. b/tsDMARDb/tsDMARDs retention was defined as the proportion of patients continuing the same biologic therapy 1 year after the flare. Additionally, we analyzed risk factors for drug discontinuation within 1 year.

2.4 | Statistical Analysis

Continuous values are presented as mean (standard deviation) for normally distributed data, or as median (interquartile range [IQR]) for non-normally distributed data. Comparisons between flare and non-flare groups were conducted using Student's *t*-test or Mann–Whitney U test for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables. Cox proportional hazard models were employed for univariate and multivariate analyses to identify predictors of flare occurrence and b/tsDMARD retention. A *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 26.0 (IBM Corp., Armonk, NY).

3 | Results

3.1 | Baseline Characteristics of Patients With RA Under b/tsDMARDs

A total of 2745 patients with RA receiving b/tsDMARDs were included in the analysis. Figure 1 depicts the overall study flow. The median age was 56.3 years (IQR, 47.0–64.1 years), with a predominance of female patients (82.3%) (Table 1). The median disease duration at the time of initiation of b/tsDMARDs was 5.4 years (IQR, 1.7–11.4 years). The median swollen joint count was 6 (IQR, 3–10), and the median tender joint count was 8 (IQR, 5–13). The DAS28-ESR score was 5.5 (IQR, 5.0–6.3).

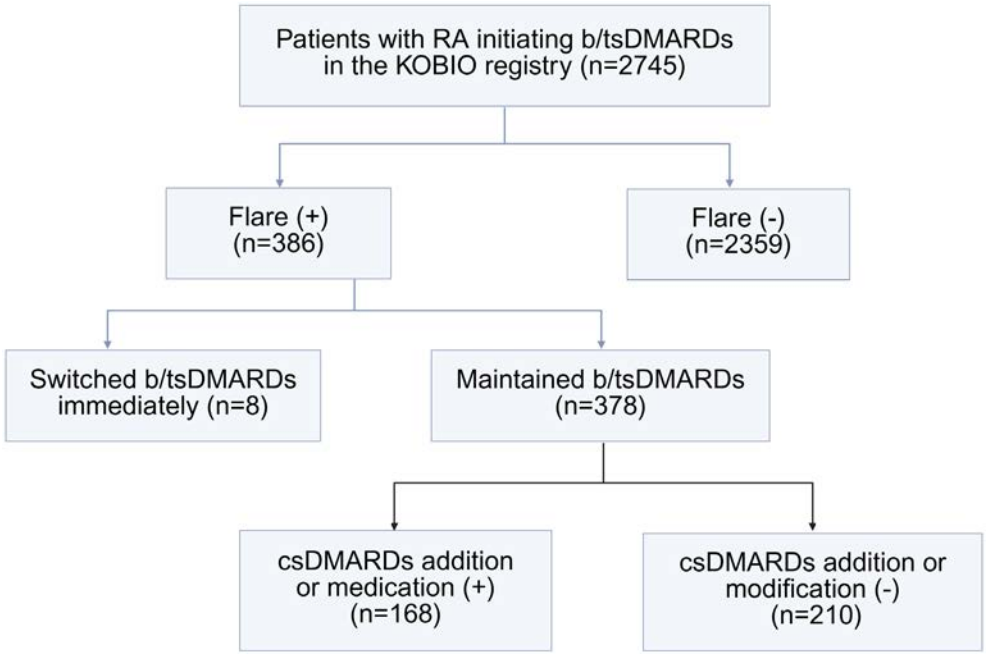

FIGURE 1 | Study flow chart.

Regarding medication use, most patients were biologic-naïve (76.9%), while 7.2% had been exposed to more than two prior biologic therapies. At enrollment, 46.7% of patients-initiated treatment with TNF inhibitors (adalimumab 16.6%, etanercept 14.3%, infliximab 8.9%, and golimumab 6.9%). Among non-TNF inhibitor users, tocilizumab was the most frequently prescribed (23.3%), followed by abatacept (12.9%). In terms of tsDMARDs, baricitinib was most commonly used (6.2%), followed by upadacitinib (2.7%). Methotrexate was the most prevalent csDMARD, used by 80.4% of patients (2208/2745), while 85.4% (2345/2745) were concomitantly using GCs. The most frequently affected joints at baseline were the hands (86.7% swelling, 88.8% tenderness), followed by the knees (34.8% swelling, 43.5% tenderness) and elbows (27.7% swelling, 38.7% tenderness).

3.2 | Comparison Between Patients With and Without RA Flare

During a median follow-up of 5.4 years (IQR, 1.7–11.4 years), 386 patients (14.1%) experienced an RA flare, while 2359 did not. The median time to flare was 2.0 years (IQR, 1.0–3.1) after b/tsDMARDsb/tsDMARDS initiation. Baseline characteristics were compared between patients with and without flares (Table 1). Patients who experienced flares were significantly younger than those who did not (54.5 [IQR, 44.5–62.9] vs. 56.6 [IQR, 47.5–64.3], $p < 0.01$). There were no significant differences between the groups in terms of sex, disease duration, and prior b/tsDMARD therapy use. However, infliximab was more frequently used in the flare group ($p = 0.04$), and leflunomide as a concomitant csDMARD was also more common among those with flares (67/386, 17.4% vs. 212/2359, 9.0%, $p = 0.02$). Although there was a trend toward more frequent shoulder swelling and tenderness at the baseline in the flare group, only shoulder swelling reached statistical significance (swelling, 14.2% vs. 13.7%, $p = 0.01$; shoulder tenderness, 41.5% vs. 38.5%, $p = 0.25$). When comparing classes of advanced therapies, no significant differences were observed in clinical characteristics—including flare rates—among patients receiving TNF inhibitors, non-TNF biologics, and tsDMARDs (14.2%, 14.0%, and 13.5%, respectively, $p = 0.200$) (Table S1).

3.3 | Predictive Factors for RA Flare After Use of b/tsDMARDs

We further investigated predictive factors for RA flares using univariate and multivariate analyses (Table 2). While prior use of b/tsDMARDs was associated with a higher risk of flare in the univariate analysis, it was not statistically significant in the multivariate analysis (HR: 1.628, 95% CI: 0.933–2.839, $p = 0.086$). Neither the specific type of b/tsDMARDs nor the concomitant use of csDMARDs was significantly associated with flare risk. Multivariate analysis identified two significant predictors of RA flares: higher baseline swollen joint count (HR: 1.125, 95% CI: 1.041–1.216, $p = 0.003$) and the presence of shoulder swelling (HR: 2.810, 95% CI: 1.460–5.410, $p = 0.002$). Conversely, baseline tenderness in the hand joints was associated with a reduced risk of flares (HR: 0.368, 95% CI: 0.175–0.774, $p = 0.008$).

3.4 | Management for RA Flares Under b/tsDMARDs

We also evaluated the management strategies employed for RA flares. Among the 386 patients who experienced flares, 8 switched b/tsDMARDs immediately. Of the remaining 378 patients, 168 added or modified their csDMARDs regimen, while 210 did not (Table 3). There were no significant differences in the time to flare after b/tsDMARDs initiation or in follow-up duration between these groups. At the time of the flare, disease activity indicators such as ESR, CRP, and DAS28-ESR levels

TABLE 1 | Baseline characteristics of patients with and without flares.

		Flare		
	Total ($n = 2745$)	**(−) ($n = 2359$)**	**(+) ($n = 386$)**	***P***
Age, years	56.3 (47.0–64.1)	56.6 (47.5–64.3)	54.5 (44.5–62.9)	**< 0.01**
Female sex, *n* (%)	2259 (82.3)	1930 (81.8)	329 (85.2)	0.08
Disease duration, years	5.4 (1.7–11.4)	5.4 (1.7–11.4)	5.3 (1.5–11.4)	0.48
Comorbidities				
Hypertension	830 (30.2)	718 (30.4)	112 (29)	0.57
Diabetes	349 (12.7)	310 (13.1)	39 (11.9)	0.75
Dyslipidemia	594 (21.6)	508 (21.5)	86 (22.3)	0.92
Previous b/tsDMARD use				0.47
0	2111 (76.9)	1831 (77.3)	280 (72.5)	
1	435 (15.8)	329 (13.9)	106 (27.5)	
2	116 (4.2)	116 (4.9)	0 (0)	
3+	83 (3)	83 (3.5)	0 (0)	
Laboratory finding				
ESR	39 (21.0–55.0)	44 (27.0–65.0)	46 (30.0–67.0)	0.27
CRP	1.4 (0.6–2.9)	1.2 (0.4–2.9)	1.5 (0.6–3.0)	0.23
Positive rheumatoid factor	2175 (79.2)	1875 (79.5)	300 (77.7)	0.51
Positive anti-CCP	1976 (72)	1719 (72.9)	257 (66.6)	0.40
Disease activity				
Swollen joint count	6 (3–10)	6 (2–9)	6 (3–9)	0.09
Tender joint count	8 (5–13)	7 (4–12)	7 (4–12)	0.17
DAS28-ESR	5.5 (5.0–6.3)	5.5 (4.9–6.3)	5.5 (5.0–6.2)	0.5
SDAI	27.3 (21.1–35.6)	27.3 (21.1–35.6)	27.2 (21.1–35.6)	0.35
CDAI	25 (19.0–33.0)	25 (19.0–33.0)	24.5 (19.0–33.0)	0.51
Biologics, *n* (%)				**0.04**
Adalimumab	457 (16.6)	384 (16.3)	73 (18.9)	
Etanercept	392 (14.3)	341 (14.5)	51 (13.2)	
Infliximab	245 (8.9)	147 (6.2)	98 (25.4)	
Golimumab	190 (6.9)	157 (6.7)	33 (8.5)	
Tocilizumab	639 (23.3)	527 (22.3)	112 (29)	
Abatacept	354 (12.9)	307 (13)	47 (12.2)	
Rituximab	202 (7.4)	199 (8.4)	3 (0.8)	
tsDMARD, *n* (%)	303			
Baricitinib	169 (6.2)	168 (7.1)	1 (0.3)	
Upadacitinib	74 (2.7)	74 (3.1)	0 (0)	
Tofacitinib	23 (0.8)	20 (0.8)	3 (0.8)	
Concomitant csDMARD, *n* (%)				
Methotrexate	2208 (80.4)	1905 (80.8)	303 (78.5)	0.26

(Continues)

TABLE 1 | (Continued)

	Total ($n=2745$)	Flare		P
		(−) ($n=2359$)	(+) ($n=386$)	
Leflunomide	279 (10.2)	212 (9)	67 (17.4)	**0.02**
Hydroxychloroquine	235 (8.6)	182 (7.7)	53 (13.7)	0.19
Sulfasalazine	172 (6.3)	144 (6.1)	28 (7.3)	0.04
Concomitant GC, *n* (%)				0.25
User	2345 (85.4)	2016 (85.5)	329 (85.2)	
Non-user	400 (14.6)	343 (14.5)	57 (14.8)	
Joint swelling				
Shoulder	379 (13.8)	324 (13.7)	55 (14.2)	**0.01**
Hand	2379 (86.7)	2043 (86.6)	336 (87)	0.16
Elbow	760 (27.7)	637 (27)	123 (31.9)	0.58
Knee	956 (34.8)	796 (33.7)	160 (41.5)	0.53
Foot	669 (24.4)	531 (22.5)	138 (35.8)	0.10
Joint tenderness				
Shoulder	1068 (38.1)	908 (38.5)	160 (41.5)	0.25
Hand	2438 (88.8)	2092 (88.7)	346 (89.6)	0.40
Elbow	1063 (38.7)	909 (38.5)	154 (39.9)	0.9
Knee	1193 (43.5)	1002 (42.5)	191 (49.5)	0.31
Foot	804 (29.3)	656 (27.8)	148 (38.3)	0.34
Drug retention rate at 1 year	2417 (88.1)	2111 (85.2)	306 (79.2)	0.10

Note: Data are shown as median (interquartile range) for continuous variables and as *n* (%) for categorical variables. Bold values indicate statistical significance ($p<0.05$).
Abbreviations: CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28, disease activity score in 28 joints; ESR, erythrocyte segmentation rate; GC, glucocorticoid; SDAI, simplified disease activity index; tsDAMRD, targeted synthetic disease-modifying antirheumatic drug.

were comparable across groups. However, patients who added or modified their csDMARDs exhibited a lower prevalence of shoulder swelling (18.5% vs. 21.0%, $p=0.04$) and foot tenderness (14.9% vs. 15.7%, $p=0.02$) compared with those who did not modify their csDMARD regimen. The 12-month retention rate of b/tsDMARDs post-flare did not significantly differ between the groups (Figure S1). However, the mean daily GC dose during the 12 months following the flare was significantly lower in patients who adjusted their csDMARDs (11.5 [IQR, 6.8–13.7] vs. 6.8 [IQR, 0.0–13.7], $p=0.02$).

3.5 | Factors Associated With b/tsDMARD Discontinuation After the Flare

Lastly, we analyzed factors associated with b/tsDMARDs discontinuation. The overall retention rate at 1 year was 88.1% ($n=2417$). Among patients in the flare group ($n=386$), the 1-year drug retention rate was 79.2% ($n=306$). In the analysis of factors associated with b/tsDMARD discontinuation within 1 year after a flare, prior biologic use was significantly associated with an increased risk of discontinuation (HR: 1.330, 95% CI: 1.030–1.717, $p=0.029$) (Table 4). Lower swollen joint count at baseline was associated with a reduced risk of discontinuation (HR: 0.971, 95% CI: 0.946–0.996, $p=0.023$). The absence of concomitant csDMARD use and the occurrence of flares within the first year did not significantly affect the likelihood of therapy discontinuation. Specific joint involvement also did not influence the risk of drug discontinuation.

4 | Discussion

This study, utilizing data from the nationwide KOBIO registry, provides important insights into disease flares in patients with RA treated with b/tsDMARDs. Approximately 14% of patients experienced a flare during treatment, highlighting the significance of baseline joint involvement, particularly shoulder swelling, as a predictor of future flares. Moreover, this study offers potential guidance on managing flares in the context of ongoing b/tsDMARD treatment.

Despite advances in b/tsDMARDs therapies, RA remains characterized by frequent flares. In our study, over a median follow-up of 5.4 years (IQR 1.7–11.4 years), 14.1% of patients experienced a flare, with hand swelling being the most frequently involved joint. Comparatively, a U.S.-based study involving 1105 patients found that 30% of those in remission reported flares,

TABLE 2 | Predictors for RA flare in patients treated with b/tsDMARDs.

	Univariate			Multivariate		
	HR	**95% CI**	**P**	**HR**	**95% CI**	***P***
Age	1.002	0.981–1.023	0.867			
Female sex	0.802	0.388–1.660	0.553			
Disease duration	0.972	0.931–1.014	0.185			
Previous biologics use	**1.374**	**1.072–1.762**	**0.012**	1.628	0.933–2.839	0.086
Disease activity at baseline						
Swollen joint count	**1.122**	**1.032–1.219**	**0.007**	**1.125**	**1.041–1.216**	**0.003**
Tender joint count	1.006	0.937–1.081	0.864			
DAS28-ESR	1.285	0.711–2.322	0.407			
SDAI	0.978	0.934–1.024	0.348			
CDAI	0.988	0.950–1.028	0.565			
Biologics or tsDMARD						
TNF inhibitor	—					
Non-TNF inhibitor	0.989	0.535–1.817	0.964			
JAKi	0.327	0.039–2.730	0.302			
Concomitant csDMARD						
Yes	—					
No	0.945	0.620–1.441	0.793			
Joint swelling at baseline						
Shoulder	**3.093**	**1.462–6.542**	**0.003**	**2.810**	**1.460–5.410**	**0.002**
Hand	0.514	0.234–1.130	0.098			
Elbow	0.768	0.406–1.452	0.416			
Knee	0.988	0.545–1.792	0.968			
Foot	0.776	0.406–1.483	0.443			
Joint tenderness at baseline						
Shoulder	1.645	0.923–2.931	0.091			
Hand	**0.349**	**0.165–0.736**	**0.006**	**0.368**	**0.175–0.774**	**0.008**
Elbow	0.982	0.559–1.724	0.982			
Knee	1.362	0.791–2.343	0.265			
Foot	0.669	0.375–1.193	0.173			

Note: Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: b/tsDAMRD, biologic or targeted synthetic disease-modifying antirheumatic drug; CDAI, clinical disease activity index; csDMARD, conventional synthetic DMARD; ESR, erythrocyte segmentation rate; JAKi, Janus kinase inhibitor; SDAI, simplified disease activity index.

defined as self-reported symptom aggravation [5]. Meta-analyses of TNF inhibitor de-escalation studies reported flare rates ranging from 8% at 24 weeks to 63% at 4 months after de-escalation [6]. Another study on etanercept in moderately active patients with RA reported an 11.3% flare rate [14], while a real-world analysis showed 56.8% of patients experienced at least one flare in the year after etanercept treatment [15]. The lower flare rates observed in our study, drawn from a nationwide b/tsDMARDs registry, may reflect differences in patient populations, flare definitions, and treatment protocols.

Interestingly, our findings did not reveal any significant association between specific types of b/tsDMARDs (TNF inhibitors, non-TNF inhibitors, or JAK inhibitors) and flare risk. While studies have primarily focused on discontinuation due to loss of efficacy, rather than flare rates, some suggest that non-TNF inhibitors such as abatacept or tocilizumab have lower discontinuation rates due to loss of effectiveness compared with TNF inhibitors [16, 17]. A Danish registry study found that drug withdrawal due to lack of efficacy was highest for infliximab and lowest for etanercept among patients with TNF inhibitors [18].

TABLE 3 | Clinical characteristics at the time of flare according to csDMARD adjustment.

	csDMARDs addition or modification		
	(−) (*n* = 210)	**(+) (*n* = 168)**	***P***
Time to flare from baseline (years)	2.0 (1.1–3.1)	2.0 (1.0–3.0)	0.55
Total follow-up time (years)	4.4(3.1–6.1)	4.1 (2.7–5.8)	0.61
Age	57.3 (47.4–65.6)	57.0 (48.4–65.2)	0.58
Female sex	179	144	0.48
Disease duration	8.2 (4.8–13.8)	8.9 (4.7–15.9)	0.90
Disease activity at flare			
ESR	31 (14.0–50.5)	34 (19.8–50)	0.27
CRP	0.5 (0.1–1.6)	0.5 (0.1–1.3)	0.34
Swollen joint count	2.0 (0.0–5.8)	2.0 (0.0–4.0)	0.54
Tender joint count	3.0 (1.0–8.8)	3.0 (1.0–7.0)	0.54
DAS28-ESR	3.7 (2.6–5.0)	3.5 (2.6–4.7)	0.59
SDAI	15.0 (8.0–27.0)	15.1 (8.9–25.2)	0.45
CDAI	16.2 (9.0–28.3)	14.5 (8.0–23.0)	0.54
Joint swelling at flare			
Shoulder	11 (5.2)	8 (4.8)	0.83
Hand	125 (59.5)	98 (58.3)	0.82
Elbow	28 (13.3)	25 (14.9)	0.67
Knee	53 (25.2)	38 (22.6)	0.56
Foot	24 (11.4)	16 (9.5)	0.55
Joint tenderness at flare			
Shoulder	44 (21.0)	31 (18.5)	**0.04**
Hand	145 (69.0)	111 (66.1)	0.48
Elbow	43 (20.5)	38 (22.6)	0.07
Knee	66 (31.4)	59 (35.1)	0.18
Foot	33 (15.7)	25 (14.9)	**0.02**
Biologics retention rate at 1 year	182 (86.7)	138 (82.1)	0.23
Mean daily GC dose over 1 year (mg/day)	11.5 (6.8–13.7)	6.8 (0.0–13.7)	**0.02**

Note: Data are shown as median (interquartile range) for continuous variables and as *n* (%) for categorical variables. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: b/tsDAMRD, biologic or targeted synthetic disease-modifying antirheumatic drug; CDAI, clinical disease activity index; csDMARD, conventional synthetic DMARD; ESR, erythrocyte segmentation rate; JAKi, Janus kinase inhibitor; SDAI, simplified disease activity index.

There have been studies examining factors associated with the discontinuation of b/tsDMARDs, including specific medications [19–22]. However, direct comparisons of flare rates across b/tsDMARDs types are scarce, and caution is warranted when drawing conclusions, given the variability in study designs and populations. Further research is needed to determine whether certain b/tsDMARDs are more likely to trigger RA flares.

In managing flares, the adjustment of csDMARDs was the predominant strategy rather than switching b/tsDMARDs.b/tsDMARDS. Although disease activity measures were comparable between those who added or modified csDMARDs and those who did not, the higher prevalence of shoulder and foot tenderness in the non-csDMARD modification group may suggest different responses to intervention. While no established guidelines exist for managing flares during b/tsDMARD therapy, some studies indicate that increasing the dosage or reintroducing it after tapering can be effective [23]. A 2002 study reported that the most common strategies for managing flares included temporary increases in GC dosage (43%) or intra-articular injections (14%), with only 8% of patients modifying their csDMARD therapy [15]. Our study found a higher rate of csDMARD addition or modification (44.4%), which was associated with a lower mean GC dose, suggesting a potential benefit in reducing GC dependence while maintaining b/tsDMARD therapy.

Baseline shoulder swelling and a higher swollen joint count were identified as significant risk factors for flares. The association between baseline shoulder swelling and increased flare risk suggests that it may serve as a clinical surrogate for a substantial systemic inflammatory burden. This is consistent with previous studies indicating that patients with large joint involvement at baseline are more likely to experience radiographic progression and less likely to achieve sustained remission [24, 25]. Beyond systemic factors, the shoulder's unique anatomical structure and susceptibility to repetitive mechanical stress during daily activities may predispose it to persistent subclinical inflammation, which eventually manifests as a flare [26].

Our finding that the choice of b/tsDMARD class did not significantly influence flare risk aligns with previous real-world registry data indicating comparable clinical effectiveness between various bDMARDs and JAK inhibitors [27]. Although individual agents may exhibit different safety profiles or drug survival rates [28, 29], the physiological propensity for clinical flares—often driven by secondary loss of efficacy—appears similar across these advanced therapies. This suggests that baseline clinical phenotypes, such as a high swollen joint count or large joint involvement including the shoulder, may be more important determinants of future flare risk than the specific pharmacologic mechanism of the drug class.

While this study provides valuable insights, several limitations should be acknowledged. The observational nature of the study limits causal inference. Additionally, reliance on registry data may introduce selection bias, as not all patients with RA in Korea are represented. Furthermore, variability in treatment protocols and clinician preferences across different centers may have introduced bias, as the management of RA flares, drug initiation, or adjustments to csDMARDs could differ between institutions. There is the possibility of underreporting flares, as the data

TABLE 4 | Factors associated with b/tsDMARD discontinuation within 1 year after flare among patients who experienced flares.

	Univariate			Multivariate		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age	1.000	0.971–1.029	0.982			
Female sex	1.545	0.574–4.159	0.389			
Disease duration	0.968	0.920–1.020	0.225			
Previous biologics use	**1.323**	**1.025–1.708**	**0.031**	**1.330**	**1.030–1.717**	**0.029**
Disease activity at baseline						
Swollen joint counts	**0.971**	**0.947–0.996**	**0.022**	**0.971**	**0.946–0.996**	**0.023**
Tender joint counts	**0.985**	**0.971–0.999**	**0.034**	1.001	0.980–1.021	0.960
DAS28-ESR	0.871	0.795–1.211	0.851			
SDAI	0.981	0.976–1.010	0.187			
CDAI	0.983	0.976–1.027	0.674			
Biologics						
TNF inhibitor	—					
Non-TNF inhibitor	1.719	0.146–2.938	0.667			
JAKi	1.844	0.203–16.748	0.587			
Flare within one year	1.826	0.641–5.205	0.260			
csDMARD						
Yes	—					
No	3.068	0.394–23.909	0.284			
Joint swelling						
Shoulder	0.784	0.310–1.986	0.608			
Hand	2.180	0.930–5.112	0.073			
Elbow	1.187	0.551–2.555	0.661			
Knee	1.068	0.526–2.170	0.855			
Foot	1.435	0.668–3.083	0.355			
Joint tenderness						
Shoulder	1.119	0.512–2.444	0.778			
Hand	2.384	0.948–5.994	0.065			
Elbow	1.258	0.584–2.710	0.558			
Knee	0.748	0.364–1.534	0.428			
Foot	0.745	0.422–1.853	0.745			

Note: Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: b/tsDAMRD, biologic or targeted synthetic disease-modifying antirheumatic drug; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28, disease activity score in 28 joints; ESR, erythrocyte segmentation rate; SDAI, simplified disease activity index; tsDAMRD, targeted synthetic disease-modifying antirheumatic drug.

were collected during scheduled follow-up visits, which may not have captured flare episodes that occurred between visits, particularly if patients did not seek medical attention for milder flares. Nonetheless, the large sample size and comprehensive data collection enhance the robustness and generalizability of our findings. Another notable limitation is that this study could not specifically account for b/tsDMARD tapering as a potential trigger of flares. Clinicians frequently attempt dose reduction or interval extension in patients with stable low disease activity or remission to minimize long-term drug exposure; however, these strategies are often associated with an increased risk of flare. As pharmacological adjustments during follow-up may have influenced flare incidence, the predictive value of baseline characteristics—such as shoulder involvement—should be interpreted cautiously. Future prospective studies incorporating predefined tapering protocols are warranted to clarify these associations.

In conclusion, 14.1% of patients treated with b/tsDMARDs experienced RA flares, with baseline swollen joint count and shoulder involvement serving as key predictors. Addition or modification of csDMARDs during flares was associated with lower mean steroid use but did not significantly impact b/tsDMARD retention rates.

Author Contributions

Young-Eun Kim: conceptualization, data curation, formal analysis, investigation, writing – original draft. **Soo Min Ahn:** investigation, methodology. **Ji Seon Oh:** investigation, methodology. **Yong-Gil Kim:** investigation, methodology. **Chang-Keun Lee:** investigation, methodology. **Bin Yoo:** investigation, methodology. **Seokchan Hong:** conceptualization, project administration, supervision, writing – review and editing. All authors have read and approved the final manuscript.

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Ethics

The protocols of this study were approved by the Institutional Review Board of Asan Medical Center (2022–0891).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article are available upon reasonable request from the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Retention rate of b/tsDMARDs at 12 months post flare. **Table S1:** Comparison of baseline characteristics and flare rates according to b/tsDMARD class.

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EDITORIAL

Rheumatology in the Era of Carbon Pricing: Low-Carbon Care and Cost Stewardship

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1 | Rheumatology Under Climate and Carbon Constraints

As carbon pricing and net-zero targets reshape health policy [1–3], rheumatology must confront its own contribution to greenhouse-gas emissions. Low-carbon models of care that preserve clinical benefit while managing costs are now a strategic priority for the specialty [4].

The intricate relationship between climate change and systemic autoimmune rheumatic diseases—such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), and systemic sclerosis (SSc)—has become a central challenge for our field rather than a peripheral concern. The American College of Rheumatology highlights how climate-amplified environmental factors can trigger or worsen these conditions, creating a feedback loop in which a warming planet drives disease activity, increasing demand for resource-intensive care and further enlarging healthcare's carbon footprint [4]. In this editorial, we focus on RA and selected systemic rheumatic diseases where links to environmental change and healthcare-related emissions are best described, and where low-carbon interventions are beginning to be quantified. For other rheumatic and musculoskeletal conditions—such as osteoarthritis, regional pain syndromes, and crystal arthropathies—the evidence base is more limited, and our proposed low-carbon strategies should be extrapolated cautiously and adapted to predominantly degenerative or mechanical conditions.

2 | Environmental Triggers: Air Pollution and Heat

Long-term exposure to fine particulate matter ($PM_{2.5}$), largely generated by fossil-fuel combustion, is associated with a *1.3-fold increased* risk of developing arthritis, including rheumatoid arthritis (RA) [5], in international cohorts. Environmental hazards amplified by climate change—such as heat and air pollution—already account for an estimated 25% of the global burden of disease [6]. Increased heat vulnerability is linked to higher odds of recurrent hospitalizations and affects up to *18% of patients* with systemic rheumatic conditions in some cohorts [7]. In Taiwan, a nationwide cohort linking National Health Insurance data with air-quality monitoring reported a modestly increased risk of incident RA in people in the highest versus lowest $PM_{2.5}$ exposure quartile (adjusted hazard ratio, $aHR \approx 1.053$) [8].

3 | The Carbon Cost of Care

Systemic autoimmune rheumatic diseases, as prototypical chronic inflammatory diseases, require frequent outpatient visits for ongoing monitoring and treatment adjustment, creating a substantial cumulative travel burden that exemplifies how sustained rheumatology care itself generates avoidable transport-related emissions when not redesigned through a low-carbon lens [9].

At the same time, our own practice contributes to the crisis. The global healthcare sector is responsible for an estimated *4.4%–5.2% of net greenhouse-gas emissions* [1]. Within rheumatology, a major contributor is the carbon-intensive supply chain for biologic therapies, whose annual carbon emissions can vary dramatically—for example, from about 1.1 kg CO_2e for benralizumab to 188.9 kg CO_2e for dupilumab (a 172-fold difference), depending on the specific agent and delivery model [10]. Broader pharmaceutical life-cycle assessments (LCAs) and monoclonal antibody manufacturing studies similarly report large differences in cradle-to-gate between

molecules and across alternative production scenarios, reinforcing that these figures should be treated as order-of-magnitude estimates rather than definitive product-level values and highlighting the need for rheumatology-specific, peer-reviewed LCAs [11, 12].

4 | Precision Medicine as a Decarbonization Strategy

To break this cycle, rheumatology must pursue a *dual transformation*: precision medicine and low-carbon care. Precision medicine—using the right drug, at the right time, for the right patient—aims to shorten ineffective treatment sequences and achieve low disease activity earlier, as shown in recent real-world and systematic treat-to-target (T2T) studies in systemic autoimmune rheumatic diseases. Achieving stricter, consistently applied targets is associated with better disease control and fewer flares, which can reasonably be expected to reduce downstream emergency visits and hospitalizations, the most carbon-intensive elements of care [13, 14]. In the UK, effective disease control that prevents a single hospitalization can avoid an estimated 246–369 kg CO_2e per patient per year [15], while switching an in-person consultation to telemedicine can save between 0.7 and 372 kg CO_2e, primarily through reduced travel-related emissions [16, 17]. In China, a recent study shows that telemedicine visits emit about 19 kg CO_2e per visit and on average reduce emissions by around 85.5 kg

TABLE 1 | The vicious cycle of carbon emissions and rheumatic diseases: Key data and proposed interventions.

Domain	Key finding/metric	Illustrative data	Source
Environmental Impact on Patients	Increased risk of Rheumatoid Arthritis (RA) with long-term $PM_{2.5}$ exposure	*1.3-fold* increased risk of arthritis	[5]
	Association between PM2.5 and incident RA in Taiwan—Taiwan nationwide cohort study.	*Adjusted hazard ratio of 1.053* for incident RA in the highest versus lowest quartile of $PM_{2.5}$ exposure	[8]
	Increased odds of recurrent hospitalizations due to heat vulnerability	*18%* of patients experienced recurrent hospitalizations in one study cohort	[7]
Healthcare's Carbon Footprint	Contribution of the global healthcare sector to total GHG emissions	*~4.4%–5.2%* of global net emissions	[1]
	Variability in carbon footprint among different biologic agents in UK (per patient, per year)	Total emissions ranged from 1.1 kg CO_2e for benralizumab to 188.9 kg CO_2e for dupilumab; a 172-fold difference (Product-level carbon footprints from [10] derive from early-stage LCAs, preprints and is therefore used here as *preliminary, order-of-magnitude indicators* rather than definitive estimates.)	[10–12]
	Travel-Related Carbon Footprint of RA in UK (per patient, per year)	Average annual travel distance is *~78 km* (vs. < 2 km for controls), generating *~12.5 kg CO_2e* (if using petrol cars)	[9]
	Carbon savings from avoiding one hospitalization through effective treatment in UK (per patient, per year)	*246–369 kg CO_2e* net annual savings	[15]
Low-Carbon Interventions	LCA of telemedicine in China (per consultation)	*19 kg CO_2e* per telemedicine section; mean *85.5 kg CO_2e reduction* per visit vs. in-person outpatient care	[18]
	Carbon footprint reduction per consultation switched to telemedicine in western countries (per consultation)	*0.7 to 372 kg CO_2e* savings per consultation	[16, 17]
	Significant Decarbonization Potential via Modal Shift in UK (per patient, per year)	– Switching to electric vehicles reduces emissions *~3.5 kg CO_2e* – Replacing 40% of petrol car travel with public transport saves up to *6.6 kg CO_2e*	[9]

CO_2e compared with in-person care, with national networks potentially cutting millions of tons of CO_2e annually and particularly benefiting patients in mountainous and remote regions [18].

Telemedicine thus exemplifies how digital transformation can support low-carbon rheumatology. For patients with stable chronic rheumatic disease, virtual consultations can safely replace many in-person visits, improving access while substantially reducing travel-related emissions and time costs. When supported by appropriate reimbursement and community-based monitoring, telemedicine can further enhance access for patients living far from tertiary centers in Taiwan and across Asia. Together with locally tailored precision-medicine strategies and a progressively decarbonized biologic supply chain, telehealth can become a cornerstone of resilient, low-carbon rheumatology care. The scale of this cycle—from environmental triggers to healthcare-generated emissions and the potential impact of targeted interventions—is summarized in Table 1.

In parallel, emerging work in "Green" Health Technology Assessment (HTA) shows how LCA can be embedded alongside clinical effectiveness and cost-effectiveness, allowing environmental metrics to be integrated into routine therapeutic decision-making [2, 3]. In rheumatology, this means that better phenotyping and earlier, targeted treatment—for example T2T RA care and biomarker-guided stratification in systemic autoimmune rheumatic diseases—can be aligned with greener delivery models to reduce emissions from high-intensity services such as emergency care and inpatient stays. Low-carbon incentives should focus on how care is delivered—by reducing low-value care, optimizing

TABLE 2 | Integrated framework for low-carbon rheumatology: BSC, HTA, and LCA.

BSC perspective	Strategy focus	Key performance indicator (KPI)	Data-driven tool
Environmental & Sustainability	Reduce total carbon footprint of rheumatology services [22]	– Annual reduction in total carbon emissions (kg CO_2e) – Supply chain LCA data transparency (%) – Medical waste reduction rate (%)	LCA [23]
Patient & Community	Improve patient health and reduce environmental exposure risks [9, 16]	– Telemedicine adoption rate (%) – Reduction in patient travel carbon emissions (kg CO_2e) – Disease flare rate (Flare Rate)	HTA [3]
Internal Processes	Establish data-driven low-carbon clinical decision-making processes: minimizing low-value care and expanding high-quality care [20]	– Proportion of Green HTA incorporated into new technology assessments (%) – Precision prescribing (T2T) rate (%) (avoiding ineffective test and treatments) – Medication Stewardship program rate (%) (promote appropriate use of medications and reduce medication-related waste) – Operating Room BSC (Adopt Sustainable Operating Room Scorecard to reduce footprint) – Reusable & Streamlined Supplies (%) (Replace single-use textiles with reusables and optimize supply management) – Improvement in cold chain logistics energy efficiency (%) – Inpatient low carbon food service rate (%) (Implement plant-forward menus and person-centered food services to minimizing food waste and including low carbon food items)	HTA [2, 3] Sustainable Operating Room Scorecard [24]
Learning & Growth	Foster sustainable healthcare culture and innovation capabilities [25]	– Staff sustainable healthcare training hours – Number of cross-departmental (clinical/community/supply chain) collaboration projects – Number of publications on low-carbon rheumatology	BSC [25, 26]

dosing and monitoring, and improving supply-chain efficiency—rather than restricting access to high-efficacy therapies.

5 | Rheumatology Balanced Scorecard

As rheumatology enters an era of carbon pricing and tighter fiscal constraints, departments need governance tools that can align clinical quality, costs, and emissions. Our proposed *Rheumatology Balanced Scorecard* builds on prior work integrating environmental indicators into hospital performance frameworks and sustainability-balanced scorecards in public healthcare systems, as well as emerging models that link *HTA* with the *Balanced Scorecard* for technology management [19–21]. In this framework, an *Environmental & Sustainability* perspective tracks total annual emissions, transparency of supplier LCA data, and reductions in medical waste, incorporating environmental impact alongside safety, efficacy, and cost in therapeutic decisions. A *Patient & Community* perspective monitors telemedicine uptake, patient travel-related emissions, flare rates, and rural–urban differences in access, allowing services to see whether low-carbon interventions are narrowing rather than widening inequities.

An *Internal Processes* perspective follows the proportion of new technologies evaluated using Green HTA, and metrics such as *first-time-right* and *Treat-to-Target* biologic prescribing, which capture how often patients receive effective therapy early in the disease course and are expected to reduce preventable flares, hospitalizations, and their associated carbon emissions. A *Learning & Growth* perspective measures staff training in sustainable care, cross-departmental projects between clinicians and supply-chain teams, and research output in low-carbon rheumatology, embedding decarbonization into organizational culture. Importantly, environmental metrics in this Balanced Scorecard are not intended to justify restricting access to high-efficacy therapies such as biologic disease-modifying drugs, but to identify and eliminate low-value and wasteful care—for example, redundant investigations, unnecessary routine visits, or avoidable supply-chain inefficiencies. By linking environmental data (LCA) and evidence-based appraisal (HTA) to strategic goals through the *Rheumatology Balanced Scorecard*, rheumatology services can move from rhetoric to accountable implementation in a carbon-priced world [19–21] (Table 2).

6 | Conclusion

The fight against climate change is fundamentally a fight for our patients' health. By embracing a data-driven strategy that combines *precision medicine*, *supply-chain accountability*, *Green HTA*, and the *intelligent integration of telemedicine* within a *Rheumatology Balanced Scorecard*, our community can lead rather than follow. A low-carbon future for rheumatology is not only an environmental imperative—it is a clinical obligation to protect both our patients and the planet on which they depend.

Author Contributions

G.-N.K. conceived the study idea, All authors designed the research framework, and led the overall project administration. G.-N.K. collected and curated the data, conducted the formal analysis, and interpreted the results. G.-N.K. drafted the original manuscript and revised it critically for important intellectual content. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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LETTER TO THE EDITOR

Case Report: Successful Treatment of Refractory Relapsing Polychondritis with Anti-CD20 Therapies

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Dear Editor,

Relapsing polychondritis (RP) is a rare immune-mediated disorder characterized by recurrent inflammation of cartilaginous and proteoglycan-rich tissues, with a highly variable clinical course and significant morbidity in severe cases [1–3]. Management remains challenging because of disease rarity, clinical heterogeneity, and the lack of standardized treatment protocols, with only French guidelines currently providing formal recommendations [4]. Treatment responses are often variable, and therapeutic options are limited in relapsing or treatment-resistant disease. We report a patient with steroid-dependent relapsing polychondritis who failed multiple immunomodulatory therapies and achieved remission with anti-CD20 agents, including successful disease control with rituximab and obinutuzumab.

A 29-year-old woman was diagnosed with RP at age 13 after presenting with scleritis, hoarseness, costochondritis, and painful auricular chondritis. Immunologic work-up and inflammatory markers were unremarkable. Initial treatment with prednisone and azathioprine resulted in only partial clinical response, with persistent scleritis and recurrent auricular inflammation. Methotrexate was subsequently introduced; however, disease control remained inadequate, as auricular chondritis progressed and eventually led to cauliflower ear deformity (Figure 1a). Chronic corticosteroid exposure also resulted in treatment-related adverse effects. Rituximab was then administered, resulting in significant disease control and allowing tapering and eventual discontinuation of prednisone. Over the following years following a year of rituximab-induced remission, she experienced intermittent mild to moderate flares with recurrent costochondritis, auricular pain and swelling, and occasional scleritis, without major organ involvement, managed with mycophenolate mofetil (MMF) or parenteral methotrexate with only partial symptom relief while requiring potent analgesics; she consistently refused corticosteroids.

In April 2023, she developed fatigue, costochondritis, polyarthritis, intermittent scleritis, tinnitus, and nail pitting (Figure 1b). Her symptoms worsened, requiring codeine for pain control, and significantly interfering with quality of life. Treatment with NSAIDs and adalimumab was ineffective. High-dose corticosteroids, methotrexate injections, and upadacitinib were attempted but discontinued due to adverse effects. Laboratory evaluation, including inflammatory markers, ANA, anti-dsDNA, anti-CCP, and rheumatoid factor, was unremarkable. A lymphocyte panel showed increased CD20+ (994 cells/cu.mm) and CD19+ (994 cells/cu.mm) B-cell counts, exceeding the laboratory reference ranges (CD20+: 139–347; CD19+: 118–322 cells/cu.mm) (Table 1). There were no clinical or laboratory features suggestive of an underlying clonal hematologic disorder.

Given her relapsing course, elevated B-cell levels, and prior favorable though brief complete response to rituximab, she opted to try obinutuzumab (1 g infusions on days 0 and 15). Marked clinical improvement was observed after the first dose, with significant reduction in joint pain and costochondritis and resolution of scleritis. Following the second infusion, all symptoms resolved completely without adverse events. She was able to discontinue analgesics and taper off prednisone (from 20 mg/day) and was maintained on MMF 1 g/day. A repeat lymphocyte

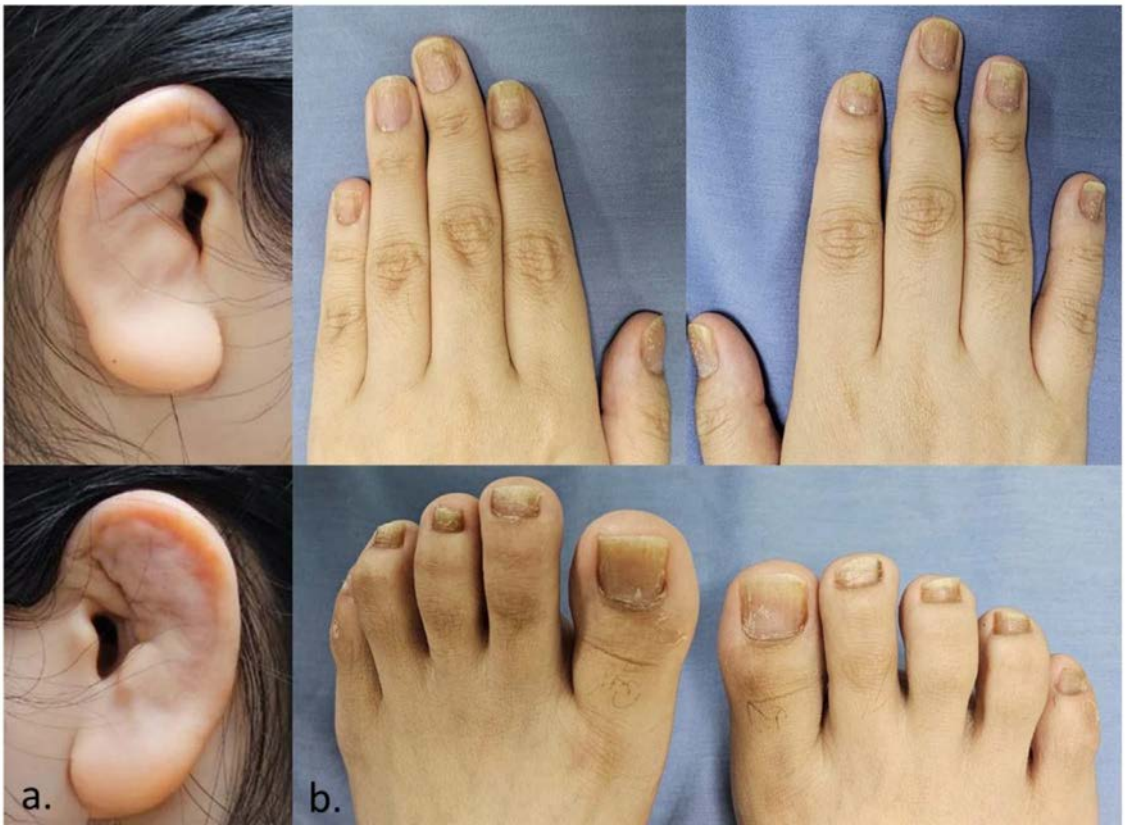

FIGURE 1 | (a) Cauliflower ear deformity of both ears and (b) nail pitting on both hands and feet.

TABLE 1 | Lymphocyte counts before and 6 months after obinutuzumab (OBN).

	Lymphocyte counts, cells/cu.mm		
	Before OBN	**6 months after OBN**	**Reference values**
CD3 Pan T lymphocytes	3290	2143	1220-2256
CD4 T helper cells	1638	964	581–1177
CD8 T suppressor cells	1649	1150	490–1031
CD20+ B cells	994	21	139–347
CD19+ B cells	994	21	118–322

Abbreviation: OBN, Obinutuzumab.

panel 6 months post-obinutuzumab showed marked depletion of CD20+ and CD19+ cells (Table 1). As of this writing, 18 months after obinutuzumab, she remains in clinical remission.

Although the pathogenesis of RP remains incompletely understood, both genetic susceptibility and immune dysregulation contribute to disease expression. HLA-DR4 has been identified as a major susceptibility allele [5], and both humoral and cellular immune mechanisms are implicated. In particular, B cells play a central role through autoantibody production, antigen presentation, and amplification of inflammatory cascades targeting cartilage-associated proteins [1, 4]. Murine models of RP fail to develop disease in B-cell-deficient mice, supporting their pathogenic role [6].

Treatment is guided by disease severity. NSAIDs, colchicine, and glucocorticoids are used in mild disease, whereas methotrexate, cyclophosphamide, azathioprine, and MMF are employed in moderate to severe cases [1, 3]. Refractory RP remains challenging and often requires biologics. TNF-α inhibitors (e.g., infliximab and adalimumab) are most commonly used and have shown efficacy, whereas abatacept and tocilizumab have shown promise as second-line therapies [2–4].

Though the role of rituximab, an anti-CD20 agent, remains variable and debated in RP [7], the patient's earlier favorable response to rituximab and the availability of the new anti-CD20 agent obinutuzumab prompted the decision to use the latter for the recent severe RP flare refractory to other immunosuppressive/immunomodulating agents. Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody that induces B-cell depletion through enhanced antibody-dependent cellular cytotoxicity and direct, caspase-independent apoptosis [8]. Compared with rituximab, which relies primarily on complement-dependent cytotoxicity (CDC), obinutuzumab mediates stronger FcγRIIIa-dependent cellular cytotoxicity and reduces CDC-related effects [8]. Given limited options for steroid-dependent RP despite multiple immunomodulatory therapies, this case consistently illustrates achievement of disease control with anti-CD20 therapy chimeric rituximab, which was later re-established with humanized obinutuzumab during relapse, supporting continued responsiveness to B-cell-targeted therapy and reinforcing the role of B cells in RP pathogenesis.

Author Contributions

F.P.K.L. and S.V.N. contributed to conceptualization and patient management. F.P.K.L. performed data collection and drafted the manuscript. S.V.N. supervised and critically revised the manuscript. All authors approved the final version.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Fayanne Patricia K. Lim
Sandra V. Navarra

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ORIGINAL ARTICLE

Recombinant Human Tumor Necrosis Factor Receptor Fusion Protein as Treatment for Gout Flare

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ABSTRACT

Objectives: A single-center, prospective, random, open-label study of acute gout patients treated with etanercept.

Methods: The treatment protocol involved subcutaneous administration of etanercept at a dose of 25 mg twice in five days. The control group received 20 mg of methylprednisolone administered intravenously every day for a total of five days. Baseline assessments, conducted at the initiation of etanercept included visual analogue scale (VAS) scores and C-reactive protein (CRP) levels. The levels of CRP and VAS in the gout patient after being injected with etanercept or methylprednisolone for 5 days. Adverse events were diligently recorded throughout the study period.

Results: Etanercept demonstrated rapid and substantial alleviation of pain and inflammatory responses in all 12 acute gout patients. Its effect is comparable to that of methylprednisolone.

Conclusion: Etanercept might be contemplated for "off-label" use in gout patients who do not respond to standard therapy or glucocorticoid therapy, encounter severe side-effects and contraindications.

1 | Introduction

Gout is a form of inflammatory arthritis characterized by the deposition of monosodium urate crystals in joints [1]. Currently, a limited number of therapeutic drugs are available for treating gout, including colchicine, nonsteroidal anti-inflammatory medications, and corticosteroids. However, the use of these drugs at an optimal dosage may pose challenges for some patients with pre-existing conditions such as diabetes, renal, cardiovascular, or gastrointestinal diseases, due to significant and severe side effects or contraindications [2, 3] and these traditional medicines may not be effective in treating acute gout. Despite guidelines recommending the consideration of the IL-1β antibody as a treatment for gout flares, canakinumab is not readily available in China. Anakinra was approved in China in 2024 for the treatment of familial Mediterranean fever, cryopyrin-associated periodic syndromes, and Still's disease, but gout is not included in its indications. Firsekibart, as the IL1β monoclonal antibody drug approved for treating gout in China in July 2025, is expensive. Therefore, the exploration of alternative therapeutic options is commonly encountered in clinical practice.

One of the key players in the inflammatory process associated with gout is tumor necrosis factor-alpha (TNF-α). In gout, uric acid crystals are deposited in tissue and are phagocytosed by parenchymal cells, which subsequently induce a series of apoptosis through activating the necrotic RIPK1, RIPK3, and MLKL pathways. The resulting cell necrosis leads to the release of damage-associated molecular patterns (DAMPs), thereby activating immune cells to secrete proinflammatory cytokines such as IL-1β, IL-6, and TNF-α. Additionally, proinflammatory cytokines like TNF-α can further stimulate the necrotic RIPK1, RIPK3, and MLKL pathways via TNFR1. This self-amplifying cycle between cell death and inflammation is referred to as necroinflammation

Statement of Significance

Etanercept exhibited prompt and significant pain relief, and reduction of inflammatory reactions in all patients with acute gout in this study. The study reported no adverse effects among the participants. The success of etanercept in this study highlights its potential in managing acute gout by interrupting the necroinflammatory cycle.

and ultimately results in exacerbated tissue damage and potential organ failure [4]. The connection between TNF-α and gout has prompted exploration into anti-TNF-α therapies as a potential treatment option for gouty arthritis. Medications targeting TNF-α, such as etanercept, infliximab, and adalimumab, have been utilized in various inflammatory conditions, including rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel diseases. Several studies and case reports have investigated the efficacy of these anti-TNF agents in managing gout symptoms and reducing the frequency of gout attacks [5]. In this report, we present a single-center, random, open-labeled study of acute gout patients treated using etanercept.

2 | Study Design

This was an exploratory, proof-of-concept open-label, prospective, randomized, parallel-controlled trial, conducted between September 2020 and June 2022 at the Jiangxi Provincial People's Hospital. Given the absence of prior published data on the use of etanercept specifically for acute gout flares at the time of the study design, we were unable to reliably estimate an expected effect size for a formal power calculation. The sample size of 30 patients (15 per group) was chosen pragmatically as a convenience sample to generate preliminary data on efficacy and safety to inform the design of future larger-scale trials. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, and the protocol was reviewed and approved by the Ethics Committee of Jiangxi Provincial People's Hospital.

To be eligible for the study, patients had to be ≥18 years of age, have gout according to the ACR/European League Against Rheumatism (EULAR) 2015 classification criteria [6]. In addition, patients had to have had ≥1 episode of intolerance or nonresponsiveness to NSAIDs and colchicine or have had these treatments judged to be contraindicated or not appropriate. Signs of nonresponsiveness to NSAIDs and colchicine were prespecified and included lost efficacy over time, failure to treat acute gout pain, inadequate/unsatisfactory pain relief, or incapacity to achieve/maintain an adequate dose regimen of these agents. Patients taking specified pain relief medications or biologic agents prior to randomization were excluded. Exclusion criteria included patients with an active, untreated infection, uncontrolled diabetes, uncontrolled heart failure, or chronic renal failure with a creatinine clearance less than 30 mL/min. Consent for etanercept or methylprednisolone administration was obtained from all patients.

The random number generator was used to create a randomization list for the eligible participants, who were randomly assigned in a 1:1 ratio to either the Methylprednisolone group or the etanercept group. The treatment protocol included subcutaneous administration of etanercept at a dose of 25 mg twice in 5 days (Day 1 and Day 3). The dosing regimen of etanercept 25 mg subcutaneously, administered twice with a 3 day interval, was selected based on two main factors. First, it aligns with the standard China's Food and Drug Administration approved dosing schedule for etanercept in its indicated chronic inflammatory conditions (like rheumatoid arthritis), representing a clinically relevant and well-understood exposure. Second, this regimen was chosen to provide rapid and sustained TNF inhibition over the typical 5–7 day duration of an acute, severe gout flare, with the second dose serving to consolidate the response. The methylprednisolone group received 20 mg of methylprednisolone administered intravenously every day for a total of five days. According to the 2024 Update of Chinese Guidelines for Management of Hyperuricemia and Gout Part II and the 2020 American College of Rheumatology (ACR) guideline, systemic glucocorticoids (including intravenous and oral administration) are recommended as alternative first-line treatments for acute gout flares in patients with contraindications to colchicine and NSAIDs [7]. Since etanercept is administered subcutaneously, we selected an intravenous corticosteroid regimen to maintain consistency in the route of administration (both parenteral) and to ensure bioequivalence in terms of absorption. This approach allowed us to isolate the treatment effect without introducing variability related to oral bioavailability. The 5-day treatment regimen is temporally aligned with the etanercept dosing schedule in the treatment group, which covers a similar period of approximately one week. The updated "Gout Management Guidelines" by EULAR in 2016 proposed recommended first-line options for acute flares include oral corticosteroid (30–35 mg/day of equivalent prednisolone for 3–5 days) [8]. Although oral glucocorticoids are more commonly recommended in international guidelines, short-term intravenous pulse or intravenous therapy remains a widely accepted and effective clinical practice in hospitalized patients with severe, refractory gout flares.

Baseline assessments, conducted at the initiation of etanercept or methylprednisolone, included visual analog scale (VAS) scores and C-reactive protein (CRP) levels. The level of CRP and VAS in the gout patient after being injected with etanercept or methylprednisolone for 5 days, and adverse events were diligently recorded throughout the study period. The study was registered at ClinicalTrials.gov (identifier NCT NCT05925166).

2.1 | Statistical Analysis

Demographic and clinical features were displayed using standard descriptive statistics, including mean ± S.D., number (percentage) where appropriate, or Fisher's exact test. The comparison between the two groups was conducted using Mann–Whitney *U* test, and two-way mixed ANOVA. The intra-group comparison uses the Wilcoxon signed-rank test.

3 | Results

3.1 | Patient Characteristics

Two groups each had 3 participants withdraw from the study; we did not include them in the statistics. The baseline

characteristics of gout patients are detailed in Table 1, indicating mean durations of gout, serum uric acid, visual analogue scale (VAS) scores, C-reactive protein (CRP), hospitalization period, short-term relapse rates, and creatinine at 10 years (SD 29.0), 400 μmol/L (SD 96.3), 8.33 (SD 1.16), 98.4 mg/L (SD 46.7), 10 days (SD 2.27), 16.67%, and 150.5 μmol/L (SD 82.5) in etanercept group, 10.01 (SD 8.52), 366.4 (SD 145.3), 7.5 (SD 0.67), 99.88 (SD 55.83), 9 days (SD 5.25), 0%, and 106 μmol/L (SD 42.3) in methylprednisolone group respectively. Among the two groups of patients, the number of those with hypertension, diabetes, coronary artery disease and chronic kidney disease were respectively 41.67%, 33.3%, 16.67%, and 75% in the etanercept group and 25%, 8.3%, 8.3%, and 41.67% in the methylprednisolone group. There were 41.67% patients with febuxostat at enrollment in etanercept group and 83.33% patients with febuxostat at enrollment in methylprednisolone group.

3.2 | Outcome

Following etanercept treatment, a significant reduction was observed in the mean VAS score from 8 (SD 1.2) at baseline to 3.1 (SD 0.7) ($p = 0.0005$). Similarly, in the methylprednisolone group, the VAS score also showed a significant reduction from 7.5 (SD 0.67) to 3.17(SD 0.72) ($p = 0.0005$). There was no difference between the two groups (Figure 1a). Additionally, the mean CRP showed a significant decrease from 98.4 mg/L (SD 46.7) at baseline to 17.5 mg/L (SD 17.1) in the etanercept group ($p = 0.001$). The CRP levels in the methylprednisolone group also showed a significant decrease from 99.88 mg/L (SD 55.83) to 13.08 mg/L (SD 11.26) ($p = 0.0005$) (Figure 1b). All gout patients experienced no side effects. There was no significant difference in CRP changes between the two groups. This indicates that etanercept has the same efficacy as methylprednisolone. This also indicates that for patients with gout who are intolerant to colchicine or hormones, etanercept can be used as an alternative treatment.

4 | Discussion

The findings from this open-label study provide compelling evidence that etanercept may serve as a viable therapeutic option for acute gout, particularly in patients who exhibit poor responses or severe side effects to traditional anti-inflammatory treatments. This study is significant as it addresses a critical gap in gout management. In China, gout management is particularly challenging. Traditional treatments such as colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) can be ineffective or pose significant risks for patients with comorbid conditions like diabetes, renal, cardiovascular, or gastrointestinal diseases [9].

The inflammatory process in gout begins with the deposition of monosodium urate (MSU) crystals in the joints and surrounding tissues, which leads to a complex cascade of cellular events that result in acute inflammation and chronic tissue damage [10]. Activated macrophages and neutrophils release proinflammatory cytokines, including TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6). TNF-α is a major cytokine that plays a pivotal role in the amplification of the inflammatory response [11]. The interaction between TNF-α and its receptors further stimulates the necrotic pathways. This activation leads

TABLE 1 | Baseline characteristics of the patients.

Characteristic	Etanercept ($n = 12$)	Methylprednisolone ($n = 12$)
Median age (SD)—year	64 (16.06)	59 (16.02)
Age ≥ 65 year—no. (%)	8 (67)	6 (50)
Male sex—no. (%)	12 (100)	12 (100)
Duration of gout(SD)—year	10.08 (5.63)	10.01 (8.52)
serum urate level (SD)—μmol/L	400 (96.28)	366.4 (145.3)
Presence of tophi—no. (%)	8 (66.67)	7 (58.33)
VAS(SD)	8.33 (1.16)	7.5 (0.67)
CRP(SD)-(normal range 0–8 mg/L)	98.45 (46.66)	99.88 (55.83)
Hospitalization period (SD)—day	10 (2.27)	9 (5.25)
Short-term relapse rates (%)	2/12 (16.67)	0/12 (0)
Creatinine (SD)—μmol/L	150.5 (82.5)	106 (42.3)
Hypertension (%)	5/12 (41.67)	3/12 (25)
Diabetes (%)	4/12 (33.3)	1/12 (8.3)
Chronic kidney disease (%)	9/12 (75)	5/12 (41.67)
Coronary artery disease (%)	2/12 (16.67)	1/12 (8.3)
Febuxostat (%)	5/12 (41.67)	10/12 (83.33)*

Note: Short-term relapse rates was defined as the recurrence of acute gout symptoms requiring further active treatment within 30 days of discharge.
*$p < 0.05$.

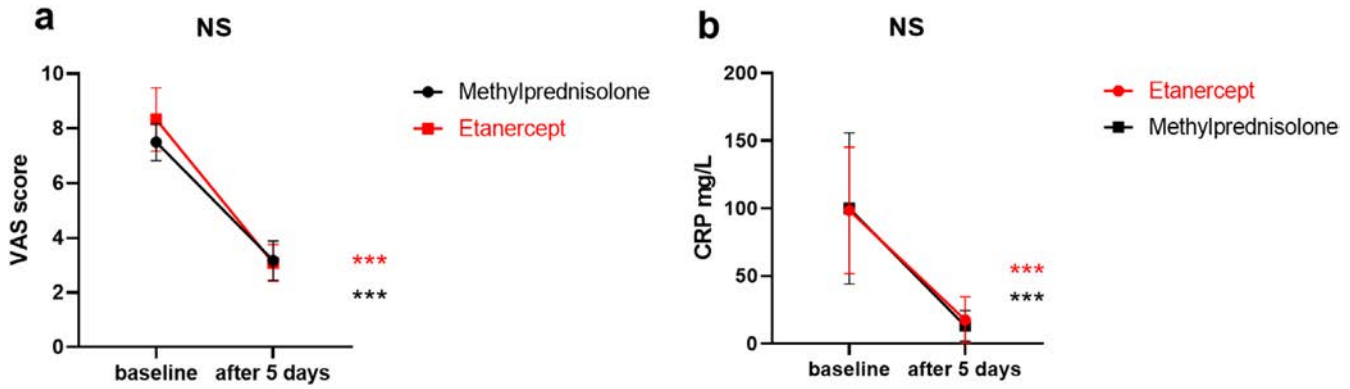

FIGURE 1 | (a) VAS scores in 12 gout patients with etanercept therapy and in 12 gout patients with methylprednisolone were compared to baseline. (b) CRP levels were compared in 12 gout patients with etanercept therapy and in 12 gout patients with methylprednisolone therapy. Wilcoxon matched-pairs signed rank test and two-way mixed ANOVA were used. ***$p < 0.001$.

to a form of programmed cell death known as necroptosis, releasing damage-associated molecular patterns (DAMPs) into the extracellular space. DAMPs perpetuate the inflammatory cycle by attracting and activating more immune cells, leading to sustained inflammation and tissue damage [12]. Chronic exposure to TNF-α contributes to the formation and maintenance of these tophi, causing joint destruction and chronic pain. Given its central role in the inflammatory cascade, TNF-α is a potential therapeutic target in gout. In this study, 24 male patients with gout flare were treated with etanercept or methylprednisolone. The results demonstrated a significant reduction in both pain (VAS scores) and inflammation (CRP levels) in the etanercept group and methylprednisolone group. The two treatments have comparable efficacy. Anti-TNF medications like etanercept, infliximab, and adalimumab have shown efficacy in conditions such as rheumatoid arthritis and ankylosing spondylitis by targeting and neutralizing TNF-α, thereby reducing inflammation and pain [13]. The success of etanercept in this study highlights its potential in managing gout flare by interrupting the necroinflammatory cycle. It is noteworthy that the study reported no adverse effects among the participants, underscoring the potential safety of etanercept in this patient population.

It is noteworthy that the study reported no adverse effects among the participants. The primary concerns with glucocorticoids in acute gout include hyperglycemia (particularly in diabetic patients), immunosuppression, fluid retention (exacerbating heart failure), osteoporosis with repeated use, and adrenal suppression. Etanercept, as a TNF-α inhibitor, carries its own distinct risks, including serious infections (particularly reactivation of tuberculosis), injection site reactions, and rare demyelinating disorders or hematologic abnormalities. Thus, we do not claim that etanercept is universally safer. However, in certain clinical scenarios—such as patients with poorly controlled diabetes where steroid-induced hyperglycemia poses a significant risk, or patients with severe heart failure where fluid retention from steroids may be deleterious—etanercept might represent a mechanistically different option with a safety profile that avoids these specific steroid-related complications. Conversely, etanercept would be contraindicated in patients with active infections or untreated latent tuberculosis. We do not advocate for etanercept as a "safer" alternative, but rather as a potential option with a different safety profile that may be suitable for specific patient subgroups.

The limitations of this study include the small sample size, which may affect the generalizability of the findings. Additionally, the follow-up period was relatively short, and longer-term studies are necessary to fully assess the safety and efficacy of etanercept in gout treatment. Further prospective studies with larger sample sizes and extended follow-up periods are imperative to validate these findings and establish comprehensive safety profiles.

In conclusion, our findings suggest that etanercept might be contemplated for "off-label" use in gout patients who do not respond to standard therapy or encounter severe side-effects and contraindications. Further prospective studies, encompassing a larger sample size, extended follow-up periods, and safety endpoints, are imperative to validate the efficacy and safety of Etanercept in the context of gout.

Author Contributions

Jiao L and Lihua D designed and drafted the manuscript. Jiao L, Zhongming X, Weizhong Z, and Sijia L performed the statistical analysis. All authors read and approved the final manuscript.

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Ethics Statement

This study was approved by the Institutional Review Board and Medical Ethics Committee of Jiangxi Provincial People's Hospital. The study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and has ClinicalTrials.gov number DLH86895639.

Consent

Written informed consent was acquired from all participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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International Journal of Rheumatic Diseases

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LETTER TO THE EDITOR

The Patient With Persistent Low Back Pain: Crystal Deposition or Lumbar Degeneration?

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Dear Editor,

A 68-year-old Chinese gentleman, with a history of hypertension and psoriasis, was initially admitted under Orthopedics for chronic low back pain lasting 6-months, which acutely worsened over the past 2 weeks with radiating pain to the dorsum of the left foot. He had no history of peripheral joint pains or podagra. On examination, he had no objective spinal tenderness or neurological deficits. The straight leg raise examination was negative. Scattered psoriatic plaques were observed over bilateral inguinal folds, upper, and lower limbs. There were no gouty tophi.

Initial investigations revealed a normal full blood count, inflammatory markers, and renal function. The uric acid level was significantly elevated at 472 umol/L. X-ray of the lumbar spine revealed multilevel spondylotic changes. Magnetic resonance imaging (MRI) identified the presence of L4/5 facet joint cysts compressing the left L5 traversing nerve root (Figure 1). Dual-energy computed tomography (DECT) of the lumbar spine showed monosodium urate (MSU) deposits within the L1/2 supraspinous ligament and several scattered urate deposits in the lumbar discs (Figure 2).

In view of concerns of spinal gout, a rheumatology referral was sought. Correlating the clinical and radiological findings, the nature and location of his back pain, and L5 radiculopathy symptoms were more in keeping with the identified degenerative spinal disease rather than crystal arthritis. For his lumbar spondylosis with radiculopathy, he was treated with analgesics (anarex, etoricoxib, gabapentin), and physiotherapy. However, urate-lowering therapy (ULT) in the form of allopurinol, with colchicine prophylaxis, was also commenced in shared decision-making with the patient to target uric acid levels < 360 umol/L, given that the uric acid crystals within the spine could contribute to bouts of back pain when it flares up, and more pertinently risk of neurological sequelae if hyperuricemia remains untreated. Despite 6–8 weeks of medical therapy, his symptoms persisted and affected his function. He then underwent endoscopic left lumbar 4/5 decompression with facet cyst excision, and experienced significant symptomatic improvement at 2 weeks post-surgery.

There are several learning points to be gleaned from this case.

Spinal gout is an uncommon entity which is hard to diagnose due to nonspecific symptoms. Patients may present with localized back pain, radiculopathy, or even neurological deficits from nerve root or cord compression [1]. Most cases affect the lumbar spine [1]. Although gout classically presents with sudden, severe pain in acute episodes of crystal-mediated synovitis, with interval pain-free periods, it may be particularly difficult to diagnose this condition based on symptom profile alone in patients with underlying spondylosis causing chronic baseline pain. In our patient, his radiating back pain to the dorsum of the foot suggested L5 dermatomal involvement, which correlated radiologically with the L4/5 facet cyst nerve root compression on the MRI rather than MSU deposits in L1/2 interspinous ligament on DECT. Moreover, the complete lack of symptom relief with colchicine and even after optimizing uric acid levels with urate-lowering treatment further went against spinal gout as the driver of his back pain. A meta-analysis of 17 studies on DECT use in gout found that it had a pooled sensitivity of 85%

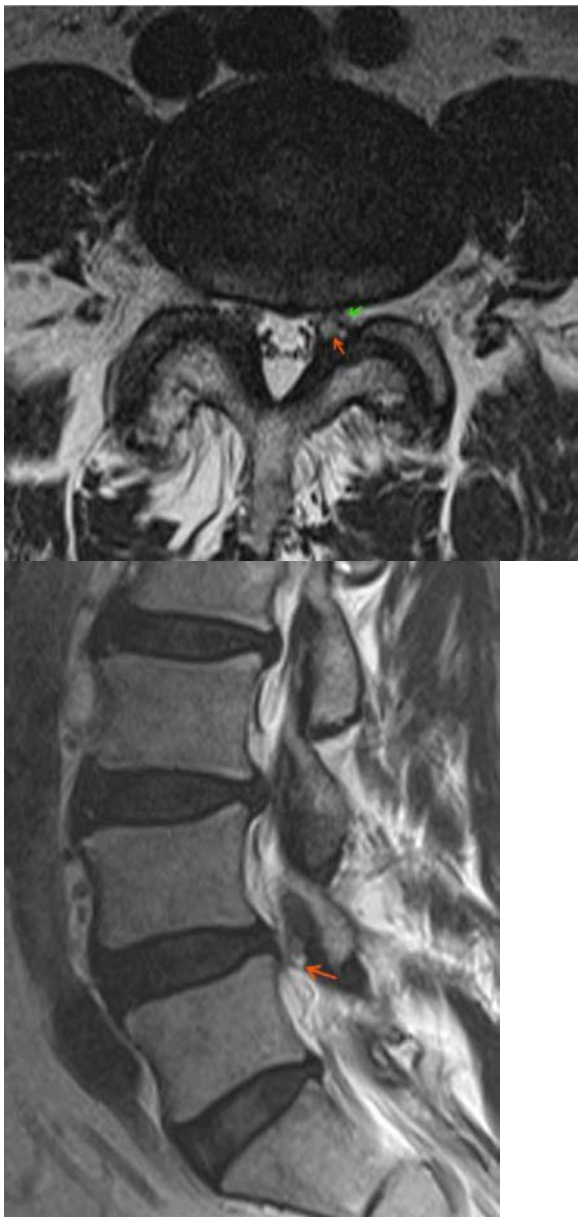

FIGURE 1 | Magnetic Resonance Imaging of the Lumbar Spine showing L4/5 Facet Joint Cysts compressing on the Left L5 traversing Nerve Root in both (A) Axial, and (B) Sagittal Views. *Red arrows indicate the facet cyst, and the green arrow is pointing at the compressed left L5 traversing nerve root.

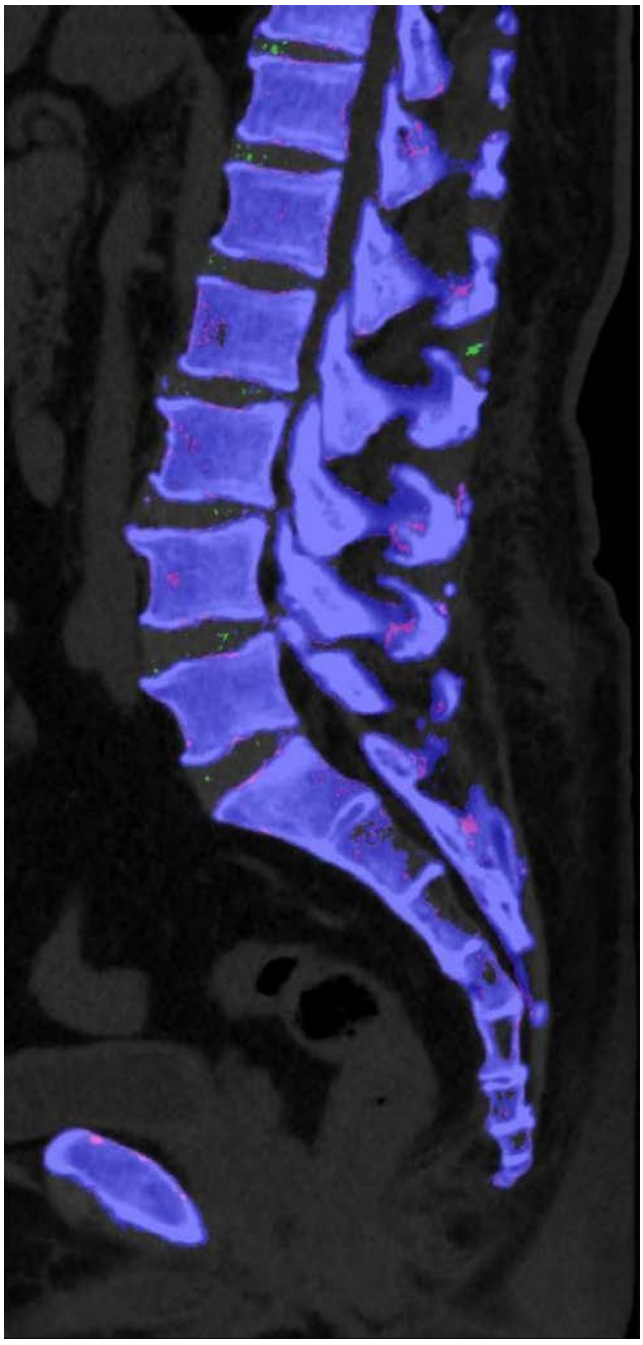

FIGURE 2 | Dual-Energy Computed Tomography Scan of the Lumbar Spine showing Urate Deposits at the L1/2 Supraspinous Ligament and Lumbar Discs, on Background of Degenerative Disease.

and specificity of 88% in the diagnosis of gout, with higher diagnostic accuracy in established gout than in recent gout [2]. False positives may occur in the presence of advanced osteoarthritis, artifacts (e.g., nailbed, skin, beam hardening, image noise), and vascular calcifications, whereas false negatives may occur in the first flare or acute symptoms, post-urate lowering therapy, and overly low parameter ratio setting [3]. This underscores the importance of correlating radiological findings with the clinical context.

Treatment decision-making in spinal gout is challenging for two main reasons. Firstly, there is often a lack of clarity in diagnosis due to the nonspecificity of symptoms and the inability to obtain synovial fluid for definitive crystal diagnosis [4]. In equivocal cases like our patient, the clinical significance of his MSU deposits on DECT and serum hyperuricemia (likely driven by psoriasis with high cell turnover) is unclear. While he does not meet the conventional criteria for urate-lowering therapy in gout, spinal MSU deposits were reportedly much more prevalent in gout patients compared to healthy individuals [5], and have the potential to grow and cause spinal cord/nerve root compression if hyperuricemia is left untreated. Further studies are necessary to clarify the treatment threshold for ULT initiation in patients with spinal-limited gout or MSU deposits.

Author Contributions

I.K.S.N. wrote the manuscript draft. J.N., C.C. critically reviewed and edited the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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ORIGINAL ARTICLE

Cross Cultural Validation of Work Productivity and Activity Impairment Questionnaire in Lupus Patients From Latin America

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ABSTRACT

Objective: The objective of this study is to perform a cross-cultural validation of the Work Productivity and Activity Impairment (WPAI-Lupus v2.0) questionnaire in Latin American individuals with systemic lupus erythematosus (SLE), using data from the GLADEL cohort.

Methods: GLADEL 2.0 is an observational cohort of SLE patients ≥18 years old. Clinical data, disease activity (SLEDAI-2K), damage index (SDI), physician's global assessment (PGA) and patient-reported outcomes (WPAI-Lupus v2.0, LupusQoL), were assessed at baseline and during follow-up. Construct validity was evaluated through Spearman correlations with SLEDAI-2K, SDI and LupusQoL. Internal consistency was assessed using Cronbach's alpha and responsiveness over 12 months was analyzed using the Wilcoxon signed-rank test. Appropriate statistical tests ($p < 0.05$) were performed using R software, version 4.4.0.

Results: Among 1083 patients, 684 were evaluated at baseline and at 12 months. Cronbach's alpha values were: absenteeism 0.54; presenteeism 0.64; overall work impairment 0.62; activity impairment 0.62. WPAI-Lupus v2.0 scores correlated with SLEDAI-2K ($p < 0.001$) and negatively with LupusQoL domains. Moderate correlations were observed between activity impairment and physical health, pain and planning ($r \approx -0.52$ to -0.58). Presenteeism and overall work impairment also showed moderate correlations with physical health and pain domains ($r \approx -0.49$ to -0.53). WPAI-Lupus v2.0 was sensitive to change over 12 months ($p = 0.001$) for all domains except intimate relationship.

Conclusions: WPAI-Lupus v2.0 demonstrated good validity, internal consistency, and responsiveness. It correlated with disease activity and quality of life, supporting the WPAI-Lupus v2.0 as a valid tool to assess work and activity impairment in Latin American patients with SLE.

For affiliations refer to page 9.

Significance and Innovations

- This is the first study to validate the WPAI-Lupus v2.0 questionnaire in a large, multi-national Latin American cohort of patients with systemic lupus erythematosus.
- The instrument demonstrated good internal consistency, construct validity, and responsiveness with significant associations between work/activity impairment, disease activity, and quality of life.
- The study provides the first validated tool for assessing work productivity loss and activity limitations in Latin American individuals with SLE.
- It fills a critical gap by providing a validated patient-reported outcome measure for use in clinical practice and research across diverse settings in the region.

1 | Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by immune dysregulation, autoantibody and immune complex formation, and a wide spectrum of clinical manifestations, ranging from mild to major organ involvement. This disease predominantly affects women of childbearing age and has a profound impact on quality of life, work productivity, and survival [1].

Latin America is a region characterized by linguistic, cultural, and socioeconomic diversity. It includes populations of mixed ancestry and varying degrees of access to healthcare, education, and employment. As a result, SLE may affect patients differently depending on their country of residence, income level, and available social support. Culturally valid instruments allow healthcare professionals to accurately assess disease burden, monitor treatment response, and design interventions that reflect the lived experiences of patients. In Latin America, SLE patients tend to present with greater severity and earlier onset compared to other populations, in part due to socioeconomic disparities, delayed diagnoses, and limited access to specialist care [2]. Lupus nephritis represents one of the major complications affecting patients with lupus in Latin America, where disease burden tends to be more severe and access to specialized care is often limited. This condition imposes a substantial burden on patients' work productivity and can adversely affect their activity levels and productivity [2, 3].

Moreover, although advances in the treatment of LN have improved clinical outcomes, the impact of these treatments on work productivity remains understudied. This gap underscores the need for culturally adapted and psychometrically robust tools to assess productivity loss in Latin American patients with SLE.

Given that SLE commonly affects individuals during their most productive years, assessing work-related and activity-related impairment is essential for capturing the broader impact of the disease. Patient-reported outcomes (PROs) have emerged as critical tools in understanding disease burden beyond clinical and laboratory parameters. Among them, the Work Productivity and Activity Impairment (WPAI) questionnaire is an instrument to measure impairments in both paid work and unpaid work, designed to measure disease-related effects on absenteeism, presenteeism, overall work productivity, and activity impairment during the past seven days [4, 5]. It has been validated to quantify work impairments for numerous diseases such as asthma, psoriasis, irritable bowel syndrome (IBS), ankylosing spondylitis (AS) and Crohn's disease [6–8]. In addition, the linguistic validity of the WPAI General Health (WPAI:GH) has been previously established for the U.S. Spanish translation among a diverse U.S. Spanish-speaking population, including individuals with minimal education, as well as for the Brazilian Portuguese version [9, 10]. A disease-specific version of this tool, the WPAI-Lupus v2.0, was developed to better reflect the unique impairments faced by individuals living with SLE.

While the WPAI-Lupus v2.0 has been used in global studies, its measurement properties have not been evaluated in a large Latin American SLE population. This is a critical limitation, as applying PROs without proper validation can lead to inaccurate interpretations and potentially misleading results. Cultural factors, socioeconomic disparities, and variability in healthcare access may influence how patients perceive and report work limitations and activity impairment. Therefore, validating such tools in specific regional contexts is crucial to ensure their relevance and measurement accuracy.

The Latin American Group for the Study of Lupus 2.0 (GLADEL 2.0) is a multicenter, observational study that includes both incident and prevalent cases of SLE patients from several Latin American countries. The geographic, ethnic, and socioeconomic diversity of the cohort makes it a unique and valuable resource for developing regionally valid outcome measures [11].

To date, no studies have specifically validated the WPAI-Lupus v2.0 in Latin American SLE patients, nor explored its responsiveness to disease activity in this context. By conducting a cross-cultural validation of the WPAI-Lupus v2.0 in this population, we aim to ensure the reliability and appropriateness of this tool for use in both clinical settings and research initiatives across the region. Taking advantage of this diverse and representative dataset, our study aims to perform a cross-cultural validation of the WPAI-Lupus v2.0 questionnaire and its ability to capture the real-life burden of lupus on work and activity performance in Latin American patients with SLE, based on data from the GLADEL 2.0 cohort. Our hypothesis is that impaired work productivity and reduced quality of life are logically associated with higher disease activity in patients with SLE.

2 | Methods

2.1 | Patient Selection

GLADEL 2.0 is an observational cohort of SLE patients ≥18 years of age with diagnosis of SLE according to either the 1982/1997 American College of Rheumatology (ACR) [12, 13] and/or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) [14] classification criteria. Participants provided informed consent and were enrolled between May 2019 and October 2023. Baseline data on clinical features, laboratory parameters, and comorbidities were collected using

ARTHROS-Web, with follow-up at 6 months and annually thereafter. Patients were stratified into four groups based on lupus nephritis (LN) status: Group I: SLE, without LN (never); Group II: SLE, with prevalent LN (at any time during their disease course), currently inactive; Group III: SLE, with prevalent LN (at any time during their disease course), currently active; and Group IV: SLE, with incident LN (≤ 3 months since onset) [11].

2.2 | Inclusion Criteria

Patients enrolled in the cohort who completed the WPAI-Lupus v2.0 questionnaire at baseline and at 12 months were included in the present analysis. Work-related domains of the WPAI (absenteeism, presenteeism, and overall work productivity loss) were evaluated only in patients who reported being employed at the time of assessment. Accordingly, analyses examining associations with these work-related domains inherently included only employed patients. The activity impairment domain was assessed in all patients, regardless of employment status, in accordance with the WPAI instrument guidelines.

2.3 | WPAI-Lupus v2.0 Instrument

The WPAI-Lupus v2.0 questionnaire [4] assesses work productivity impairment related to SLE over the previous 7 days through six items grouped into four domains: 1- absenteeism (percentage of work time missed due to SLE; a higher percentage corresponds to more time missed from work); 2- presenteeism (reduced productivity while at work; a higher percentage corresponds to worse productivity while at work); 3- overall work impairment (a composite of absenteeism and presenteeism domains); and 4- activity impairment (limitations in regular daily activities outside of work). All scores are expressed as percentages, with higher values indicating greater impairment.

Data collection within the GLADEL 2.0 cohort was performed using an electronic case report form (eCRF), ARTHROS_web, which was completed by the investigator. Patient-reported outcomes (PROs), including the WPAI-Lupus v2.0 questionnaire, were administered according to local practice at each participating center. Questionnaires were completed by patients electronically (e.g., in PDF format) or with assistance from trained study personnel when required, particularly to ensure adequate comprehension without influencing patient responses.

This study is being conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH). The protocol has received Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study at all participating centers. All patients signed the informed consent. Confidentiality of all participants is being maintained.

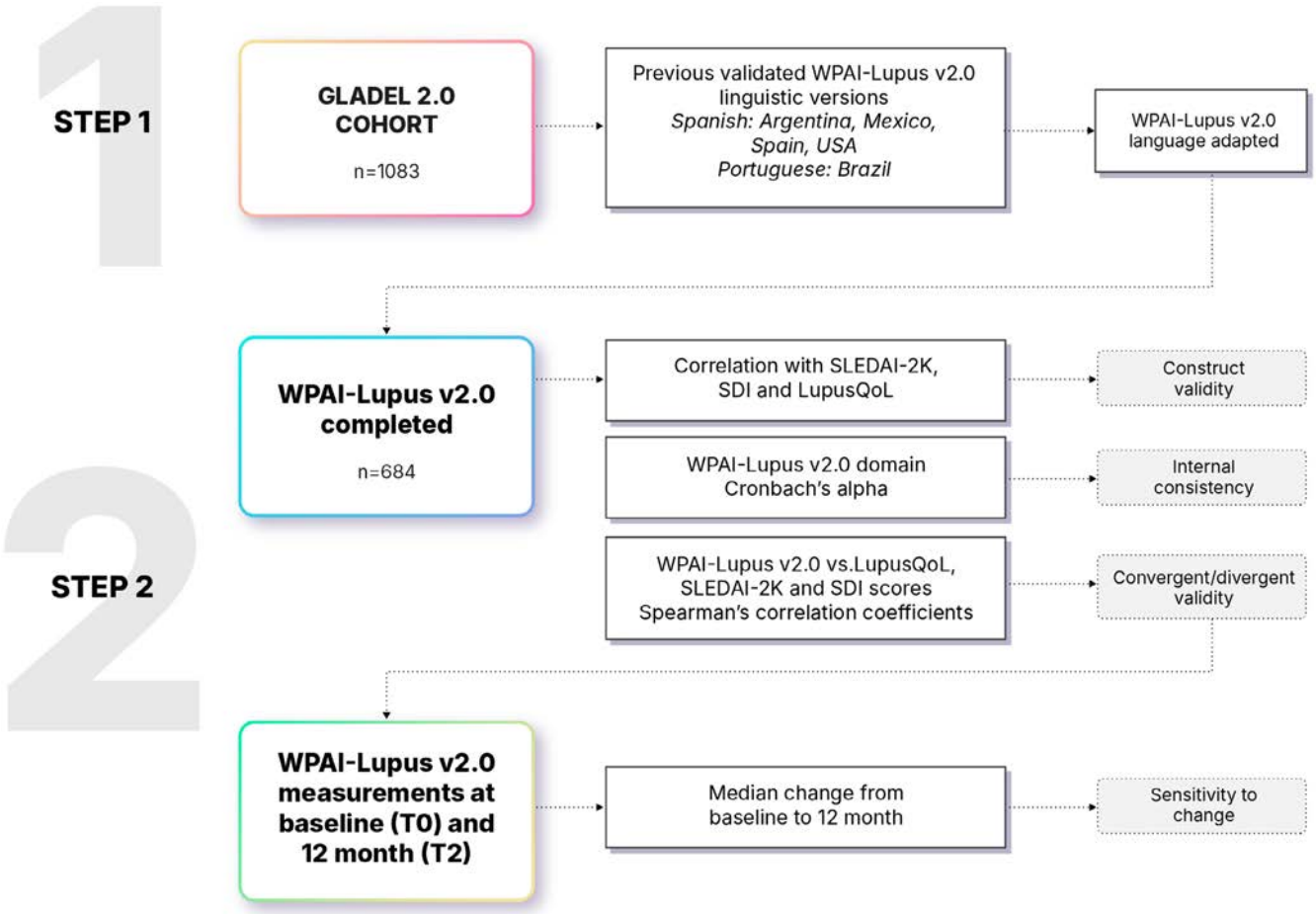

FIGURE 1 | Flow diagram of the WPAI-Lupus v2.0 validation process.

TABLE 1 | Sociodemographic and Clinical Characteristics at Baseline.

Variable	Frequency ($N = 684$)
Age at diagnosis, mean (SD)	29.1 (11.7)
Age at enrollment, mean (SD)	37.0 (12.6)
Female sex, *n*(%)	612 (89.5)
Education (years) ($n = 805$), mean (SD)	13.4 (3.9)
Ethnicity, *n*(%)	
Mestizo	451 (66)
Caucasian	181 (26.5)
Afro-Latinoamerican	46 (6.7)
Indigenous	4 (0.6)
Other	1 (0.1)
Socioeconomic status, *n*(%)	
Low	70 (10.4)
Lower-Middle	194 (28.7)
Middle	246 (36.4)
Upper-middle	148 (21.9)
High	17 (2.5)
Employment status, *n*(%)	
Full-time employed	280 (43)
Part-time employed	101 (15.5)
Unemployed (seeking work)	95 (14.6)
Unemployed due to illness	91 (14.0)
Student	56 (8.6)
Retired	28 (4.3)
Marital status, *n*(%)	
Single	311 (46.3)
Married/Living with partner	307 (45.8)
Separated-Divorced	42 (6.3)
Widowed	11 (1.6)
Health insurance, *n*(%)	
Full coverage	382 (56.5)
No coverage	216 (32.0)
Partial coverage	78 (11.5)
SLE Groups[a], *n*(%)	
Without nephritis	289 (42.3)
With prevalent inactive LN	143 (20.9)
With prevalent active LN	142 (20.8)
With incident (LN active)	110 (16.1)
Comorbidities, *n*(%)	348 (51.0)
Arterial hypertension	179 (26.2)
Diabetes	25 (3.7)
Dyslipidemia	83 (12.3)
Body mass index (BMI), *n*(%)	
Underweight	20 (1.3)
Normal weight	307 (44.8)
Overweight	229 (33.512)
Obesity	128 (18.7)
Secondary Cushing's Syndrome, *n*(%)	78 (11.4)
SDI ≥ 1, ($n = 665$), n(%)	246 (37.0)
SLEDAI-2 K ($n = 680$), median (Q3-Q1)	4.0 (0.8; 10.0)
PGA, *n*(%)	
Mild	201 (20.5)
Moderate	183 (33.8)
Severe	87 (46.5)

[a]At cohort entry.
Abbreviations: LN: lupus nephritis, BMI: Body Mass Index, SDI: SLICC/ACR damage index, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, PGA: patient global assessment.

3 | Statistical Analysis

Sociodemographic characteristics, clinical variables, disease activity (SLEDAI-2 K), organ damage (SDI), Physician's Global Assessment (PGA), and patient-reported outcomes (WPAI-Lupus v2.0 and LupusQoL) were assessed at baseline and at 12-month follow-up. This study was based on WPAI-Lupus v2.0, a questionnaire that had been previously validated and linguistically adapted, establishing semantic and cultural equivalence in both Spanish and Portuguese [9, 10]. As no gold standard exists to assess and compare the impact on work productivity in lupus patients, validated instruments were used for comparison. The construct validity was assessed by examining correlations between the WPAI-Lupus v2.0 and established disease measures, including the LupusQoL questionnaire for quality of life [15], the SLEDAI-2 K for disease activity [16], the SLICC/ACR damage index (SDI) for organ damage [17], and the Physician's Global Assessment (PGA). Internal consistency of WPAI domains was evaluated using Cronbach's alpha based on tetrachoric correlations among items. Convergent and divergent validity were examined using a correlation matrix of Spearman's correlation coefficients. Sensitivity to change was evaluated through the median change from baseline to month 12, and its significance was tested using the Wilcoxon signed-rank test (Figure 1). Normality of continuous variables was assessed using the Shapiro–Wilk

TABLE 2 | WPAI:lupus v2.0 questionnaire results at baseline and at 12-month follow-up.

	At cohort entry ($N=684$)		At 12 months ($N=684$)	
Variable	***n***	**%**	***n***	**%**
1- Currently employed, n%	310	45.3	295	43.1
	n	Median (Q3-Q1)	*n*	Median (Q3-Q1)
2- Work hours missed due to SLE	302	0 (0.0;8.0)	295	0 (18)
3- Work hours lost due to other causes	310	0 (0.0;3.8)	293	0 (18)
4- Actual hours worked per week	310	32 (10.5;43.5)	294	36 (20.0;45.0)
5- Impact of lupus on ability to work (0 a 10)	310	2 (0.0;5.8)	295	0 (0.0;3.0)
6- Impact of lupus daily activities (0 a 10)	684	4 (1.0;7.0)	683	2 (0.0;5.0)
WPAI:Lupus v2.0 Score				
Absenteeism	302	0 (0.0;24.4)	286	0 (18)
Presenteeism	310	20 (0.0;57.5)	295	0 (0.0;30.0)
Work productivity loss	302	30 (0.0;70.0)	286	10 (0.0;42.4)
Activity impairment	684	40 (10.0;70.0)	683	20 (0.0;50.0)

Note: Absenteeism: percent work time missed due to health, Presenteeism: percent impairment while working due to health, Overall work productivity loss: combined percent of absenteeism and presenteeism, Activity impairment: percent impairment in non-work-related daily activities.

TABLE 3 | Cronbach's alpha for WPAI: Lupus v2.0 components at baseline and 12-month follow-up.

Domains	Time	*n*	Alpha	95% CI (LL)	95% CI (UL)
Percent work time missed due to health	T0	302	0.54	0.47	0.59
	T2	285	0.62	0.55	0.68
Percent impairment while working due to health	T0	310	0.64	0.59	0.68
	T2	293	0.71	0.65	0.75
Percent overall work impairment due to health	T0	302	0.62	0.56	0.66
	T2	285	0.70	0.65	0.74
Percent activity impairment due to health	T0	302	0.62	0.56	0.66
	T2	285	0.70	0.65	0.74

Abbreviations: CI: Confidence Interval; LL: Lower Limit; UL: Upper Limit; T0: baseline; T2: 12-month follow-up.

test. Correlation analyses were performed using Spearman's correlation coefficients according to data distribution. A p-value <0.05 was considered statistically significant. All statistical analyses were conducted using R version 4.4.0 [18].

4 | Results

Of the 1083 patients enrolled in the cohort, 684 completed the WPAI-Lupus v2.0 questionnaire and were evaluated at baseline and at 12 months. Overall, 89.5% were female. The median age at diagnosis was 27 years (Q3-Q1 20–36), and at cohort entry, 36 years (Q3-Q1 27–45). Most patients (66.0%) were of Mestizo ethnicity, the median of years of formal education was 13 (Q3-Q1 11–16) years, and 39.1% had low or low-middle socioeconomic status. At baseline, 57.8% of patients had renal involvement. Median disease activity (SLEDAI-2k) was 4 (Q3-Q1 0.8–10.0), and cumulative damage (SDI) was 0 (0.0–1.0). Based on PGA, 33.8% were classified as moderate and 46.5% severe (Table 1).

Findings from the WPAI-Lupus v2.0 questionnaire at baseline and 12 months are summarized in Table 2. At cohort entry, 45.3% of patients were employed. Among employed patients at baseline, the median (Q3; Q1) number of work hours lost due to SLE was 0 (0.0;8.0), and due to other causes, 0 (0.0;3.8). Patients worked a median (Q3; Q1) of 32 (10.5;43.5) hours per week. The impact of SLE on work ability and daily activities, measured on a 0–10 scale, was 2 (0.0;5.8) and 4 (1.0;7.0), respectively. At 12 months, 43.1% of patients remained employed. Among them, the median (Q3; Q1) hours lost due to SLE and other causes were 0 [18] and 0 [18] respectively, with 36 (20.0;45.0) hours worked per week. The median impact of SLE on work and daily activities decreased to 0 (0.0;3.0) and 2 (0.0;5.0), respectively. Figures S1 and S2 in the Supporting Information show box plots of WPAI-Lupus

TABLE 4 | Correlation Between WPAI: Lupus v2.0 Domains and SLEDAI-2K and SDI Scores.

Time	Score WPAI – SLEDAI-2K	Correlation[a]	95% CI	*p*-value
Baseline	Absenteeism	0.45	0.36; 0.54	0.001
	Presenteeism	0.41	0.30; 0.51	0.001
	Work productivity loss	0.48	0.39; 0.58	0.001
	Activity impairment	0.32	0.25; 0.39	0.001
12-month	Absenteeism	0.20	0.08; 0.32	0.001
	Presenteeism	0.22	0.11; 0.33	0.001
	Work productivity loss	0.27	0.15; 0.38	0.001
	Activity impairment	0.27	0.20; 0.34	0.001
Time	Score WPAI – SDI	Correlation	95% CI	*p*-value
Baseline	Absenteeism	0.00	−0.11; 0.13	0.943
	Presenteeism	−0.03	−0.15; 0.10	0.580
	Work productivity loss	−0.03	−0.13; 0.11	0.665
	Activity impairment	0.03	−0.02; 0.14	0.476
12-month	Absenteeism	0.11	−0.01; 0.24	0.065
	Presenteeism	0.03	−0.08; 0.15	0.617
	Work productivity loss	0.07	−0.05; 0.18	0.286
	Activity impairment	0.11	0.03; 0.18	0.009

[a]Spearman Correlation Coefficient(r)between WPAI:Lupus v2.0 domains and disease activity (SLEDAI-2K) and organ damage (SDI); CI: Confidence interval; WPAI: Work productivity and activity impairment.

v2.0 responses (items 1, 4, 5, and 6) and domain scores, respectively, at cohort entry and at 12 months.

Internal consistency of each WPAI-Lupus v2.0 domain at baseline was assessed using Cronbach's alpha. Values (95% CI) were: absenteeism 0.54 (0.47–0.59), presenteeism 0.64 (0.59–0.68), overall work impairment 0.62 (0.56–0.66), and activity impairment 0.62 (0.56–0.66) (Table 3). Correlation matrices between WPAI-Lupus v2.0 questions and each domain of the score are shown in the Supporting Information (Figures S3–S10).

At baseline, WPAI-Lupus scores and disease showed significant correlations with disease activity (SLEDAI-2K): absenteeism ($r = 0.45$), presenteeism ($r = 0.41$), overall work impairment ($r = 0.48$), and activity impairment ($r = 0.32$); all $p < 0.001$. These correlations persisted at 12 months: absenteeism ($r = 0.20$), presenteeism ($r = 0.22$), overall work impairment ($r = 0.27$), and activity impairment ($r = 0.27$); all $p < 0.001$. No significant correlations were observed with SDI (Table 4).

WPAI-Lupus v2.0 domains showed strong positive correlations among themselves, particularly between presenteeism and overall work impairment ($r = 0.91$), and between overall work impairment and activity impairment ($r = 0.76$). All WPAI-Lupus v2.0 domains were negatively associated with LupusQoL domains, supporting convergent validity. Moderate correlations were observed between activity impairment and physical health ($r = -0.58$), pain ($r = -0.52$), and planning ($r = -0.57$). Presenteeism and overall work impairment also showed moderate correlations with physical health and pain domains (r ranging from −0.49 to −0.53) (Table 5).

Sensitivity to change from baseline to 12 months was assessed using the Wilcoxon signed-rank test. Median (Q3-Q1) changes were: absenteeism ($n = 223$): 0 (−0.1; 0.0), presenteeism ($n = 235$): 0 (−0.3; 0.0), overall work impairment ($n = 223$): 0 (−0.4; 0.0), and activity impairment ($n = 683$): 0 (−0.3; 0.1). All changes were statistically significant ($p = 0.001$ for all domains) (Table 6).

5 | Discussion

This is the first study to perform a cross-cultural validation of the WPAI-Lupus v2.0 questionnaire in a large, multicenter Latin American cohort of patients with SLE, using data from the GLADEL 2.0 cohort. Our findings support the instrument's content validity, internal consistency, construct validity, and responsiveness to clinical changes, establishing it as a valid tool to assess work productivity and activity impairment in SLE patients from diverse cultural and socioeconomic backgrounds.

At baseline, over half of the patients had renal involvement and moderate disease activity according to the SLEDAI-2K, while two-thirds were classified as having moderate-to-severe disease by PGA. Despite this, most had no cumulative damage as per SDI. Nearly 15% were unemployed due to the disease.

TABLE 5 | Correlation Matrix Between WPAI:Lupus v2.0 Domains and LupusQoL Dimensions at Baseline (Spearman's Correlation Coefficients).

Domain	Absenteeism	Presenteeism	Overall work impairment	Activity impairment	Pysical health	Pain	Planning	Intimate relationships	Burden to others	Emotional health	Body image	Fatigue
Absebteeism	1.00	0.53	0.75	0.49	−0.32	−0.33	−0.27	−0.22	−0.30	−0.29	−0.28	−0.29
Preseneesism		1.00	0.91	0.78	−0.53	−0.52	−0.49	−0.38	−0.39	−0.48	−0.46	−0.46
Overall work impairment			1.00	0.76	−0.49	−0.50	−0.46	−0.35	−0.39	−0.45	−0.39	−0.45
Activity impairment				1.00	−0.58	−0.52	−0.57	−0.43	−0.44	−0.49	−0.47	−0.49
Physical health					1.00	0.79	0.63	0.58	0.60	0.71	0.63	0.70
Pain						1.00	0.58	0.60	0.60	0.71	0.63	0.70
Planning							1.00	0.63	0.61	0.65	0.68	0.59
Intimate relationships								1.00	0.49	0.60	0.58	0.59
Burden to others									1.00	0.74	0.64	0.61
Emotional health										1.00	0.74	0.73
Body image											1.00	0.66
Fatigue												1.00

TABLE 6 | Change in WPAI: Lupus-v2.0 Domain Scores from Baseline to 12 Months.

Domains	Statistics	*p*-value[a]
Absenteeism (n)	223	
Median (Q3-Q1)	0.0 (−0.1;0.0)	0.001
Presenteeism (n)	235	
Median (Q3-Q1)	0 (−0.3;0.0)	0.001
Overall work impairment (n)	223	
Median (Q3-Q1)	0 (−0.4;0.0)	0.001
Activity impairment (n)	683	
Median (Q3-Q1)	0 (−0.3;0.1)	0.001

[a]*p*-value derived from the Wilcoxon signed-rank test.

Internal consistency of the WPAI-Lupus v2.0 was acceptable, with Cronbach's alpha ranging from 0.54 to 0.64 at baseline and exceeding 0.70 at 12-month follow-up. Although the baseline values did not exceed the conventional threshold of 0.70, they should be interpreted in the context of clinimetric evaluations and the nature of the construct being measured. The WPAI-Lupus v2.0 assesses multiple dimensions of work productivity and activity impairment, which are not necessarily expected to show high internal homogeneity. In instruments addressing social, behavioral, or functional outcomes, lower Cronbach's alpha values have been reported and considered acceptable or moderate. Similar findings have been described in the original WPAI validation studies and in other PRO measures [4]. These values are comparable to those reported in WPAI validation studies in other chronic conditions, including rheumatoid arthritis, axial spondyloarthritis, and Crohn's disease [7, 8, 19]. Similarly, a Brazilian validation study of the WPAI-GH reported high internal consistency (Cronbach's alpha = 0.74), confirming its reliability across domains [10].

Regarding construct validity, significant positive correlations were observed between WPAI-Lupus v2.0 domains and disease activity, particularly for absenteeism ($r = 0.45$), presenteeism ($r = 0.41$), and work productivity loss ($r = 0.48$), indicating that greater disease activity is associated with increased productivity loss. In contrast, the weak correlation with cumulative damage suggests that WPAI-Lupus v2.0 primarily captures current functional burden rather than long-term irreversible outcomes. These findings are consistent with previous studies in large lupus cohorts, where disease activity showed a stronger association with quality of life and functional status than accumulated damage [20].

We observed moderate to strong negative correlations between WPAI-Lupus v2.0 scores and health-related quality of life as measured by the LupusQoL, demonstrating a coherent and clinically meaningful pattern. As hypothesized, all WPAI domains were negatively correlated with LupusQoL domains, indicating that greater work and activity impairment was associated with poorer health-related quality of life. The strongest correlations were observed between activity impairment and physical health ($r = -0.58$), planning ($r = -0.57$), and pain ($r = -0.52$). These findings are in agreement with previous research demonstrating that pain and fatigue are key drivers of reduced productivity and functional impairment in SLE [2]. Similarly, a previous validation study of the WPAI-GH found significant correlation coefficients between work impairment, global productivity loss, activity impairment and all SF-36 domains [10]. On the other hand, the Spanish version of the WPAI:Pain was validated in a cohort of 577 patients from two university hospitals in Spain. It demonstrated excellent internal consistency (Cronbach's alpha = 0.896; Guttman split-half = 0.921) and strong test–retest reliability. Construct validity was supported by significant correlations with pain severity on a visual analog scale, further highlighting the instrument's utility in assessing pain-related work productivity [21].

Crucially, the WPAI-Lupus v2.0 demonstrated sensitivity to change, with significant reductions in absenteeism, presenteeism, overall work impairment and activity impairment at 12-month follow-up. Although effect sizes were modest, these changes reflect the instrument's ability to detect clinical improvement or stabilization over time, supporting its use in longitudinal research and clinical trials.

Regional validation of the WPAI-Lupus v2.0 score is particularly relevant given the socioeconomic and healthcare disparities in Latin America. In our cohort, a substantial proportion of patients were unemployed due to lupus and nearly half reported limited access to healthcare. Validating patient-reported outcome measures in this context ensures their reliability and applicability in both clinical and policy decision-making.

Strengths of our study include the large sample size, geographic diversity across Latin America, use of validated instruments (SLEDAI-2K, SDI, LupusQoL) and a longitudinal design. However, several limitations should be noted. First, the WPAI-Lupus v2.0 relies on self-report, which may be influenced by personal perception and cultural attitudes regarding work. Second, a notable proportion of patients were unemployed, limiting the applicability of work-related domains in some cases.

6 | Conclusions

The WPAI:Lupus v2.0 is a valid, reliable, and responsive instrument for evaluating work and activity impairment in Latin American patients with SLE. It demonstrated strong content validity, moderate internal consistency, and meaningful correlations with disease activity and quality of life, supporting its use in clinical practice and research to better understand lupus-related functional impairment and to inform patient-centered care and health resource planning.

Supporting Information include box plots of WPAI-Lupus v2.0 responses and domain scores, as well as scatter plots and correlation matrices between questionnaire items and domain scores at different time points, supporting the psychometric evaluation of the instrument.

Author Contributions

R.E.N. and I.P.-B. conceived and designed the project, performed the analyses, interpreted the results and wrote the manuscript. L.H.

performed the formal analyses. I.P.-B. supervised the execution of the project. All authors listed in this manuscript were involved in the generation of GLADEL cohort and drafting or revising this article critically for important intellectual content. All authors approved the final version to be published.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Box Plot of responses to the WPAI-Lupus v2.0 questionnaire. **Figure S2:** Box Plot of the WPAI-Lupus v2.0 Score Domains. **Figure S3:** and S4. Scatter plots and Correlation Matrices between the WPAI-Lupus v2.0 Questionnaire questions and domain 1 of the WPAI-Lupus v2.0 Score (at T0 and T2 respectively). **Figure S5:** and S6. Scatter plots and Correlation Matrices between the questions of the WPAI-Lupus v2.0 Questionnaire and domain 2 of the WPAI-Lupus v2.0 Score (at T0 and T2 respectively). **Figure S7:** and S8. Scatter plots and Correlation Matrices between the WPAI-Lupus v2.0 Questionnaire questions and domain 3 of the WPAI-Lupus v2.0 Score (at T0 and T2 respectively). **Figure S9:** and S10. Scatter plots and Correlation Matrices between the WPAI-Lupus v2.0 Questionnaire questions and domain 4 of the WPAI-Lupus v2.0 Score (at T0 and T2 respectively).

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LETTER TO THE EDITOR

Lower C-Reactive Protein and Preserved Cortisol Levels at Disease Onset Are Associated With Favorable Short-Term Prognosis in Polymyalgia Rheumatica

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Dear Editor,

Polymyalgia rheumatica (PMR) responds well to oral prednisolone (PSL); however, some patients experience recurrence during PSL tapering [1–5]. Relative adrenal insufficiency may be involved in disease development and progression [6, 7]. We aimed to assess recurrence risk factors, including adrenal function, in patients with PMR.

We enrolled patients diagnosed with PMR based on previously published criteria [8] between 2023 and 2025 at Takikawa Municipal Hospital and uniformly subjected them to a short-term treatment protocol: 15 mg PSL tapered by 2.5 mg every 4 weeks and discontinued after 24 weeks. Adrenocorticotropic hormone (ACTH) loading tests were performed 0, 4, 12, and 24 weeks after treatment initiation, and at recurrence (Figure 1A). Disease-modifying antirheumatic drugs were not used. In accordance with the 2012 European League Against Rheumatism/American College of Rheumatology provisional classification criteria for polymyalgia rheumatica, we collected clinical findings such as morning stiffness lasting 45 min or more, buttock pain or limited range of motion of the hip joint, and the presence or absence of joint symptoms other than those involving the shoulder or hip joints, as well as blood findings, such as rheumatoid factor and anti-cyclic citrullinated peptide antibodies, and ultrasound findings [8]. Autoantibodies associated with connective tissue diseases were measured to exclude an alternative diagnosis. Matrix metalloproteinase-3 (MMP-3), being reportedly increased in PMR [9], was also measured as an exploratory marker to assess its association with relapse and adrenal function. This prospective cohort study was conducted following the ethical tenets of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the Takikawa Municipal Hospital Ethics Committee (approval number: 22–06). Statistical significance was set at $p < 0.05$. All analyses were performed using the JMP Student Edition software (SAS Institute Inc., Cary, NC, USA).

No patients with PMR tested positive for rheumatoid factor or anti-cyclic citrullinated peptide antibodies. To exclude connective tissue diseases, antinuclear antibodies, anti-SS-A antibodies, anti-ARS antibodies, MPO-ANCA, and PR3-ANCA were measured at the initial consultation, and these tests were confirmed to be negative in all cases. Among the 16 patients included in the study, nine patients (56.3%) experienced recurrence: one at 1–4 weeks (15 mg PSL), one at 16–20 weeks (5 mg PSL), five at 20–24 weeks (2.5 mg PSL), and two at 25–28 weeks (no PSL). Seven patients (43.7%) did not experience recurrence and remained in remission until week 48 (Figure 1B). Although C-reactive protein (CRP) levels were significantly higher in the recurrence group compared with those in the non-recurrence group, the MMP-3 levels did not differ significantly between groups (median CRP: 8.6 vs. 1.9 mg/dL; $p = 0.0025$) (median MMP-3: 280.1 vs. 175.7 ng/mL; $p = 0.1986$) (Table 1). Evaluation of the ROC curve for recurrence and CRP level at disease onset yielded an AUC of 0.92. When a CRP level of 4.2 mg/dL was used as the cut-off, the sensitivity and specificity for predicting the recurrence rate were 85.7% and 100%, respectively. Kaplan–Meier analysis revealed significantly higher recurrence rate in the group with a baseline CRP level of ≥4.2 than that in the group with a

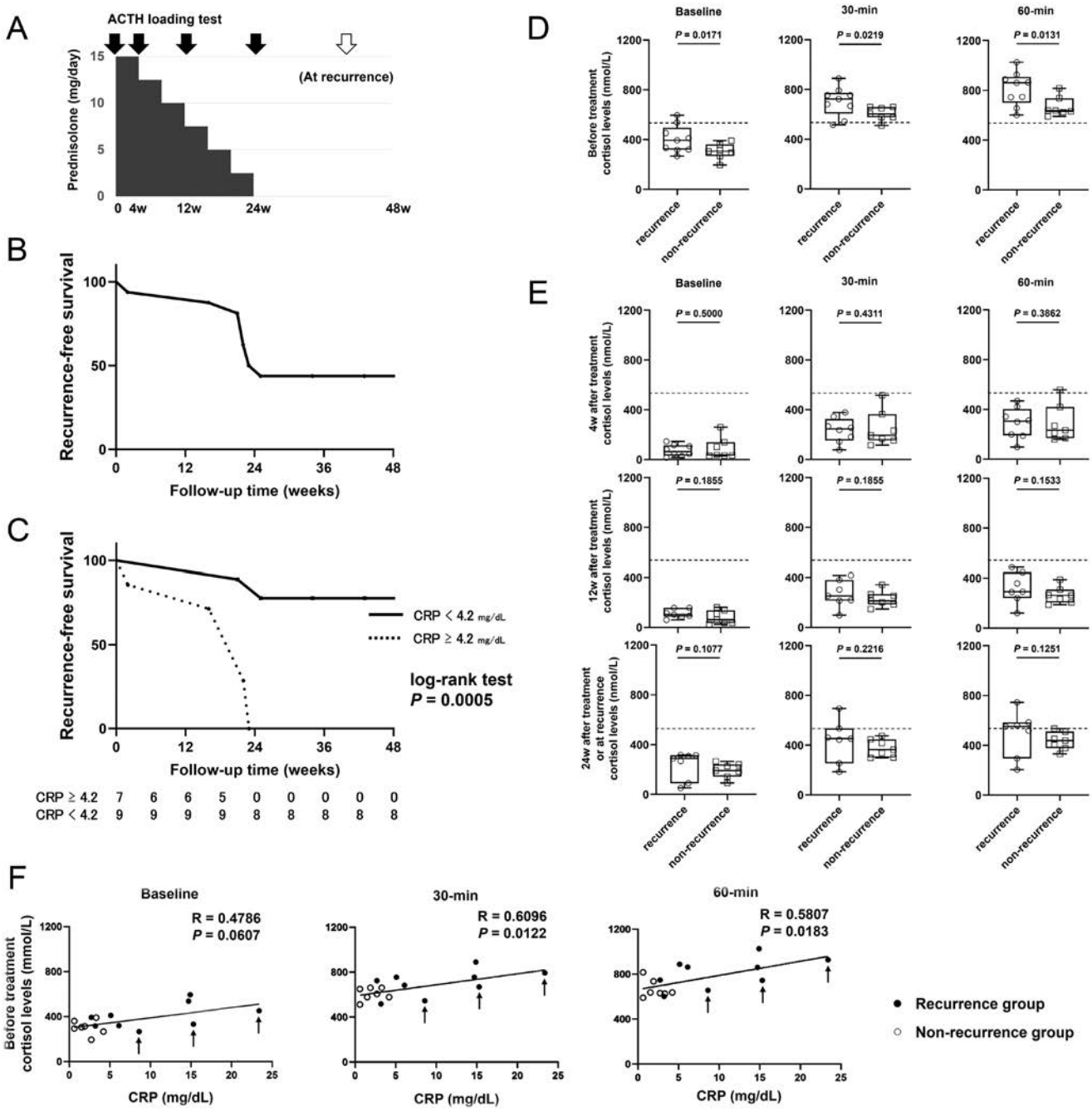

FIGURE 1 | Short-term treatment success in patients with polymyalgia rheumatica showing low C-reactive protein levels and adequate endogenous cortisol secretion. (A) Patients with polymyalgia rheumatica (PMR) were uniformly subjected to a short-time treatment protocol: Prednisolone (PSL) was started at a dose of 15 mg/d, the dose was reduced by 2.5 mg every 4 weeks, and PSL administration was discontinued at week 24. Adrenocorticotropic hormone (ACTH) loading tests were performed to evaluate adrenal function before treatment; at 4, 12, and 24 weeks after treatment initiation; and at the time of recurrence. Participants received tetracosactide acetate (250 μg; Cotrosin, Daiichi Sankyo Inc., Tokyo, Japan) at baseline and again at 30- and 60-min thereafter. (B) A Kaplan–Meier curve showing the recurrence-free survival rate in all patients with PMR. (C) Kaplan–Meier curves showing cumulative recurrence-free survival among patients with PMR, stratified by baseline CRP levels. (D) Comparison of cortisol levels between the recurrence and non-recurrence groups at disease onset by using the Wilcoxon rank sum test. The dotted line shows the 500 nmol/L indication of adrenal insufficiency. (E) Comparison of cortisol levels between the recurrence and non-recurrence groups at 4, 12, 24 weeks after treatment, or at recurrence by using the Wilcoxon rank sum test. (F) Correlation between C-reactive protein (CRP) and cortisol levels assessed using the Spearman's rank correlation coefficient and with regression lines in patients with PMR.

baseline CRP level of < 4.1 ($p = 0.0005$; Figure 1C). As clinical symptoms or ultrasound findings did not differ between the two groups, these factors were not useful for predicting recurrence (Table 1).

At disease onset, patients with PMR did not show signs of adrenal insufficiency, defined as a cortisol level of < 500 nmol/L (18 μg/dL) at either 30- or 60-min following ACTH loading [10]. Cortisol levels at baseline, 30, and 60 min after ACTH loading

TABLE 1 | Factors associated with recurrence in patients with PMR.

Recurrence		Yes ($n=9$)	No ($n=7$)	p*
Age (years)	Median [quartile]	79 [74–82.5]	76 [71–84]	0.5596
Observation time (weeks)	Median [quartile]	22 [18.5–24]	80 [43–96]	
Female	*n* (%)	6 (66.7)	6 (85.7)	0.3827
ESR	mm/h [quartile]	90 [70–109]	56 [25–89]	0.0221
CRP	mg/dL [quartile]	8.6 [4.1–15.1]	1.9 [0.6–3.3]	0.0025
MMP-3	ng/mL [quartile]	280.1 [113.2–454.1]	175.7 [76.9–292.4]	0.1986
Bilateral upper arm tenderness	*n* (%)	8 (88.9)	6 (85.7)	0.8489
Hip pain or limited range of motion	*n* (%)	7 (77.8)	6 (85.7)	0.6866
Morning stiffness > 45 min	*n* (%)	9 (100)	6 (85.7)	0.2416
No other joint involvements	*n* (%)	8 (88.9)	6 (85.7)	0.8489
Ultrasonography in shoulders				
Biceps tenosynovitis	*n* (%)	8 (88.9)	6 (85.7)	0.8489
Subdeltoid bursitis	*n* (%)	5 (55.5)	3 (42.8)	0.6143
Glenohumeral synovitis	*n* (%)	0 (0)	0 (0)	

Abbreviations: CRP, C-reactive protein; ESR, serum erythrocyte sedimentation rates; MMP-3, matrix metalloproteinase-3; PMR, polymyalgia rheumatica. Data are shown as the median [quartile] or number (%).
*p-value, chi-squared test for categorical variables or Wilcoxon rank sum test for continuous variables.

were significantly higher in the recurrence group than those in the non-recurrence group at disease onset (Figure 1D). No significant differences in cortisol levels existed between the recurrence and non-recurrence groups at 4, 12, and 24 weeks after treatment and at the time of recurrence (Figure 1E). Cortisol levels before treatment were positively correlated with CRP levels at 30-min ($p=0.0122$, $r=0.6096$) and 60-min ($p=0.0183$, $r=0.5807$) after ACTH loading (Figure 1F). In contrast, no significant correlation was found between cortisol and erythrocyte sedimentation rate.

This study showed that PMR recurrence was significantly more frequent in the patient group with higher CRP levels. In our patients with PMR whose pretreatment CRP level was ≥4.2 had a significantly higher recurrence rate. Our patients with low CRP levels at onset entered remission after receiving a short treatment protocol. Because PMR primarily affects individuals aged > 60 years, the potential benefits of early PSL discontinuation, which may contribute to vascular risk, are significant in this population.

Previous studies have examined adrenal function in relation to PMR and showed that cortisol levels in response to inflammation may be low in patients with PMR [11–14]. A recent study reported a high rate of adrenal insufficiency in patients with PMR during PSL treatment, which requires continued oral PSL therapy [15]. In the present study, none of the patients with PMR met the criteria for adrenal insufficiency. Therefore, endogenous cortisol secretion was preserved in both the recurrence and non-recurrence groups. Cortisol levels were positively correlated with the CRP levels and were higher in the recurrence group. However, cortisol secretion was relatively low in some patients with recurrent PMR at disease onset. These patients had lower cortisol levels than the estimated levels from a CRP-cortisol regression line (arrows on Figure 1F), suggesting they may have "relative" adrenal insufficiency, that is, inadequate cortisol response despite the hyperinflammatory condition (higher CRP levels).

This study was limited by the small sample size as the requirement for an ACTH loading test under fasting and resting conditions before treatment initiation restricted patient enrolment. Accordingly, this study should be considered a small-scale pilot study, and further research is needed. Another limitation of this study is that because ACTH has been used as an alternative to oral glucocorticoids and may have had an augmenting effect, the ACTH injection itself could have influenced the clinical course of PMR.

In conclusion, CRP levels at disease onset are useful in predicting PMR recurrence. Short-term treatment may be possible in patients with low CRP levels and preserved cortisol secretion.

Author Contributions

Y.O. contributed to study design and data collection. M.B., K.B., R.H., and H.N. contributed to the interpretation of data. Y.O. wrote the original draft, the other authors edited it, and all the authors approved the final version.

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The authors have nothing to report.

Ethics Statement

This study was approved by the Takikawa Municipal Hospital Ethics Committee (approval number: 22-06).

Consent

The patients provided informed consent for participating in this study and also consented to the use and publication of patient data and images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data included in this article will be shared by the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Exploring the Correlation Between Genotypes of Drug-Metabolizing Enzymes and the Therapeutic Efficacy and Adverse Reactions of Cyclophosphamide in Childhood-Onset Lupus Nephritis: A Chinese Cohort Study

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ABSTRACT

Objective: To investigate the association between genetic polymorphisms (CYP2B6, CYP2C19, GSTP1) and haplotypes of cyclophosphamide (CTX)-metabolizing enzymes with therapeutic efficacy and adverse drug reactions (ADRs) in pediatric patients with lupus nephritis (LN).

Methods: A retrospective cohort study was conducted on 46 childhood-onset LN patients treated with CTX pulse therapy at Peking Union Medical College Hospital. Genetic polymorphisms of CYP2B6, CYP2C19, and GSTP1 were analyzed using blood samples. Patients were stratified into effective ($n = 38$) versus ineffective ($n = 8$) groups based on 3-month clinical outcomes, and adverse reaction ($n = 13$) versus control ($n = 33$) groups. Genotype/allele frequencies and haplotype distributions were compared using χ^2 tests, Hardy–Weinberg equilibrium, and PHASE 2.1 software.

Results: Mutations in CYP2C19 (rs4244285) and GSTP1 (rs1695) were associated with reduced therapeutic efficacy ($p < 0.05$). No significant differences in genotype/allele frequencies were observed between adverse reaction and control groups ($p > 0.05$). Haplotype distribution frequencies showed no association with ADRs and efficacy.

Conclusion: CYP2C19 ×2 and GSTP1 polymorphisms may reduce CTX efficacy in pediatric LN patients. Genetic variations showed no correlation with ADRs. These findings highlight the potential of pharmacogenetic testing to guide CTX therapy, though larger prospective studies are needed for validation.

Clinical Trial Number: Not applicable.

1 | Introduction

Systemic lupus erythematosus (SLE) is the most common systemic autoimmune disease, and lupus nephritis (LN) represents one of the most severe complications of SLE [1]. According to the 2003 classification criteria established by the International Society of Nephrology/Renal Pathology Society (ISN/RPS), LN is classified into types I, II, III, IV, V, and VI. A composite diagnosis is made when type V lesions coexist with type III or IV lesions, designated as type III + V or type IV + V, respectively [2]. In 2018, revisions were made to the original ISN/RPS pathological classification, including updates to the assessment of renal tubular lesion severity and definitions of vascular lesions [3, 4]. Current clinical guidelines primarily base treatment strategies

on renal histopathological classification. Glucocorticoids, immunosuppressive agents, and biological agents are commonly used therapeutic regimens. However, these treatments demonstrate suboptimal efficacy in some patients, and long-term medication use increases the risk of adverse drug reactions [5].

Cyclophosphamide (CTX), a commonly used immunosuppressive agent, exerts therapeutic effects by leveraging its alkylating properties to bind human DNA, thereby reducing serum levels of dsDNA-anti-dsDNA immune complexes and minimizing their deposition in glomeruli. However, CTX is associated with severe adverse effects [6], and some patients exhibit poor therapeutic responses. The interindividual variability in CTX efficacy and toxicity correlates with genetic polymorphisms of its metabolic enzymes. Key genes influencing CTX metabolism include CYP2B6, CYP2C19, CYP3A4, CYP3A5, GST, and GSTA1 [7]. Notably, polymorphisms in CYP2B6, CYP2C19, and GST critically impact CTX pharmacokinetics [8]. This study focuses on investigating the relationship between CYP2B6, CYP2C19, GST, and their haplotypes with therapeutic outcomes and adverse effects in CTX-treated LN patients, aiming to guide precision individualized therapy for children. The study cohort comprised LN pediatric patients who received CTX pulse therapy at our hospital from January 2012 to January 2018. Genetic analyses of CTX metabolic enzymes were performed, followed by comparative assessments of drug-related genotypes and haplotype distributions across subgroups stratified by treatment efficacy and adverse reactions.

2 | Materials and Methods

2.1 | Study Design and Inclusion/Exclusion Criteria

This study was approved by the Ethics Committee of Peking Union Medical College Hospital (PUMCH) (NO. 2019-1-22), individual consent was signed by the parents. A total of 408 SLE children admitted to pediatric department of PUMCH from January 2012 to January 2018 were included. Inclusion criteria: (1) Meet the 1997 revised classification criteria of the American College of Rheumatology (ACR) [9] and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [10] for both SLE and LN ($n = 116$). The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification [2] was used as a reference standard for the pathological classification of childhood-onset LN in this study. On the basis of being diagnosed with SLE, if the child has any of the following renal involvement symptoms, it can be diagnosed as LN [11]: ① If the urine protein test meets any of the following criteria: 3 qualitative urine protein tests positive within 1 week; Or 24-h Urinary Total Protein (24 h UTP) quantification > 150 mg; Or protein/urinary creatinine > 0.2 mg/mg, or urinary microalbumin levels higher than normal three times within a week; ② Centrifuge urine with more than five red blood cells per high-power field of view; ③ Abnormal glomerular and/or tubular function; ④ Renal biopsy (hereinafter referred to as renal biopsy) shows abnormalities, consistent with the pathological changes of LN. (2) Age ≤ 18 years old. (3) Induction therapy using glucocorticoids (GC) + CTX. (4) 3 months clinical indicators were collected in our hospital. (5) Willing to accept drug metabolism enzyme gene testing. Exclusion criteria: (1) Primary or secondary immunodeficiency disease. (2) Hematological Malignancies or history. (3) Tuberculosis or other potential infectious diseases. (4) Incomplete medical history data. After admission and exclusion, a total of 46 LN patients were included in the study (Figure 1).

2.2 | Data Collection and Grouping Criteria

Clinical data were collected from all enrolled patients. Treatment efficacy was categorized at the 3-month follow-up into three groups based on laboratory findings: complete remission, partial remission, and non-remission. The criteria were defined as follows: complete remission: Normalization of all laboratory parameters, including blood routine tests, renal function, serum albumin (Alb), complement levels, and erythrocyte sedimentation rate (ESR), with 24-h urinary protein < 150 mg. Partial remission [12]: (1) ≥ 50% reduction in urinary protein (non-nephrotic range) or (2) ≥ 50% improvement in serum creatinine and urinary protein-to-creatinine ratio or (3) serum creatinine improvement accompanied by urinary protein-to-creatinine ratio < 1.0, alongside amelioration of all other laboratory markers compared to baseline. Non-remission [13]. Failure to meet any of the above criteria. Patients achieving complete or partial remission were classified as the effective group, while those with non-remission constituted the ineffective group.

Adverse drug reactions (ADRs) observed during CTX therapy included the following categories [14, 15]:

(1) Gastrointestinal disturbances: Manifested as nausea or vomiting within 1 week of CTX administration, after excluding acute/chronic gastroenteritis. (2) Menstrual irregularities: Development of irregular menstrual cycles post-treatment in patients with regular menstrual cycles and duration prior to therapy. (3) Alopecia: Hair loss attributed to CTX therapy, after excluding SLE-related hair loss. (4) Hemorrhagic cystitis: Occurring post-CTX administration. (5) Myelosuppression: Defined as laboratory findings within 2 weeks of CTX treatment meeting any of the following criteria: Leukocyte count $< 4.0 \times 10^9$/L or Neutrophil count $< 2.0 \times 10^9$/L or Platelet count $< 100 \times 10^9$/L, after excluding SLE-related cytopenia or viral infection-induced hematologic abnormalities. (6) Infection: Clinically diagnosed within 2 weeks post-CTX therapy based on: presence of fever, rhinorrhea, cough, or sputum production. Physical examination findings of pulmonary rales or radiologic evidence of pneumonia. (7) Hepatic dysfunction: elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels. ADR severity was graded using the 2021 Common Terminology Criteria for Adverse Events (CTCAE v 5.0) by the U.S. Department of Health and Human Services/National Institutes of Health/National Cancer Institute (HHS/NIH/NCI) [16]. Patients with ADRs graded ≥ 1 were classified into the adverse reaction group, while others were assigned to the control group.

2.3 | Drug Treatment Plan

All enrolled patients received GC therapy [oral prednisone at 2 mg/(kg/day) with a maximum dose of 60 mg/day, and intravenous methylprednisolone at 15–30 mg/(kg/day) with a maximum dose of 500 mg/day for 3 consecutive days, administered

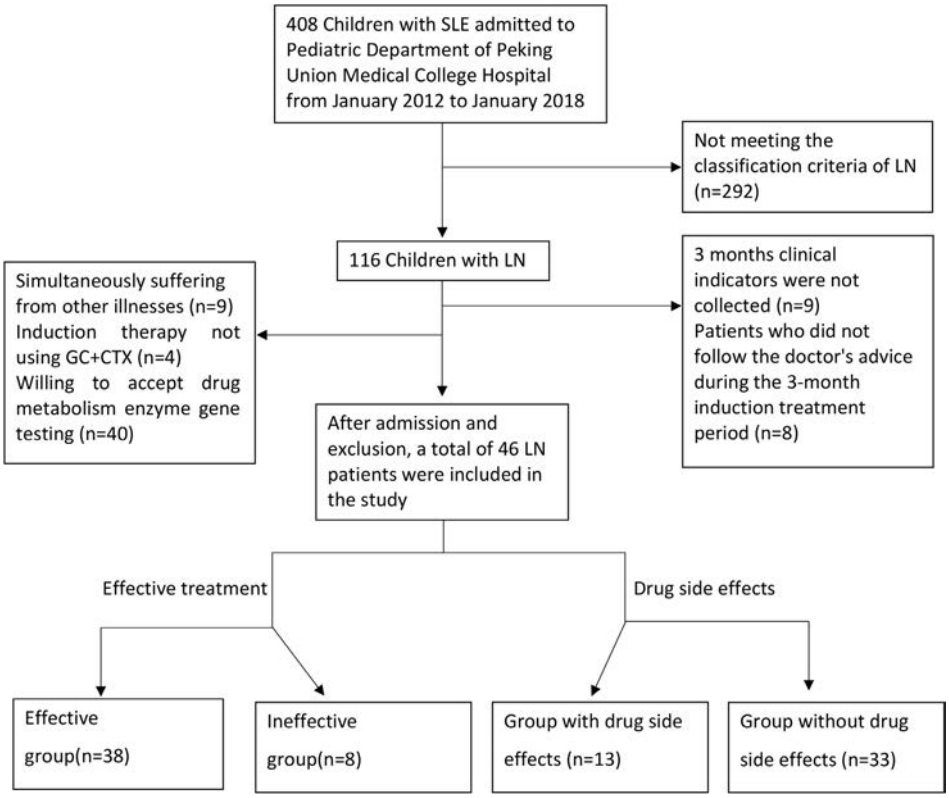

FIGURE 1 | Study flow diagram.

once weekly for 2 weeks] combined with intravenous CTX pulse therapy every 2 weeks [each cycle lasting 2 days at 8–12 mg/(kg/day), with a maximum dose of 1 g per administration]. After 3 months of CTX treatment, patients transitioned to sequential mycophenolate mofetil (MMF) therapy [20–30 mg/(kg/day)] or switched to monthly CTX pulse therapy for an additional 3 months before transitioning to MMF. Alternatively, oral prednisone was administered for 6–8 weeks, with gradual dose tapering based on therapeutic response until reaching a maintenance dose of 5–10 mg/day. Other immunosuppressants, such as hydroxychloroquine (HCQ), were used as additional baseline therapies [11].

2.4 | Gene Detection of Drug Metabolizing Enzymes

All enrolled pediatric patients underwent collection of 2.0 mL venous blood for CTX-metabolizing enzyme-related genetic testing. The procedures including peripheral blood DNA extraction, DNA concentration measurement and purification, PCR amplification, and genotyping were conducted by Beijing Majorbio Gene Technology Co. Ltd.

2.5 | Statistical Analysis

Continuous variables were presented as mean ± standard deviation (mean ± SD) or median (Q1-Q3), with between-group differences analyzed using independent samples *t*-test or Mann–Whitney *U* test via SPSS 25.0. Categorical variables were expressed as proportions (%), analyzed by χ^2 test. χ^2 test was also employed to assess genotype distribution conformity to Hardy–Weinberg equilibrium. Statistical significance was defined as $p < 0.05$. Haplotype analysis of CYP2B6, CYP2C19 and GSTP1 was performed using PHASE 2.1 software.

3 | Results

3.1 | Demographic Characteristics

The median age of 46 LN patients at disease onset was 10.5 (8.5–13.0) years, while the median age at diagnosis was 11.8 (9.2–13.1) years. The interval from symptom onset to diagnosis was 0.1 (0.0–0.75) years. The cohort comprised eight males and 38 females (male-to-female ratio 1:4.8). Six patients (13.0%) reported a family history of autoimmune diseases.

3.2 | Genotype and Allele Frequencies of Different SNPs

This study analyzed genetic variants in 46 pediatric patients. CYP2B6 ×5, CYP2B6 ×8, and CYP2C19 ×17 showed no mutations in the study population and were therefore excluded from further analysis. The heterozygous mutation rates were as follows: CYP2B6-750T > C (rs4802101) 56.5% (heterozygous) and 34.8% (homozygous); CYP2B6 ×2 8.7% (heterozygous) with no homozygous mutations; CYP2B6 ×9 47.8% (heterozygous) and 4.3% (homozygous); CYP2B6 ×4 45.7% (heterozygous) and 8.7% (homozygous); CYP2C19 ×2 32.6% (heterozygous) and 10.9% (homozygous); CYP2C19 ×3 10.9% (heterozygous) with no homozygous mutations; GSTP1 13.0% (heterozygous) and 2.2%

(homozygous). Genetic loci with mutation frequencies exceeding 50% included CYP2B6-750T>C (rs4802101), CYP2B6 ×9, and CYP2B6 ×4, while CYP2B6 ×2, CYP2C19 ×3, and GSTP1 exhibited mutation frequencies below 50%. All SNP loci underwent Hardy–Weinberg equilibrium (HWE) testing, with results demonstrating compliance with population genetic principles ($p > 0.05$) for all analyzed loci in this cohort (Table 1).

3.3 | Therapeutic Response Stratification and Clinical Characteristics

Based on laboratory tests and clinical manifestations at 3 months, patients were classified into three groups: complete remission (CR, $n = 14$), partial remission (PR, $n = 24$), and non-remission (NR, $n = 8$). CR and PR patients were defined as the

TABLE 1 | Genotype and allele frequencies of different SNPs.

Allele	SNP	Genotype frequency		Allele frequency		Allele frequency in Chinese reference population	*p*-value of Hardy–Weinberg equilibrium test
		Genotype	Number of cases	Allele	Proportion		
CYP2B6 rs4802101	−750T > C	TT	4/8.7%	T	37.0%	—	0.15
		CT	26/56.5%	C	63.0%	—	
		CC	16/34.8%				
CYP2B6 × 2 rs8192709	64C > T	CC	42/91.3%	C	95.7%	96.4%	0.76
		CT	4/8.7%	T	4.3%	3.6%	
		TT	0/0.0%				
CYP2B6 × 9 rs3745274	516G > T	GG	22/47.8%	G	71.7%	82.4%	0.22
		GT	22/47.8%	T	28.3%	17.6%	
		TT	2/4.3%				
CYP2B6 × 5 rs3211371	1459C > T	CC	46/100.0%	C	100.0%	/	/
		CT	0/0.0%	T	0.0%	/	
		TT	0/0.0%				
CYP2B6 × 4 rs2279343	785A > G	AA	21/45.7%	A	68.5%	75.3%	0.70
		AG	21/45.7%	G	31.5%	24.7%	
		GG	4/8.7%				
CYP2B6 × 8 rs12721655	415A > G	AA	46/100.0%	A	100.0%	—	—
		AG	0/0.0%	G	0.0%	—	
		GG	0/0.0%				
CYP2C19 × 2 rs4244285	681G > A	GG	26/56.5%	G	72.8%	70.3%	0.23
		GA	15/32.6%	A	27.2%	29.7%	
		AA	5/10.9%				
CYP2C19 × 17 rs12248560	4195C > T	CC	46/100.0%	C	100.0%	—	—
		CT	0/0.0%	T	0.0%	—	
		TT	0/0.0%				
CYP2C19 × 3 rs4986893	636G > A	GG	41/89.1%	G	94.6%	94.8%	0.70
		GA	5/10.9%	A	5.4%	5.2%	
		AA	0/0.0%				
GSTP1 rs1695	Ile105Val	AA	39/84.8%	A	91.3%	80.2%	0.23
		AG	6/13.0%	G	8.7%	19.8%	
		GG	1/2.2%				

effective group ($n=38$), while NR patients comprised the ineffective group ($n=8$). The cumulative CTX dose showed no statistically significant difference between groups (ineffective group: 4.3 ± 1.2 g vs. effective group: 4.4 ± 1.1 g, $p>0.05$). No significant differences were observed in age, gender, or renal pathology between groups ($p>0.05$). However, hemoglobin levels were significantly lower in the ineffective group compared to the effective group [93 (55–108) g/L vs. 105 (91–123) g/L, $p=0.04$], with no significant differences in other laboratory parameters (Table 2).

3.4 | Adverse Event Stratification and Clinical Characteristics

A total of 13 patients experienced CTX-related adverse drug reactions (ADRs), constituting the adverse reaction group (ADR group, $n=13$), while the remaining 33 patients formed the control group. The ADRs included gastrointestinal discomfort ($n=2$), menstrual disorders ($n=1$), leukopenia/neutropenia ($n=4$), thrombocytopenia ($n=1$), alopecia ($n=2$), hepatic dysfunction ($n=4$), and infections ($n=1$). Notably, two patients experienced two distinct adverse reactions. The cumulative CTX dose showed no statistically significant difference between groups (ADR group: 4.0 ± 1.1 g vs. control group: 4.6 ± 1.1 g; $p=0.11$). Baseline characteristics including gender, age, and laboratory parameters were comparable between groups ($p>0.05$). Additionally, no significant differences were observed in age at onset, renal pathology types, or other clinical features between the groups (Table 3).

3.5 | Comparison of Genotypes and Gene Frequencies Among Different Groups

Under the premise of no differences in clinical characteristics or laboratory tests between the effective and ineffective groups, a comparison of genotypes and gene frequencies was conducted. The results revealed differences in the genotypes and gene frequencies of CYP2C19 ×2 (rs4244285) and GSTP1 (rs1695) between the two groups. For CYP2C19 ×2 (rs4244285), the GG genotype was significantly more frequent in the effective group than in the ineffective group, while the AA genotype was significantly less frequent. The allele G frequency was also significantly higher in the effective group. For GSTP1 (rs1695), the AA genotype was significantly more frequent in the effective group than in the ineffective group, while the AG genotype was significantly less frequent. The allele A frequency was significantly higher in the effective group. These findings suggest that the CYP2C19 ×2 allele (rs4244285 A) is associated with reduced therapeutic efficacy, and the GSTP1 rs1695 G allele may also influence efficacy. Additionally, the study found

TABLE 2 | Therapeutic response stratification and clinical characteristics.

Related parameters	Effective group ($n=38$)	Ineffective group ($n=8$)	Univariate analysis (p-value)	Multifactor analysis(p-value)
General information				
Age of onset	11.4 (9.8–13.7)	11.8 (8.6–12.3)	0.46	>0.05
Gender (Female/Male)	30/8	8/0	0.15	>0.05
Renal pathology (Present/Absent)	25/13	6/2	0.61	>0.05
Class III	3	0	0.37	—
Class IV	17	5	0.46	—
Class III + V	3	1	0.76	—
Class IV + V	2	0	0.47	—
Laboratory parameters				
White blood cells ($\times10^9$/L)	5.1 (2.7–7.5)	5.2 (1.9–9.9)	0.90	>0.05
Hemoglobin (g/L)	105 (91–123)	93 (55–108)	0.04	>0.05
Platelets ($\times10^9$/L)	210 (97–274)	176 (133–382)	0.72	>0.05
24-h Urine protein (g/day)	2.99 (1.71–4.9)	2.98 (1.12–6.64)	0.91	>0.05
Serum creatinine (μmol/L)	57 (37.5–72.5)	50 (42–54.5)	0.79	>0.05
Blood urea nitrogen (mmol/L)	7.47 (3.85–11.44)	7.65 (5.61–12.78)	0.13	>0.05
Elevated ESR	29 (76.3%)	8 (100.0%)	0.13	>0.05
Low complement 3	33 (86.8%)	5 (83.3%)	0.82	>0.05
Low complement 4	30 (78.9%)	5 (83.3%)	0.81	>0.05
Anti-dsDNA antibody positive	27 (71.1%)	6 (75.0%)	0.13	>0.05

Note: Continuous variables were presented as mean ± standard deviation (mean ± SD) or median (Q1–Q3). Categorical variables were expressed as proportions (%).

TABLE 3 | Adverse reaction stratification and clinical characteristics.

Related parameters	Adverse reaction group ($n=13$)	Control group ($n=33$)	Univariate analysis (p-value)	Multifactor analysis(p-value)
General information				
Age of onset	10.6 ± 3.0	11.4 ± 2.5	0.37	> 0.05
Gender (Female/Male)	12/1	26/7	0.28	> 0.05
Renal pathology (Present/Absent)	7/6	24/9	0.22	> 0.05
Class III	1	2	0.64	—
Class IV	6	16	0.33	—
Class III + V	0	4	0.25	—
Class IV + V	0	2	0.43	—
Laboratory parameters				
White blood cells ($\times 10^9$/L), median (Q1–Q3)	7.6 (1.9–9.9)	7.6 (4.5–10.2)	0.60	> 0.05
Hemoglobin (g/L), Median (Q1–Q3)	103 (91–110)	100 (84–120)	0.96	> 0.05
Platelets ($\times 10^9$/L), median (Q1–Q3)	198 (82–273)	176 (82–269)	0.62	> 0.05
24-h urine protein (g/day), median (Q1–Q3)	3.47 (2.30–5.60)	2.52 (1.58–4.96)	0.89	> 0.05
Serum creatinine (μmol/L), median (Q1–Q3)	57 (43–76)	55 (41–75)	0.38	> 0.05
Blood urea nitrogen (mmol/L), median (Q1–Q3)	7.5 (4.3–10.1)	8.1 (5.1–13.6)	0.35	> 0.05
Elevated ESR, *n* (%)	9 (69.2%)	24 (72.7%)	0.81	> 0.05
Low complement C3, *n* (%)	13 (100.0%)	27 (81.8%)	0.13	> 0.05
Low complement C4, *n* (%)	11 (84.6%)	26 (78.8%)	0.65	> 0.05
Anti-dsDNA antibody positive, *n* (%)	10 (76.9%)	23 (69.7%)	0.62	> 0.05

Note: Continuous variables were presented as mean ± standard deviation (mean ± SD) or median (Q1–Q3). Categorical variables were expressed as proportions (%).

no significant differences in genotypes or gene frequencies between the adverse drug reaction group and the normal group for any of the tested genes. This indicates that homozygous mutations or genotypes containing wild-type alleles at these polymorphic loci do not affect the occurrence of adverse drug reactions (Table 4).

3.6 | Haplotype Analysis

Haplotype analysis for CYP2B6, CYP2C19, and GSTP1 was performed using PHASE 2.1 software. The polymorphic loci included in the analysis were CYP2B6 (rs4802101, rs8192709, rs3745274, rs2279343), GSTP1 (rs1695), and CYP2C19 (rs4986893, rs4244285). The results identified 14 haplotypes among the 46 pediatric patients. The most frequent haplotype consisted of wild-type alleles of CYP2B6, GSTP1, and CYP2C19, with an observed frequency of 23.9% and a predicted population frequency of 18.7%. The second most common haplotype included CYP2B6 (mutant rs4802101, wild-type rs8192709, mutant rs3745274, mutant rs2279343), GSTP1 (wild-type rs1695), and CYP2C19 (wild-type rs4986893, wild-type rs4244285), with an observed frequency of 20.7% and a predicted population frequency of 16.7%. Another haplotype with a higher frequency comprised CYP2B6 (mutant rs4802101, wild-type rs8192709, wild-type rs3745274, wild-type rs2279343), GSTP1 (wild-type rs1695), and CYP2C19 (wild-type rs4986893, wild-type rs4244285), with an observed frequency of 15.2% and a predicted population frequency of 20.5%. The haplotype CYP2B6 (mutant rs4802101, wild-type rs8192709, wild-type rs3745274, wild-type rs2279343), GSTP1 (wild-type rs1695), and CYP2C19 (wild-type rs4986893, mutant rs4244285) showed an observed frequency of 9.8% and a predicted population frequency of 9.0%. The remaining haplotypes were rare (Table S1).

TABLE 4 | Comparison of Genotypes and Gene Frequencies.

Allele	Genotype and Allele Frequency	Genetic models(Additive Model)	Effective Group($n=38$)	Ineffective Group($n=8$)	OR	95% CI	p Value	p Value (Benjamini–Hochberg FDR)	Adverse Reaction Group($n=13$)	Normal Group ($n=33$)	OR	95% CI	p Value	p Value (Benjamini–Hochberg FDR)
CYP2B6 rs4802101	TT	2	4	0	—	—	0.18	0.36	1	3	—	—	0.89	1.0
	CT	1	19	7					8	18				
	CC	0	15	1					4	12				
	C	Allele	49	9	1.41	0.47–4.21	0.58	0.789	16	42	1.09	0.43–2.79	0.85	1.0
	T		27	7					10	24				
CYP2B6 × 2 rs8192709	CC	2	36	6	6.0	0.70–51.1	0.134	0.327	11	31	0.355	0.044–2.832	0.565	1.0
	CT	1	2	2					2	2				
	TT	0	0	0					0	0				
	C	Allele	74	14	5.29	0.69–40.7	0.14	0.327	24	64	0.375	0.004–2.43	0.284	1.0
	T		2	2					2	2				
CYP2B6 × 9 rs3745274	GG	2	17	4	—	—	1.0	1.0	7	15	—	—	0.597	1.0
	GT	1	20	4					6	16				
	TT	0	1	0					0	2				
	G	Allele	54	12	1.22	0.35–4.21	0.75	0.875	20	46	1.45	0.51–4.15	0.49	1.0
	T		22	4					6	20				
CYP2B6 × 4 rs2279343	AA	2	17	4	—	—	1.0	1.0	7	14	—	—	1.0	1.0
	AG	1	18	4					6	16				
	GG	0	3	0					0	3				
	A	Allele	52	12	0.72	0.21–2.47	0.62	0.789	20	44	1.67	0.59–4.74	0.34	1.0
	G		24	4					6	22				
CYP2C19 × 2 rs4244285	GG	2	24	2	—	—	0.002	0.007	8	18	—	—	1.0	1.0
	GA	1	13	2					4	11				
	AA	0	1	4					1	4				
	G	Allele	61	6	6.78	2.13–21.6	0.00026	0.004	20	47	1.35	0.47–3.91	0.34	1.0
	A		15	10					6	19				

(Continues)

TABLE 4 | (Continued)

Allele	Genotype and Allele Frequency	Genetic models(Additive Model)	Effective Group($n=38$)	Ineffective Group($n=8$)	OR	95% CI	*p* Value	*p* Value (Benjamini–Hochberg FDR)	Adverse Reaction Group($n=13$)	Normal Group ($n=33$)	OR	95% CI	*p* Value	*p* Value (Benjamini–Hochberg FDR)
CYP2C19 × 3 rs4986893	GG	2	33	8	—	—	0.569	0.789	12	29	0.759	0.121–4.747	1.0	1.0
	GA	1	5	0					1	4				
	AA	0	0	0					0	0				
	G	Allele	71	16	—	0–8.07	0.284	0.497	25	62	1.61	0.006–131.41	1.0	1.0
	A		5	0					1	4				
GSTP1 rs1695	AA	2	35	3	—	—	0.001	0.006	12	27	—	—	0.753	1.0
	AG	1	2	5					1	5				
	GG	0	1	0					0	1				
	A	Allele	72	11	8.06	1.96–34.6	0.0012	0.006	25	59	2.97	0.3–103.18	0.39	1.0
	G		4	5					1	7				

3.7 | Comparison of Haplotype Distribution Frequencies Among Different Groups

No significant differences were observed in the distribution frequencies of haplotypes between the effective and ineffective groups. Additionally, there were no significant differences in haplotype distribution frequencies between the adverse drug reaction group and the normal group (Table S2).

4 | Discussion

Cyclophosphamide (CTX) exerts its immunosuppressive effects and exhibits toxicity only after being metabolized by various enzymes in the body. Genes encoding enzymes involved in CTX metabolism include CYP2B6, CYP2C19, CYP3A4, CYP3A5, ALDH, and GST. Studies have shown that polymorphic mutations in CYP2B6, CYP2C19, and GST genes occur at higher frequencies in the Chinese population. This study focuses on investigating the association of CYP2B6, CYP2C19, and GSTP1 gene polymorphisms with therapeutic efficacy and adverse drug reactions. Ten SNP loci were initially selected: CYP2B6 (rs4802101, rs8192709, rs3745274, rs2279343, rs3211371, rs12721655), GSTP1 (rs1695), and CYP2C19 (rs4986893, rs4244285, rs12248560). However, no mutant alleles were detected for CYP2B6 (rs3211371, rs12721655) or CYP2C19 (rs12248560) in any of the pediatric patients studied. Therefore, seven SNP loci were ultimately included in the analysis. To minimize the confounding effects of glucocorticoids (GC) on drug efficacy in this study, we also analyzed the association between ABCB1 gene polymorphisms (rs10276036, rs2229109, rs1045642, rs1128503, rs4148737) and the therapeutic efficacy of glucocorticoids in treating systemic lupus erythematosus (SLE). No significant differences in ABCB1 genotypes or allele frequencies were observed among the different groups (Table S3).

The study found that all SNPs included in this research conformed to Hardy–Weinberg equilibrium. The mutation rates of CYP2B6-750T > C (rs4802101), CYP2B6 ×9, and CYP2B6 ×4 exceeded 50%, while the mutation frequencies of CYP2B6 ×2, CYP2C19 ×3, and GSTP1 were below 50%. Based on laboratory tests, clinical manifestations, and adverse drug reactions at the 3-month follow-up, patients were categorized into effective group, ineffective group, adverse reaction group, and normal group. Under the premise of no differences in clinical characteristics or laboratory parameters among groups, genotype and allele frequency comparisons revealed that the CYP2C19 ×2 (rs4244285) mutation reduced therapeutic efficacy [17–19]. This aligns with prior studies reporting that CYP2C19 ×2 mutations diminish drug efficacy in CTX-treated SLE patients. One study demonstrated that when CTX doses were < 1000 mg/m^2, the CYP2C19 ×2 mutation reduced the formation of 4-hydroxy-CTX (active metabolite), thereby lowering therapeutic efficacy [18].

Notably, drug side effects often parallel efficacy outcomes. Some studies suggest that while CYP2C19 ×2 reduces CTX efficacy in SLE patients, it may also mitigate ovarian toxicity [20]. However, due to the short follow-up period in this study, the association between SNPs and ovarian toxicity was not explored. Additionally, this study observed that the GSTP1 (rs1695) mutation also reduced efficacy. However, existing research indicates

that GSTP1 primarily influences CTX-related adverse effects by detoxifying its metabolites into inactive forms for elimination. To date, no studies have linked GSTP1 (rs1695) to therapeutic efficacy. SLE patients with GSTP1-105I/V (heterozygous) or GSTP1 × −105V/V (homozygous) genotypes are reported to have an increased risk of myelotoxicity during high-dose CTX pulse therapy [21]. Nevertheless, this study found no association between these SNP polymorphisms and adverse drug reactions.

Research has found that the impact of pharmacogenetic polymorphisms on the efficacy and adverse effects of CTX treatment is not solely attributed to individual SNPs but can also arise from combinations of multiple SNPs on chromosomes, known as haplotypes [22]. One study indicates that the CYP2B6 (rs4802101 mutant) decreases blood concentrations of 4-hydroxycyclophosphamide, diminishing therapeutic effects [17], while conflicting reports suggest CYP2B6 (rs3745274 mutant) and CYP2B6 (rs2279343 mutant) enhance hepatic microsomal CYP2B6 activity in converting CTX to 4-hydroxy-CTX, a discrepancy potentially explained by divergent interactions among SNPs within haplotypes [23]. While no significant differences were observed in the distribution frequencies of haplotypes between the effective and ineffective groups. Additionally, there were no significant differences in haplotype distribution frequencies between the adverse drug reaction group and the normal group.

This study preliminarily explored the correlation between CYP2B6, CYP2C19, and GSTP1 genotypes/haplotypes with CTX therapeutic efficacy and adverse effects, providing limited evidence for clinical diagnosis and treatment. However, it has significant limitations: the small sample size may introduce result bias, and its retrospective design lacked monitoring of 4-hydroxy-CTX drug concentrations during treatment, leaving unexplored the relationships between drug concentration, genetic polymorphisms, efficacy, and adverse reactions. While glucocorticoid (GC) pharmacogenetic polymorphisms were analyzed to minimize GC-related interference, confounding factors persist in efficacy evaluation, such as unaccounted influences from concomitant medications (e.g., antihypertensive drugs) on therapeutic outcomes and toxicity. Therefore, prospective, large-scale studies incorporating drug concentration monitoring and comprehensive confounding factor analyses are required to establish more robust experimental conclusions.

5 | Conclusion

The mutations of CYP2C19 ×2 (rs4244285) and GSTP1 (rs1695) may reduce CTX efficacy. Future research should prioritize prospective, large-scale studies to generate more robust experimental data. Implementing CTX pharmacogenetic testing to guide therapeutic adjustments in pediatric patients shows promise for evaluating its impact on treatment efficacy and adverse effects, thereby establishing an evidence-based foundation for personalized treatment in LN patients.

Author Contributions

W.Q. collected clinical data and drafted the article. J.S. collected and analyzed clinical data. M.M. and W.C. helped W.Q. to collect data. W.W., Z.L. and D.Y. provided assistance in data interpretation. S.H. and W.W. designed the topic and S.H. approved the final version of the manuscript.

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Ethics Statement

The studies involving human participants were reviewed and approved by the ethics committee, and all participants provided their written informed consent prior to their involvement.

Consent

Written informed consent for publication was obtained from all participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Haplotype analysis in children with lupus nephritis. **Table S2:** Comparison of haplotype distribution frequencies. **Table S3:** Comparison of ABCB1 genotypes and allele frequencies.

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ORIGINAL ARTICLE

Appendicular Skeletal Muscle Mass Prediction Equation for Older Adults: Anthropometric, Physical, and Biochemical Indicators

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ABSTRACT

Objectives: To develop and validate an equation for estimating Appendicular Skeletal Muscle Mass (ASM) using community-accessible indicators, thereby facilitating the rapid screening of sarcopenia among older adults in primary care settings.

Methods: A total of 800 community-dwelling elders were included and randomly partitioned into a training set (80%) and a validation set (20%); an additional 200 elderly participants were independently recruited to serve as the external validation cohort. Demographic characteristics, anthropometric and biochemical parameters of the participants were collected and analyzed. Variables associated with ASM were screened via univariate analysis, and core predictors were identified using a Random Forest model. Subsequently, Least Absolute Shrinkage and Selection Operator (LASSO) regression was applied to optimize the model. Finally, Stepwise Multiple Linear Regression was utilized to develop the ASM prediction equation. Bland–Altman (B-A) plots and intraclass correlation coefficient (ICC) were used to assess the predictive validity and reliability of the model.

Results: Height, weight, gender, waist-to-hip ratio, hemoglobin concentration, left calf circumference, and left hand grip strength were ultimately selected for model development. The B–A plots revealed no significant discrepancy, with over 95% of data points falling within the limits of agreement. The ICC values for the two validation sets were 0.958 and 0.954, indicating good consistency between the model-predicted values and the actual values.

Conclusions: The ASM prediction equation, developed by integrating anthropometric indicators, physical function metrics, and laboratory biochemical parameters, provides a reliable alternative for accurate assessment of skeletal muscle mass in older adults.

1 | Introduction

Sarcopenia is a complex syndrome closely associated with older adults, primarily characterized by the progressive loss of muscle mass, reduced muscle strength, and decline in physical function. It significantly increases the risk of adverse health outcomes such as accidental falls, fractures, physical functional disabilities, and mortality [1]. Epidemiological studies report that the global prevalence of sarcopenia ranges approximately from 10% to 27%, with an estimated prevalence of approximately 12% in China [2]. As the aging of the population continues to intensify, this public health issue has become increasingly

Qian-Qian Shi and Yu-Tong Tan contributed equally to this work and should be considered co-first authors.

Key Points

- Univariate analysis, random forest, and LASSO were employed for feature selection.
- Seven variables were selected to develop the ASM prediction equation ($R^2 = 0.94$).
- The equation achieved high consistency with BIA-measured ASM in both internal and external datasets (icc = 0.96\0.95).

severe. Therefore, promoting early screening for sarcopenia in community-dwelling older adults is of critical importance.

The diagnosis of sarcopenia usually combines the assessment of muscle mass, muscle strength, and physical function [2]. Appendicular Skeletal Muscle Mass (ASM) refers to the mass of skeletal muscles in the upper and lower extremities. It serves as a key parameter for muscle health assessment and relevant diseases. Dual-Energy X-ray Absorptiometry (DXA) and Bioelectrical Impedance Analysis (BIA) are widely utilized methods for estimating muscle mass [3, 4]. However, DXA involves ionizing radiation and high equipment costs, whereas reliable BIA devices are not universally accessible in primary healthcare settings. Consequently, exploring low-cost and simple methods for assessing muscle mass will facilitate community healthcare workers quickly evaluate the muscle health status of elderly individuals in the community. Previous studies have attempted to estimate muscle mass using simple anthropometric parameters and physical function parameters [5]. However, the influencing factors of muscle mass are multifaceted and may be associated with malnutrition [6], endocrine changes [7], inflammation [8], and other factors [9]. Due to these complex interactions, unidimensional physical indicators often fail to yield sufficient predictive accuracy. Accurate measurement of ASM remains a challenge.

Machine learning (ML) has emerged as a pivotal tool for analyzing high-dimensional medical data, capturing nonlinear relationships, and improving disease prediction accuracy [10]. Concurrently, ML has demonstrated its effectiveness in various medical fields, such as detecting sepsis and diagnosing ovarian cancer early, by integrating clinical and laboratory data [11].

In this study, we aimed to develop and validate a computational model for ASM in older adults using community-accessible indicators.

2 | Materials and Methods

2.1 | Participants

The study included older adults aged 60 years and above who underwent health examinations at community health service centers in Hefei, China, from January to October 2025. All participants were able to cooperate in completing the health examinations and were willing to undergo subsequent BIA measurement. Exclusion criteria included: (1) Presence of metallic implants (e.g., cardiac pacemakers, stents, or orthopedic hardware) that contraindicate BIA measurement; (2) Inability to stand independently or failure to complete the requisite physical and laboratory examinations.

2.2 | Demographic Characteristics

General demographic data included the following items: gender, age, occupation, marital status, living arrangement, educational level and medical insurance; smoking, alcohol consumption, egg consumption frequency, sun exposure duration, sleep duration, physical activity level, and medical histories (hypertension, hyperlipidemia, hyperglycemia, joint diseases, cardio-cerebrovascular diseases). Details of the variables were given in Table S1.

2.3 | Anthropometric Measurements

The measured parameters included height, weight, waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), left and right upper arm circumferences (LUAC/RUAC), left and right calf circumferences (LCC/RCC), and left and right hand grip strength (LHG/RHG). Grip strength was measured using a dynamometer, and participants stood with feet shoulder-width apart and arms naturally pendent. Two measurements were taken for each hand, and the maximum value was recorded. ASM was measured using the Inbody DBA-210 [DongHuaYuan Medical, China] BIA device.

2.4 | Biochemical Parameters

Laboratory test data included white blood cell count (WBC), lymphocytes (Lym), neutrophils. Red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HCT), total bilirubin (TB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST/ALT, creatinine (Scr), and urea; total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Laboratory physicians obtained 5 mL of blood samples via peripheral venous puncture, and the samples were analyzed in a biochemical laboratory using standardized chemical analysis methods.

2.5 | Statistical Analysis

The model was trained on 80% of the dataset and validated on the remaining 20%, external validation was performed on an independent external cohort. Data for the external validation cohort were obtained from a region distinct from that of the model development cohort. The same inclusion and exclusion criteria were applied in both cohorts, and all anthropometric and body composition measurements were conducted using identical instruments and standardized protocols. For continuous variables, the Spearman correlation coefficient was used to calculate the correlation with ASM measured by BIA. Categorical variables were compared using independent sample *t*- tests, Welch's *t*-tests, or Kruskal–Wallis tests, as appropriate. Variables with no statistically significant correlation with ASM ($p > 0.05$) were excluded to reduce feature space redundancy. Thereafter, a Random Forest algorithm was utilized to capture complex nonlinear associations

and potential interaction effects among variables, leveraging its inherent strengths in handling high-dimensional data and evaluating feature importance. Subsequently, Least Absolute Shrinkage and Selection Operator (LASSO) regression was employed. L1 regularization term was incorporated into the loss function, and 5-fold cross-validation was utilized to identify the optimal value. This approach effectively mitigates multicollinearity, reduces the risk of overfitting, and enables the screening of key variables. Ultimately, Stepwise Multiple Linear Regression was employed to identify the final variables for constructing the ASM prediction model. To validate the predictive performance of the constructed regression equation, Bland–Altman (B-A) plot was used to analyze the distribution characteristics of random and systematic errors. Meanwhile, the intraclass correlation coefficient (ICC) was employed to quantify the degree of agreement between the ASM measured by BIA and the equation developed in this study.

All analyses were conducted with IBM SPSS Statistics 23 and Python (3.8.8).

3 | Results

3.1 | Baseline Characteristics

A total of 800 participants were included in the final analysis, including 452 females (56.9%) and 348 males (43.1%). The mean age of the cohort was 70 ± 4.63 years (Table S1). Participants were randomly allocated into a training set ($n = 640$) and a validation set ($n = 160$). No statistically significant differences in baseline characteristics were observed between the two groups (Figure S1).

3.2 | Development of the Equation

Univariate analysis identified 32 candidate variables that were significantly correlated with ASM ($p > 0.05$) (Table S1). Subsequently, a random forest model was used to select the top 11 important features, including gender, weight, height, LCC, Lym, LHG, BMI, WC, Scr, HGB, TC (Figure 1). Furthermore, LASSO regression was then employed to further refine the feature selection and mitigate multicollinearity. Post-screening analysis confirmed that the variance inflation factor for the remaining 10 variables was less than 5, indicating negligible collinearity (Figure S2). Finally, a stepwise multiple linear regression was applied to construct the predictive model (Table S2), resulting in a final equation comprising seven predictors (Table 1). Height and weight played an important explanatory role, accounting for 89% of the variance. Although WHR was not identified as a significant variable in prior variable screening steps, it was incorporated a priori into the final model based on compelling clinical and physiological rationale. Importantly, WHR entered the stepwise linear regression model at an early stage, indicating its contribution to the prediction equation. The interpretability of final model could reach 94.2% (Table S2).

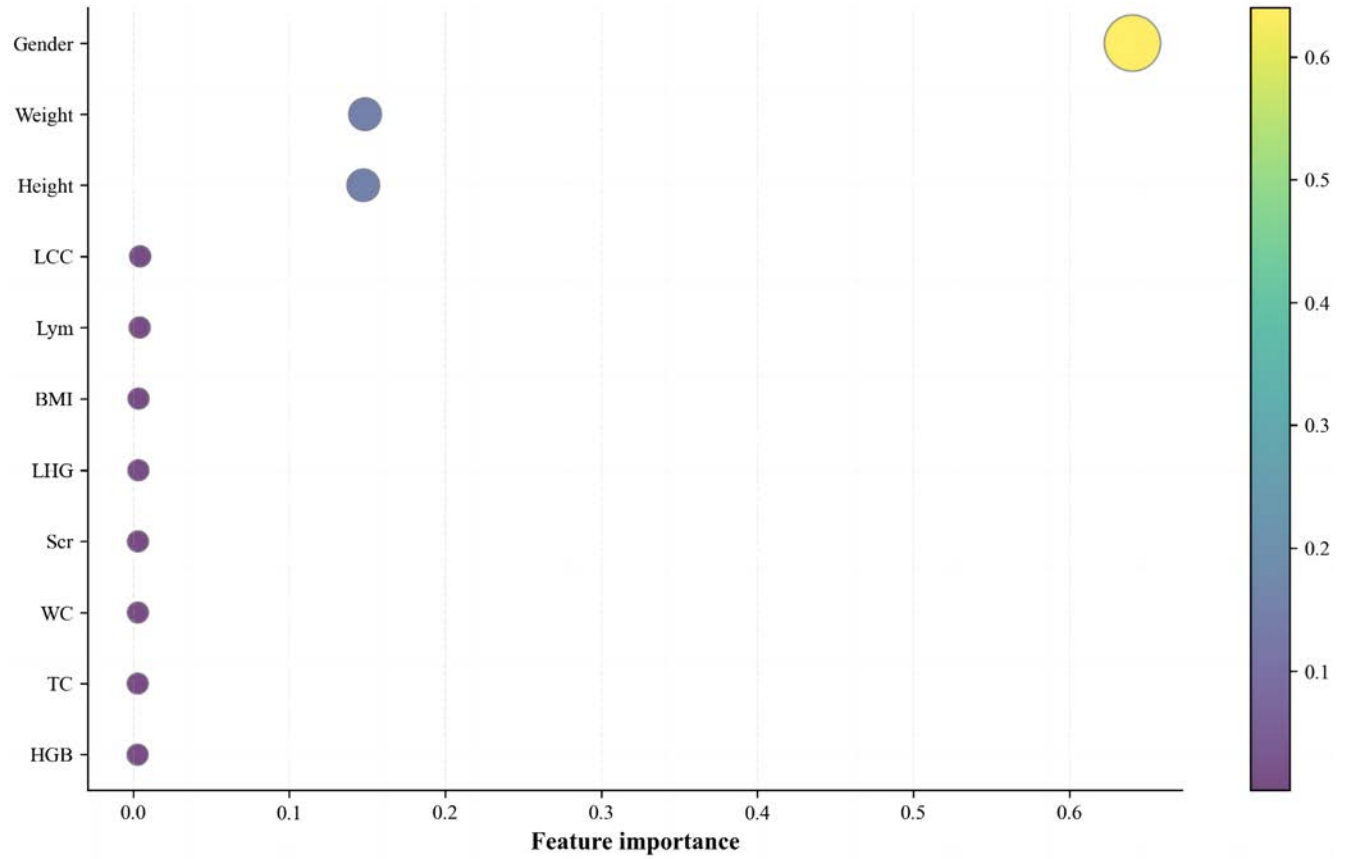

FIGURE 1 | Important features selected by random forest. BMI, body mass index; HGB, hemoglobin concentration; LCC, left calf circumference; LHG, left hand grip strength; Lym, lymphocyte count; Scr, creatinine; TC, total cholesterol; WC, waist circumference.

3.3 | Validation of the Equation

Based on the finally adopted features, we adopted a two-tier validation strategy, including internal validation and external validation. The mean value of ASM in the internal validation was 17.61 ± 3.44 kg, with a corresponding predicted mean of 17.75 ± 3.51 kg. There was a high level of consistency with the actual measured values (mean difference ± standard deviation [MD ± SD]: 0.14 ± 1.00, $p = 0.074$), and with an adjusted coefficient of determination of 0.91 and a mean absolute error of 0.81 kg (Table 2). Additionally, we compared the performance of our model against established anthropometric-based ASM prediction equations proposed by Sun et al. and Kawakami et al. (Table 2). The equation by Sun et al. showed a significant deviation from the BIA-measured ASM ($p < 0.001$), indicating poor applicability in this cohort. In contrast, no statistically significant difference was observed between the predicted values of the Kawakami et al. equation and the BIA-measured ASM ($p = 0.392$); however, the mean prediction error of this equation was relatively large, reaching 1.22 kg.

The external validation cohort was derived from an additional community health service center. No statistically significant differences were found in basic demographic characteristics (gender, occupational, smoking, alcohol consumption) or routine hematological parameters between the training and external validation sets (all $p > 0.05$). However, significant differences were observed in age, prevalence of hypertension and diabetes, and anthropometric measures (RHG, WHR) between the two groups (all $p < 0.05$) (Table S3). The mean value of ASM in the external validation was 17.62 ± 3.96 kg, with a corresponding predicted mean of 18.29 ± 3.66 kg. The predicted values demonstrated favorable agreement with the actual measurements. The MD ± SD was 0.68 ± 0.95 ($p < 0.001$). With a high adjusted coefficient of determination ($R^2 = 0.94$) and a low mean absolute error (MAE = 0.97 kg), the model exhibited strong predictive accuracy and reliability.

The results of the B-A plots showed that the majority of data points falling within the 95% limits of agreement (LOA), and a relatively small mean bias for both the internal and external validation sets (MD = −0,14, 95% LOA: −2.11–1.82; MD = −0.68, 95% LOA: −2.55–1.19). (Figure 2). Meanwhile, the ICC plots indicated a strong correlation between the predicted ASM and the BIA-measured ASM in both validation sets ($R^2 = 0.919$ and 0.944, respectively). The ICC was 0.958 (95% CI: 0.943, 0.969) for the internal validation set and ICC was 0.954 (95% CI: 0.939, 0.965) for the external validation set. Additionally, the fitted lines were close to the ideal line, indicating no significant systematic deviation between the

TABLE 1 | BIA-measured ASM estimation equation derived from anthropometric, hemoglobin, and grip strength.

	Coefficient	SE	*p*	R^2 cumulative	RMSE
Constant	−8.050	2.449	0.001	—	—
Height (cm)	0.183	0.009	< 0.001	0.798	1.739
Weight (kg)	0.159	0.007	< 0.001	0.891	1.276
Gender (Male = 1; Female = 2)	−2.401	0.124	< 0.001	0.931	1.013
WHR	−10.978	1.53	< 0.001	0.937	0.969
HGB (g/L)	−0.015	0.003	< 0.001	0.939	0.956
LCC (cm)	0.068	0.016	< 0.001	0.941	0.943
LHG (kg)	0.026	0.006	< 0.001	0.942	0.931

Abbreviations: ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; HGB, hemoglobin concentration; LCC, left calf circumference; LHG, left-hand grip strength; R^2, coefficient of determination; RMSE, root-mean-square error; SE, standard error; WHR, waist–hip ratio.

TABLE 2 | Comparison of equations for predicting ASM from the present study with previous studies.

	ASM	MD ± SD	*p*	MAE	R^2
Internal validation ($n = 160$)	17.61 ± 3.44	—	—	—	—
ASM_Pred[a]	17.75 ± 3.51	0.14 ± 1.00	0.074	0.805	0.912
Yun Sun et al.[b]	18.29 ± 3.99	0.68 ± 1.53	< 0.001	1.284	0.762
Ryoko Kawakami et al.[c]	17.50 ± 3.80	0.10 ± 1.52	0.392	1.222	0.802

Abbreviations: ASM, appendicular skeletal muscle mass (kg); ASM_Pred, the regression equation established in this study; CC, calf circumference; HGB, hemoglobin concentration; LCC, left calf circumference; LHG, left-hand grip strength; MAE, mean absolute error; MD, mean difference; R^2, coefficient of determination; SD, standard deviation; WHR, waist–hip ratio.

[a]ASM = −8.05 + 0.183 × Height (cm) + 0.159 × Weight (kg) − 2.401 × Gender (male = 1, female = 2) − 10.978 × WHR − 0.015 × HGB (g/L) + 0.068 × LCC (cm) + 0.026 × LHG (kg).

[b]ASM = −5.142 − 4.346 × sex (male = 1, female = 2) + 0.136 × Weight (kg) + 9.009 × height (m) + 0.283 × CC (cm) − 0.034.

[c]ASM = 2.955 × Gender (male = 1, female = 0) + 0.255 × Weight (kg) − 0.130 × hip (cm) + 0.308 × CC (cm) + 0.081 × Height (cm) − 11.897.

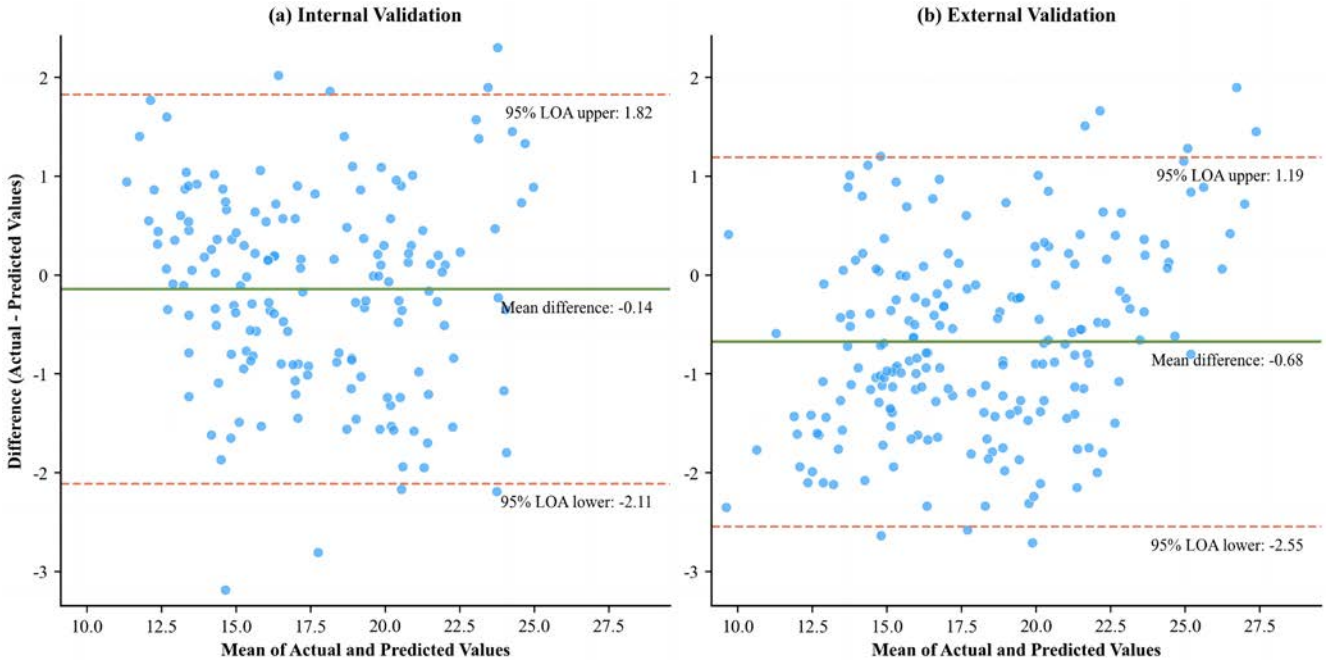

FIGURE 2 | Bland–Altman analysis of model-derived ASM compared to BIA-derived ASM in the internal (a) and external (b) validation groups. ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis. The solid green line represents the mean difference in ASM measured by BIA and the prediction model. The dashed red line denotes the upper and lower limits of the 95% limits of agreement (LOA).

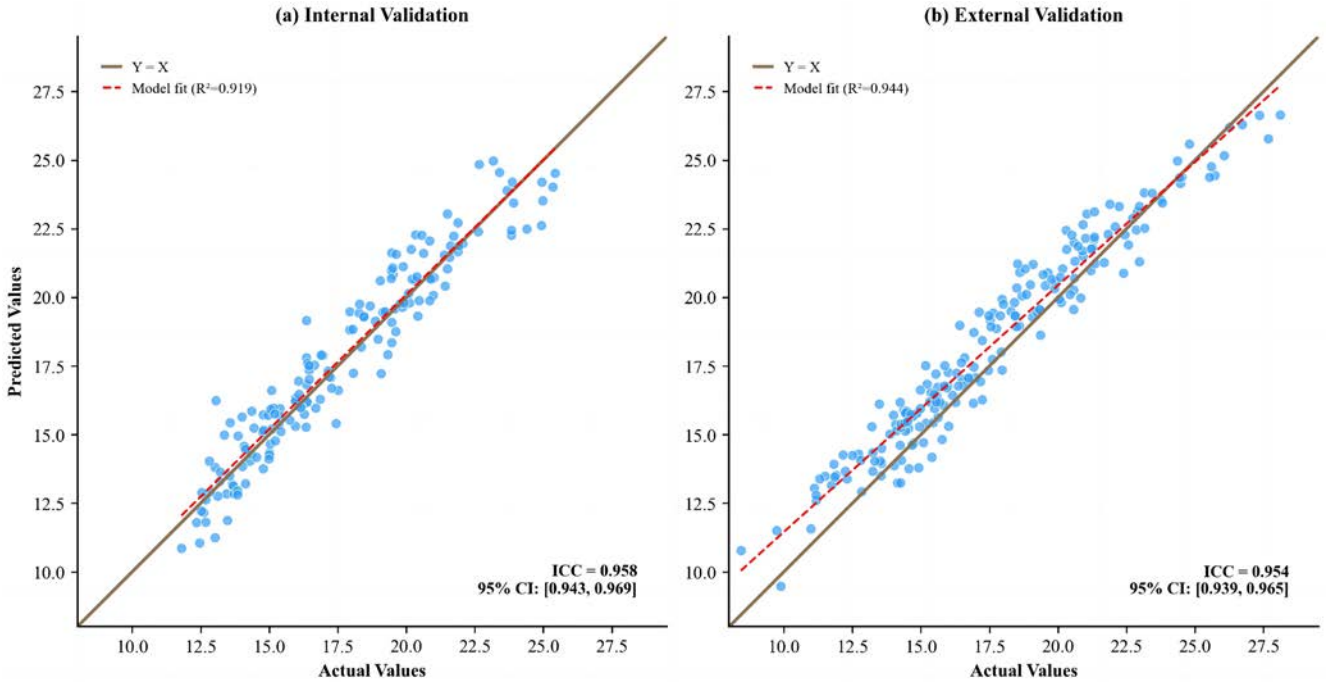

FIGURE 3 | Intraclass correlation coefficient correlation between estimated ASM by the equations and BIA-measured ASM in the internal (a) and external (b) validation groups. ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; CI, confidence interval; ICC, intraclass correlation coefficient; R^2, coefficient of determination. The ideal line (brown solid line) and the linear fitted regression line (red dashed line) with the corresponding R^2 value.

equation-predicted and actual measured values (Figure 3). These findings confirm that the proposed regression model achieves consistency with BIA measurements, supporting its utility for the rapid screening of ASM in community-dwelling older adults.

4 | Discussion

The ASM prediction equation developed in this study demonstrated excellent consistency and predictive accuracy with the ASM measured by BIA. The two sets of measurements showed

a high degree of correlation, with negligible systematic bias and random error within an acceptable range. Therefore, the ASM prediction equation established in this study can serve as an effective alternative to BIA-measured ASM.

This study indicated that weight, height, LHG, and LCC were significantly positively correlated with ASM. This finding has also been confirmed by multiple previous studies [12–17]. Weight and gender are incorporated into nearly all equations for ASM estimation that employ BIA or anthropometric measurements [15, 16, 18–21]. Additionally, females tend to have lower muscle mass compared with males, which may be attributed to the fact that females have a higher body fat content than males [5]. Aligns with the finding of the present study, individuals with higher grip strength typically exhibit greater ASM [22]. Calf circumference has been validated in multiple studies as an effective anthropometric indicator for ASM [14, 17]. Subcutaneous fat and connective tissue constitute a minimal proportion in the calf, and calf circumference is primarily determined by skeletal muscle content. Higher skeletal muscle mass corresponds to a larger measured calf circumference [23].

A higher WHR is associated with lower muscle mass, as an elevated WHR typically indicates excessive abdominal visceral fat. Abdominal adipocytes release substantial amounts of free fatty acids and inflammatory factors, which directly interfere with insulin signaling [24]. When insulin resistance develops in the body, muscle cells fail to efficiently uptake and utilize blood glucose for energy production. In response, the body compensates by increasing the breakdown of muscle protein for energy, leading to reduced muscle mass [25]. Excessive visceral fat significantly inhibits the secretion of growth hormone [26]. As a core regulatory factor governing muscle growth, fat metabolism, and cellular repair, insufficient secretion of this hormone directly impairs muscle anabolic capacity. Furthermore, visceral fat serves as a key initiating factor of chronic low-grade inflammation, and the continuous release of inflammatory factors therefrom establishes a systemic chronic inflammatory microenvironment; it directly damages muscle cells and accelerates muscle mass loss; in parallel, it inhibits post-exercise muscle repair and regeneration, which results in the deterioration of muscle mass and function in the long term [27, 28].

Importantly, HGB was incorporated in this equation. Generally, HGB has a positive association with muscle strength [6]. Previous studies have corroborated a negative correlation between HGB and sarcopenia [29]. However, contradictory correlations exist under specific circumstances: obese individuals often exhibit elevated HGB [7]. In this study, the mean BMI was 24.03 and the mean WHR was 0.96, indicating the presence of central obesity. This physique is common in older adults with reduced skeletal muscle mass, and such populations typically present with high fat mass but relatively low muscle mass. Excessive adipose tissue accumulation can elicit systemic chronic low-grade inflammation and insulin resistance, thereby promoting protein degradation and accelerating the loss of ASM [25]. Additionally, in the context of insufficient dietary protein intake but adequate iron intake, sufficient iron maintains hemoglobin synthesis [8], but skeletal muscle fails to preserve normal mass due to protein deficiency, resulting in normal or elevated hemoglobin levels concomitant with a significant reduction in ASM.

This study overcomes the limitations of traditional single-dimensional prediction models and it is the first to systematically integrate anthropometric indicators, physical function indicators, and biochemical parameters to develop a comprehensive multi-dimensional prediction model for ASM. Employing a sequential multistage variable screening and modeling approach, this study not only ensures methodological rigor and result robustness but also furnishes solid methodological underpinnings for the development of the ASM prediction equation. The ultimately derived model exhibits favorable interpretability coupled with low prediction error. Furthermore, in the present study, a comparative validation was conducted between equations established in previous studies based on simple anthropometric measurements and ASM values quantified via BIA. The results indicated that the ASM estimation equation developed herein exhibited a significantly stronger correlation with BIA-derived ASM values than prior equations relying solely on anthropometric measurements. Moreover, it demonstrated minimal total prediction error and the highest predictive accuracy, thereby further corroborating its superiority.

However, this study has several limitations. First, the data were collected from an elderly population in a single region, and the average age of the participants was relatively high. This limits the extrapolation of the results, making it difficult to directly generalize them to populations of other age groups and different geographical regions. Second, BIA was used as the reference standard for ASM measurement. While BIA is widely accepted, DXA remains the gold standard. Future studies should validate this prediction equation against DXA-derived muscle mass to further confirm its accuracy. Finally, this model incorporates grip strength, although some primary-level communities may face insufficient initial equipment allocation; grip strength dynamometers are more accessible and less costly than BIA devices. This partly mitigates the potential limitations of its application contexts.

5 | Conclusions

Concisely, the equation ($ASM = -8.05 + 0.183 \times Height\ (cm) + 0.159 \times Weight\ (kg) - 2.401 \times Gender\ (male = 1,\ female = 2) - 10.978 \times WHR - 0.015 \times HGB\ (g/L) + 0.068 \times LCC\ (cm) + 0.026 \times LHG\ (kg)$) developed in this study can provide a simple and low-cost method for ASM. This model can provide usable ASM measurements for communities unable to be equipped with BIA devices, thereby facilitating the early screening of sarcopenia at the community level.

Author Contributions

Qian-Qian Shi contributed to data curation, conducted formal analysis, devised the methodology, and wrote the original draft. Yu-Tong Tan was involved in data curation. Sheng Li performed formal analysis; Jian-Hui Xiong and Jia-Jun Deng carried out investigative work. Peng Wang and Sha-Sha Tao supervised the investigation process and provided guidance. Hai-Feng Pan not only supervised the investigation but also managed the project overall. All authors reviewed the manuscript.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

In attempt to preserve the privacy of individuals, data will not be shared; the data can be available from the corresponding author on reasonable request authors upon request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Basic variable information of participants. **Table S2:** Equations for predicting BIA-measured ASM developed by stepwise multiple linear regression analyses in the development group. **Table S3:** Comparison of Basic Variable Information Between Training Set and External Validation Set. **Figure S1:** Differences in data distribution between the train group and the test group. ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; AST/ALT, Aspartate Aminotransferase/Alanine Aminotransferase; BMI, Body Mass Index; HC, Hip Circumference; HCT, Hematocrit; HDL_C, High-Density Lipoprotein Cholesterol; HGB, Hemoglobin Concentration; KS, Kolmogorov–Smirnov; LCC, Left Calf Circumference; LDL_C, Low-Density Lipoprotein Cholesterol; LHG, Left Hand Grip Strength; LUAR, Left Upper Arm Circumference; Lym, Lymphocyte Count; Neut, Neutrophil Count; RBC, Red Blood Cell Count; RCC, Right Calf Circumference; RHG, Right Hand Grip Strength; RUAC, Right Upper Arm Circumference; Scr, Creatinine; TB, Total Bilirubin; TC, Total Cholesterol; TG, Triglycerides; WBC, White Blood Cell Count; WC, Waist Circumference; WHR, Waist-Hip Ratio. **Figure S2:** VIF values of variables selected by LASSO regression. BMI, Body Mass Index, HGB, Hemoglobin Concentration, LASSO, Least Absolute Shrinkage and Selection Operator, LCC, Left Calf Circumference, LHG, Left Hand Grip Strength, Lym, Lymphocyte Count; Scr, Creatinine, TC, Total Cholesterol, VIF, variance inflation factor, WC, Waist Circumference.

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REVIEW

Management of Polyarticular Course Juvenile Idiopathic Arthritis and Temporomandibular Joint Arthritis: A Systematic Literature Review and Meta-Analysis Informing the APLAR Consensus Recommendations

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ABSTRACT

Introduction: Juvenile idiopathic arthritis (JIA) is one of the most common chronic rheumatic diseases and requires coordinated and targeted treatment strategies to avoid long-term disability. Existing guidelines from Western countries may not address region-specific factors, including genetic heterogeneity, limited treatment availability, and limitations in healthcare infrastructure, in the Asia Pacific region. The aim of this systematic literature review (SLR) and meta-analysis was to provide up-to-date evidence for the Asia Pacific League of Associations for Rheumatology (APLAR) recommendations for managing polyarticular course JIA (pcJIA) and temporomandibular joint (TMJ) arthritis.

Methods: This systematic review followed PRISMA guidelines, with searches conducted on MEDLINE, Embase, Web of Science, Scopus, and CENTRAL through January 2025. Included studies addressed pharmacologic or non-pharmacologic treatments for pcJIA and TMJ involvement. Studies were limited to publications not already covered in existing guidelines. The Cochrane Rob2 tool and GRADE approach were used to assess quality and evidence certainty. Meta-analyses were performed where applicable.

Results: Of the initial 9424 records, 86 studies were included in the qualitative analysis. Methotrexate remains the csDMARD of choice, and subcutaneous administration may be more advantageous. Biological DMARDs, particularly abatacept and tocilizumab, have evidence for good efficacy and acceptable safety profiles. Emerging evidence supports the use of JAK inhibitors. Biosimilars were reported to have efficacy and safety comparable to those of originator biologics in observational studies. Limited

evidence suggests that gradual medication tapering after achieving inactive disease status reduces the risk of flares. Evidence for physiotherapy, occupational therapy, and complementary medicine was of very low certainty due to methodological heterogeneity. **Conclusion:** This SLR offers new evidence to support region-specific clinical practice in JIA. While many findings support global recommendations, important evidence gaps remain, particularly in tapering, biosimilar use, TMJ management, and non-pharmacological therapies. These insights will directly inform APLAR's upcoming clinical practice guideline for pcJIA and TMJ arthritis.

1 | Introduction

Juvenile Idiopathic Arthritis (JIA) is one of the most common childhood chronic rheumatic diseases, characterized by persistent arthritis of unknown cause that begins before the age of 16 and lasts for at least 6 weeks [1]. The current International League of Associations for Rheumatology (ILAR) classification criteria divide JIA into seven mutually exclusive categories. Effective treatment of JIA aims to control inflammation, prevent joint damage, maintain functional ability, and optimize the patient's quality of life [2]. Current recommended treatment involves a multidisciplinary approach that entails pharmacologic agents such as non-steroidal anti-inflammatory medications (NSAIDs), conventional synthetic disease-modifying antirheumatic medications (csDMARDs), biological treatments, and supportive measures that include physiotherapy and occupational therapy [3].

These guidelines provide thorough recommendations for diagnosis, treatment, and monitoring of disease activity, mainly based on data from Western populations. Despite these guidelines, an unmet need remains in providing focused guidelines for the Asia Pacific (AP) region. This region has variable genetic, environmental, socio-economic, and healthcare aspects that could affect the presentation of disease, the treatment response, access to care, and adherence [4]. Therefore, the credibility and generalizability of Western developed guidelines in this population remains unclear.

Recognizing this gap, the Asia Pacific League of Associations for Rheumatology (APLAR) has initiated the development of a regional clinical practice guideline for JIA. The first section focuses on non-systemic polyarticular course JIA (pcJIA) and TMJ arthritis, with the second section covering systemic JIA, and the final section providing information on oligoarticular JIA, enthesitis-related arthritis, and psoriatic arthritis. A systematic literature review (SLR) and meta-analysis have been developed as part of this process to provide a comprehensive evidence base for region-specific recommendations. This manuscript aims to outline the methods of the SLR and meta-analysis, to present the main results and highlight the implications in providing evidence-based clinical practice guideline for the pediatric rheumatology community in the Asia Pacific region.

2 | Methods

2.1 | Search Strategy

This SLR was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (www.prisma-statement.org) [5, 6]. The protocol for this SLR was registered in PROSPERO (CRD420251036584), which included the research question, search strategy, inclusion and exclusion criteria as well as risk of bias assessment. An online search was conducted on MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify relevant studies from the beginning until September 2024. A combination of Medical Subject Headings (MeSH) and free-text terms was used for each search. A manual review of the reference lists from the identified studies helped locate additional relevant studies that were missed in the initial search. The search was updated in January 2025. The detailed search strategy is provided in Appendix S1.

2.2 | Eligibility Criteria

The research question was developed using the Population, Intervention, Comparator, and Outcome (PICO) framework. The included populations consisted of patients with pcJIA, defined as children with arthritis starting before age 16 and affecting more than four joints. This included children from various ILAR JIA categories, as long as more than four joints were involved. Another group was patients with TMJ involvement. Interventions included (1) NSAIDs (both nonselective and cyclooxygenase-2 [COX-2] selective NSAIDs); (2) glucocorticoids (oral, intravenous, or intra-articular); (3) csDMARDs (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, lenalidomide); (4) tumor necrosis factor inhibitors (TNFi) and their biosimilars (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol); (5) other biological DMARDs (bDMARDs) and their biosimilars (abatacept, tocilizumab, anakinra, canakinumab, rilonacept, rituximab, secukinumab, ustekinumab, ixekizumab); (6) targeted synthetic DMARDs (tsDMARDs) such as tofacitinib, baricitinib, upadacitinib, and ruxolitinib; (7) non-medical interventions including physical therapy, exercise, occupational therapy, and dietary modifications; (8) traditional and complementary medicine (T&CM). Comparators were any other active drug or placebo. The outcomes of interest included all relevant efficacy and safety data. Articles not published in English were excluded. Due to the scarcity of randomized controlled trials (RCTs) in juvenile idiopathic arthritis, we included not only RCTs, but also quasi-RCTs, cohort studies, case–control studies, cross–sectional studies, and case series with more than six cases. Narrative reviews, case reports, conference abstracts, and animal studies were excluded from the analysis. Details on the eligibility criteria are available in Appendix S2.

2.3 | Study Selection

The results of the initial searches were uploaded to Covidence software. After removing duplicates, titles and abstracts were reviewed independently without date restrictions. The full texts of all potentially relevant studies were then screened independently to determine the final study selection. All title, abstract, and full-text search results were independently examined by two reviewers, with a third reviewer resolving any disagreements. The number of records included and excluded at each stage is reported in the PRISMA flowcharts (Figure 1). Since the clinical practice guideline development process followed an adaptation framework (ADAPTE) using previously published high-quality international guidelines, the present systematic review focused on identifying additional studies not included in prior guideline evidence synthesis. This approach was intended to update and supplement the existing evidence base rather than replicate earlier reviews. As such, the final studies selected were those not included in previous guidelines [7].

2.4 | Data Collection and Quality Assessment

Two independent reviewers carefully reviewed the selected articles for their eligibility criteria. Data collection was conducted using a pre-designed form. For each outcome of interest, either the absolute frequencies or the mean and standard deviation were recorded, depending on the data type. Quality assessment was done separately for each outcome using the GRADE approach, which assigns one of four evidence grades reflecting confidence in the effect estimate: high, moderate, low, and very low [8]. The GRADE method begins with the study design: clinical trials are initially rated as high quality, while observational studies are initially rated as low quality.

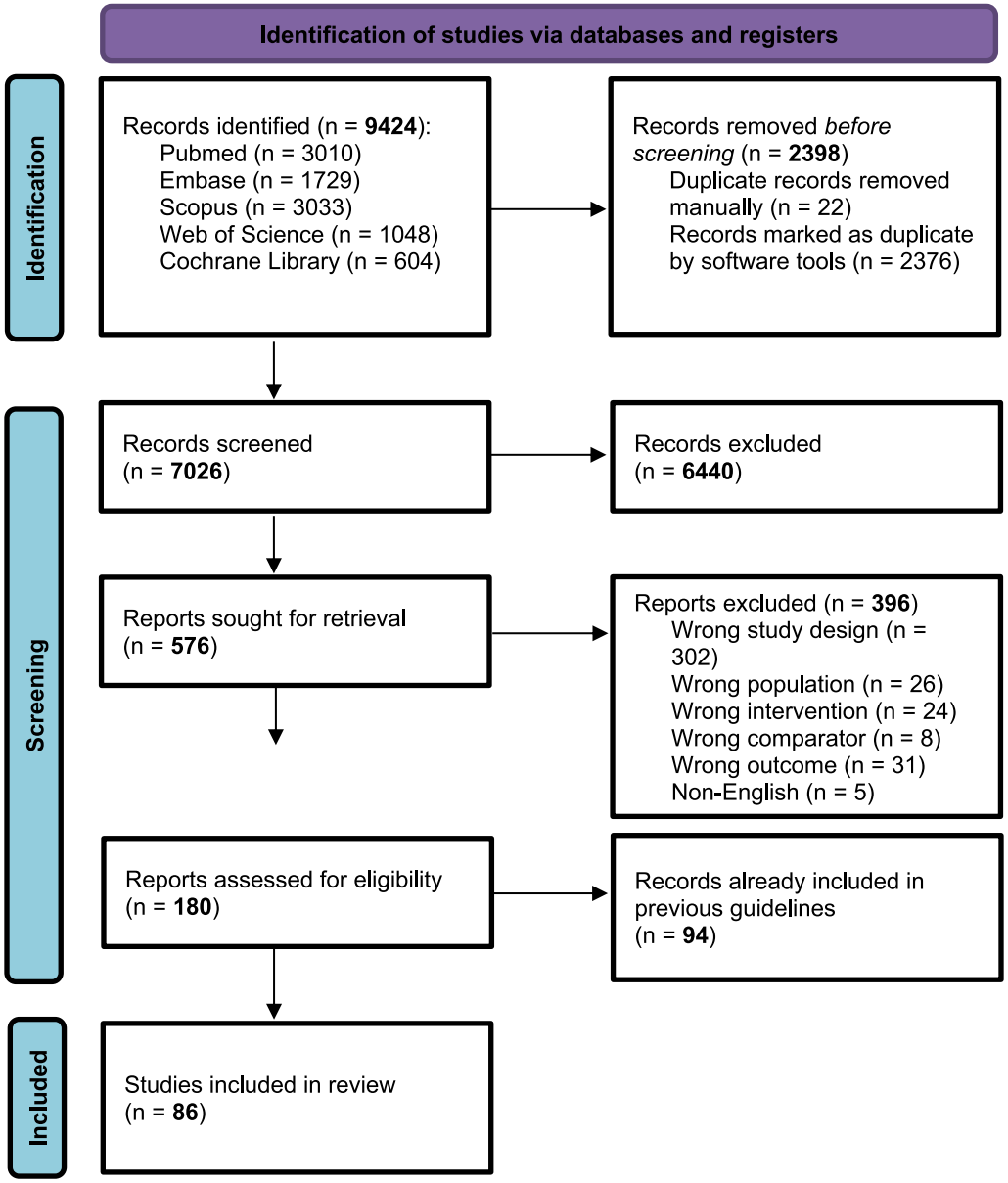

FIGURE 1 | PRISMA flowchart.

It then considers five reasons for potentially lowering the evidence quality and three reasons for possibly raising it. The five factors that can downgrade the evidence include risk of bias, inconsistency, indirectness, imprecision, and publication bias. The risk of bias (RoB) in RCTs and clinical controlled trials was evaluated using the Cochrane Collaboration's RoB tool for RCTs and clinical trials (version 2) [9]. The domains assessed include the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain is rated as low risk, some concerns, or high risk.

2.5 | Statistical Analyses

Meta-analysis was conducted when appropriate. Relative risk (RR), odds ratio (OR), or mean differences (MDs) along with 95% confidence intervals (CIs) were displayed using forest plots. Heterogeneity was measured with the I^2 statistic. Random effect model was used to adjust for heterogeneity across studies. Reasons for heterogeneity were explored during interpretation of the results. When the criteria for meta-analysis were not met, a qualitative assessment was used to summarize study outcomes and the level of evidence across studies. The meta-analyses were performed using the RevMan software.

3 | Results

3.1 | Search Results

The initial search yielded 9424 records. After removing 2398 duplicates, 7026 potential records were screened for eligibility based on the title and abstract. This initial screening resulted in 576 records for full-text review. Following this review, 396 records were excluded, leaving 180 studies deemed suitable for inclusion. The reasons for exclusion included incorrect study population, inappropriate study designs, insufficient outcome data, non-original research, and irrelevant interventions and comparators. After removing studies included in previous guidelines, 86 studies were selected for qualitative analysis in this systematic review (Figure 1).

3.2 | Overview of Included Studies

The 86 studies were broadly categorized into six main themes based on their primary clinical focus: pharmacological management of pcJIA ($n = 32$), TMJ arthritis ($n = 5$), outcome measures in JIA ($n = 18$), use of biosimilars ($n = 6$), tapering strategies for pharmacological treatments ($n = 8$), and non-pharmacological interventions including T&CM and physiotherapy ($n = 17$). Among the 86 included studies, randomized controlled trials accounted for 25 studies (29%), while the remaining 61 studies (71%) were observational studies and non-randomized trials. The predominance of observational evidence and non-randomized trials in several therapeutic domains contributed to the overall low or very low certainty ratings assigned using the GRADE framework.

3.3 | Polyarticular Course Juvenile Idiopathic Arthritis

3.3.1 | Nonsteroidal Anti-Inflammatory Drugs

Three RCTs assessed the effectiveness of various NSAIDs. One RCT showed a non-significant trend favoring piroxicam over naproxen (RR 1.87; 95% CI, 0.83–4.19) for clinical improvement at Week 12, while another comparing meloxicam and naproxen found no significant differences in ACR responses or adverse event rates [10, 11]. Similarly, celecoxib showed comparable effectiveness and safety to naproxen [12]. The overall certainty of evidence from these studies remained very low, mainly due to small sample sizes and indirectness (Table 1).

3.3.2 | Glucocorticoids

Additional evidence on glucocorticoid use in pcJIA remains scarce. One randomized controlled trial specifically assessed intravenous pulse dexamethasone (3 mg/kg/day, up to a maximum of 100 mg/day for 3 days) compared to placebo [13]. This study found no significant differences in ACR response rates between the dexamethasone group and placebo at 16 weeks (RR for ACR30 1.07, 95% CI 0.81–1.41; RR for ACR50 0.99, 95% CI 0.65–1.50; RR for ACR70 1.17, 95% CI 0.62–2.20). Concerning the use of oral glucocorticoids as bridging therapy, three RCTs compared initial csDMARD monotherapy to concomitant oral prednisolone with csDMARD. All three RCTs showed no significant benefit from adding bridging oral prednisolone, and side effects did not significantly increase either [14–16]. Although these were RCTs, the overall certainty of evidence across these studies was very low due to concerns about RoB, small sample sizes, and population heterogeneity, which included non-pcJIA patients (Table 1).

3.3.3 | Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs

One additional non-randomized observational study compared oral and subcutaneous methotrexate (Bakry 2022). The ACR responses at Month 24 were significantly higher in patients receiving subcutaneous methotrexate (mean ± SD dose 13.3 ± 4.5 mg/m^2/week) compared to oral methotrexate (mean ± SD dose 13.5 ± 5.3 mg/m^2/week). However, the proportion of patients who achieved JADAS remission and the time to remission did not differ between the two groups. The subcutaneous methotrexate group had more elevated liver enzymes (18.4% vs. 10%, OR 1.9, 95% CI 1.3–2.9, $p = 0.001$), as well as nausea and vomiting (51% vs. 25%, OR 1.9, 95% CI 1.47–2.6, $p < 0.001$). There was no mention of folic acid use in this study. Notably, patients on subcutaneous methotrexate had higher baseline disease activity. Despite this confounding factor, the results showed that patients on subcutaneous methotrexate achieved a greater response compared to those on oral methotrexate. Therefore, this study was graded up one level of certainty. The other RCT comparing methotrexate monotherapy with combination methotrexate/leflunomide therapy demonstrated no significant advantage for the combination regimen

TABLE 1 | Summary of included articles for polyarticular juvenile idiopathic arthritis.

Theme	Authors (date)	Study design	Sample size	Intervention	Comparator	Outcomes	RoB	CoE
NSAID	Garcia-Morteo (1987)	RCT	26	Piroxicam	Naproxen	Clinical improvement at Week 12		Very low
	Foeldvari (2002)	Non-RCT	34	Meloxicam	—	PRINTO outcome criteria at Week 12		Very low
	Foeldvari (2009)	RCT	242	Meloxicam	Naproxen	ACR responses at Week 12		Low
GC	Bhardwaj (2022)	RCT	60	Pulse dexamethasone	Placebo	ACR responses at Week 16		Very low
	Hissink Muller (2017)	RCT	64	csDMARD with oral steroid	csDMARD monotherapy	ACR responses at Week 6		Very low
	Muller (2019)	RCT	64	csDMARD with oral steroid	csDMARD monotherapy	Inactive disease at Month 24		Very low
	Spekking (2023)	RCT	64	csDMARD with oral steroid	csDMARD monotherapy	VAS pain score at Month 24		Very low
csDMARD	Bakry (2022)	Non-RCT	794	SC MTX	Oral MTX	ACR responses at Month 24, transaminitis		Moderate
	Rezaieyazdi (2023)	RCT	18	MTX with Leflunomide	MTX monotherapy	ACR responses, active joint counts, adverse events at Week 12		Very low
bDMARD	Brunner (2018)	Single-arm trial	219	SC Abatacept	—	ACR responses, clinical inactive disease at Week 16		Low
	Hara (2019)	Single-arm trial	20	IV Abatacept	—	ACR responses, clinical inactive disease at Week 16		Low
	Brunner (2023)	Single-arm trial	219	SC Abatacept	—	ACR responses, clinical inactive disease at Week 52		Low
	Ruperto (2023)	Single-arm trial	219	SC Abatacept	—	ACR responses, CHAQ-DI, PtGA, VAS pain at Month 24		Low
	Gronlund (2020)	Observational study	56	Tocilizumab	—	JADAS-10 score at Month 24		Very low
	Malattia (2020)	Non-RCT	188	Tocilizumab	—	Radiographic progress at Weeks 52 and 104		Very low
	Brunner (2021)	Non-RCT	188	Tocilizumab	—	CHAQ, VAS pain, HRQoL at Weeks 16, 40, and 104		Very low

(Continues)

TABLE 1 | (Continued)

Theme	Authors (date)	Study design	Sample size	Intervention	Comparator	Outcomes	RoB	CoE
	Illowite (2009)	Withdrawal trial	50	Anakinra	Placebo	Adverse events, disease flare at Week 28		Very low
	Kearsley-Fleet (2019)	Observational study	36	Rituximab	—	cJADAS-71, active joint counts at first follow-up		Very low
	Alexeeva (2021)	RCT	68	Etanercept and MTX	csDMARD monotherapy	ACR responses at Week 12		Very low
	Muller (2019)	RCT	62	Etanercept and MTX	csDMARD monotherapy	ACR responses, inactive disease at Month 24		Low
	Spekking (2023)	RCT	62	Etanercept and MTX	csDMARD monotherapy	VAS pain at Month 24		Low
	Tarkiainen (2019)	RCT	40	Infliximab and MTX	csDMARD monotherapy	Psyschosocial and physical summary score at Week 54		Very low
	Tynjala (2011)	RCT	40	Infliximab and MTX	csDMARD monotherapy	ACR responses at Week 54		Low
	Kimura (2021)	Observational study	143	Combination bDMARD and csDMARD	bDMARD monotherapy	Inactive disease, JADAS-10, ACR responses at Month 12		Very low
	Klein (2019)	Observational study	584	Combination adalimumab and MTX	Adalimumab monotherapy	ACR responses, inactive disease at Month 12		Very low
JAKi	Ruperto (2021)	RCT	142	Tofacitinib	Placebo	ACR responses at Week 44		Moderate
	Ramanan (2023)	RCT	163	Baricitinib	Placebo	ACR responses at Week 33		Moderate
	Brunner (2025)	Open label phase 1 trial	57	Upadacitinib		ACR responses at Week 12		Very low
	Rahman (2022)	Observational study	8	Tofacitinib		JADAS-27 at Week 12 and 24		Very low

Note: Green = low risk of bias, yellow = moderate risk of bias, red = high risk of bias.

Abbreviations: ACR, American College of Rheumatology; bDMARD, biologic disease modifying anti-rheumatic drug; CHAQ, childhood health assessment questionnaire; CoE, certainty of evidence; csDMARD, conventional disease modifying anti-rheumatic drug; GC, glucocorticoid; HRQoL, health related quality of life; IV, intravenous; JADAS, juvenile arthritis disease activity score; JAKi, janus kinase inhibitor; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drugs; PRINTO, Pediatric Rheumatology INternational Trials Organization; RCT, randomized controlled trial; RoB, risk of bias; SC, subcutaneous; VAS, visual analogue scale.

in disease control or safety outcomes [17]. The certainty of evidence was low, despite this being an RCT, due to differences in baseline characteristics between the groups, heterogeneity in the patient population, and a small sample size (Table 1).

3.3.4 | Biological Disease-Modifying Anti-Rheumatic Drugs

Four articles covered abatacept, including two different single-arm phase III studies [18–21]. The Pediatric Rheumatology International Trials Organization (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG) investigated the use of subcutaneous abatacept, while another Japanese study examined intravenous abatacept in pcJIA patients. Brunner et al. reported high rates of patients achieving ACR responses at Month 4 [21]. The median (Interquartile range, IQR) Juvenile Arthritis Disease Activity Score (JADAS)-71–CRP improved from baseline to Month 4 [cohort 1, ages 6–17 years, from 21.0 (13.5–30.3) to 4.6 (2.1–9.4); cohort 2, ages 2–5 years, from 18.1 (14.0–23.1) to 2.1 (0.3–4.4)]. No unexpected adverse events were reported. The authors also examined the long-term maintenance of clinical response [19]. The proportions of patients meeting low disease activity and minimal pain composite endpoints increased from 44.7% at Month 4 to 54.8% at Month 21. Ruperto et al. also described early and sustained improvements in patient-reported outcomes using subcutaneous abatacept in this patient cohort [20]. Hara et al. enrolled 20 patients who received intravenous abatacept [18]. Week 16 JIA-ACR30 response rate was 90.0%. At Week 52, JIA-ACR30 response and inactive disease rates were 89% and 44%, respectively. All adverse events were mild or moderate, and no anti-drug antibodies were detected through Week 16. In a pooled analysis of the outcomes from both trials, the proportion of ACR30 responses at Week 16 was 84.3% (95% CI, 79.1–89.4).

Two RCTs were included for tocilizumab [22, 23]. Patients from both RCTs were enrolled in the CHERISH trial, a 2-year, phase 3 randomized withdrawal study assessing the efficacy and safety of tocilizumab in patients with pcJIA [24]. This trial consisted of a 16-week open-label, lead-in period, a 24-week double-blind, placebo-controlled withdrawal phase, and a long-term extension. The first RCT demonstrated slower radiographic progression in patients with pcJIA receiving tocilizumab, while the second RCT reported significantly reduced disability and pain, along with improved health-related quality of life (HRQoL). Another observational study on tocilizumab was included [25]. It involved 56 patients with pcJIA, with tocilizumab typically started as a third-line biological agent. The median JADAS-10 score decreased from 7.6 (IQR 5.4–12.1) at baseline to 1.2 (IQR 0–2.5) at 24 months ($p < 0.001$). The overall certainty of evidence across critical outcomes for tocilizumab remains very low due to a high risk of bias.

One placebo-controlled withdrawal trial evaluated the efficacy of anakinra compared to placebo; however, the primary outcome was later changed to a safety analysis due to the small sample size for efficacy [26]. While there were no significant differences in adverse events, there was also no statistically significant difference in efficacy. Regarding rituximab, an observational study reported a median change in active joint count of 1 (IQR, 4 to 0; $p < 0.05$) and a median change in clinical JADAS (cJADAS)-71 of 9 (IQR, −14 to 2), although limited data were available for some variables [27].

Additional evidence from five RCTs examined combination therapies with bDMARD versus csDMARD monotherapy. Three RCTs comparing etanercept combined with methotrexate to csDMARD monotherapy found no significant differences in achieving ACR30 responses or inactive disease states (Figure S1) [15, 16, 28]. In contrast, two RCTs assessing infliximab plus methotrexate showed improved ACR responses and inactive disease rates, without an increase in adverse events. However, patient-reported outcomes revealed no significant difference compared to csDMARD monotherapy [29, 30].

Regarding the use of bDMARD as monotherapy, a prospective observational study compared the effectiveness of three consensus treatment plans for untreated pcJIA [31]. The combination bDMARD/methotrexate plan did not offer additional benefits over bDMARD monotherapy in achieving clinically inactive disease at Month 12 (25% vs. 11%). Similarly, Klein et al. showed comparable efficacy between adalimumab monotherapy and combination therapy with adalimumab and methotrexate [32]. In fact, patients on the combination had a higher risk of elevated transaminases (RR, 3.98; 95% CI, 1.53–10.30) and gastrointestinal events (RR, 4.93; 95% CI, 2.92–8.34) (Table 1).

3.3.5 | Janus Kinase Inhibitors

Two pivotal phase 3 RCTs evaluated JAK inhibitors (tofacitinib and baricitinib) in patients who failed csDMARD therapy. In the tofacitinib double-blind, placebo-controlled, withdrawal phase 3 trial, patients who continued to take tofacitinib had lower flare rates at Week 44 than those who switched to placebo [33]. The proportion of patients with ACR30/50/70/90 responses was also higher in the tofacitinib arm, with no significant differences in adverse events. Similarly, baricitinib demonstrated robust efficacy, with significant improvements in disease activity and health-related quality of life measures compared to placebo, along with an acceptable safety profile observed across studies involving 219 patients who received baricitinib during the open-label lead-in period; 74% achieved at least a JIA-ACR30 response by Week 12 [34]. The time to disease flare was significantly shorter for patients switched to placebo than for those who continued baricitinib [HR 0.241 (95% CI 0.128–0.453), $p < 0.0001$]. In another interim analysis of a phase 1 open-label trial evaluating upadacitinib, the ACR 30/50/70 response rates at Week 12 were 91.8%, 89.8%, and 69.4%, respectively, with sustained efficacy through Week 48 [35]. The overall certainty of evidence supporting JAK inhibitor efficacy and safety was moderate, primarily limited by short follow-up durations. In a separate prospective observational study by Rahman et al., assessing the efficacy and safety of tofacitinib in 27 refractory pcJIA patients, the proportion of patients with improvement in the JADAS-27 score was 83%, 91%, and 96% at 6, 12, and 24 weeks, respectively (Table 1, Figure 2) [36].

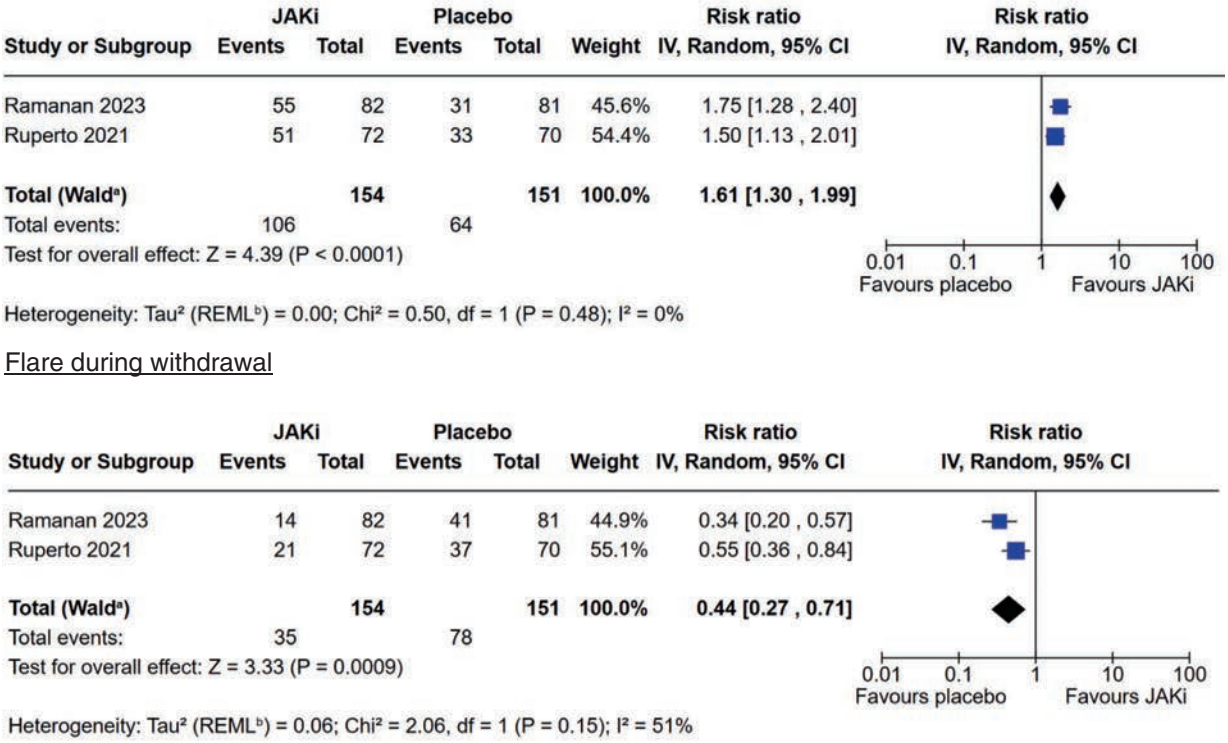

FIGURE 2 | Meta-analysis for JAK inhibitors (combining both baricitinib and tofacitinib studies). [a]CI calculated by Wald-type method. [b]Tau^2 calculated by Restricted Maximum-Likelihood method. ACR, American College of Rheumatology; JAKi, janus kinase inhibitor.

3.4 | Temporomandibular Joint Arthritis

Five observational studies examined the management of TMJ arthritis in patients with JIA. Of these, four focused on intra-articular therapy. Arabshahi et al. reported improved maximal incisal opening in 43% of patients who received CT-guided corticosteroid injections of the TMJ, while 77% experienced complete pain resolution [37]. This study lacked a comparator arm. Antonarakis et al. investigated the effects of intra-articular lavage in JIA patients with clinical and radiographic signs of TMJ arthritis [38]. The study was modified midway to include TMJ lavage combined with intra-articular steroid injections, as the effectiveness of lavage alone was limited. MRI at 6 months showed that 18 of 42 joints (42.9%) improved in the lavage with intraarticular steroid group, compared to 31.3% (5 out of 16) in the lavage-only group and 27.8% (5 out of 18) in the no-treatment group. In two retrospective studies, intra-articular infliximab did not show significant improvement in TMJ arthritis imaging compared to intra-articular glucocorticoids [39, 40]. Finally, Alqanatish et al. reported a single-center experience in managing TMJ arthritis in children with JIA [41]. Nearly 100% of patients with TMJ involvement received biological medication, resulting in complete improvement in 95% of cases. However, there were no comparisons with patients not on biological or targeted synthetic DMARDs. Besides these retrospective studies, no new evidence was found on the pharmacological management of TMJ arthritis using NSAIDs, csDMARDs, or bDMARDs. Additionally, no studies were identified regarding the use of dental occlusal splints or the utility of MRI in monitoring disease activity (Table 2).

3.5 | Outcome Measures

Eighteen studies focused on outcome measures used to assess disease activity and response to treatment in JIA. The JADAS was the most extensively evaluated instrument. JADAS was shown to have strong construct validity, demonstrating high correlations with core JIA activity measures, including swollen joint counts ($r = 0.44–0.82$), tender joint counts ($r = 0.50–0.73$), and the Childhood Health Assessment Questionnaire (C-HAQ) ($r = 0.43–0.51$) [42]. The JADAS-CRP and JADAS-ESR had a very high correlation ($r = 0.99$) [43]. Multiple studies also validated various versions of the JADAS, including JADAS-71, JADAS-27, JADAS-10, and cJADAS-10. Among these, the cJADAS-10 was especially emphasized due to its simplicity and proven validity [44–47]. The diagnostic properties of suggested cutoff values for clinical decision-making and disease activity thresholds were also assessed across various studies. These cutoff values and their diagnostic properties are summarized in Table 3.

Apart from the JADAS, Sontichai et al. investigated the use of the CHAQ disability index (CHAQ-DI) in 139 patients with JIA [49]. The CHAQ-DI showed a significantly stronger correlation with disease activity parameters during active disease compared to inactive disease ($r = 0.73$ vs. $r = 0.21$). Nicoara et al. examined the potential use of the systemic immune-inflammation index (SII) and found that SII was independently associated with JADAS-10 ($p = 0.690$, using multiple regression analysis) [50]. Additionally, SII effectively distinguished patients with high disease activity from other severity groups (AUC = 0.827, sensitivity 81.5%, specificity

66%). Finally, Doeleman et al. investigated a self-assessment tool using the EuroQol five-dimensional "youth" questionnaire with five levels (EQ-5D-Y-5L) to identify JIA patients requiring treatment adjustments [51]. They demonstrated that the EQ-5D-Y-5L could differentiate between patients with inactive or minimally active disease and those with moderate to high disease activity with good sensitivity (85%), specificity (89%), and negative predictive value (86%).

3.6 | Tapering of Medication

Eight studies (two RCTs and six observational studies) investigated strategies for tapering medications in patients with JIA after they reached clinical inactive disease (CID). The evidence primarily focused on tapering approaches for methotrexate and TNFi.

For methotrexate tapering, Foell et al. found no difference in flare rates between withdrawing methotrexate at 6 and 12 months of inactive disease [48]. Although observational data suggest that a longer duration (> 12 months) of CID before methotrexate withdrawal significantly lowers the risk of flare (HR 0.50; 95% CI 0.34–0.74), the strength of evidence in these observational studies was lower compared to the RCT [52, 53]. Overall, pooled results showed no significant difference in flare rates after methotrexate discontinuation between early and late withdrawal (RR 1.19; 95% CI 0.66–2.15).

Regarding TNFi tapering, five studies (one RCT, four observational) evaluated various withdrawal strategies. Garcia-Fernandez et al. demonstrated significantly lower flare rates following gradual tapering compared to abrupt withdrawal at both 6 months (RR = 0.26, 95% CI 0.16–0.41) and 12 months (RR = 0.39, 95% CI 0.29–0.54), with moderate certainty of evidence due to the large effect size [54]. In an RCT by Tsulukiya et al. comparing TNFi dose reduction to interval prolongation, there was no significant difference in remission maintenance at 6 months (RR = 0.96; 95% CI 0.63–1.47) and 12 months (RR = 0.72; 95% CI 0.29–1.78) [55]. Additionally, Teh et al. compared outcomes of a short (every 4 weeks for 6 months before stopping) and long weaning strategy (extending dosing interval by 2 weeks for three cycles until reaching 12-week intervals and then stopping) of TNFi in a prospective JIA cohort [56]. The total flare rate after stopping TNFi (RR = 1.41, 95% CI 0.98–2.02) and the time to flare after stopping TNFi showed no difference ($p = 0.639$), suggesting that weaning over a longer duration does not confer additional benefits. Other observational data indicated that the order of medication withdrawal may be important; discontinuing methotrexate before TNFi in patients on combination therapy significantly reduced flare risk at 12 months compared to stopping TNFi first (RR = 0.27, 95% CI 0.13–0.56), although the certainty of evidence is low due to the non-randomized nature of this study [57]. The details of the included studies are presented in Table S1.

3.7 | Biosimilars

Five observational studies were identified, specifically focusing on TNFi [58–62]. These studies examined biosimilar

TABLE 2 | Summary of included articles for temporomandibular joint arthritis.

Theme	Authors (date)	Study design	Sample size	Intervention	Comparator	Outcomes	RoB	CoE
IA	Arabshahi (2005)	Observational	13	IA glucocorticoid	Standard of care	Pain, MIO, MRI improvement post injection		Very low
	Antonarakis (2018)	Observational	41	IA glucocorticoid and lavage	IA lavage	Anamnestic dysfunction index score, clinical dysfunction index score post injection		Very low
	Stoll (2015)	Observational	33	IA infliximab	IA glucocorticoid	MRI improvement post injection		Very low
	Stoll (2013)	Observational	24	IA infliximab	IA glucocorticoid	MIO post injection		Very low
bDMARD	Alqanatish (2021)	Observational	123	bDMARD	—	Clinical improvement		Very low

Note: Red = high risk of bias.

Abbreviations: bDMARD, biologic disease modifying anti-rheumatic drug; CoE, certainty of evidence; IA, intraarticular; MIO, maximal incisal opening; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drugs; RoB, risk of bias.

TABLE 3 | Summary of included articles for outcome measures.

Authors (year)	Population	Cutoff values	Diagnostic performance
JADAS (overall)			
Consolaro (2009)	Four samples of patients comprising 4578 JIA patients		The JADAS demonstrated good construct validity and strong correlations with JIA activity measures not included in the score, such as the swollen joints ($r = 0.44–0.82$), tender joint counts ($r = 0.50–0.73$), and C-HAQ ($r = 0.43–0.51$). JADAS scores may also predict radiographic progression ($r = 0.47$ for JADAS-71 and $r = 0.50$ for JADAS-10, $p < 0.001$)
Consolaro (2012)	609 JIA patients for derivation cohort, 1323 for validation	IDA: 1 Physician assessed Remission: 2 MiDA: 3.8	Sensitivity: 83.4%, Specificity 88.2% Sensitivity: 82.8%, Specificity 94.5% Sensitivity: 96.5%, Specificity 91.3% *Cutoffs for JADAS-10/27/71 are the same*
Nordal [48] (2012)	389 JIA patients including 99 polyarticular JIA	—	JADAS-ESR and JADAS-CRP have good correlation ($r = 0.98$ for JADAS-10, $r = 0.99$ for JADAS-27 and $r = 0.99$ for JADAS-71) Strong correlation between remission status and JADAS, with a median JADAS27-CRP of 0 (IQR 0–0) for children in remission off medication and a median JADAS27-CRP of 2.0 (IQR 0.4–5.2) for children not in remission off medication
McErlane (2013)	956 JIA patients including 205 polyarticular JIA	—	Correlation between JADAS-10, JADAS-27 and JADAS-71 was high ($r = 0.87–1.0$) Correlation with ESR was poor
Consolaro (2014)	609 JIA patients for derivation cohort, 1378 for validation	Cutoffs for HDA JADAS-10: 10.5 JADAS-27: 8.5 JADAS-71: 10.5	Sensitivity 89.1%, Specificity 92.7% Sensitivity 91.5%, Specificity 91% Sensitivity 89.1%, Specificity 92.7%
JADAS-10			
Ringold (2010)	97 polyarticular JIA	—	AUC (95% CI) for prediction of ACR measure and flare Flare: 0.90 (0.85–0.95) ACR30: 0.89 (0.84–0.93) ACR50: 0.92 (0.88–0.96) ACR70: 0.92 (0.88–0.96) ACR90: 0.86 (0.81 - 0.92)

(Continues)

TABLE 3 | (Continued)

Authors (year)	Population	Cutoff values	Diagnostic performance
Consolaro (2014)	609 JIA patients for derivation cohort, 485 patients for validation	cJADAS-10 IDA: ≤1 LDA: ≤2.5 MDA: 2.51–8.5 HDA: >8.5	
Horneff (2014)	1315 treatment courses, including 474 polyarticular JIA	Improvement cutoff based on baseline disease activity Low: 4 Moderate: 10 High: 17	Sensitivity 76.1%, specificity 81.6% Sensitivity 76.0%, specificity 73.6% Sensitivity 77.1%, specificity 87.9%
Backstrom (2016)	513 JIA patients including 33 polyarticular JIA	JADAS-10 CID: 0.0–0.7 IDA: 0.8–3.9 MDA: ≥4.0 cJADAS-10 CID: 0.0–0.7 IDA: 0.8–3.9 MDA: ≥4.0	CCR: 70.2% CCR: 49.5% CCR: 82.0% CCR: 70.2% CCR: 49.0% CCR: 81.0%
Backstrom (2018)	513 JIA patients including 233 polyarticular JIA	JADAS-10 HDA: ≥15.2 cJADAS-10 HDA: ≥14.0	CCR 84.5% CCR 82.8% Must also fulfill at least 3 of the following: Six or more active joints, ESR above normal, PGA of overall disease activity ≥4, PtGA of well-being ≥2
Shoop-Worrall (2018)	832 JIA patients including 269 polyarticular JIA	—	Achieving CID was superior to achieving MDA in terms of short- and long-term pain (RR (CI): −6.5 (−12.1, −0.9) and −5.5 (−10.1, −0.9)) and the absence of joints with limited range of motion (OR (CI): 2.4 (1.3, 4.5) and 1.7 (1.0, 2.7)).
Backstorm (2019)	337 non-systemic JIA patients including 140 polyarticular JIA	JADAS-10 CID: 0.0–0.7 IDA: 0.8–5.0 MDA: >5.0	CCR 65.3% CCR 81.8% CCR 69.6% CID must exclude patients with active joints

(Continues)

TABLE 3 | (Continued)

Authors (year)	Population	Cutoff values	Diagnostic performance
Trincianti (2021)	1936 JIA patients	JADAS-10 ID to MiDA: ≤2.7 MiDA to MoDA: 6 MoDA to HDA: 17 cJADAS-10 IDA to MiDA: 2.5 MiDA to MoDA: 5 MoDA to HDA: 16	Sensitivity 79.1%, specificity 90.2% Sensitivity 79.8%, specificity 88.6% Sensitivity 82.6%, specificity 92.3% Sensitivity 81%, specificity 89% Sensitivity 76%, specificity 92.2% Sensitivity 81.5%, specificity 93.9%
JADAS-27			
Ringold (2010)	97 polyarticular JIA	—	AUC (95% CI) for prediction of ACR measure and flare Flare: 0.92 (0.88–0.97) ACR30: 0.85 (0.79–0.91) ACR50: 0.87 (0.81–0.92) ACR70: 0.87 (0.81–0.92) ACR90: 0.76 (0.66–0.85)
Mourao (2014)	358 JIA patients	—	JADAS27-CRP and JADAS27-ESR have good correlation (correlation coefficient 0.967, $p < 0.0001$) JADAS27-ESR and JADAS27 without ESR have good correlation (correlation coefficient 0.97, $p < 0.0001$)
Bulatović Calasan (2014)	270 JIA patients with 92 polyarticular JIA	Clinically important difference for disease improvement −5.5 (IQR −9.5 to −2.7) Clinically important difference for flare +1.7 (IQR +0.3 to 5.0) Cutoffs LDA: ≤2.7 HDA: ≥6.0	AUC 0.86 (95% CI 0.83–0.90) AUC 0.84 (95% CI 0.80–0.88) Sensitivity 76%, specificity 62%, PPV 42%, NPV 88% Sensitivity 77%, specificity 77%, PPV 41%, NPV 94%
JADAS-71			
Ringold (2010)	97 polyarticular JIA	—	AUC (95% CI) for prediction of ACR measure and flare Flare: 0.92 (0.88–0.97) ACR30: 0.83 (0.77–0.90) ACR50: 0.84 (0.77–0.90) ACR70: 0.85 (0.79–0.91) ACR90: 0.75 (0.67 - 0.83)

(Continues)

TABLE 3 | (Continued)

Authors (year)	Population	Cutoff values	Diagnostic performance
Swart (2018)	74 polyarticular JIA	cJADAS-71 that predict MTX failure At 3 months: > 7 At 6 months: > 4	Accuracy 75.6%, Sensitivity 81.3%, Specificity 72.0% Accuracy 75.6%, Sensitivity 70.6%, Specificity 78.6%
CHAQ-DI			
Sontichai (2018)	139 JIA patients including 30 polyarticular JIA	—	CHAQ-DI correlation with JADAS-27 during active disease using Spearman correlation: 0.73 ($p < 0.005$) CHAQ-DI correlation with JADAS-27 during inactive disease using Spearman correlation: 0.21 ($p < 0.005$) CHAQ-DI correlated significantly more with disease activity parameters during active than inactive disease and had moderate to strong correlations with JADAS27 during active disease
*Systemic immune inflammation index (SII)**			
Nicoara (2024)	74 JIA patients including 25 polyarticular JIA	—	SII associated with JADAS-10 ($p = 0.004$)
EuroQol five-dimensional "youth" questionnaire with five levels (EQ-5D-Y-5 L)			
Doeleman (2021)	68 JIA patients	Cutoff to discriminate moderate to high disease Sum score > 6	Accuracy 87%, Sensitivity 85%, Specificity 89%

*SII=neutrophil count (10^9/L)×platelet count (10^9/L)/lymphocyte count (10^9/L).

formulations of adalimumab, etanercept, and infliximab. All but one study showed no significant difference between biosimilars and originators in head-to-head comparisons of disease activity measured using JADAS. One study demonstrated significantly lower JADAS-10 scores at Months 3, 6, and 12 for biosimilar agents compared to originators ($p < 0.05$), alongside lower anti-drug antibody levels at Month 3 ($p = 0.04$ for adalimumab and $p = 0.0007$ for etanercept) [58]. A pooled analysis of adverse event data across these studies revealed no significant difference between the biosimilar and originator groups (OR, 0.78; 95% CI 0.52–1.17). Similarly, switching from originators to biosimilars did not significantly affect disease activity (OR 0.71, 95% CI 0.34–1.50). Overall, the certainty of this evidence remains low, primarily due to the lack of randomized controlled trials and the potential for confounding inherent in observational designs (Table 4).

3.8 | Non-Pharmacologic Management

Seven studies (five RCTs and two observational studies) evaluated the effectiveness of physiotherapy and occupational therapy interventions [63–70]. The included RCTs showed significant variability in intervention types (land-based versus aquatic exercise), duration, and measured outcomes. Among them, only one RCT assessing an aquatic fitness training program reported significant improvements in the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) and the Juvenile Arthritis Functional Assessment Scale (JAFAS) scores [63]. The other land-based exercise RCTs found no statistically significant differences in functional or quality-of-life outcomes compared to the control group. Observational studies have produced mixed results. For instance, a single-arm observational study evaluating a 6-month exercise program aimed at improving bone and muscle strength did not demonstrate sustained clinical improvements, with a notably low adherence at 47% [68]. Conversely, another observational study reported significant reductions in disease severity indices (mean Articular Severity Index: 28.9 to 17.6) and pain scores after an 8-week weight-bearing physical conditioning program [69]. Overall, the evidence supporting the use of physiotherapy and occupational therapy for JIA remains very limited, primarily due to methodological limitations, imprecision, and inconsistency across studies (Figure S2). The details of the included studies are presented in Table S2.

3.9 | Traditional and Complementary Medicine

Nine studies (three RCTs and six observational studies) evaluated complementary and alternative therapies in patients with JIA. Two studies assessing the use of massage and yoga therapy demonstrated reductions in the number of active joints and morning stiffness at Week 4; however, no conclusive results were obtained for improvements in pain scores at Week 8 [71, 72]. One RCT reported that adjunctive Vitamin D supplementation (2000 IU/day for 24 weeks) effectively increased serum vitamin D levels but did not lead to clinically meaningful reductions in disease activity or improvements in bone mineral density [73]. Another RCT demonstrated that blueberry supplementation, combined with etanercept, significantly improved ACR30/50/70

TABLE 4 | Summary of included articles for biosimilar.

Theme	Authors (date)	Study design	Sample size	Intervention	Comparator	Outcomes	RoB	CoE
Comparative study	Gicchino (2024)	Observational	81	Etanercept and Adalimumab biosimilar	Etanercept and Adalimumab originator	JADAS-10, flare and anti-drug antibodies at Months 3, 6, and 12		Very low
	Kearsley-Fleet (2024)	Observational	328	TNFi biosimilar	TNFi originator	Drug survival probability, JADAS-71 at Month 6		Very low
	Ulu (2023)	Observational	76	Adalimumab biosimilar	Adalimumab originator	JADAS-10, adverse events at Months 3, 6, 12, 18, and 24		Very low
Switching study	Maccora (2022)	Observational	45	Etanercept and adalimumab switched to biosimilar	Etanercept and adalimumab originator	Inactive disease, JADAS-10, flare rate at Months 3, 6, 12		Very low
	Thiele (2021)	Observational	57	Etanercept switched to biosimilar	Etanercept originator	Drug discontinuation, JADAS-10, adverse events at last followup		Very low

Note: Red = high risk of bias.
Abbreviations: CoE, certainty of evidence; JADAS, juvenile arthritis disease activity score; RoB, risk of bias; TNFi, tumor necrosis factor inhibitor.

response rates compared to etanercept alone, along with reductions in pro-inflammatory cytokines (IL-1α, IL-1β) [74]. Observational data on other supplements, including Radix Tripterygium Wilfordii Hook F and Kre-Celazine (an oral, non-prescription, nutritional supplement made from a proprietary alkali-buffered creatine monohydrate and acetylated fatty acids mixture), indicated improvements in pain and active joints for patients with JIA, but these are non-randomized studies with small sample sizes [75, 76]. One observational study examining mind–body interventions (relaxation training, biofeedback) demonstrated significant improvements in self-reported pain, although the very small sample size limited certainty [77]. A broader observational analysis found no association between the use of T&CM and improved health-related quality of life or reduced pain scores among JIA patients [78]. Overall, the certainty of evidence across these studies remains very low, limited by study heterogeneity, small participant numbers, and methodological weaknesses (Table S3).

4 | Discussion

This systematic review and meta-analysis compile the latest evidence on the management of pcJIA and TMJ arthritis. The present systematic review should also be interpreted in the context of the guideline adaptation process used by our task force. Rather than conducting a de novo synthesis of all historical evidence, the review focused on identifying additional studies not already incorporated in previous international guideline evidence syntheses. Importantly, the vast majority of studies are still from Western countries, and fewer studies are from the Asia Pacific region, highlighting a considerable regional evidence gap. Our review confirms that methotrexate remains the cornerstone of csDMARDs therapy in pcJIA. Consistent with current guideline recommendations, methotrexate continues to show the superior efficacy–safety balance [79, 80]. However, our review shows an important nuance in practice: the subcutaneous route seems to yield higher ACR response rates than oral dosing but has more gastrointestinal intolerance and elevated hepatic enzymes. The evidence also shows no additive benefit from combination csDMARD regimens. Given these findings, in pcJIA patients who do not respond to methotrexate, escalation to early bDMARD therapy may be considered, rather than adding csDMARD combination therapy.

The bDMARDs landscape is changing rapidly. With TNFi already demonstrating effectiveness in pcJIA patients, there has been increased focus on abatacept and tocilizumab over the past decade [81]. Both drugs demonstrate high clinical response rates in clinical trials, with no major safety concerns. These findings support the 2021 ACR recommendations to initiate bDMARDs earlier in non-systemic JIA phenotypes, and will increase confidence in their adoption in regions with slower regulatory approval. Notably, we also found combination therapy of a bDMARD with methotrexate, showed no incremental advantages in clinical response and disease control compared with bDMARD monotherapy [31, 32]. This aligns with a recent Cochrane review, which found that 70% of JIA patients on methotrexate and 90% on TNFi plus methotrexate achieved a treatment response, with no statistically significant difference between the groups (RR 1.29, 95% CI 0.93 to 1.77) [81]. However, It is important to note that this SLR did not consider the formation of anti-drug antibodies as an outcome in comparing bDMARD monotherapy and bDMARD and methotrexate combination regimens.

Cost considerations limit the use of bDMARDs, especially in resource-limited countries [82]. Biosimilars have no clinically meaningful differences in terms of safety and efficacy compared to their originators, but are generally cheaper [83]. With the expanding use of biosimilars, our SLR examined five head-to-head observational studies that concluded equivalent disease control and adverse event profiles compared with TNFi originators. Despite the overall low certainty of evidence due to the non-randomized design of these studies, the findings align with adult rheumatology experience and support formulary substitution policies that could possibly decrease treatment costs and improve access to biological therapies—an important step in emerging Asia–Pacific economies [84–86].

The emergence of JAK inhibitors is a promising development in the management of refractory pcJIA. Baricitinib, tofacitinib, and upadacitinib all provide moderate-certainty evidence for meaningful clinical improvements, accompanied by acceptable short-term safety profiles. Being taken orally also makes JAK inhibitors an attractive alternative to bDMARDs for children and young adolescents with JIA, especially when their prices are expected to be more competitive in the future. However, it is important to note that long-term safety data in pediatric populations are still emerging. Careful post-marketing surveillance and long-term observational studies will be essential to examine their safety profile in children with JIA.

The increasing use of a treat-to-target (T2T) strategy in JIA care makes a stronger case for standardized outcome measures [87]. Multiple validation studies of the JADAS and its shortened version, the cJADAS, are reflective of their validity, feasibility, and utility in clinical practice. The practicality of cJADAS to make real-time clinical decisions and treatment adjustments can be especially helpful in those without laboratory equipment and settings with a slow turnaround time. In T2T approaches, treatments are modified to reach established goals. However, multiple cutoffs for different disease activity levels and remission criteria necessitate future work and consensus to standardize these treatment targets for improved comparability across clinical settings.

While the use of T2T approach in JIA management has gained increasing momentum, less is known about tapering and withdrawal of medication. Evidence informing medication tapering and withdrawal remains fragmentary. Our SLR suggests that tapering of methotrexate or TNFi after sustained inactive disease may be feasible. However, strategies vary and there is a lack of clarity on the optimal tapering regimen. Gradual dose reduction, rather than abrupt cessation, was associated with lower rates of flare-ups. As the outcomes of JIA patients continue to improve and more patients achieve remission, there is an increasing need for pragmatic clinical trials to determine the best approach to drug tapering [88].

Our SLR also emphasizes the ongoing knowledge gap concerning the management of TMJ in JIA patients. TMJ arthritis contributes to significant craniofacial morbidity, yet there is a

limited understanding of the best systemic and/or local treatments. There are only five new observational studies, mostly focused on intra-oral procedures, that met our inclusion criteria. The lack of high-quality studies limits definitive conclusions about the best systemic or local treatments for TMJ arthritis. Nevertheless, there is potential consequences of TMJ involvement on craniofacial growth, mandibular development, and long-term functional outcomes. Multidisciplinary management involving pediatric rheumatologists, dentists, orthodontists, and maxillofacial specialists remains essential.

Non-pharmacologic interventions, though recommended in all current guidelines, still lack substantial evidence. The existing data are inconsistent, limited by small sample sizes and high variability in patient populations, interventions, and outcomes measured. Similarly, while interest in T&CM remains high among families in the Asia Pacific, the evidence is limited and methodologically weak. These areas require urgent further research.

One limitation of our SLR is the heterogeneity in study designs and outcome definitions, which restricts the ability to perform quantitative analysis. Additionally, excluding non-English literature may have resulted in missing important data from key East Asian sources. This restriction may have introduced language bias and may limit the regional representativeness of the evidence base. However, the APLAR JIA guideline development task force included pediatric rheumatology experts from multiple countries across the Asia-Pacific region, many of whom are actively involved in regional research networks and national registries. During the evidence review, task force members were invited to highlight key studies from their respective regions that may not have been captured in the initial search strategy. This process helped ensure that important regional evidence was considered in the interpretation of findings and formulation of recommendations. Lastly, the predominance of observational studies and small sample sizes in several themes reduces overall confidence in the findings.

The findings from this SLR have several implications. First, the weight of evidence supports adopting a treat-to-target framework that escalates from methotrexate to bDMARD or tsDMARDs when remission is not achieved, mirroring Western algorithms yet mindful of local pharmacoeconomics. Second, the equivalent effectiveness of approved biosimilars should encourage greater access to treatment in resource-limited countries. Third, significant evidence gaps, particularly regarding tapering, TMJ disease, and non-pharmacologic care, outline a clear research agenda for the region.

5 | Conclusion

In summary, this SLR provides a strong foundation for developing the first APLAR clinical practice guideline on pcJIA. While many therapeutic principles align with global standards, our findings highlight the importance of region-specific factors and the need for high-quality studies across various areas. By identifying and synthesizing evidence not previously included in existing guidelines, this review contributes to an updated and contextually relevant framework for caring for JIA patients in the Asia Pacific region.

Author Contributions

K.L.T. drafted the manuscript. L.D. was the methodologist supervising the systematic review. All authors reviewed and edited the manuscript. T.A. supervised the overall project and provided the final edits to the manuscript.

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Disclosure

Patient and Public Involvement Statement: The Task Force on this project involved two patient research partners, who participated in the Task Force meeting where the results of this SLR were presented and discussed.

Ethics Statement

This article analyzed de-identified individual participant data from previously published studies. Therefore, formal ethical approval and informed consent are not required. No new data involving human participants or animals were collected by any of the authors.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors have declared no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Search strategies. **Appendix S2:** Search inclusion. **Table S1:** Summary of included articles for tapering of medications. **Table S2:** Summary of included articles for non-pharmacologic interventions. **Table S3:** Summary of included articles for traditional and complementary medicine. **Figure S1:** Combination Etanercept/MTX versus csDMARD monotherapy. **Figure S2:** Non-pharmacologic interventions.

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LETTER TO THE EDITOR

ELISA Detects Anti-MDA5 Antibodies Missed by Line Blot: Two Cases and a Cohort Review

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Dear Editor,

Anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibodies are key biomarkers for dermatomyositis (DM), particularly in patients with rapidly progressive interstitial lung disease (RP-ILD) [1]. Timely recognition is crucial, as affected patients often require early and aggressive immunosuppressive therapy to reduce morbidity and mortality [2]. While characteristic cutaneous ulcers may suggest this disease phenotype, antibody confirmation remains essential for diagnostic confidence and treatment decisions. However, discrepancies between clinical progression and serological findings may occur and necessitate heightened clinical vigilance.

Line blot immunoassays (LIA), though widely used as first-line screening tools, may miss low-titer antibodies. We report two clinically significant cases where anti-MDA5 antibodies were not detected by LIA but were subsequently identified by enzyme-linked immunosorbent assay (ELISA), supported by findings from a retrospective cohort review. The first case involved a 66-year-old man presented with refractory rashes on his fingers, elbows, and face, initially misdiagnosed as dyshidrosis. He later developed dyspnea and hoarseness, with violaceous rashes and shallow ulcers suggestive of DM. High-resolution computed tomography (HRCT) revealed ILD; however, initial myositis antibody testing using a commercial line blot immunoassay (LIA, Euroimmun, 16 antigens) was positive only for anti-Ro52. Given the strong clinical suspicion of anti-MDA5–associated disease, confirmatory testing using ELISA (Medical & Biological Laboratories Co. Ltd.) [3] was performed, revealing a markedly elevated anti-MDA5 antibodies titer (94 AU, ref. < 32 AU), thereby establishing the diagnosis. Prompt immunotherapy (high-dose steroids, cyclophosphamide, calcineurin inhibitor, rituximab) led to clinical improvement. In this case, ELISA confirmation was obtained approximately 2 weeks after symptom onset, allowing prompt escalation of immunosuppressive therapy.

The second case was a 66-year-old woman with ILD who was initially managed conservatively following a negative LIA. She later developed worsening hypoxemia and required ICU care. Despite late administration of cyclophosphamide and nintedanib for suspected RP-ILD, she deteriorated and opted for palliative care, passing away within 4 weeks. Retrospective ELISA testing demonstrated high anti-MDA5 antibodies (100 au), suggesting that the initial negative LIA result may have contributed to delayed diagnostic confirmation. In contrast, ELISA testing was performed only after clinical deterioration, by which time the therapeutic window may have been missed.

These cases highlight the diagnostic challenges of anti-MDA5 DM and emphasize the importance of integrating clinical suspicion with laboratory findings. While immunoprecipitation (IP) is regarded as the reference standard for detecting myositis-specific antibodies [4], its limited accessibility and dependence on technical expertise often necessitate alternative methods in clinical practice. Commercial line blot immunoassays (LIA), despite their convenience and broad antigen panel, may yield false-negative results due to differences in epitope conformation and reduced sensitivity to low-titer antibodies, as previously reported for anti-TIF1γ by Mulhearn et al. [5] To summarize the underlying mechanisms, we provide a comparative overview of potential causes for false-positive and false-negative LIA results in Table 1. In contrast, ELISA-based assays have been validated in Japanese cohorts [6] and provide a valuable confirmatory tool, although broader validation in diverse populations is needed. Moreover, the semi-quantitative nature of line blot assays means

TABLE 1 | Potential causes of false-negative and false-positive results in line blot immunoassays (LIA) for anti-MDA5 detection.

Category	False negative	False positive
Antigen conformation	Denatured antigens may lose conformational epitopes [5]	Misfolded proteins may expose non-native epitopes [5]
Antibody titer	Low-level antibodies may fall below LIA detection threshold [6]	High total IgG or polyclonal activation may bind nonspecifically [4]
Epitope coverage	Targeted epitopes may be absent in strip design [4]	Cross-reactive epitopes may bind related antigens [4]
Platform sensitivity	Semi-quantitative format lacks resolution for low signals [6]	Inappropriate cutoffs may misclassify weak bands as positive [5]
Assay interpretation	Visual reading may overlook faint bands [4]	Borderline bands may be overinterpreted as positive without confirmation [4]
Technical issues	Insufficient washing or incubation may impair signal development [7]	Residual background signal may produce spurious bands [7]

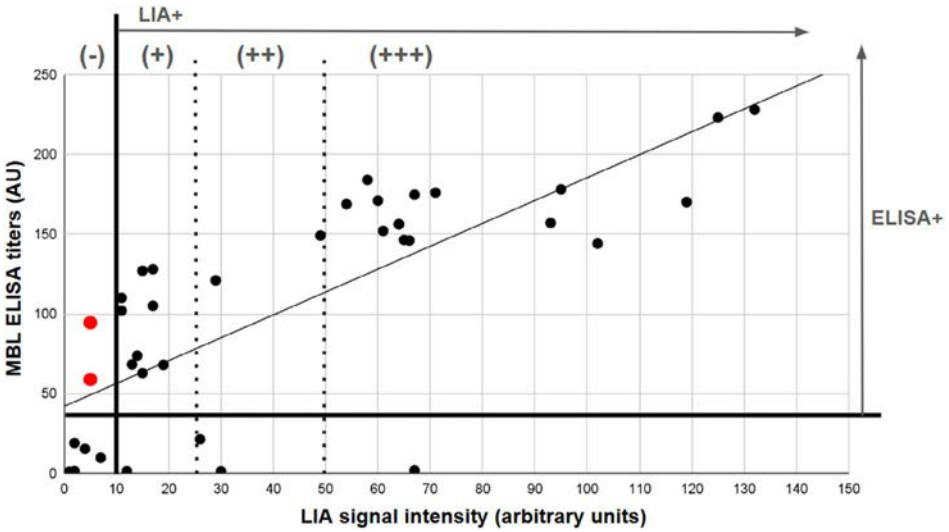

FIGURE 1 | Relationship between line blot signal intensity and ELISA titers for anti-MDA5 antibodies.

signal intensity may not reflect antibody burden and clinical severity, whereas ELISA-based assays have been associated with clinical outcomes [6] and may serve as an additional risk factor to predict RP-ILD and survival.

To further explore this diagnostic discrepancy, we retrospectively reviewed a predefined cohort of 37 patients with DM-associated ILD who underwent both LIA (Euroimmun) and ELISA (MBL Co., Japan) between January 2020 and September 2023. Patients were consecutively identified from our institutional DM-ILD cohort who had tested by both LIA and ELISA as part of routine clinical evaluation. ELISA testing was performed either concurrently with or subsequent to LIA when clinical suspicion for anti-MDA5 DM remained high. Among them, two patients (5.4%) were ELISA-positive but LIA-negative, confirming the discrepancy observed in our index cases. Immunoprecipitation was not routinely available at our institution during the study period and therefore could not be used as a reference standard; clinical diagnosis served as the comparator. LIA was performed using a commercial Euroimmun line blot assay according to the manufacturer's instructions. Anti-MDA5 ELISA (MBL Co., Japan) positivity was defined as ≥ 32 AU, as specified by the manufacturer. While infrequent, these cases highlight the potential for misdiagnosis when relying solely on LIA in high-risk clinical settings. Figure 1 illustrates the relationship between ELISA antibody titers and LIA signal intensities, highlighting the complementary diagnostic value of ELISA in selected cases. The concordance between LIA and ELISA results is summarized in Table 2. Agreement between LIA and ELISA was moderate (Cohen's $\kappa = 0.50$). McNemar's test did not demonstrate a

TABLE 2 | Concordance between line blot immunoassay and ELISA for anti-MDA5 antibodies in patients with dermatomyositis-associated interstitial lung disease.

	ELISA+	ELISA−	Total
LIA+	26	4	30
LIA−	2	5	7
Total	28	9	37

statistically significant systematic difference between the two assays ($p = 0.69$). Summary statistics of ELISA titers and line blot signal intensities are provided to illustrate the distribution of assay results within the cohort, while individual-level data are not publicly shared due to institutional data protection policies.

In summary, we describe two cases of anti-MDA5 DM with RP-ILD where LIA failed to detect anti-MDA5 antibodies, leading to delayed diagnosis and suboptimal management. These cases emphasize the potential for false-negatives in LIA and support the use of ELISA as a complementary confirmatory assay, particularly in high-risk patients. More importantly, they underscore the role of clinical judgment when serological results do not align with disease progression. *This retrospective study was approved by the institutional review board of National Taiwan University Hospital (approval no. 202004111RINB), with a waiver of informed consent*. The data that support the findings of this study are available in aggregated form within the article. Individual-level data are not publicly shared due to institutional and ethical restrictions.

Author Contributions

Wan-Hao Tsai: conceptualization, data collection, data analysis, manuscript drafting, and revision. **Ting-Yuan Lan:** data interpretation and critical revision of the manuscript. **Ko-Jen Li:** study supervision, conceptualization, and critical revision of the manuscript. All authors approved the final version of the manuscript.

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Ethics Statement

This study was conducted in accordance with institutional ethical guidelines. Ethical approval was waived due to its retrospective nature and anonymized data.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Wan-Hao Tsai
Ting-Yuan Lan
Ko-Jen Li

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LETTER TO THE EDITOR

Case Report: Refractory Lupus Intestinal Pseudo-Obstruction Successfully Treated With Obinutuzumab

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Dear Editor,

Standard-of-care therapies of systemic lupus erythematosus (SLE) often prove insufficient for a subset of patients, necessitating the development of novel therapeutic approaches. Here, we report a case of severe, treatment-refractory SLE with intestinal pseudo-obstruction, hydronephrosis, cystitis, and class V lupus nephritis. Treatment with obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, resulted in the resolution of intestinal pseudo-obstruction and hydronephrosis, and improvement of proteinuria after failure of cyclophosphamide and belimumab combination therapy.

A 46-year-old woman presented with persistent watery diarrhea, foamy urine, leg edema, and skin rash. Image study revealed intestinal pseudo-obstruction, splenic infarction, and bilateral hydronephrosis (Figure 1A,D). Laboratory tests showed active serology (high-titer ANA, anti-dsDNA, low complements), antiphospholipid antibodies, and nephrotic-range proteinuria (13.7 g/g). A renal biopsy was contraindicated due to significant bilateral severe hydronephrosis. The patient was diagnosed with SLE with clinical lupus nephritis (LN), presenting with an initial SLEDAI score of 15. Initial therapy was initiated with intravenous methylprednisolone 10 mg every 6 hours. Concurrently, six-monthly cycles of low-dose intravenous cyclophosphamide (500 mg) and intravenous belimumab (400 mg on Day 1, 15, and 29, then monthly) were given. However, she had persistent severe ileus (Figure 1B), refractory diarrhea requiring diaper use, and significant weight loss, despite a reduction in proteinuria (from 13.7 g/day to 7 g/day) and resolution of her skin rash. A renal biopsy remained unfeasible due to persistently severe bilateral hydronephrosis (Figure 1E).

Given the refractory nature of her disease, treatment was switched to obinutuzumab with mycophenolate mofetil (MMF) (starting at 250 mg/day and gradually up-titrated to 1 g/day), with background prednisolone (10 mg/day) and hydroxychloroquine (200 mg/day). Obinutuzumab (1 000 mg) was administered intravenously on Days 1 and 15, followed by maintenance courses at Months 6 and 12 (Weeks 24, 26, 50, and 52). Following initiation, hydronephrosis and bladder wall thickening resolved by Month 6 (Figure 1F), while intestinal pseudo-obstruction resolved completely by Month 13 (Figure 1C). Her proteinuria decreased to 0.75 g/day at Month 13. A kidney biopsy was finally able to be performed after the resolution of her hydronephrosis and confirmed the diagnosis of membranous lupus nephritis (ISN/RPS Class V, Activity Index 1, Chronicity Index 3). During obinutuzumab therapy, she could tolerate MMF only up to 1 g/day despite gradual improvement of gastrointestinal symptoms. MMF was discontinued after six months due to patient intolerance. Despite the sub-therapeutic dosage and early discontinuation of MMF, the patient remained clinically stable without relapse and demonstrated sustained reduction of proteinuria and resolution of pseudo-obstruction, suggesting the potential therapeutic benefit of obinutuzumab. At the latest follow-up (four months after the third cycle of obinutuzumab), proteinuria was 0.69 g/day. She is currently on maintenance therapy with cycle 3 obinutuzumab, 200 mg hydroxychloroquine (5 mg/kg/day), and low-dose prednisolone (5 mg/day).

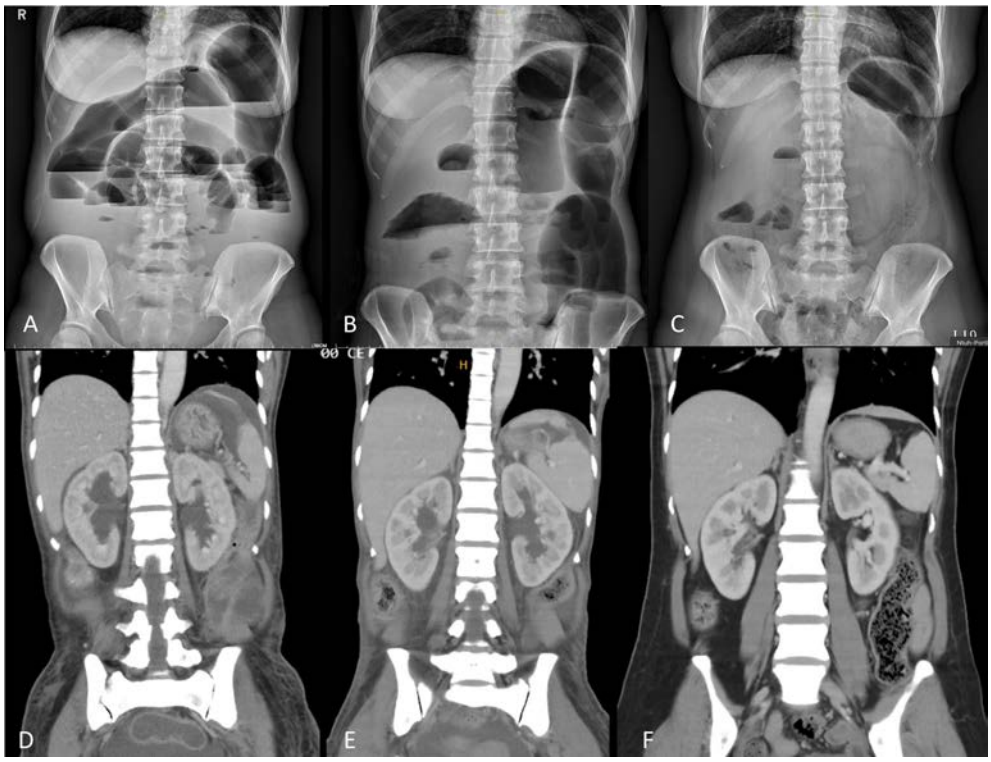

FIGURE 1 | Serial standing abdominal plain films (A–C) and coronal computer tomography (CT) of the abdomen (D–F) of this patient. A (2023/10/10): Prior to induction therapy with cyclophosphamide (CYC) and belimumab (BEL), there is marked evidence of severe ileus, manifesting as pronounced bowel distention and air-fluid levels; B (2024/04/01): After four CYC + BEL cycles, improvement in ileus is noted, with decreased but persistent bowel dilatation; C (2025/08/28): Post three cycles of obinutuzumab, there is marked resolution of ileus, with normalization of bowel gas pattern and absence of distended loops, indicating substantial clinical improvement. D (2023/10/11): Initial CT scan reveals grade 4 bilateral hydronephrosis; E (2024/04/11): After four CYC + BEL cycles, there is improvement to grade 3 hydronephrosis bilaterally; F (2025/01/16): Following one cycle of obinutuzumab, imaging demonstrates near-complete resolution: Grade 1 hydronephrosis on the right and grade 0 (normal) on the left.

B-cell depletion therapy is a cornerstone in managing refractory SLE. While rituximab, a type I anti-CD20 antibody, has been used off-label for over a decade with extensive real-world evidence of efficacy, obinutuzumab achieves superior and more sustained B-cell depletion through enhanced antibody-dependent cellular cytotoxicity and minimizes CD20 internalization—a key mechanism of rituximab resistance in SLE [1]. Emerging data from failed rituximab trials, as well as recent experiences with chimeric antigen receptor (CAR) T cells and other next-generation B-cell–directed approaches, indicate that clinical efficacy in SLE is closely related to the depth and tissue penetration of B-cell depletion, with deep and sustained depletion being associated with durable remission and normalization of autoantibody levels [2, 3]. Given the severity of this patient's refractory multi-organ involvement, we elected to use obinutuzumab as the first-line B-cell depleting agent to ensure maximal potency and avoid potential resistance associated with rituximab. While randomized controlled trials (NOBILITY and REGENCY) have demonstrated improved renal outcomes with obinutuzumab in proliferative lupus nephritis, evidence regarding severe extra-renal manifestations is scarce. Although the ongoing ALLEGORY trial addresses non-renal SLE, patients with severe and life-threatening manifestations, such as intestinal pseudo-obstruction, may not be enrolled [4, 5]. Therefore, this case addresses that gap by documenting robust extra-renal responses—including resolution of lupus enteritis, lupus cystitis, and intestinal pseudo-obstruction—in a patient with refractory multi-organ SLE [6–8].

In conclusion, obinutuzumab may represent a promising therapeutic option for patients with refractory SLE extending beyond renal involvement. Its capability for potent and sustained B-cell depletion may offer clinical benefit across gastrointestinal, genitourinary, and renal manifestations unresponsive to conventional immunosuppressive and biologic therapy.

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T.-Y.L., T.-J.L. and Y.-S.C. patient care and clinical data acquisition. C.-H.W. and I.-S.C. literature review and initial drafting. C.-H.W., I.-S.C. and T.-Y.L. critical revision and final approval.

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Consent

Informed patient consent was obtained for the publication of this article.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All relevant clinical data are presented in the manuscript.

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EDITORIAL

Chimeric Antigen Receptor T Cells in Autoimmune Disease: Mechanistic Insights, Safety Challenges, and Trial Design Imperatives

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1 | Introduction

Chimeric antigen receptor (CAR) T cell therapy, initially developed for hematologic malignancies, has recently been applied to refractory autoimmune diseases (AID) [1]. Early experience in systemic lupus erythematosus (SLE) demonstrated durable clinical remission following a single B cell–directed infusion in heavily pretreated patients [2]. These findings have prompted reconsideration of the risk–benefit balance, mechanistic underpinnings, and trial design strategies specific to autoimmunity.

2 | Conceptual Impact of Small Cohorts

Reports of transient CAR T expansion coinciding with sustained drug-free remission introduced the hypothesis of functional immune recalibration rather than simple B cell depletion [3]. Activity observed in antisynthetase syndrome-associated myositis and interstitial lung disease supports cross-disease applicability of B lineage targeting [4]. Feasibility was further demonstrated in severe systemic sclerosis; CAR T therapies showed their effectiveness in severe patients, such as candidates for lung transplantation [5]. An RNA-engineered, transiently expressed CAR strategy showed promising activity in myasthenia gravis, highlighting alternative persistence-tuning approaches [6]. Early anti-BCMA experience in neuromyelitis optica spectrum disorder broadened the therapeutic target space beyond CD19 [7]. Collectively, these uncontrolled but diverse reports support the possibility of a generalizable immune "reset."

3 | Risk–Benefit Distinctions in Autoimmunity

Toxicity thresholds acceptable in oncology, where short-term mortality was high, were less tolerable in autoimmune conditions characterized by prolonged morbidity and near-normal life expectancy. For patients with AID, lower ceilings for cytokine release syndrome (CRS) and neurotoxicity were warranted, as outlined by consensus grading frameworks [8]. Concerns regarding long-term sequelae, for example secondary malignancies, persistent hypogammaglobulinemia, or chronic cytopenias are further amplified by younger age at treatment. These considerations justified a stratified approach, initially prioritizing organ-threatening refractory phenotypes.

4 | Mechanistic Questions Requiring Trial Embedding

Several mechanistic issues remain unresolved and must be embedded into clinical trial protocols. These include the extent and durability of B cell repertoire remodeling relative to clinical remission; minimal expansion thresholds required to destabilize autoreactive networks; the relative contributions of T follicular helper

modulation versus direct B cell contraction; the role of tissue-resident immune niches in systemic recalibration; and predictive biomarkers such as plasmablast proportion, interferon signatures, and BAFF levels [9]. In addition, insights from senescence-directed cellular interventions suggest that selective clearance of pathogenic stromal or immune subsets may synergize with antigen-specific tolerization strategies [10].

5 | Engineering Priorities Beyond Oncology Models

Optimization of CAR T therapy for AID requires a departure from oncology paradigms. Priorities include the integration of modular safety switches, attenuation or redesign of lymphodepletion regimens, and reduction of immunogenicity to enable retreatment [11]. Development of allogeneic, genome-edited products seeks to reduce vein-to-vein time while mitigating host-versus-graft responses and innate rejection through multiplex editing and HLA modulation [12]. Emerging constructs such as chimeric autoantibody receptor (CAAR) T cells and regulatory T cell–based approaches may allow immunomodulation to be confined to culprit clones, reducing broad hypogammaglobulinemia risk. Transient expression systems or in vivo gene delivery may further refine persistence.

6 | Trial Design: Moving From Anecdote to Evidence

Future trials must adopt adaptive, biomarker-rich designs. Key features should include early ($\leq$90 days) safety and pharmacokinetic endpoints, intermediate (3–12 months) organ-specific indices, and long-term ($\geq$24 months) durability and infection outcomes. Integrated biospecimen schedules—including single-cell profiling, BCR/TCR sequencing, and soluble mediator panels—are critical. Standardized infection prophylaxis and immunoglobulin replacement protocols should be mandated, with toxicity reporting harmonized using consensus frameworks. Bayesian or response-adaptive designs can minimize unnecessary exposure in lower mortality settings while efficiently validating efficacy signals.

7 | Ethical and Health-System Considerations

High manufacturing cost and limited treatment center capacity raise concerns regarding equitable access. The absence of validated predictive biomarkers increases the likelihood of overtreatment in patients who might otherwise respond to emerging biologics or small molecules. Prospective long-term registries, beginning at phase II, are essential for monitoring late cytopenias, oncogenic transformation, and persistent immune dysregulation. Transparent patient counseling must distinguish CAR T therapy as an effectively irreversible cellular intervention, in contrast to cyclical and reversible immunomodulators.

8 | Path Toward Controlled Clinical Integration

Transition from experimental therapy to standard practice requires reproducible multicenter evidence of durable drug-free remission, validated predictive biomarker panels, and clearly defined long-term safety parameters. Manufacturing innovations that reduce cost and time without compromising quality will further influence feasibility. Until these conditions are met, CAR T therapy in autoimmunity should remain restricted to rigorously designed clinical trials with embedded translational analyses.

9 | Conclusion

Early experiences with CD19- and BCMA-directed CAR T therapy in autoimmunity suggest the possibility of single-intervention immune recalibration. Nevertheless, the biological, ethical, and economic contexts of autoimmunity differ fundamentally from oncology, requiring bespoke developmental strategies. Mechanistic clarity, safety-focused engineering, and stratified trial design will determine whether CAR T becomes a transformative therapeutic modality or remains limited to exceptional salvage cases.

Author Contributions

Conceptual framing (all authors); draft preparation (C.Y.W., H.Y.C.); critical revision (S.B.Y., C.Y.W.); final approval (all authors).

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Consent

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Conflicts of Interest

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LETTER TO THE EDITOR

Paradoxical Vitiligo Induced by Adalimumab in Ankylosing Spondylitis With Uveitis: Clinical Management and Therapeutic Considerations

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Dear Editor,

Tumor necrosis factor-α inhibitors (TNFi) are widely used and highly effective in treating ankylosing spondylitis (AS), significantly improving disease activity, functional outcomes, and quality of life. However, despite their established efficacy, TNFi may paradoxically induce autoimmune phenomena, most commonly affecting the skin. The prevalence of such paradoxical cutaneous reactions is reported to range from 0.6% to 5.3% [1]. Psoriasiform and eczematous eruptions represent the most frequent manifestations, while less common inflammatory dermatoses, including lupus-like reactions, vasculitis, sarcoidosis-like and other granulomatous disorders, and lichenoid eruptions [2], have also been described. Recognition of these reactions is clinically significant, as they may complicate disease management and necessitate therapeutic modifications. This report presents a case of AS and recurrent anterior uveitis that developed vitiligo after starting adalimumab.

A 47-year-old male patient had been followed for 9 years with a diagnosis of ankylosing spondylitis. He had previously used sulfasalazine but was on NSAIDs at the time of admission. He presented with inflammatory neck and low back pain. His past medical history revealed recurrent anterior uveitis, the last episode occurring 1 year prior. He had no other chronic illnesses and was a non-smoker. Laboratory tests showed C-reactive protein 12 mg/L and erythrocyte sedimentation rate 32 mm/h. HLA-B27 was positive. Pelvic radiography demonstrated bilateral grade 4 sacroiliitis, and spinal radiography revealed a bamboo spine appearance (Figure 1a,b). His Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score was 6.5, and adalimumab was initiated. One month later, the patient developed new depigmented lesions on the dorsal aspects of both hands (Figure 1c). Dermatological evaluation confirmed vitiligo. Adalimumab was discontinued, and topical tacrolimus was prescribed. The patient was subsequently switched to secukinumab, with significant improvement in axial complaints, partial repigmentation of vitiligo lesions, and no further uveitis recurrences during follow-up.

Although TNF-α inhibitors are effective in managing AS, paradoxical autoimmune reactions, including psoriasis, sarcoid reaction, and rarely vitiligo, have been reported. The exact mechanisms remain unclear, but proposed pathways include disruption of cytokine balance and compensatory activation of type I interferons [3]. Genetic predisposition may further increase the likelihood of this autoimmune phenomenon in susceptible patients. TNF-α inhibition may decrease Treg production and activation, leading to increased T cell autoreactivity against melanocytes [4].

Younger patients and those receiving etanercept appear to have a higher risk of developing vitiligo [5]. A case of AS has been reported in which previously stable vitiligo showed rapid deterioration within 3 months of initiating adalimumab therapy, with marked improvement following TNFi withdrawal [6]. Another report described adalimumab-induced vitiligo in a patient with plaque psoriasis, where switching to secukinumab led to the resolution of both psoriasis and the presumed drug-induced vitiligo [7]. Furthermore, elevated IL-17 levels and increased IL-17A mRNA expression have been demonstrated in vitiligo lesions [8]. Based on these findings, IL-17 inhibition was considered an appropriate therapeutic option for our patient, whose axial manifestations were predominant and who had remained free of uveitis for the preceding

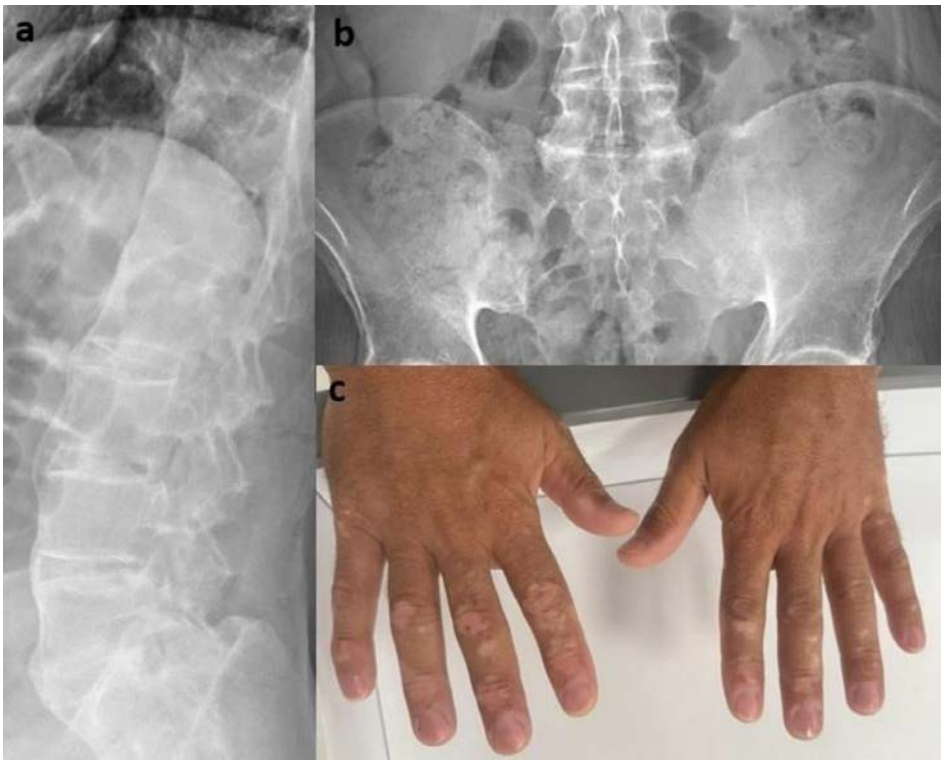

FIGURE 1 | (a) Lumbar radiograph of a patient with ankylosing spondylitis demonstrating the characteristic "bamboo spine" appearance; (b) Pelvic radiograph showing bilateral grade 4 sacroiliitis according to the modified New York criteria; (c) Hypopigmented patches on the dorsal surfaces of both hands, consistent with vitiligo.

year. Nevertheless, cases of new-onset vitiligo or progression of pre-existing vitiligo have also been documented during secukinumab therapy [9]. If uveitis or axial complaints could not be controlled under secukinumab treatment, tofacitinib or upadacitinib could also be considered potential therapeutic options [10].

This case highlights vitiligo as a rare paradoxical reaction to adalimumab in a patient with ankylosing spondylitis and recurrent anterior uveitis. Transition to secukinumab provided effective control of axial symptoms, partial repigmentation of vitiligo, and sustained uveitis remission. While IL-17 blockade may be a rational therapeutic option in this context, reports of paradoxical vitiligo under secukinumab emphasize the need for careful monitoring. Awareness of such paradoxical autoimmune manifestations is essential to optimize management strategies and guide individualized treatment decisions in patients receiving biologic therapies.

Acknowledgments

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Ethics Statement

Written informed consent was obtained from the patient before writing the report.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Tuba Yuce Inel

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LETTER TO THE EDITOR

Case Report: Secondary Osteoporosis With Extensive Bone Marrow Edema Mimicking Axial Spondyloarthritis in a Young Woman

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Dear Editor,

Axial spondyloarthritis (axSpA), particularly radiographic axSpA (ankylosing spondylitis, AS), is a chronic inflammatory disease mainly involving the axial skeleton and sacroiliac joints, typically presenting in young adults with inflammatory back pain (IBP) and characteristic imaging findings [1, 2]. Laboratory features such as HLA-B27 positivity [3] and elevated inflammatory markers may support the diagnosis, while bone marrow edema (BME) on MRI is regarded as a key feature of active sacroiliitis and is incorporated into the Assessment of SpondyloArthritis International Society (ASAS) classification criteria [2, 4]. However, BME is not disease-specific and may also occur in mechanical stress, trauma, metabolic bone disease, or osteoporosis (OP).

OP reduces bone mass and disrupts microarchitecture. Common in older adults, secondary OP also affects younger individuals due to nutritional, endocrine, or mechanical factors [5]. The resulting BME can mimic inflammatory lesions on imaging, complicating diagnosis. Here, we first report a young woman with extensive OP-related BME initially misdiagnosed as axSpA and discuss the key distinctions between the two conditions.

An 18-year-old woman presented with low back pain for over 6 months (Figure 1). In 2023, she experienced Achilles tendon pain with normal MRI findings. In September 2024, MRI at Hospital A revealed extensive BME in both sacroiliac joints changes and small bilateral hip effusions (Figure 1a–c). She was HLA-B27 positive and suspected of having axSpA. In October 2024, Hospital B diagnosed axSpA based on the ASAS criteria (Figure 2) and initiated adalimumab. After six injections, there was no clinical or radiologic improvement.

In January 2025, she was admitted again for persistent low back pain. Further review of her medical history revealed scoliosis and a suspected occult S1 fracture in 2021. From September 2022, after ridiculed for "thick legs," she had undergone extreme dieting and 5–6 h of daily high-intensity exercise, losing 10 kg (160 cm/50 kg to 161 cm/40 kg, BMI 15.43 kg/m^2). She was subsequently diagnosed with anorexia nervosa and sleep disorder and developed fatigue, alopecia, and secondary amenorrhea for over 1 year. Leukopenia (2–3 × 10^9/L) was noted in May 2023. Imaging at that time demonstrated multifocal BME involving the femoral head, acetabulum, and epiphyseal regions, which are rich in trabecular (cancellous) bone (Figure 1d–h). Dual-energy X-ray absorptiometry revealed OP (*Z*-score: −3.0). Serum 25-hydroxyvitamin D (25-OH-VitD, including D2 and D3) measured by LC-MS/MS was markedly reduced at 7 ng/mL (reference range: < 12 ng/mL, deficient; 12–20 ng/mL, insufficient; ≥ 20 ng/mL, sufficient). On reassessment, spinal mobility was preserved (modified Schober's test within normal limits), and sacroiliac provocation tests were unremarkable. Clinically, the pain was aggravated by physical activity and relieved by rest, without typical nocturnal pain or significant morning stiffness. Therefore, she did not fulfill the ASAS definition of IBP [6]. Given the markedly reduced bone mineral density (BMD), symptomatic BME, and persistent hypoestrogenism, treatment with alendronate

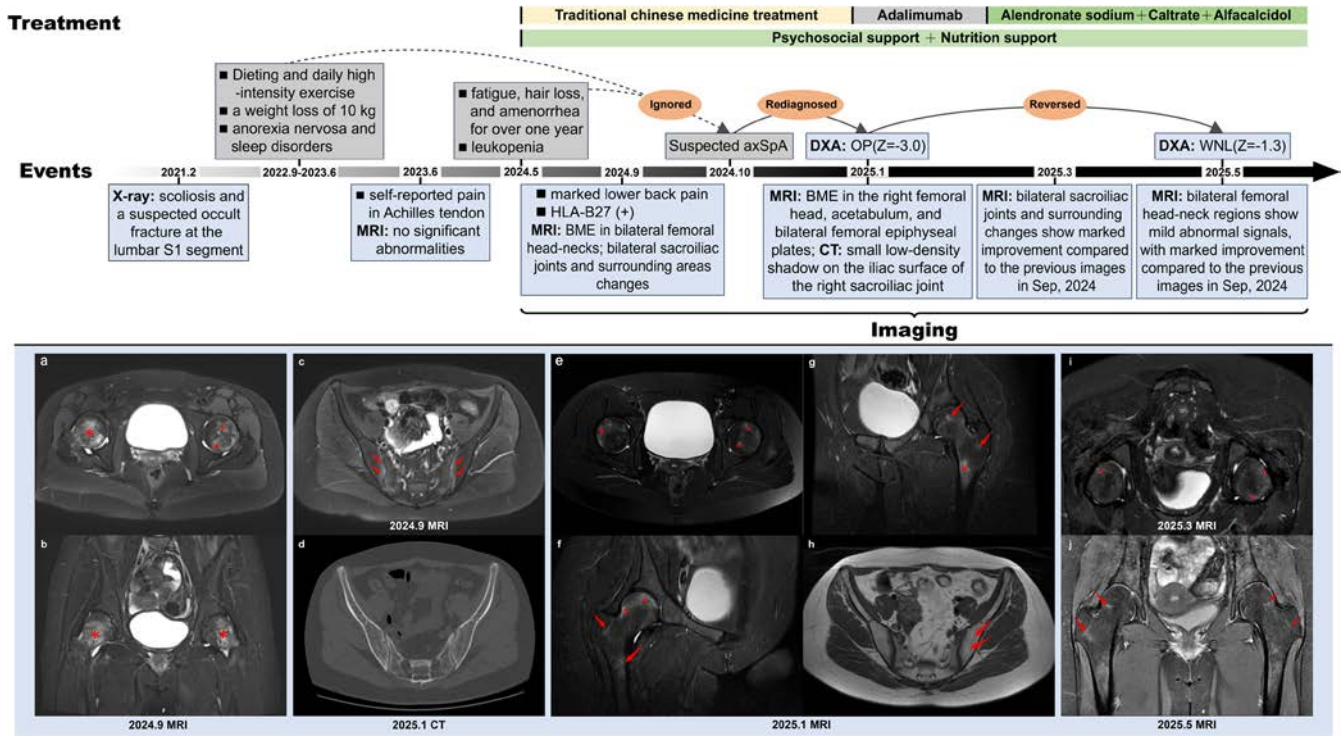

FIGURE 1 | Timeline of key diagnostic and treatment information and imaging changes in this case. Images (a–c) and (e–g) showed visible BME; (d) revealed significant OP; (h) showed uniformly distributed fatty high signals associated with OP on T1-weighted imaging, distinguishing it from the localized bone destruction and fat deposition related to AS; (i, j) were follow-up MRIs showing marked improvement and near resolution of previously noted BME. As shown in Image (h), by January 2025, the BME around the sacroiliac joints had significantly improved, with only partial fat infiltration remaining. On follow-up in March 2025, the BME in the femoral heads also showed marked improvement. Subsequently, in May 2025, a targeted follow-up MRI of both hip joints was performed, and Image (j) demonstrated that the BME had almost completely resolved compared to Image (b). BME, bone marrow edema; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; HLA-B27, human leukocyte antigen B27; MRI, magnetic resonance imaging; OP, osteoporosis; WNL, within normal limits.

sodium 70 mg/qw, caltrate 1#/qd, and alfacalcidol 0.25 μg/qd was initiated after a multidisciplinary risk–benefit evaluation to improve BMD, reduce fracture risk, and stabilize bone turnover. Follow-up MRI in March (Figure 1i) and May 2025 (Figure 1j) demonstrated marked resolution of sacroiliac and hip BME. BMD improved substantially (Z-score: −1.3), and serum 25-OH-VitD increased to 11.8 ng/mL. Inflammatory markers (ESR, hsCRP), autoimmune panels, endocrine tests, and infection screening were all normal. A final diagnosis of secondary OP-related mechanical insufficiency BME was established based on clinical evolution, imaging response, and multidisciplinary evaluation. The most likely etiology was energy deficiency-related functional hypothalamic amenorrhea caused by prolonged extreme dieting and excessive exercise. Chronic energy imbalance suppresses the hypothalamic–pituitary–gonadal axis, leading to hypoestrogenism, which disrupts bone remodeling homeostasis, accelerates trabecular bone loss, compromises mechanical strength of cancellous bone, and increases skeletal fragility. This pathophysiological mechanism aligns with that described in the Female Athlete Triad and Relative Energy Deficiency in Sport (RED-S) [7, 8]. The distinguishing features from axSpA are summarized in Figure 2 based on the literature review (Tables S1 and S2 and Figure S1) and multidisciplinary consultation.

AxSpA typically affects young individuals and presents with chronic low back pain, sacroiliac involvement, BME, and HLA-B27 positivity, features that initially led to misdiagnosis in this case. According to the ASAS criteria of axSpA, the diagnosis follows two pathways (Figure 2): one based on sacroiliitis detected by X-ray or MRI and the other on HLA-B27 positivity [2, 4]. Among these, bilateral sacroiliitis of grade ≥2 or unilateral sacroiliitis of grade ≥3 on X-ray, or the presence of BME or osteitis on MRI, constitute the imaging basis for the diagnosis of sacroiliitis [9, 10]. However, only subchondral BME on the sacroiliac joint surface qualifies as "positive MRI for sacroiliitis" [5]. In this patient, early imaging showed nonspecific periarticular edema without definite erosions, followed by fatty changes that blurred bony margins, highlighting a well-recognized diagnostic pitfall in daily practice.

A key factor in the misdiagnosis was the insufficient consideration of metabolic bone disease. The patient's significant weight loss and amenorrhea due to extreme dieting and excessive exercise suggested hormonal and bone metabolic dysregulation. Estrogen deficiency and potential glucocorticoid exposure may accelerate bone loss but are often overlooked [11]. In 2025, low BMD and severe 25-OH-VitD deficiency further supported the diagnosis of secondary OP. Although trabecular bone score and bone turnover markers (e.g., β-CTX and P1NP) were not assessed, the profound reduction in BMD combined with clinical features such as low BMI and amenorrhea strongly indicated impaired bone quality and active metabolic bone loss.

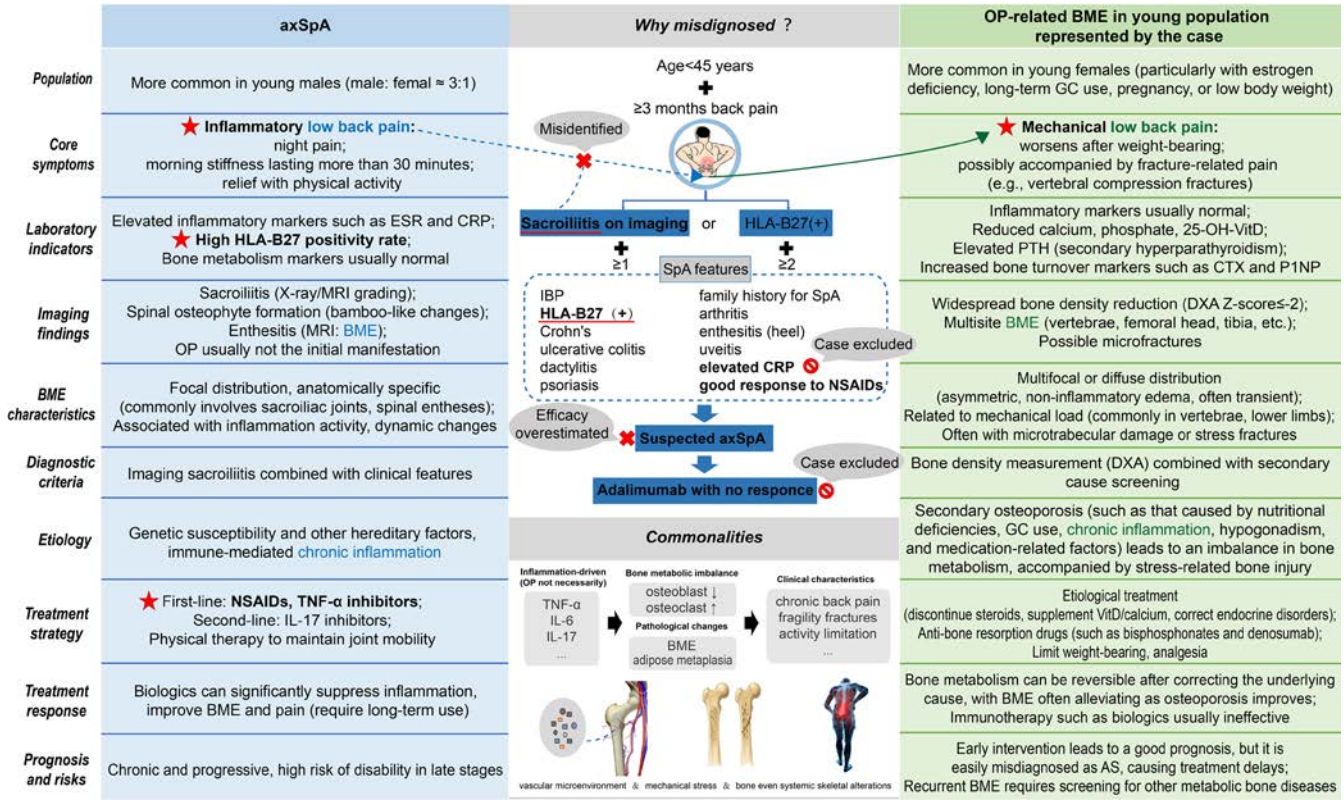

FIGURE 2 | Commonalities and comparison of clinical features between axSpA and OP-related BME. BME, bone marrow edema; CRP, C-reactive protein; CTX, C-terminal telopeptide of type I collagen; DXA, dual-energy X-ray absorptiometry; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; HLA-B27, human leukocyte antigen B27; IBP, inflammatory back pain; IL, interleukin; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; OP, osteoporosis; PTH, parathyroid hormone; P1NP, procollagen type I N-terminal propeptide; SpA, spondyloarthropathy; TNF-α, tumor necrosis factor-alpha; 25-OH-VitD: 25-hydroxyvitamin D.

Overinterpretation of HLA-B27 positivity also contributed to misdiagnosis. The HLA-B27 positivity rate in the general population is 5%–8% [3]. When combined with age under 45 and chronic low back pain [4], this can easily lead to a misdiagnosis of axSpA. However, this patient lacked characteristic IBP features (nocturnal pain, morning stiffness), persistently normal inflammatory markers (hsCRP, ESR), and showed no response to biologic therapy [12], all of which contradict the typical disease course of axSpA.

Overreliance on MRI-detected BME without considering alternative causes such as mechanical stress, trauma, infection, or metabolic bone disease may also lead to misdiagnosis [9]. Notably, BME in axSpA exhibits "anatomically site-specific distribution", primarily concentrated in the sacroiliac joints, vertebral endplates, and entheses [13], reflecting localized inflammatory responses. In contrast, OP-associated BME demonstrates a "mechanically related distribution," typically involving weight-bearing areas such as vertebral bodies, femoral heads, and proximal tibiae, often accompanied by trabecular microfractures or imbalanced bone remodeling [14]. In this case, the multifocal and asymmetric edema pattern (involving femoral heads, acetabula, and bilateral femoral epiphyseal plates) radiographically aligns with the characteristics of OP-related BME. Unlike acute osteoporotic fractures, the gradual onset in this case characterizes a bone stress injury, where repetitive strain exceeds the repair capacity of the osteoporotic bone, leading to insidious pain and microdamage accumulation.

The temporal evolution of imaging findings further aids differential diagnosis. In axSpA, BME correlates with disease activity and requires biological agent intervention for resolution [2], whereas OP-related edema is often self-limiting, gradually subsiding with anti-resorptive therapy or mechanical load adjustments [14]. Notably, although current classification criteria facilitate axSpA identification, their overall performance remains suboptimal [15–17], with reported sensitivity of 82.9% and specificity of 84.4% [4].

From a clinical perspective, misdiagnosis carries therapeutic consequences. AxSpA treatment targets inflammation via NSAIDs or biologics [12], but long-term NSAID use may exacerbate OP [11]. Conversely, OP management addresses underlying causes (e.g., calcium/VitD supplementation) and uses anti-resorptive or bone-forming agents [18]. OP-related BME requires bone repair and mechanical protection, including short-term analgesia, bracing, or weight-bearing restriction during the acute phase [11]. For patients with concomitant mental health disorders, multidisciplinary care and psychosocial support are essential.

Overall, this case highlights the importance of integrating clinical history, laboratory data, bone metabolism assessment, and

MRI distribution patterns in young patients with BME to distinguish inflammatory from metabolic etiologies and avoid inappropriate treatment.

Author Contributions

Xinyue Zhang conducted the literature review, collected the data, and drafted the manuscript; Shaozhe Cai and Guifen Shen critically reviewed and revised the manuscript; Min Wang contributed to the interpretation and review of the radiological findings; Lingli Dong was responsible for the patient's clinical management and revised the manuscript. All authors read and approved the final manuscript.

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Ethics Statement

This study was reviewed and approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. TJ-IRB202510024). All procedures involving human participants were conducted in accordance with the principles stated in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). No identifying information or personal data that could reveal the patient's identity is included in the manuscript.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The informed consent form and related documentation can be made available to the journal's editorial office upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data available in article Supporting Information.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Flowchart of literature selection. **Table S1:** Search strategy used for the literature review. **Table S2:** Summary of reported cases of osteoporosis-related bone marrow edema with spondyloarthritis-like clinical features. **Data S1:** apl70619-sup-0001-Supinfo.docx.